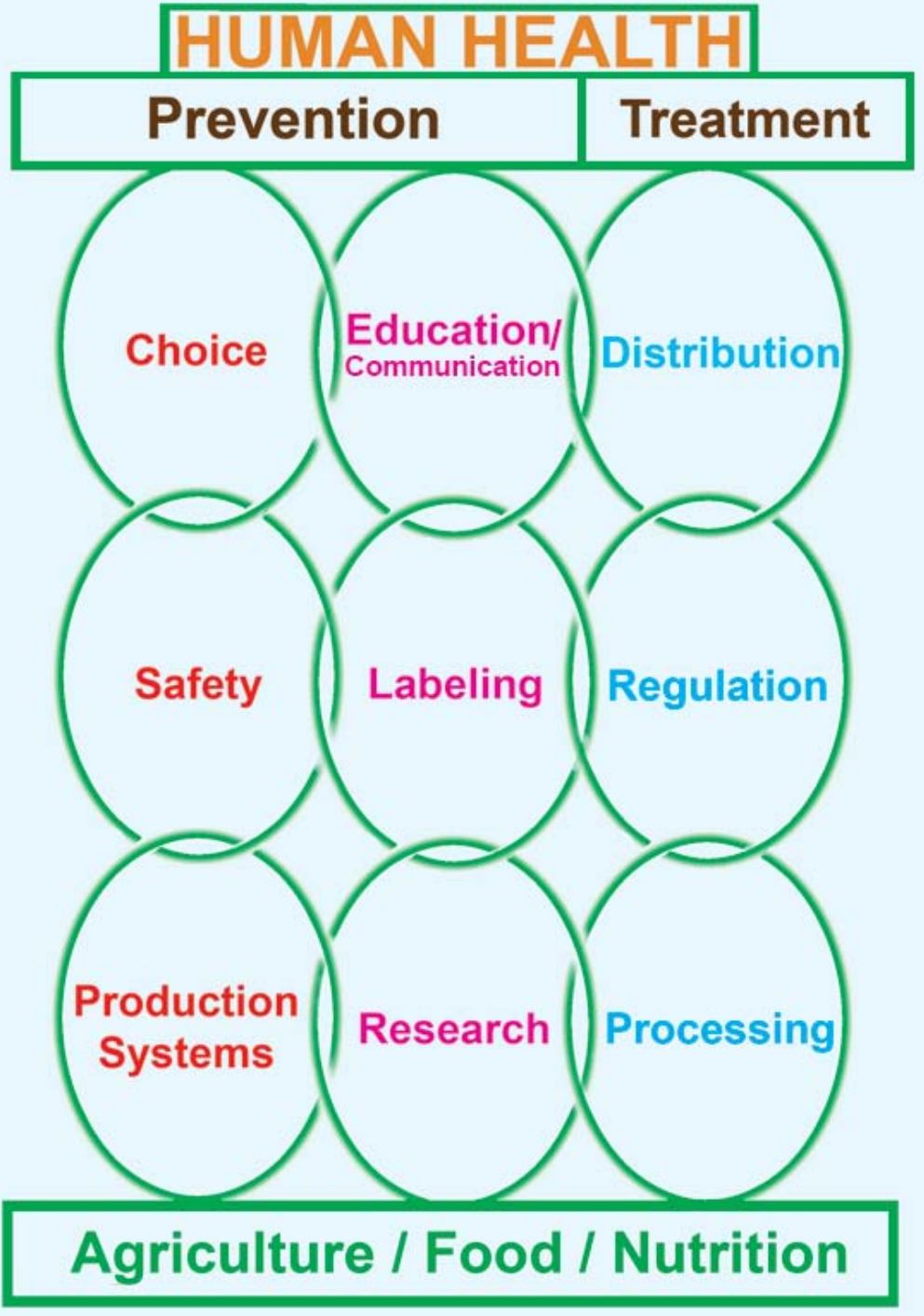
NABC Report 22

Promoting Health by Linking Agriculture, Food, and Nutrition



Edited by Allan Eaglesham, Alan B. Bennett & Ralph W.F. Hardy

2010

National Agricultural Biotechnology Council Report

The cover illustration indentifies the multiple linkages that tie agriculture, food and nutrition together for—especially—prevention, but also treatment, of disease for the improvement of human health. Speakers at NABC's twenty-second annual conference, and other attendees during breakout workshops, addressed all of these linkages, as recorded in this report. Research in agriculture, food and nutrition is the underpinning component for improvements in production systems, inputs, crops and in processing for more healthful diets. Research also underpins safer food sources, labeling and regulation, including identifying biomarkers for human disease. Finally, education, communication and distribution play key roles in assisting consumers in choosing more healthful foods. The multiple links dictate the necessity of an interdisciplinary and interinstitutional research structure for effective coupling of agriculture, food and nutrition to the goal of improved human health.

NABC Report 22

Promoting Health by Linking Agriculture, Food, and Nutrition

Proceedings of the twenty-second annual conference of the National Agricultural Biotechnology Council, hosted by the University of California, Davis, June 16–18, 2010

Edited by
Allan Eaglesham, Alan B. Bennett and Ralph W.F. Hardy

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NABC Report 22

Promoting Health by Linking Agriculture, Food, and Nutrition

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Providing an open forum for exploring issues in agricultural biotechnology

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ACKNOWLEDGMENTS

NABC's twenty-second annual conference—*Promoting Health by Linking Agriculture, Food and Nutrition*—was hosted by Neal Van Alfen at the University of California, Davis (UCD), in Davis, CA, with program development by Alan Bennett and event planning by Carrie Cloud and Chris Akins, to all of whom we are extremely grateful for a highly successful conference.

Thanks are due to the members of the planning committee[1] for an excellent agenda and first-rate choice of speakers: Alan Bennett (program chair), Lindsay Allen, Charlotte Biltekoff, Clare Hasler-Lewis, Carl Keen, Kirk Klasing, Jim Seiber and Tom Tomich (all UCD), Mark McLellan (University of Florida) and Kenneth Swartzel (North Carolina State University).

Seamless operation of the proceedings resulted from the excellent efforts of the following:

Moderators and Workshop Facilitators: Alan Bennett, Carl Keen and Tom Tomich (all UCD), Mark McLellan (University of Florida) and Kenneth Swartzel (North Carolina State University).

Workshop Recorders and Reporters:* Ashley Burns (Clemson University), Vannessa Da Silva and Cindy Montero (both University of Florida), Amanda Martin (University of Minnesota), Mark McLellan* (University of Florida), Lauren Ritchie* (Texas A&M University) and Laurie Steed* (North Carolina State University).

Student Voice Program Administrator: Susanne Lipari (NABC).

Student Voice Reporters: Rosalee Hellberg (North Carolina State University) and Watchareeya Kuldamrong (McGill University).

Special thanks go to Monsanto Co. for defraying costs of meals and refreshments.

On behalf of NABC, we thank Mark McLellan (University of Florida) for exemplary leadership as NABC's chair, 2009–2010.

Ralph W.F. Hardy
President
NABC

Allan Eaglesham
Executive Director
NABC

November 2010

[1]RWFH and AE served on the planning committee.

PREFACE

In 2002, NABC's fourteenth annual conference—hosted by the University of Minnesota—had the theme *Foods for Health*. The resulting proceedings volume, *NABC Report 14*, was titled *Integrating Agriculture, Medicine and Food for Future Health.* Since then, delivery of healthcare has become one of the most pressing social, economic, technical and political challenges of our time. In 2007, expenditure on healthcare in the United States was 16% of the GDP, growing at twice the rate of inflation. Diet-related chronic ailments—diabetes, heart disease, stroke, cancer, obesity, asthma, *etc*.—account for about 75% of the expenditure. Recognizing that emphasis has been on therapeutic and surgical interventions rather than on prevention through improved diet, in March 2009 NABC published *Food and Agricultural Research: Innovation to Transform Human Health*[1], a white paper proposing a 21st-century plan to make food and agriculture a full partner in the endeavor to improve human health.

Building on the themes presented in *Food and Agricultural Research*, NABC's twenty-second conference, *Promoting Health by Linking Agriculture, Food and Nutrition*, brought attendees representing academia, industry and government agencies to the University of California's Davis campus, June 16–18, 2010. Speakers at NABC 22 addressed the science linking agriculture, food, and nutrition to health, with the goal of informing both research priorities and government policies that seek to improve human livelihoods.

Agriculture and conventional food systems have provided the basis for long and healthy lives, which have improved dramatically over the last century, and much of that improvement can be traced to healthier diets. At the same time, we are faced with a growing critique that conventional food systems are a significant contributor to the health crisis that developed countries are facing, particularly related to obesity and diabetes. With this dichotomy—agriculture and diet being both the problem and the solution to an increasing health crisis—NABC 22 was framed, focusing on research strategies to better promote health through food and diet as well as on how governmental regulatory systems are providing oversight of the relationship between food and health.

The conference was organized in five sessions:

I. Agriculture, Food, and Health: The Problem and the Solution

- *Food and Nutrition: The Good, the Bad, and the Ugly*–Carl Keen (UC Davis)
- *Trends, Innovations and the Future of Food-Product Development*–Clare Hasler-Lewis (UC Davis)
- *The American Diet: Voluntary Action vs. Government Action*–Michael Jacobson (Center for Science in the Public Interest)

[1]Appendix, pages 257–268.

II. Food for Health Successes and Prospects

- *The Pipeline of a New Generation of Foods*–Marlin Edwards (Monsanto Co.)
- *Mammalian Milk Genomics: Knowledge to Guide Diet and Health in the 21st Century*–Jennifer Smilowitz (UC Davis)
- *Opportunities for Biofortification of Cassava: The BioCassava Plus Program*–Martin Fregene (Donald Danforth Plant Science Center)

III. Choosing Foods for Health

- *Functional Foods For Health: Negotiation and Implications*–Charlotte Biltekoff (UC Davis)
- Farm2School: *Giving Children a Healthy Choice for Lunch*–Robert Knight (Old Orange Grove)
- *Putting People First: Designing for Healthy Product Choices*–Lauren Shimek (IDEO)

IV. Regulatory Framework for Food Health Claims

- *Food-Labeling: Where Science, Health and Policy Meet*–Barbara Schneeman(US Food and Drug Administration)
- *The Science Behind the Claims and Why the Product that Bears a Claim Needs to be "Healthy"*–Joanne Lupton (Texas A&M University)
- *The EU Regulation on Nutrition and Health Claims: Current and Future Trends*–Miguel da Silva (European Advisory Services)

V. Food for Health Strategies and Programs

- *Alimentary Pharmabiotics: Common Ground for Academia with the Food and Pharmaceutical Industries*–Fergus Shanahan (University College Cork)
- *A National Network for Advanced Food and Materials*–Rickey Yada (University of Guelph)
- *Where Will Business Find the Next Best Food and Nutrition Innovations?*–Will Rosenzweig (Physic Ventures)

Martina Newell-McGloughlin (UC Davis) provided the banquet presentation, *Plant Biotechnology: The Answer to your Nutrition Needs!*

Thus, an excellent cross-section of interdisciplinary talks was presented to 159 attendees. Most of the linkages among agriculture, food, nutrition and human health were covered: research aspects, production and distribution systems, processing, safety, regulation, labeling, communication, education and choice.

As is traditional for NABC meetings, participants gathered in smaller "breakout" workshops for further discussions of issues raised in the plenary and Q&A sessions.

The *Student Voice at NABC* program provides grants of up to $750 to graduate students at NABC-member institutions (one student per institution) to offset travel and lodging expenses. Also, registration fees are waived for grant winners. The *Student Voice* delegates attended the plenary sessions and breakout workshops, and then met as a group to identify current and emerging issues relevant to the conference subject matter.[2]

This volume contains an overview of the conference, a summary of the break-out-workshop discussions, manuscripts provided by the speakers, including the banquet presentation, and the *Student Voice* report. Transcripts of the Q&A sessions are included.

In 2011, NABC's annual conference will return to the University of Minnesota, St. Paul, MN, with food again as the underpinning theme—*Food-Security: The Intersection of Sustainability, Safety and Defense*, June 15–17.[3]

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Executive Director
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Davis

Ralph W.F. Hardy
President
NABC

[2]Information on the *Student Voice at NABC 23* will be available at http://nabc.cals.cornell.edu/studentvoice.

[3]Further information may be accessed via http://nabc23.umn.edu.

[4]Public Intellectual Property Resource for Agriculture

CONTENTS

PART II–BREAKOUT SESSIONS

Workshops Summary

Ashley Burns[1]
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Vanessa Da Silva[2]
University of Florida

Amanda Cece Martin[3]
University of Minnesota

Mark McLellan[4]
University of Florida

Cindy Montero[5]
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Lauren Ritchie[6]
Texas A&M University

Laurie Steed[7]
North Carolina State Univ.

Ken Swartzel[8]
North Carolina State Univ.

Tom Tomich[9]
University of California–Davis

Two breakout sessions were held at NABC 22 on days 1 and 2—each comprising three parallel workshops—and oral reports (see footnotes) were delivered on day 3. The objective of the workshops was to provide all conferees the opportunity to speak, to listen and to learn about promoting health by linking agriculture, food and nutrition. The reports are summarized, using terminology from the cover page.

Research Topics

- Use all tools—plant breeding, biotechnology, radiation, preservation *etc*.—to produce more healthy foods.
- Provide funding for specialty crops, *e.g.* fruits, vegetables.
- Encourage production of more healthy crops, *e.g.* canola, high oleic soybean, as food sources.
- Biofortification.
- Biomarkers.
- Genomics, metabolomics, nutrigenomics for personalized foods.

[1]Recorder, workshop 1; [2]recorder, workshop 2; [3]recorder, workshop 3; [4]discussion facilitator, workshop 3, and verbal reporter at the conference; [5]recorder, workshop 3; [6]recorder, workshop 2, and verbal reporter at the conference; [7]recorder, workshop 1, and verbal reporter at the conference; [8]discussion facilitator, workshop 2; [9]discussion facilitator, workshop 1.

- Post-harvest shelf life.
- Food supply/security with challenges from emerging pests/diseases, climate change, water supply.
- Identify the bases of consumer choice with a view to modifying taste/flavor, cost, and culture-affected eating habits.
- Attention is needed to framing problems. For example, improving human nutrition may require data on median income and food costs.

Research Structure

- Major programs should be interdisciplinary and interorganizational, *i.e.* involving academia, industry, government and farmers.
- Include anthropological, social, economic, behavioral and communication skills, and relevant sciences in interdisciplinary programs.
- Nurture interdisciplinary conversations to help generate collaborative programs.
- National R&D support should be allocated specifically for interdisciplinary and interorganizational programs [similar to Canada's Agricultural Bioproducts Innovation Program (ABIP), for example].
- Provide incentives to academics to collaborate, including joint appointments and participation in joint graduate programs.

Research Training

- Redress the shortage of food scientists.
- Expose students to multidisciplinary collaborative efforts.
- Provide a full repertoire of practical skills to students as part of science-capacity building.
- Develop skills in communicating with consumers (see also *Communication* below).
- Follow the recommendations laid out in the National Research Council's 2009 report, *A New Biology for the 21st Century*.

Regulation

- Credible, science-based.
- Reduce the high cost of regulatory hurdles for low-acreage biotech-modified specialty crops, *e.g.* fruits and vegetables important for human health.
- Elucidate biomarkers to appraise human-health claims for foods.

Labeling

- Develop easy-to-understand profiling of food healthfulness, *e.g.* a smiley face for "healthy."
- Assess the effectiveness of current food labeling.

Education

- Promote education in food, nutrition and health for consumers (adults and K–12), food preparers (*e.g.* chefs), and health-service providers (nurses, physicians).
- Graduate students in the applied sciences should be exposed to political science and learn skills for communicating with lay people.

Choice

- Provide incentives to growers and processors to provide, stepwise, more healthy food, *e.g.* reduced in calorie, salt and sugar contents and containing improved oils.
- Replicate applicable aspects of the anti-smoking campaign to encourage healthy food choices.
- Use all available media—print, radio, television, Internet—to encourage people to consume fewer calories, less salt and less sugar.
- Structure food-stamp programs to encourage purchase of healthy foods.
- Identify forces shaping health and food choices by consumers.

Communication

- Encourage dialog between consumers and academics involved with agriculture, food and nutrition.
- Fund behavioral/communication-based research to develop effective tools to motivate consumers to make more-healthy food selections.
- Communicate the advantages of improved quality of life and savings in medical costs that result from choosing healthy foods.

PART III–PLENARY SESSIONS

Agriculture, Food and Health: The Problem and the Solution

Food and Nutrition: The Good, The Bad, and The Ugly

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The 19th century in the United States was a period of great expansion of population and of cities and territory. With the establishment of the railroad and enhanced food-preservation technologies, a variety of food products soon became available across the country. By the end of the century, markets began to replace the personal or local farm as the primary source of food attainment (Williams, 2006). New techniques in agriculture and food preservation were developed to meet new demands for greater food choices at modest prices. In the 1890s, Wilbur O. Atwater at the USDA established the first compositional and requirement tables for food (Welsh et al., 2002). During the same time period, the US government expanded research into nutrition and food safety for the military (Friedl and Hoyt, 1997). In part, as a consequence of the above, by the early 1900s a set of demands that met the needs of the average consumer, public health officials, government entities, and the food industry was established. These demands were, and continue to be, for foods and diets that are safe, nutritious, well balanced, and modestly priced, while affording those in industry a profit. Although initially the primary demands on the food industry were that the products they provided be safe and reasonably priced, the expectation today is that foods we consume will also protect against a wide variety of age-related diseases. Thus, changing concepts in the expectations of food in the past century have moved beyond the reduction of well-recognized nutritional deficiencies (*e.g.* scurvy, rickets, and pellagra) to that of food providing "optimal health" (Figure 1).

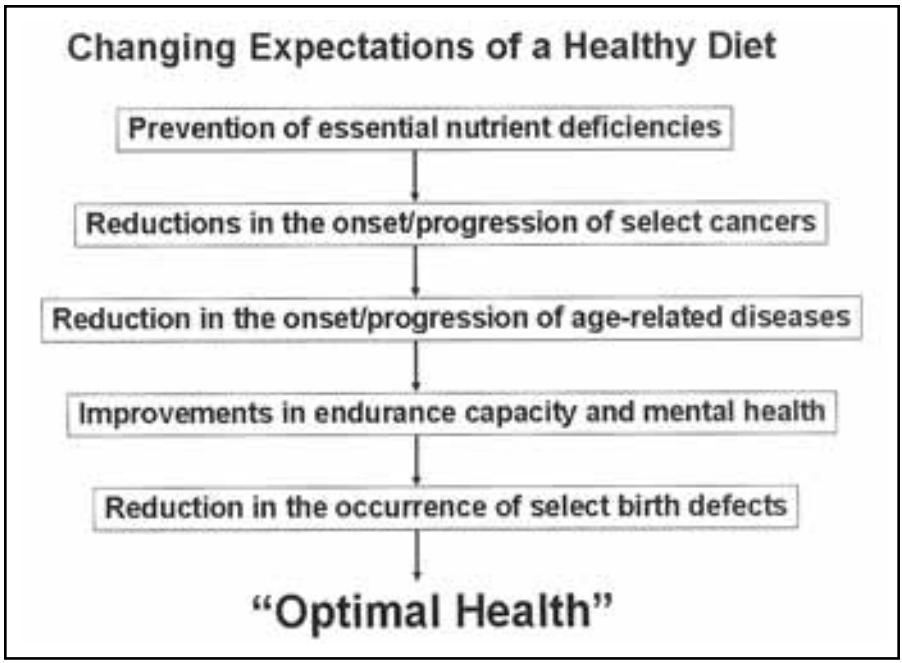

Figure 1. The changing expectations from a healthy diet: From prevention of essential nutrient deficiencies to achieving optimal health.

It is important to note that consistent with these new expectations of diet by the public, a major part of the rationale driving the development of current US and Canadian Dietary Reference Intakes (DRIs) is that nutrient intakes should ideally be set at levels that reduce the risk for select chronic diseases, such as diabetes, heart disease and cancer (IOM, 1997; Chung *et al.*, 2010). This expanded the mission of public-health policy from setting nutrient levels to prevent deficiencies that cause well-defined diseases to the establishment of dietary recommendations for the prevention of chronic disease states that are multifactorial in etiology, and for which established biomarkers are not yet well defined (Chung *et al.*, 2010; IOM, 2010). As part of the DRI process, in addition to the identification of the adequate intakes (AI) and recommended dietary allowances (RDA) for essential nutrients, when possible the committees also identify tolerable upper intake levels (UL) for these nutrients, which are defined as the amount of the nutrient that can be consumed on a daily basis with no evidence of harm. Inherent to the UL concept is that there is a U-shaped curve for any essential nutrient. While the concept of U-shaped curves and the importance of ULs are well accepted by nutritionists, how the general public will interpret them is unknown. While common in the drug industry, in general the agricultural industry at large, and the food industry specifically, has minimized discussions concerning risks and benefits. A reasonable question is whether this is an issue that food companies should address in the near future. For the food industry, this new

goal of the DRIs can be viewed as a huge opportunity or a daunting challenge. We would submit that the DRIs represent a major step forward in nutrition sciences; how the food industry will use them and communicate the potential value of the DRIs to the general public is yet to be determined. Below, we present examples where foods have been modified to reduce the risk of select diseases, and we discuss some of the potential benefits and hazards that can occur when this approach is taken.

The Good: Early Nutrition Successes

In the past 100 years, a number of public-health agencies, and later the government, had numerous significant successes with respect to nutrition and health and the prevention of well-recognized primary nutritional deficiency disorders, by working in concert with the food industry. An example of this in the United States is the addition of iodine to table salt in 1924 to prevent goiter. Iodized salt was initially limited to the state of Michigan, as the Michigan State Medical Society was first to work with their state's salt producers to reduce industry concerns and advance the technology to bring this product to the public. Subsequent data showing a successful decline of goiter influenced the rest of the industry to iodize salt throughout the country, lest they lose a market opportunity. By no more then a decade later, iodine deficiency in the United States had been largely eliminated as a public health problem (Backstrand, 2002; Bishai and Naluba, 2002). Although this is a clear success story for the food industry, with respect to the general public there is little appreciation of the critical role that iodized salt has played in the prevention of iodine-deficiency disorders. Unfortunately, in part as a consequence of the current trend for salt avoidance, there are increasing reports that marginal iodine deficiency may be reemerging as a public health issue (Perrine *et al.*, 2010; Tayie and Jourdan, 2010). How health agencies and food companies might deal with the seemingly conflicting messages of the need to increase one's iodine intake, as well as the need to reduce salt intake, is at present unclear. It is worth noting that the potential problem of iodine deficiency could be further amplified if individuals, in a desire to use more "natural products," elect to use sea salt in place of iodinated table salt, as the former typically contains only trace amounts of iodine (Dasgupta *et al.*, 2008).

The medical community "encouraged" salt iodization whereas industry initiated the establishment of vitamin-D fortification. Rickets was a common childhood disorder in the northeast, with 339 associated deaths reported in the United States in 1933 (Backstrand, 2002). Prior to isolation of vitamin D to combat the disease, a variety of products was available on the market including irradiated milk, cod-liver oil preparations, and milk from yeast-fed cattle. With the isolation of vitamin D, the dairy industry was able to begin to fortify milk by 1932. A combination of industry advertising and promotion by the American Medical Association raised awareness of the preventative benefits of consuming vitamin-D-fortified milk (Bishai and Naluba, 2002).

While rickets and goiter were considered substantial health issues by the general public, beri beri and pellagra were of less concern. These micronutrient deficiencies were not addressed until 1941, when President Roosevelt convened the Committee on Food and Nutrition of the National Research Council for a National Nutrition Conference for

Defense. At this conference the first RDAs were presented. The committee also expressed concerns with the lack of regulatory oversight with regard to fortification of foods, and established guidance for fortification under the authority of the FDA. The FDA established standards for flour enrichment with iron, thiamin and niacin in 1942, and riboflavin in 1943 (Backstrand, 2002). In 1942, the US army began purchasing enriched flour only, and by the end of the 1940s several states enacted laws mandating flour enrichment (Bishai and Nalubola, 2002). For the most part, the above food-fortification strategies were widely successful, significantly reducing the frequency and severity of what were once common nutritional deficiency diseases throughout the United States.

Regrettably, the above public-health successes have largely been forgotten, as has the critical role that the food industry has played in the prevention of these nutritional deficiency diseases. One often hears that diets 100 years ago were typically better than they are today, and that "natural foods" are typically superior to the modified foods one finds in today's grocery stores. While these views are clearly flawed, less evident are the actions that are needed to correct these misperceptions. Education campaigns in this area could have multiple benefits, ranging from a greater awareness of the historical role food companies have had in improving the general public health, to potentially creating an environment where the public is more responsive to the concept that, through relatively simple food modifications (fortification, raw-ingredient sourcing, food processing, *etc*.), further marked improvements in the health of the general population are likely to be achieved. It is reasonable to suggest that a greater acceptance of this concept would help agriculture and the food industry meet, in a timely fashion, many of the objectives that are shown in Figure 1. However, it must be stressed that the last objective in Figure 1 (a condition of "optimal health") cannot realistically be achieved through diet alone. Although most individuals accept this point, the extent to which they think that diet is the key to optimal health varies considerably. This variation is due in part to how one defines the phrase "optimal health." Is it a sense of good health and well being, a reduction in the initiation and progression of certain chronic diseases, the achievement of one's genetic potential, or the ability to play tennis and win at the age of 80? Depending on how the phrase is defined, the extent to which the food industry can help the general population meet this goal varies tremendously. Equally important, industry needs to help manage expectations regarding how quickly we think significant specific changes in health through diet modifications should occur. For example, given what is already known concerning the influence of several nutrients on vascular function, most would agree that reductions in blood pressure across the general population could be achieved through some relatively simple diet modifications. However, there is a dearth of information on how select nutrients might influence one's risk for many age-related chronic diseases, such as dementia. Thus, measurable progress in this area is bound to be slower.

The Good: "Let Food Be Thy Medicine, Let Thy Medicine Be Thy Food"

Hippocrates told his students 2,500 years ago that food can heal through a proper diet (Halsted, 1998). To this day, nutrition research is still focused on how diet can reduce

risk of onset and progression of a number of chronic diseases. However, a major problem facing the food industry with respect to the design of "healthy foods and diets" is that multiple factors can influence an individual's nutrient needs. These factors include

- age,
- sex,
- genetic background,
- reproductive status,
- lifestyle habits,
- presence of disease(s), and
- general environment.

Clearly, on a practical basis, foods, much less diets, cannot be specifically tailored to each individual's needs. While this is not a major issue, if one is simply producing foods that are good for one's general health, it is an issue if the food, and specific components in it, is being touted as a means of reducing the risk for select diseases or health conditions. Although this concept is well accepted in medicine, the extent to which it can complicate dietary recommendations for the general public has received surprisingly little attention. This is, in part, understandable, given that many diet recommendations in the past were relatively generic (rich in plant foods and low in salt and saturated fat, *etc*.), but in the future this will become a greater issue as we increasingly view food and diet as tools for reducing the risk for a variety of diseases or health conditions.

An example of the above is the relatively recent folic-acid fortification of cereal products in the United States and Canada. The target population for this diet modification was pregnant women—to reduce the risk of children being born with neural tube defects (NTDs)—yet the entire population is affected by it. Furthermore, it is thought that the pregnant women who will benefit most are those who have genetic polymorphisms that affect folate absorption and metabolism (Blom, 2009), therefore, the subset of women benefitting from folate supplementation might be quite small. On the other hand, folate-fortification programs in the United States and Canada have been very successful with respect to the primary goal, a reduction (approximately 50%) in the incidence of infants born with NTDs (De Wals *et al*., 2007; Obican *et al*., 2010). The above outcome can certainly be heralded as an excellent example of the successful use of food as a means to reduce the risk for a severe health complication, yet others have argued that widespread folate fortification might increase the risk of other health complications, including the development of some cancers (Lucock and Yates, 2009). At present, this is still an issue of debate, although current data suggest an increase in cancer attributable to the folate fortification program has not occurred. While the authors of the current paper support folate-fortification programs, the question that needs to be addressed is, to what extent should the potential risks and benefits of food-fortification programs, such as that for folate, be communicated to the general public? In a similar vein, to what extent, if any, does the food industry have a responsibility to provide the public with a variety of foods that contain various amounts of select nutrients?

It would be wrong to dismiss the food folate-fortification issue as unique. Similar issues have been raised with respect to iron fortification of foods, and more recently vitamin D. Major concerns were once raised that iron fortification could present a significant health challenge to individuals with hereditary hemachromatosis. With respect to vitamin D, during the past five years increasing attention has been given to the idea that typical dietary vitamin-D intakes are suboptimal (Holick, 2010). This change in thinking by some experts has come about due to recent data suggesting that vitamin D has positive physiological actions above and beyond bone health. Indeed, some experts are arguing that vitamin-D intakes should be higher than the UL that was set by the Food and Nutrition Board in 1997 (IOM, 1997). The current paper is not the place for a debate on the relative pros and cons of increasing dietary vitamin-D recommendations, but rather we cite it as an example of where new expectations of a nutrient (*e.g.* high levels of vitamin D have been postulated to reduce the risk for colon cancer) may significantly influence current food-fortification programs. The key question that we ask here is, to what extent should the general public be involved, or aware, of this debate? Specifically, to what extent should the public be informed of potential risks, as well as potential benefits, of a marked increase in vitamin D in commonly consumed foods? Assuming that we continue to develop new foods (changes in raw product sources, processing, formulation, *etc*.) that are aimed at substantially reducing the risk for select diseases in some population groups, the probability that some adverse effects will be associated with their use in other populations will undoubtedly increase. How do we communicate this risk, and who should be responsible for the communication?

The Good: Evolution of Diet Recommendations, and Our Expectations of Food

During the past decade there has been a resurgence in the idea that shifts in our diet can translate into marked changes in our risk for certain diseases. Illustrative is the increasing research on phytochemicals that are thought to have vascular health properties. Observational studies have suggested that large intakes of fruits and vegetables (5–8 servings per day) are associated with reduced risk of cardiovascular disease (Liu *et al.*, 2000; Joshipura *et al.*, 2001; Dauchet *et al.*, 2006); further analyses have shown even stronger associations with certain foods and specific phytochemicals (Erdman Jr. *et al.*, 2007; Mink *et al.*, 2007). For example, interventional studies have suggested that the consumption of foods high in specific subclasses of the large flavonoid family, the flavanols and procyanidins, can improve a number of measures of vascular health, including vascular and platelet reactivity, and markers of inflammation (Holt *et al.*, 2006; Selmi *et al.*, 2006; Heiss *et al.*, 2010) (Figure 2). Intake of select purified phytochemicals, such as the flavanol (-)-epicatechin, provided in similar amounts to those found in food, has been shown to have positive vascular effects (Schroeter *et al.*, 2006). The type of work described above is critical as it is well established that the flavonoid and flavanol contents and profiles in foods can greatly vary depending on the agricultural and food processes from which the food product originated. Illustrative is that the effects of food processing might be especially important with respect to the availability of bioactive (-)-epicatechin, as it can epimerize with heating

and alkalization to (-)-catechin (Gotti *et al.*, 2009; Ritter *et al.*, 2010). While the extent to which a shift in the flavanol profile of a food (*e.g.* from (-)-epicatechin to (-)-catechin) might alter its health effects is still an issue of debate, this is an example of the new way that phytochemicals in foods are being investigated. The recent work with flavanol- and procyanidin-rich foods is also important as the consumption of such foods has been reported to improve the vascular health even of diabetics and patients with coronary artery disease (Heiss *et al.*, 2010). Taken together, this body of work is just one example of how a food product that is well characterized for its nutrient content can produce robust and consistent changes in specific biomarkers; and it is demonstrative of how current research on nutrition has moved towards the Institute of Medicine's goal of defining nutrients that will slow or prevent the onset of chronic disease (Chung *et al.*, 2010). Clearly, evidence is accumulating that food can, indeed, be part of one's medicine.

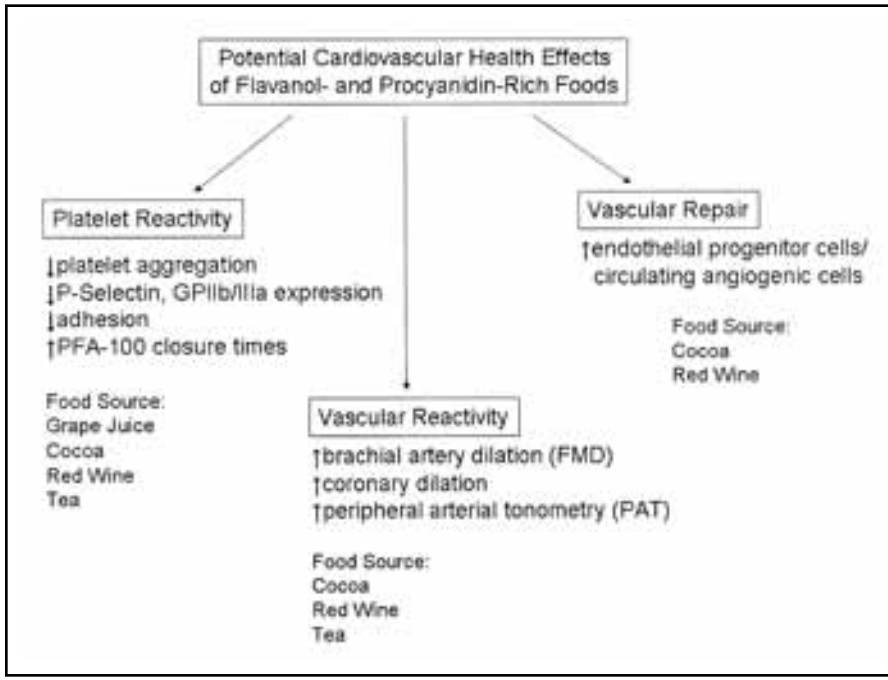

Figure 2. Reported cardiovascular health effects after intake of indicated foods that are rich in flavanols and procyanidins (see Holt *et al.*, 2006; Heiss *et al.*, 2010).

The Bad: How Good is Our Food?

A common question from the lay public is: are our diets better today than they were 50 or even 100 years ago? As is outlined above, a critical review of the facts shows that the answer to this question is an easy, "Yes." However, despite the many examples that

show our diets are better today, many consumers feel otherwise. We would submit that an understanding of this divergence of views is critical as we seek to improve popular perception of the agricultural industry in general, and the food industry more specifically. As discussed above, we suggest that the public's sometimes negative view of the food industry as it relates to their provision of "nutritious foods" is due in part to an evolution in our thinking as to what constitutes a healthy diet. A hundred years ago, the concept that our diet could be a key factor in the prevention, much less the treatment, of numerous disease states received minimal attention. Today, diet is viewed increasingly as a key player in the initiation, progression, and treatment of numerous diseases. As we change expectations of our diets, it should not be surprising that they are at times found wanting. As discussed above, an example of this is our limited ability at the present time to define the multiple factors that contribute to the positive vascular health effects of diets rich in plant foods. A predictable consequence of this is that intervention trials in which the effects of select plant foods are studied on biomarkers thought to reflect vascular health will, at times, be negative. When the information from negative trials is not carefully presented, it can lead to cynicism in the public, and fuel the belief that some foods are not as beneficial as we have preached. On the positive side, the above issue is one that can be managed with appropriate educational campaigns. However, on the negative side, for the most part, the agricultural industry has not taken a leadership role in the development of such campaigns.

Food safety is another area where there can be striking differences of opinion between the lay public and health professionals. While the vast majority of experts in the broad field of food safety would endorse the statement that our food supply is safer today than it was 50 years ago, we increasingly hear concerns over food safety from the general public. These concerns span a wide range of issues from the potential risks of pesticide residues on fruits and vegetables, to genetically modified foods, to the increasing use of nanomaterials in food products (Borchers *et al.*, 2010). In the absence of strong educational campaigns, unease over food safety will only increase. It is imperative that we find ways to communicate to the public food-safety messages that can, at times, be complex. An example of this problem can be drawn from current ongoing debates concerning pesticide residues, where distinctions are typically not made between variables such as exposure versus risk. As a consequence, one often hears the argument that organically grown fruits and vegetables are "healthier" than conventional counterparts. While there are a number of reasons why one might prefer organically grown foods, the fear that conventional grown crops are unsafe should not be one of them. Again, proactive educational campaigns are needed.

Another major issue facing agriculture and the food industry today is an increasingly prevalent opinion that the food industry is primarily driven by a quest for profit, even when it is to the detriment of the health of the general public. Illustrative of this, a commonly heard theme in the United States is that irresponsible food companies are largely to blame for the current obesity epidemic (Parloff, 2003; Ludwig and Nestle, 2008). This claim is often based on the idea that many of the low-cost foods available in the marketplace today have little to offer in the way of "good nutrition," but rather are simply inexpensive sources of energy (Drewnowski and Darmon, 2005). It has been argued that

these nutrient-poor low-cost foods are being disproportionately consumed by individuals in lower socioeconomic groups, with the result that these individuals are at a heightened risk for nutritional deficiencies, as well as numerous diseases including obesity and diabetes (Drewnowski and Darmon, 2005; Drewnowski, 2009). At its worst, one increasingly sees and hears terms, such as "toxic food corridors," being used to describe how components of the food industry are in effect a major cause of the obesity epidemic. Clearly, this is an area where the food industry again needs to be part of coordinated educational campaigns. The message that the "food industry" is putting out "toxic foods" is one that demands urgent attention. While some food industries might view this issue as one that only concerns fast-food restaurants, this is not the case. An example of how the concept of toxic foods can take hold, beyond the issue of obesity, can be drawn from the "*trans* fats" story. In the early 1900s, it was discovered that liquid oils could be hydrogenated to form *trans* fatty acids, and *trans* fat became the first man-made fat to be widely used in the food supply. In the 1950s, *trans* fats were viewed by many, including the American Heart Association, as a positive factor in the diet. However, in the early 1990s a series of papers suggested that diets high in *trans* fats might be a risk factor for vascular disease. Although the extent to which *trans* fats are causal in the initiation and progression of vascular disease is still a subject of debate, in 2003 the FDA required *trans* fat labeling on the *Nutrition Facts* label. In 2006, New York City banned the use of *trans* fats in restaurants, and multiple other cities have since followed their lead (Okie, 2007) . Whether or not the removal of *trans* fats from the food supply will have a measurable effect on the risk for vascular disease in the general population is not the issue here. Rather it is that the food industry was widely portrayed as being a culprit in the story, adding *trans* fats to foods in order to increase their bottom line. That *trans* fats were initially viewed by many public health officials as being good is a part of the story that was largely ignored, and to this day many view *trans*-fat-containing foods as toxic.

The Ugly? Changing Expectations of Food: Evolution of Biomarkers.

A major problem in the food industry is that health claims are often made for products on the basis of minimal or no data. Recently, the public has been exposed to one story in the media after another in which food companies are pilloried for making unsubstantiated health claims about their products. This is a problem that is bound to increase, as the demands for health-promoting products will certainly expand as individuals look to their diets as a means of reducing their risks for the development, and treatment, of select chronic diseases. While it is easy to make the argument that food companies should provide at least some data in support of their claims that their products do indeed have health-promoting effects, far more contentious is the question of how extensive this data base should be. In contrast to the pharmaceutical industry, intellectual property, as it relates to potentially newly discovered health benefits of common nutrients in the food supply, is hard to define. Historically, this has not been an issue, but if we increasingly turn to diet (and select foods) as a form of medicine, this is an issue that merits attention. In this regard, a National Academy of Sciences Institute of Medicine committee recently pub-

lished a monograph entitled *Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease* (IOM, 2010) that deserves special attention. This comprehensive report provides a number of observations and recommendations concerning the use of biomarkers in nutrition and disease studies. In Figure 3, we highlight three of these recommendations. On the surface all are reasonable, but if they were to be implemented it could potentially have a chilling effect on research in the area of functional foods. Given the low costs of food relative to pharmaceuticals, the expenditure involved in conducting studies according to these recommendations would in most cases be prohibitive. Therefore, there is a real risk that many food companies will scale back their research efforts on ways to improve the "nutritional value" of foods if they perceive no competitive advantage to this type of work. A conundrum facing the general agricultural industry, and more specifically the food industry, is how, from an economic perspective, private companies can justify the development of new foods that substantially improve human health. We would submit that it is imperative that this issue is addressed with alacrity, for if it is not, there is a real concern that many in the food industry will reduce their efforts with respect to the future development of impactful health-promoting foods.

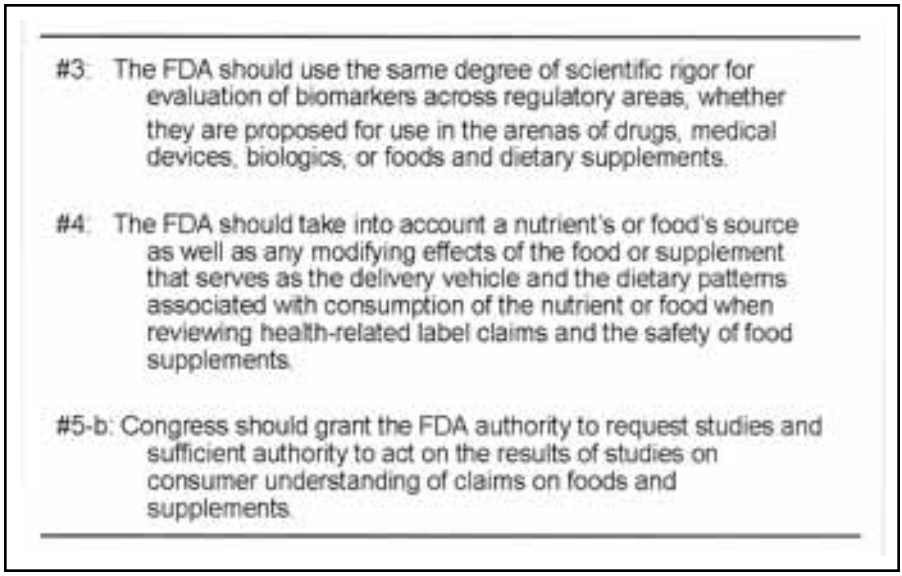

Figure 3. Biomarker evaluation process recommendations (IOM, 2010)

Conclusion

The concept that one's health is in part dictated by diet is well recognized. Regrettably, the focus of too many discussions in this area is often on the putative negative effects of "bad diets" and "bad foods," rather than on the identification of diets and foods that may confer significant positive health effects. There is a clear need for the development

of new educational programs that not only inform the public about the potential health benefits of foods, but that communicate, in an easy-to-understand way, the principles of benefit-risk analysis. The agricultural industry in general and the food industry specifically are poised to make significant new advancements in the generation of what might be viewed as revolutionary health-promoting foods; after 2,500 years we are getting closer to meeting Hippocrates's challenge.

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Trends, Innovations and the Future of Food-Product Development

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Without question, health is on the front burner of trends, innovations and future food-product development efforts (Rahavi and Kapsak, 2010). More than ever before, consumers are interested in how to get healthier through diet: the secrets of eating smarter and the science of staying healthy. What really makes us fat? Do low-carb diets really work? What should we eat to help us live longer (Park, 2010)?

Diet trends are not new. And, unfortunately, many diet trends of the past 70 years have not been healthful—some even unsafe (Younger, 2009). For example, in response to a 1929 *Lucky Strike* cigarette advertising campaign ("Reach for a Lucky instead of a Sweet"), smoking became the approach to weight loss for many in the 1930s and '40s (Watlins, 1959). In the 1950s, people prayed for weight loss. Support groups and cabbage soup were strategies in the 1960s. In the 1970s diet pills (McBee, 1968) were the rage, followed by the Scarsdale diet (Tarnower, 1979) in the 1980s. And who can forget the low-carb craze of the 1990s (Atkins, 1992)? During the last decade "lite" foods were hot (Heasman, 1993) and more recently the "100 calorie" snack (Sloan, 2006). Foods provided in 100-calorie portion sizes have impacted food categories ranging from nuts to crackers to soups—even candy (Figure 1)—in an effort to address escalating obesity.

Escalating Obesity

Obesity has grown into a major public-health crisis over the last 25 years (Flegal *et al.*, 2010). In 1985, only 10% of the US population was obese. In 2008, obesity exceeded 20% in all but one state (Colorado); it exceeded 30% in more than half a dozen others. The health consequences of obesity are numerous (CDC, 2009a), contributing to heart disease, stroke, several types of cancer (including colon, prostate and breast cancers) and diabetes. Obesity also increases surgery risk and causes gastrointestinal problems, and it shortens life by 6 to 7 years.

Figure 1. An answer to the obesity problem?

Obesity has reached epidemic proportions on a global scale, and public-health organizations are taking action. In 2009, the Centers for Disease Control and Prevention (CDC) hosted *Weight of the Nation*, an inaugural conference on obesity prevention and control (CDC, 2009b). Of particular concern is the incidence of childhood obesity (Daniels, 2009), which has tripled in the last 30 years (CDC, 2010). A study in the *New England Journal of Medicine* found that about 80% of children who were overweight at age 10–15 years were obese adults at age 25 (Whitaker *et al.*, 1997). In February 2009, First Lady Michelle Obama launched *Let's Move*, an anti-obesity campaign targeted at children (White House Office of the First Lady, 2010). If childhood obesity continues to increase unabated, some public-health experts speculate that this will be the first generation that has a shorter life expectancy than their parents' (Olshansky *et al.*, 2005). Therefore, it is not surprising that the one of the top-ten functional food trends is "foods for ailing adolescents" (Sloan, 2010a). We can expect to see many more functional-food products targeted at children, particularly for weight control.

Food-Consumption Trends

According to the *2009 Food & Health Survey* from the International Food Information Council (IFIC), 71% of adults are changing the *amounts* of food they eat to lose or maintain weight (IFIC, 2009a). They are also changing the *types* of foods or food components they eat. But fewer than 20% are counting calories and only 11% of consumers correctly estimated their daily caloric intake; 47% overestimated their energy needs (IFIC, 2009a).

According to the June 2010 report of the Dietary Guidelines Advisory Committee, "it is time for everyone in this country to know how many calories they need in a day" (DGAC, 2010).

Another food-innovation strategy that companies have used to address the obesity epidemic is the development of products containing bioactive components that increase energy metabolism. One example is Enviga—a line of sparkling green-tea beverages jointly marketed by the Coca-Cola company and Nestlé (http://www.enviga.com). Enviga contains a unique combination of bioactive ingredients (green-tea antioxidants and caffeine) that burn calories by increasing metabolism. Product claims state that consuming three cans burns 60 to 100 calories. Not surprisingly, these claims are highly controversial (CSPI, 2007). Of course an equivalent number of calories can be expended by walking a mile, which is more healthful and also free.

Eating to Lose Weight

Certain foods or food categories are also being investigated for weight-loss benefits, including dairy products (Lanou and Barnard, 2008). A recent meta-analysis of thirteen randomized, controlled trials found that increasing daily calcium intake from dairy by 1,241 mg/day was associated with an increase in excretion of fecal fat of 5.2 g/day compared with low calcium (<700 mg/day), which could be relevant for weight management (Christensen *et al.*, 2009). However, the clinical evidence for the role of dairy products in weight loss is still relatively modest (Zemel, 2009). Almonds are also being investigated for their role in weight management. They are a good source of fiber, which increases satiety, and recent evidence from clinical studies showed no weight gain even when adding in excess of 300 almond calories a day to the diet (Hollis and Mattes, 2007).

Getting away from highly processed foods and back to whole foods, "whole health eating," is a leading diet trend. Consumers are interested in foods that not only aid weight loss, but also help them live a healthier, longer life, referred to as "functional foods" (Hasler and Brown, 2009). A 2005 expert-panel report from the Institute of Food Technologists (IFT) defined these as "foods and food components that provide a health benefit beyond basic nutrition" (IFT, 2005). Interest in naturally functional foods and whole-food nutrition is likely to be one of the strongest health trends for the next 10 years (Sloan, 2009).

Several factors are driving the healthy-eating trend, including wellness-focused consumers, an epidemic of chronic disease driven in part by aging demographics, rising healthcare costs, food innovation, public-health policy, a business opportunity, and an overwhelming body of literature linking diet to health and wellness (Hasler and Brown, 2009).

According to a recent article in *Prepared Foods Magazine*, health and wellness will continue to be top priorities for consumers, and their interest will continue to drive the functional-foods sector (Rahavi and Kapsak, 2010). A recent "State of the Industry" report in *Food Technology Magazine*, "What, When and Where America Eats," stated that 66% of consumers are eating to manage specific health issues (Sloan, 2010b). According to the IFIC *2009 Foods for Health Consumer Trending Survey*, cardiovascular disease—including heart disease, cholesterol level, blood pressure and stroke—was cited as the leading health concern by 48% of consumers (IFIC, 2009b).

Heart Disease

Salt

Consumers *should* be concerned about heart disease, as it continues to be the leading killer of men and women in the United States (AHA, 2010). One of the next product-development challenges to address growing concerns about heart disease will be sodium reduction (Katz and Williams, 2010; Kuhn, 2010). A study recently published in the *New England Journal of Medicine* showed that cutting salt intake by just 3 g a day—the equivalent of half a teaspoon—could reduce the number of new cases of coronary heart disease each year by 60,000–120,000 and save an estimated $10–$24 billion in healthcare costs yearly (Bibbins-Domingo *et al.* 2010) (Figure 2).

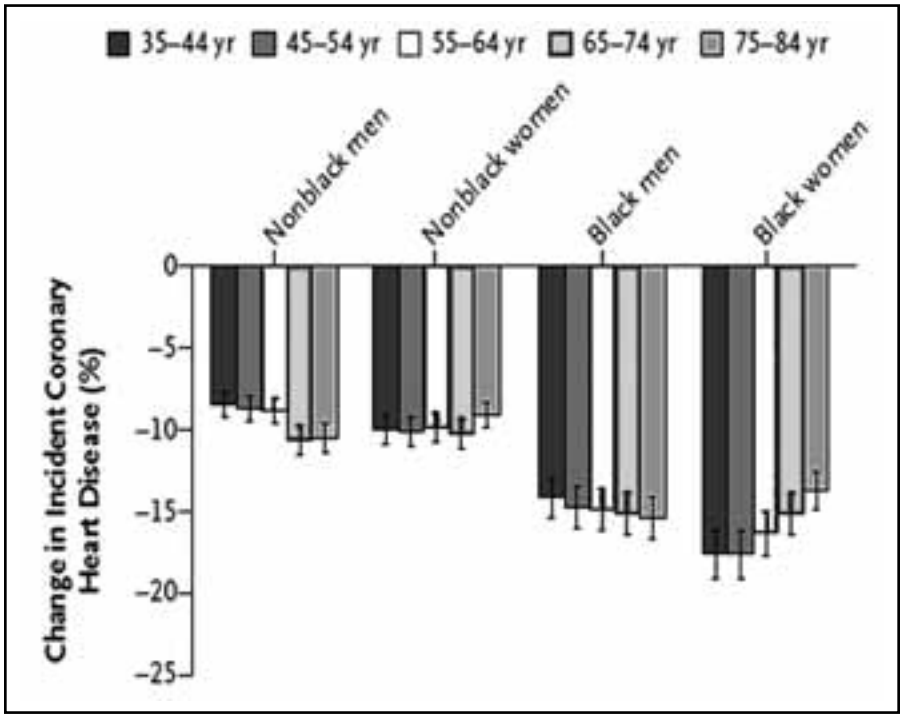

Figure 2. Potential effects of cutting salt intake by 3 g/day (Bibbins-Domingo *et al.*, 2010).

Although the contribution of excess sodium to morbidity and mortality from cardiovascular disease is considered to be fairly well established (Strazzullo *et al.*, 2009), not all experts agree that there is a comprehensive need for sodium restriction in prepared foods (Alderman, 2010). The current dietary guidelines recommend an upper daily intake of 2,300 mg of sodium, whereas the average American consumes nearly 3,500 mg/day (USDA, 2008). For people with hypertension, all African-Americans and those over 40 years of age, the recommendation is 1,500 mg. Approximately 70% of the US popula-

tion falls into this lower-sodium group. Furthermore, nearly 80% of individuals don't know the current recommended daily amount of sodium that an average adult should consume (IFIC, 2010).

The number of food products with low sodium claims has soared in the last few years (Scott-Thomas, 2010a). With sodium restriction a major focus of the 2010 dietary guidelines (USDA-DHHS, 2010), we can expect the development of many more restricted sodium products in the future. In March, Kraft announced that it will cut sodium in products by 10% over the next 2 years (Kraft, 2010). Other companies, including General Mills, are following suit (Scott-Thomas, 2010b). In April 2010, the New York City Department of Health launched the *National Salt Reduction Initiative*—a partnership of cities, states and national health organizations guiding a voluntary reduction of salt levels in packaged and restaurant foods (Katz, 2010). The food-innovation challenge is: how will mandatory sodium reduction in foods affect taste? Taste is still the leading factor influencing purchases of foods and beverages—more important than even price or healthfulness (IFIC, 2009a).

Vitamin D

Another future product-development focus will likely be vitamin-D fortification. In addition to its essential role in bone health, vitamin D may reduce the risk of various types of cancer (Krisnan *et al.*, 2010) and also boost immune function (Maruotti and Cantatore, 2010). Many individuals have suboptimal vitamin-D levels (Kennel *et al.*, 2010), and emerging research suggests that they are at greater risk of mortality from cardiovascular disease or other causes (Melamed *et al.*, 2008; Ginde *et al.*, 2009). Recently, an Institute of Medicine committee was named to undertake a study to assess current relevant data and update as appropriate dietary reference intakes (DRIs) for vitamin D and calcium (http://www.iom.edu/Activities/Nutrition/DRIVitDCalcium.aspx). The current recommendation for vitamin D intake established by the Food and Nutrition Board ranges from 200 to 600 IU. Some experts believe we may need 1,000 to 2,000 IU/day for optimal health (Landers, 2009). Vitamin-D intake recommendations are very likely to increase in the near future, which will result in supplementation of many more food products on the market or promotion of their natural vitamin-D content. An innovative strategy enhances vitamin-D content in mushrooms (*e.g.* Figure 3), the only known commodity crop that naturally contains vitamin D. A serving of conventionally cultivated mushrooms (*i.e.* grown in the dark) contains ~4% of the daily value (DV) of vitamin D (http://www.ars.usda.gov/SP2UserFiles/Place/12354500/Data/SR22/nutrlist/sr22a324.pdf). However, brief exposure to UV light can increase that to over 800% of the DV (Koyyalamudi, 2009). In 2009, *Good Housekeeping* awarded one of its first annual VIP (Very Innovative Product) awards to vitamin-D enhanced mushrooms (http://www.goodhousekeeping.com/product-testing/reviews-tests/appliances-electronics/innovate-products-awards).

In Summary

Interest in whole-food nutrition will be a leading trend in the food industry for the foreseeable future. More and more consumers are proactively influencing their own health by

including functional foods in their diets. Future food-product development efforts will include a focus on weight loss and sodium reduction. Vitamin D will be the new "hot" food ingredient. Taste still reigns, and foods must be fun! Americans are still not willing to give up all indulgences in the name of a healthy lifestyle (Anonymous, 2009).

Figure 3. Mushrooms enhanced in vitamin-D content.

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The American Diet: Voluntary Action vs. Government Action

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Food. Its customary purpose for millennia was to sustain life. Each species, from bacteria to humans, has evolved so that it instinctively consumes a diet that is most beneficial, from the specialized diets of pandas to the omnivorous diets of chimpanzees and humans.

But in the past few centuries, due to technological developments and other factors, *Homo sapiens* has gotten off track. While technologically advanced nations have largely solved the age-old problem of hunger, many, including the United States, have come to treat food as entertainment, rather than as something that should be keeping our bodies running optimally. Our food, sad to say, is contributing in a major way to diet-related diseases.

There's general agreement that too many calories are promoting weight gain, and two-thirds of American adults are overweight or obese. Obesity, in turn, increases the risks of heart disease, diabetes, strokes, and numerous forms of cancer, with concomitant medical costs estimated to be around $150 billion annually.

Numerous factors have contributed to the obesity epidemic over the past 30 years, but key is that we're simply eating too much. According to the United States Department of Agriculture (USDA), the number of calories available in the food supply jumped by 20 percent—from about 3,200 in the 1970s to 3,900 calories in the 2000s. And if those calories are there, you can bet that someone is going to eat them. Where are those calories coming from? Unfortunately, largely from such nutritional weaklings as soda pop and pizza and from the huge portions served by countless restaurants.

Probably the next most harmful substance in the food supply is salt, or, rather, sodium. Too much sodium is contributing to high blood pressure, which afflicts almost 90 percent of elderly Americans. High blood pressure is a silent killer that causes heart

attacks, strokes, and kidney disease. The average American is consuming about twice as much sodium as he or she should, with the vast majority of it coming from packaged and restaurant foods. Although most adults are advised to consume no more than 1,500 milligrams of sodium per day, major chain restaurants like Denny's and IHOP sell meals with two, three, or even four times as much. A typical can of soup provides at least two-thirds of a day's sodium.

With sodium, there's no one major culprit—not even potato chips or canned soup. Practically everything on grocery store shelves is a source of sodium. The bottom line, according to the former head of the National Heart, Blood, and Lung Institute and two colleagues, is that reducing sodium levels in packaged and processed foods by half would save about 150,000 lives per year (Havas *et al.*, 2004).

Next on the list of dietary problems are saturated fat and *trans* fat, which contribute to heart disease. Prior to 1990, *trans* fat was thought to be pretty innocuous, whereas it is now generally recognized to be, on a gram-for-gram basis, the most harmful fat in the food supply. Researchers at the Harvard School of Public Health estimated in 2006 that *trans* fat was causing 72,000 to 228,000 fatal and non-fatal heart attack, and probably 50,000 to 100,000 deaths, per year (Mozaffarian *et al.*, 2006).

Saturated fat is a separate problem. We get a good deal of that fat from red meat and cheese. Add to that the cholesterol from eggs and most other animal products. If we replaced much of the saturated fat in our diet with polyunsaturated fats, and reduced consumption of cholesterol, that would save, according to one conservative estimate, as many as 20,000 lives each year (Danaei *et al.*, 2009).

Too much refined sugars, from cane, beets, and corn, cause tooth decay and obesity. While it recommends that the average person consume no more than about eight teaspoons (32 grams) of sugar a day, USDA estimates that Americans are consuming about 28 teaspoons (112 grams) a day. The most harmful source of refined sugars is soft drinks, both because they bathe teeth in a cariogenic solution for long periods of time and because beverages appear to be more conducive to weight gain than solid foods.

Also impairing our diet is that we consume mostly refined grains in place of whole grains. Several recent studies indicate that refined carbohydrates, both simple and complex, may contribute about as much to heart disease as does saturated fat (Jakobsen *et al.*, 2010).

Together, excess salt, *trans* fat, saturated fat, and added sugars cause about 200,000 premature deaths every year. Because the illnesses that cause those deaths take decades to develop, and because the deaths cannot be pinned on specific foods, the awesome toll of diet-related deaths rarely makes for headlines. The story would be entirely different if a failed heart had a little label that said "cheese & steaks."

In any case, the challenge before health officials is to identify and implement means of changing both personal habits and tastes and the composition of foods marketed by manufacturers and restaurants.

One thing that has become abundantly clear is that voluntary action, by itself, simply doesn't work. Regrettably, good words are typically not followed by good deeds. Let me present several examples and suggest measures that would help protect the public's health.

Trans and Saturated Fat

To help educate consumers about *trans* fat in packaged foods, in 2006 the US Food and Drug Administration (FDA), after a 12-year gestation period, required food manufacturers to disclose the amount of *trans* fat on *Nutrition Facts* labels. That spurred many of them to switch to healthier oils. I estimate that, overall, the amount of artificial *trans* fat has declined by almost two-thirds over the past decade. Still, though, hundreds of millions of pounds of partially hydrogenated oil, with its *trans* fat, are being consumed each year and causing perhaps 10,000 to 20,000 deaths due to heart disease and diabetes.

But progress was slower in the restaurant world, because menus and menu boards don't list *trans* fat. To tackle the restaurant problem, New York City's health department mounted a year-long campaign to encourage restaurants to use oils that contain little or no *trans* fat. The result after one year? Zero percent change! The health department didn't waste its time again. Instead it, and subsequently the New York City Council, severely limited the *trans*-fat content of restaurant foods, and within 18 months the problem was solved. *Trans* fat was gone…and, yes, restaurants and bakeries survived perfectly well. Indeed, McDonald's said that it did not receive a single complaint when it changed its frying oil. But restaurants didn't necessarily use healthier oils elsewhere in the country.

Another factor promoting the exodus of *trans* fat from restaurants was that a San Francisco lawyer and my organization sued, or threatened to sue, Kraft, McDonald's, Burger King, and KFC. That encouraged those companies to get into high gear and get rid of most of their *trans* fat throughout the country. Other restaurants took notice.

At the same time, about a dozen cities and states—including California, Boston, Philadelphia, and Seattle—followed New York City's example and passed laws barring *trans* fat from restaurant foods. To this day, though, some large-chain restaurants and probably thousands of small ones in jurisdictions that have not passed *trans*-fat laws, continue to serve food loaded with *trans* fat.

Consider that the American Heart Association recommends that people consume fewer than 2 grams of *trans* fat a day, and the Dietary Guidelines for Americans advises people to "keep *trans* fatty acid consumption as low as possible." Now consider that at Bob Evans restaurants, an order of Stacked & Stuffed Caramel Banana Pecan Hotcakes has 7 grams of *trans* fat; and a standard order of three Buttermilk Hotcakes has 9 grams. At White Castle, the French fries, onion chips, and onion rings have between 2 and 10 grams of *trans* fat per order, depending on the product and the size. And at Long John Silver's, battered fish and shrimp have up to 4.5 grams of *trans* fat, while a fish dish with fries has 7 grams.

The FDA should simply ban partially hydrogenated oil to get rid of the remaining artificial *trans* fat. Denmark did that six years ago. Fortunately, oil processors, seed developers, and farmers have provided a sufficient supply of alternative oils that should work in every food in the marketplace. Replacing frying oils is easy; it takes more effort to replace shortenings that serve a structural purpose in such foods as doughnuts and frostings. Legally, all the FDA needs to do is declare that it no longer considers partially

[1]Information obtained from company Web sites.

hydrogenated to be "generally recognized as safe" and then give industry a year or so to switch to healthier oils.

Cutting saturated fat is much harder than cutting *trans* fat. After all, saturated fat is abundant in meat and dairy products. Ideally, animals would be raised in ways that result in meat and dairy products that are lower in saturated fat. That could be accomplished by using certain breeds of dairy cows and beef cattle, keeping beef cattle on grass for more of their lives, and feeding dairy cows conjugated linoleic acid (leads to lower-fat milk) and rapeseed (leads to more unsaturated and less saturated fatty acids). Giving subsidies to growers for producing milk and meat in those ways would be one avenue. Meanwhile, consumers need to read labels.

Salt

In 1969, the White House Conference on Nutrition recommended that salt intake be reduced. A decade later, an FDA advisory committee reviewed the safety of salt and concluded that it was not "generally recognized as safe" at the levels consumed. Since then, countless other health authorities have urged people to consume less salt: the National Academy of Sciences, the American Medical Association, the World Health Organization, the National Heart, Lung, and Blood Institute…the list goes on and on. Unfortunately, for 40 years, the food industry has ignored requests by government officials and health agencies to cut the salt. How much progress have they made on their own? None. We're actually consuming more salt now than we did 20 or 30 years ago, though that's partly due to increased overall food consumption. Lately, spurred by the imminent release of targets set by dozens of city and state health departments and of a major report by the Institute of Medicine, some of the big food processors have announced that they are going to cut the salt. And a few companies have actually made progress. Campbell has reduced sodium by about 30 percent in many soups and V8 juice.

But overall, progress has been meager. In 2005, the Center for Science in the Public Interest identified the sodium contents of about 500 foods. Three years later we checked the sodium contents once again. The change? Negligible. Some foods did contain less—but a roughly equal number of products contained *more* sodium.

Two months ago, a committee of the Institute of Medicine published a landmark report that said that, in light of 40 years of wasted opportunity while the food industry did almost nothing but say "leave it to us," the government should set limits on sodium levels in packaged and restaurant foods. And what is industry's response?: let us lower salt voluntarily! As the Grocery Manufacturers Association said, it's okay for government to regulate sodium in school foods, "but it's less clear that the government has a role with regard to products that are sold widely throughout the marketplace." If you think they're trying to play government officials for suckers, I suspect you're right.

Though salt may be the single most harmful substance in the food supply, the solution, of course, is not banning it and other sodium-containing food additives, but rather limiting the amount of sodium in various categories of foods, from bacon to bread. The British government, which has been mounting a serious and sophisticated sodium-reduction campaign, has set specific sodium targets for about 85 categories of foods and is

pressing industry to comply. Achieving those targets would lead to a one-third reduction of sodium intake. Improvements to date amount to about a 10 percent reduction…and the saving of roughly 7,000 lives each year.

It's important to realize that there is a lot of "low-hanging" salty "fruit." Although some companies might be using the least amount of salt and other sodium-containing additives feasible, many other companies are using far too much. For example, Banquet chicken pot pies contain 50 percent more sodium (per 100 grams) than Marie Callender's chicken pot pies, and Ken's Steakhouse Caesar salad dressing contains twice as much sodium as Walmart's Caesar salad dressing. It's clear that many companies can dramatically lower their sodium levels and still have perfectly marketable products.

Whole Grains

The 2005 Dietary Guidelines for Americans emphasized the value of consuming whole grains. General Mills began using more whole grains in all of its cereals, but, otherwise, progress has been spotty at best. According to the nonprofit Whole Grains Council, "Americans eat only about 11 percent of their grains as whole grains, despite government guidelines recommending that all of us make at least half our grains whole."

I'm not saying that white flour and white rice should be banned, or that consumers should be required to eat foods that they don't like. But companies could voluntarily replace some of the white flour with whole grain flour in almost everything they make—from pancakes to pasta. Depending on the food, probably up to 25 percent or so whole grain flour would not even be detectable. Government agencies—ranging from the Department of Defense to state departments of corrections—could play a role by requiring that more whole grains be served in cafeterias. The FDA should require that the percentage of whole grains in grain foods be disclosed prominently on labels. Foods that brag "made with whole grains" should be required to disclose just how much—or little—whole grains is in their products. And the Centers for Disease Control could be mounting national media campaigns explaining the health—and taste—benefits of whole grains.

Calories

Cutting calories is something that most Americans need to do. While that is something that each of us can do on our own, the federal government has begun encouraging industry to cut unnecessary calories from its offerings. Companies participating in the Healthy Weight Commitment Foundation have agreed to cut 1.5 *trillion* calories per year from their products by 2015. At first blush that sounds great, but once you get out your calculator, it doesn't look so wonderful. For starters, about 440 trillion calories are put into the food supply each year. Next, the industry took credit for supposedly removing about 500 billion calories from their products between 2008 and spring 2010—before the program even began! So you end up with supposed cuts that amount to only about *five or ten*[2] *calories* per person per day. But you shouldn't even believe that, because no company is going to handcuff its marketing whizzes and tell them that the company has

[2]Depending on how it is calculated.

hit its annual calorie limit and can't ship any more foods. This Healthy Weight Commitment Foundation may be more smoke and mirrors than substance. As for other voluntary action, few restaurants have cut their humongous portion sizes and few voluntarily list calories on their menus.

A few companies have been marketing 100-calorie packets of cookies and soft drinks, as if those are the answer to obesity. But something that the restaurant industry vehemently opposed could have a real impact: calorie disclosures on the menus and menu boards of chain restaurants. Because of local and state laws that industry fought for years, people in New York City, Philadelphia, Seattle, and California are already seeing such information. A federal law (that industry accepted only because it preempted the proliferating state and local laws) will kick into effect in the next year or so.

Beyond menu labeling, the FDA should require warning labels on soft drinks, otherwise known as "liquid candy." Soft drinks, quintessential junk foods, are a major source of calories and contributor to obesity. They should bear label statements noting their contribution to obesity and tooth decay and suggesting that people drink water or diet soft drinks instead. Congress also should consider disallowing the use of food stamps (from the Supplemental Nutrition Assistance Program, SNAP) for buying soft drinks. Currently, the several billion dollars a year that SNAP users spend on soft drinks can be seen as a subsidy to the industry, while it undermines low-income consumers' health.

Food Dyes

One other area that indicates the insufficiency of voluntary action is artificial food dyes. A good index of the junkiness of our food supply is the *per-capita* consumption of food dyes, like Red No. 40 and Yellow No. 5. Americans are consuming about five times as much of those dyes—primarily in breakfast cereals, frozen desserts, candies, and other foods marketed for children—as we did 50 years ago. Research that is too-little-discussed has examined the effect of food dyes on children's behavior. Numerous studies and a meta-analysis have shown that dyes like Red 40 and Yellow 5 cause hyperactivity and degrade learning in some children. The British government commissioned two large studies and concluded that dyes simply do not belong in the food supply. It asked companies to stop using most dyes before January 1, 2010. The European Union is requiring most foods that contain dyes after July 2019 to bear a label warning of effects on children's activity levels. That likely will be the death knell of artificially dyed packaged foods in Europe.

Beyond their behavioral effects, studies have demonstrated that some dyes, such as Yellow No. 5 and Yellow No. 6, cause allergic reactions. More troubling is the evidence that several dyes (such as those two yellow ones) contain carcinogenic contaminants (such as benzidine) or cause cancer in animals (the evidence is most accepted for Red No. 3) (CSPI, 2010).

Companies also should voluntarily eliminate dyes from their products in the United States. But what we have now is a situation in which Kellogg's strawberry Nutri-Grain bar is naturally colored in Britain but colored with dyes in the United States, and McDonald's strawberry sundae is naturally colored in Britain, but colored with Red No. 40 in the United States. Fortunately, a wide range of natural colorings can be used instead of syn-

thetic dyes. At least two companies, the maker of NECCO Wafers and Starbucks, have eliminated dyes from all their products.

I am highly skeptical of depending primarily on voluntary industry action to solve America's dietary woes. Regrettably, perhaps sincerely felt good words typically have not been followed by good deeds. That's not to oppose voluntary actions—they're invaluable. And it's certainly not to let each and every person off the hook—we all bear ultimate responsibility for what goes into our mouths. But experience has shown that if we're going to lose some pounds and reduce rates of diet-related diseases, government action is an essential ingredient.

Regulation Versus Voluntary Action

Although I've emphasized the need for legislative or regulatory action to improve the American diet, I don't want to leave the impression that that is the only strategy that should be used. Companies absolutely should undertake voluntary actions on any number of fronts, ranging from providing more readable and informative labels to reducing sodium levels. Industry can move a lot faster than government regulators—but government is often needed to provide the level playing field that would not disadvantage the more conscientious companies. And each and every consumer must make an effort to choose a healthier diet. After all, it is our bodies that will benefit.

Past and Possible Future Successes

While the scientists and regulators battle things out in Washington, agriculture schools and others certainly can play a role in affecting the American diet. Just think of some past successes:

- Trimmed carrots have created a new market for the carrot industry.
- Bagged, washed salad greens contributed to a tripling of consumption over the past 20 years, according to USDA food consumption statistics (USDA-ERS, 2010). Modified-atmosphere packaging has been a key technology to make that happen.

What are future blockbuster marketing advances? Laboratory researchers should certainly be funded to develop new products, such as:

- Salt substitutes, or salt enhancers, or new kinds of salt crystals to enable reductions in sodium levels in different kinds of foods.
- How about a safe, high-potency sweetener that actually tastes good?
- And how about meat replacements made from safe plant products? That would help reduce meat consumption and the associated health problems.

I must say, though, that even if such products were developed, we shouldn't expect too much. For instance, even though consumption of *non-caloric* sweeteners has increased over the years, consumption of *caloric* sweeteners has not decreased (Lempert, 2004; BNET, 2010) Moreover, cancer questions swirl around aspartame, acesulfame-K, and saccharin. Even with meat substitutes, there can be problems: one meat substitute, which is made

from a fungus and marketed as Quorn frozen foods, causes severe and fairly common allergic reactions, ranging from projectile vomiting to hives to anaphylactic reactions. Such products should not even be allowed on the market.

Agricultural economists could be contributing to the debate, as well:

- What are the health and economic costs of eating meat, instead of getting protein from plant products? And what are the environmental costs of meat production, considering the costs of producing fertilizer and pesticides to grow feed, soil erosion, and air and water pollution from feedlots and hog and poultry factory farms?
- How could support programs for the dairy industry be re-jiggered to encourage dairy farmers to feed cows in ways (discussed above) that reduce the saturated-fat content of milk?
- Economists need to examine how taxes and subsidies could be used to promote healthier diets: excise taxes on soft drinks; taxes levied at slaughterhouses on fatty beef cattle; subsidizing fruit and vegetable consumption via SNAP, school meals, and other federal food and feeding programs. Economists can estimate how much such economic measures would nudge the American diet in a healthier direction.

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Michael Jacobson is co-founder and executive director of the Center for Science in the Public Interest (CSPI), a nonprofit health-advocacy organization supported largely by the 850,000 subscribers to its *Nutrition Action Healthletter*. CSPI is a key player in battles against obesity, cardiovascular disease, and other health problems, using tactics ranging from education to legislation to litigation. Jacobson has written numerous books and reports, including *Nutrition Scoreboard*, *Six Arguments for a Greener Diet*, *Salt: the Forgotten Killer*, and *Liquid Candy: How Soft Drinks are Harming Americans' Health*.

Agriculture, Food and Health: The Problem and the Solution

Q&A

Moderator: Mark McLellan
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Mark McLellan: If you were the secretary of the Department of Health and Human Services, what is the one thing you would have happen, starting tomorrow? Michael?

Michael Jacobson: One specific thing is to set limits on salt. That would have the single greatest health benefit.

Clare Hasler-Lewis: I would make vegetables very cheap and junk food very expensive. When you can buy a triple burger for ninety-nine cents, there's something wrong with the food paradigm in this country.

Carl Keen: Augment the NIH budget and ask for some studies to be done, because, for the most part, we have thoughts, we don't have information.

McLellan: Let's go to the audience for questions.

Kathleen Nolan (UC Cooperative Extension, Monterey County): Dr. Keen, please comment on whether a virus or other microorganism may influence maintenance of an individual's weight.

Keen: There are good data from experimental animals, mainly chickens, that some viruses can cause significant increases in fat mass. Rick Atkinson, who used to be at UC-Davis, was one who isolated viruses from obese humans and obese monkeys. Cross injection studies looked promising. Workers at the Pennington continue to pursue this. Some believe that it's silly. On the other hand, the idea that a virus or a specific bacterium can cause some sorts of disease states is now well established. Ulcers provide an excellent example. It's provocative, but it's receiving a lot of scientific interest.

Tom Tomich (University of California, Davis): Everyone rightly raised the issue of the health crisis here in the United States. Carl stated that the evidence is thin that consumption of fruits and vegetables is linked to heart disease. Scientific evidence is surprisingly thin regarding many of the important causal relationships between food and health outcomes. Carl just made the predictable call for more research, but my question is a little different. I wonder if we are framing the questions in the right way. As an economist, I worry a lot about the right unit of analysis. We use the phrase "health-promoting foods," but I could say "health-promoting diets," "health-promoting communities," or I could say, "health-promoting society." My question is—and I hope that clear compelling messages about priorities for work will come out of this meeting—what's the right balance? I suspect it's probably "and" rather than "or," across those, but how do we get that right? I hear us talking a lot about foods, but is that the right unit?

Keen: I agree with you. But the thing that's very impressive is that the proof is in the vegetable-fruit literature, although it's not as robust as many think it is. If multiple factors in fruits and vegetables are driving it, not all fruits and vegetables are the same. The real issue is not to show that something is not a good fruit or a good vegetable, but if we take our blinders off and say, "Can we identify the family of nutrients that, in orchestration, are actually giving beneficial effects, and start finding out how to increase them in the diet?" The tricky part here is that most people are uncomfortable with the concept that one fruit is better than another or one vegetable is better than another, and we must get that out of our minds if we are to make big changes.

Jacobson: You're right when you say, "Let's look at a higher level." There is pretty clear evidence that certain diets are much better than others, in terms of health standards. [Audio lost.] A virus may contribute to obesity, as may BPA and *trans* fats, but my hunch is that these are pimples on an elephant in comparison with a twenty percent increase in calories available, which is a huge thing that dwarfs these laboratory curiosities.

Hasler-Lewis: We mustn't ignore energy expenditure, which is a large part of the problem. Michael said something that Steve Cooper stated a number of years ago: "We've engineered activity out of daily life." We need to educate people, not to spend an hour and a half in the gym, but to walk more, which could burn up twenty percent more calories.

Jacobson: The secretary of Health and Human Services stated the need for taking ten thousand steps per day. That's difficult; about five miles. It's not just leaving your car a little further out in the parking lot.

Audience Member: My questions are for Michael. The organic segment of the food industry markets its products as "safer," "healthier," "tastier" and "better for the environment." Since CSPI has a record of going after false assertions, and it's become clear over the last few years from meta-analysis that none of these claims holds up, will CSPI go after these claims?

Jacobson: If you see clear-cut, dishonest, claims that violate the law—made by large companies—send them to me. We don't play favorites. My organization, for instance, has been supportive of agricultural biotechnology, unlike most consumer and environmental groups. We work with facts, and, if we see dishonesty, we may go after it.

Audience Member: Thank you for that. My second question: Regarding your "suitable substitute" statement about *trans* fats, I am wondering if CSPI is planning to make a public statement in favor of transgenic oilseed crops that allow increased oleic acid replacement of *trans* fats.

Jacobson: We haven't commented on that particular type of seed, but we have been supportive of agricultural biotechnology. This is the second time I have spoken at an NABC conference. Ralph Hardy knows full well that we have been supportive of agbiotech. When it comes to particular seed, I don't know how necessary it may be.

Ken Swartzel (North Carolina State University): David Kessler has suggested that we need to control our own diets.[1] On the other hand, Michael suggests that the government regulations are needed, that people can't do it themselves. The *trans*-fat issue is an example. The late Peter Jennings presented a documentary titled, "How to Get Fat Without Really Trying," the point of which was simply that, on one hand we have a food pyramid and on the other hand we have government subsidies, which don't line up. We should eat more of certain foods and less of others, and most of the government subsidies go to foods we should be eating less of. Fruits and vegetables get practically no government subsidies. Clare, regarding your one issue of cheap fruits and vegetables and expensive burgers—government subsidies are controlling this.

Hasler-Lewis: That's a great point. And there should be categories for people who are given food stamps, and they should not be able to exchange food stamps for items that are not healthful. That would be an edgy move, begging the question of how much we want government involved in our lives. It's a controversial issue.

McLellan: We are the government and we are here to tell you what to eat! Michael?

Jacobson: I think you got David Kessler's book exactly wrong. His main point was how industry is engineering foods to make them virtually addictive, through smart, tested combinations of sugar, fat and salt. He didn't give a good prescription of what to do about it, because it's hard to imagine companies not trying to make their foods as tasty as possible. On the subsidy issue, there are misconceptions. The ag economists that I am familiar with have said that the subsidies to corn growers have negligible effects on the prices of

[1]Kessler D (2009) The End of Overeating: Taking Control of the Insatiable American Appetite. Emmaus, PA: Rodale Books.

corn, corn syrup and soft drinks. The reason for inexpensive food in general in the United States—corn, soybean, and even fruits and vegetables—is successful agricultural research. To make food more expensive, we would have to stop funding ag research. Regarding government mandates on one hand and functional foods on the other to prevent colon cancer through vitamin D, *etc*., in reality it's not a case of either-or. Big forces are in play. There needs to be judicious involvement, not suicidal involvement. Industry needs to do what it can do. Take salt as an example. A level playing field put out by government can be extremely helpful. Company A is unlikely to lower its sodium content since its foods would not taste as good as Company B's, unless government dictates that everyone has to meet a certain limit, although sometimes companies do the right thing on their own. And I believe that government is subsidizing the fruit and vegetable industries with the food stamp, school-lunch and WIC programs. Direct subsidies have screwed up the corn and soybean industries. If subsidies of the fruit and vegetable industries are necessary, they should be applied smartly so that more fruits and vegetables are consumed. Clearly, individuals have a role. We need to control our impulses, in large and small ways. If you have good, healthy foods around your house, you will probably eat them. If you have junk foods around the house, you'll eat those first. So we all need to contribute at different levels. It's not all government; it's not all industry; it's not all consumers.

Barbara Schneeman (Food and Drug Administration): A recently published article stated that claims on food packages are simply marketing, creating the notion that we can somehow eat our way out of a chronic disease problem or eat our way out of obesity. You were talking about the idea of funding more research and being able to make more of those kinds of claims. But are such claims useful?

Hasler-Lewis: The issue of claims has been interesting to me for a long time. The good side is if it does what it's intended to do: educate consumers at the point of purchase, such as choosing cholesterol-lowering Cheerios. I am a firm believer in information being available to people who choose to use it, provided that it's based on science.

The Pipeline of Future Foods

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Working in agriculture, we have been at the center of some of the most significant and hottest debates in society. In 6 out of the last 10 years, grain consumption has exceeded grain production. We have seen energy costs quadruple, and concern over global warming has escalated greatly, with the last 10 years representing the warmest on modern record. These issues are central to agriculture, and we all face the question of how to overcome these obstacles and continue to provide the food supply the world needs. At Monsanto, we believe that innovation will be key, and we believe that we have a role to play, as an input producer in agriculture, in helping to meet these challenges.

Food Quantity

Global population is increasing dramatically, and is expected to be over 9 billion by the middle of this century. Many experts agree that the food supply will need to double to meet the demands of that increased population. We have made an evaluation of how this is likely to affect our business. We have observed that corn consumption has increased by 34% in the last 10 years, while soybean consumption has increased by 52%. As incomes increased in developing nations consumption of grain-fed beef has increased by 21%. At the same time 55% of the habitable land is now used for agriculture and two thirds of annual fresh-water withdrawals are used in irrigation. These forces are creating critical challenges, and we need to focus on how to improve agricultural sustainability.

A few years ago, we began conversations with stakeholders to try to determine how we could best contribute to solutions to these challenges, and 2 years ago we launched a commitment comprising three primary factors and that we called our *Commitment to Sustainable Yield*. It includes the component of how to meet the need for an increased food supply and we committed to working with farmers to double yields of major food

and fiber crops by the year 2030, relative to year 2000. It included an evaluation of how to reduce environmental and resource impacts while achieving this increased food production. And we committed to reducing agricultural inputs to a third lower than they are today per unit of output. We believe that there are many ways to increase crop output per unit of input, and we want to improve the economic viability of farming, to improve the lives of farmers, their families and their communities.

Food Quality

Although much of our effort is focused on the capability of producing enough food with the minimum impact to the environment, many of our initiatives are focused on improving food quality.

Soybean comprises almost two thirds of the US diet of edible oils, more than half of which is used in processes in which they are partially hydrogenated for stability. This partial hydrogenation leads to formation of *trans* fats, which are now widely recognized as undesirable in the human diet. So, we have opportunities to modify the composition of soybean oil to help address some issues concordant with it being a major source of fats in the human diet.

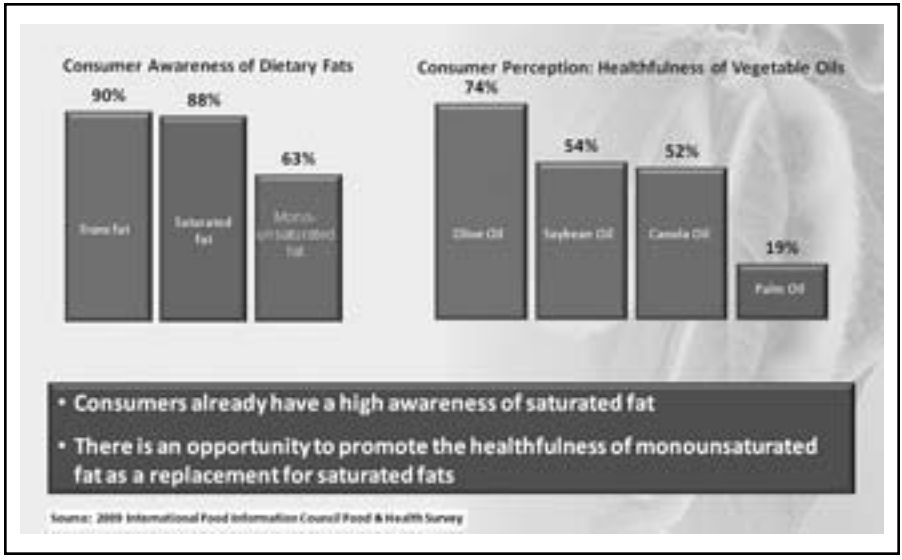

Figure 1. Consumer awareness of dietary fat.

Consumers are aware of the various oil compositions and have clear perceptions of their desirability; nearly 90% of consumers understand the significance of *trans* fats (Fig. 1). They are aware of saturated fat and they also have perceptions about the relative health merits of various vegetable sources of edible oils. We believe that we have an opportunity to promote the healthfulness of mono-unsaturated fats as an alternative to saturated fats, which are now abundantly present in the human diet. The American Heart Association

has recommended that saturated fats comprise only 7% of dietary energy, and recently, the Dietary Guidelines Advisory Committee proposed that saturated fats be reduced from the current guideline of 10% of dietary energy intake to 7%. In reality, the current saturated fat composition in the diet is about 12% and a 5% reduction to the recommended 7% would significantly reduce the risk of cardiovascular and other diseases. A majority of consumers read the nutritional labels on products they consider for purchase. They are aware of the significance of the information on dietary fats, and, in a 2009 survey by the International Food Information Council, 63% claimed to be trying to reduce their intake of saturated fats.

We have worked with a number of food-company representatives to design specifications for what we thought would be an improved composition of soybean oil. We defined significant reductions in the saturated fatty acids palmitic and stearic, a significant increase in the mono-unsaturated oleic and a reduction in linoleic acid to improve stability, and less linolenic to reduce *trans* fat (Fig. 2). We are at the pre-launch phase, and, within 2 or 3 years, we will release Vistive® Gold seeds, which will produce oil with this composition.

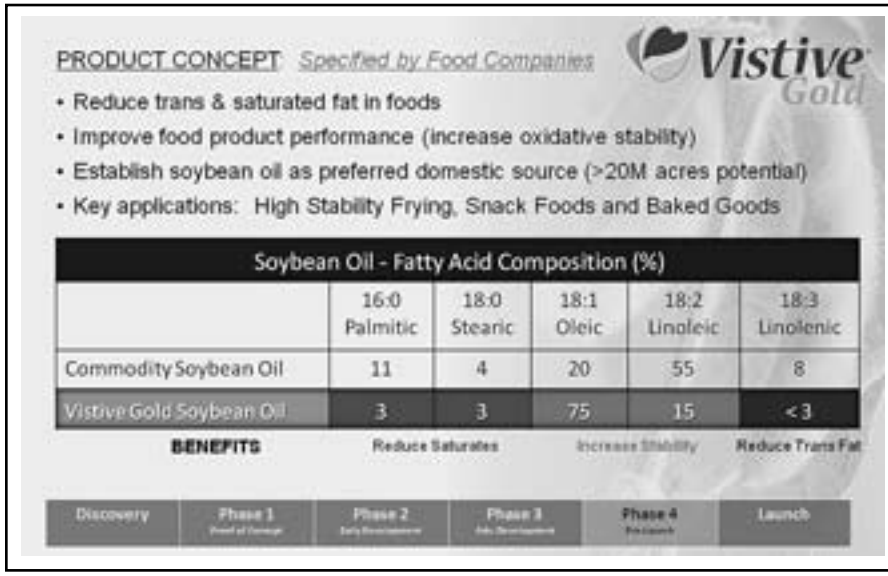

Figure 2. Vistive® Gold soybean will provide low-saturate, high-stability and zero-*trans*-fat oil.

To achieve this, we reduced the activity of three enzymes that are involved in the biosynthesis of oil in soybean. The first is FATB thioesterase; by reducing its activity, we allow more of the fatty acids to be shunted toward oleic acid. Reduction in FAD2 desaturase results in an elevation in oleic acid. Both of these changes are delivered by RNA inactivation of genes that naturally exist in soybean. And the third change is a FAD3-desaturase reduction through conventional breeding, using a mutant in soybean that reduces the level of linolenic acid, which again promotes stability.

With these three changes, soybean produces an oil that is almost identical in properties to high-oleic canola oil, an expensive specialty oil that is available in much less abundance than is soybean oil. This will be a major contribution to the abundance of oil with improved properties for food applications. French fries cooked in Vistive® Gold soybean oil versus conventional partially hydrogenated soybean oil show a reduction of 23% in saturated-fat content and a 98% reduction of *trans* fats. Importantly, this allows food companies to provide labels that indicate zero *trans* fats, no partially hydrogenated oil and lower saturated-fat content.

This oil, importantly, could go into a range of food products, including those designated with the Vistive® Gold emblem in Figure 3, and reduce the saturated-fat levels in those processed food products. We can still get our fix of saturated fats through steak, ice cream, cheese and cheesecake and various other sources that we like to eat. The bigger picture is that 40% of the saturated fats in our diet come from prepared foods such as potato chips, French fries, margarines, and salad dressings, in all of which Vistive® soybean oil could be substituted for currently used oils. Therefore, without making any changes in consumer habits, dietary preferences, if current oil sources are replaced by Vistive® Gold in these processed foods, it could result in a 9% decrease in dietary intake of saturated fat for the average individual. And, for those in the top 10% of the population for intake of saturated fats, it would result in a 13% decrease in saturated fat. This is a significant opportunity for us to help food companies help consumers improve their diets.

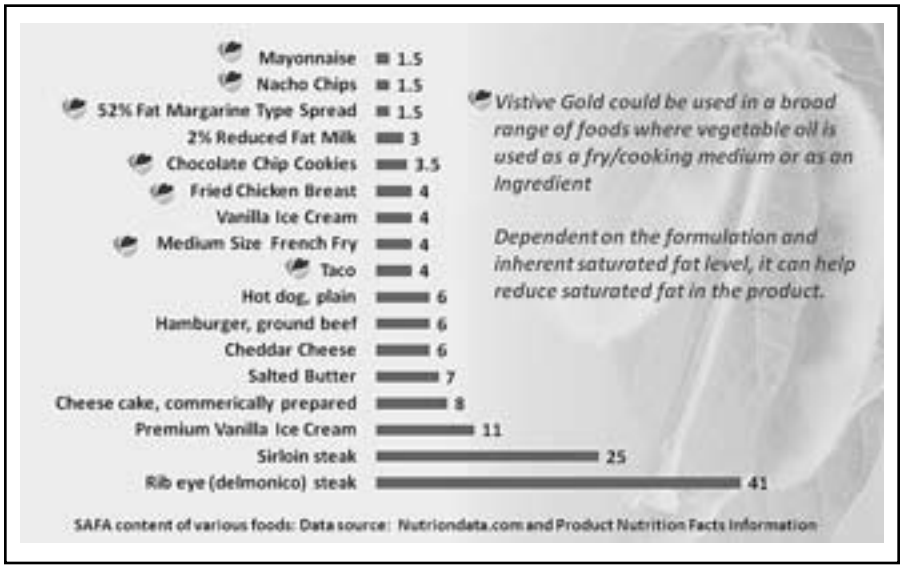

Figure 3. Vistive® Gold could be incorporated into many foods with varied levels of saturated fat (SAFA=saturated fatty acid, g/serving) (Commercialization is dependent on many factors, including successful completion of the regulatory process.)

In addition to reductions in consumption of saturated and *trans* fats, it is also recognized by health experts that cardiovascular health would be improved by increasing the level of omega-3-fatty acids in our diet (Fig. 4). Currently, these omega-3 fatty acids come predominantly from fish and a recent analysis showed that, of the risks leading to death in the American population, the sixth largest is an excessively low dietary intake of omega-3 fatty acids. In this analysis, that single risk was associated with 100,000 deaths per year in the US population. Of course, consumers are addressing this risk in increasing numbers by taking fish-oil supplements, and we are looking at what we may do by changing the composition again of soybean oil, the major oil that is used in processed food manufacturing in the United States. We have defined a way by which the composition of soybean oil may be modified to contain 20% stearidonic acid (SDA), an omega-3 fatty acid that currently comes from consumption of fish fat. The fish obtain it by eating algae, which possess the biosynthetic pathway to produce the SDA.

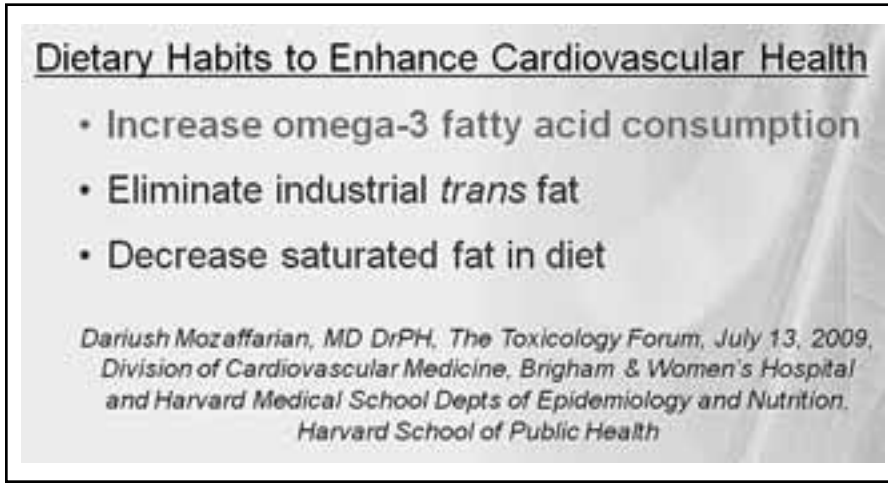

Figure 4. Dietary changes endorsed by experts in health and nutrition.

We want to reproduce in soybean the biosynthetic pathway that exists in algae, by adding two enzyme steps, achieved by borrowing a gene from a plant and one from a microbe, that allow the conversion of fats normally produced in soybean oil to the 18:4 fatty acid, SDA (Fig. 5). This, we believe, is the preferable point at which to stop in the biosynthesis of omega-3 in soybeans, due to improved stability. It doesn't have the off flavor or undesirable aroma that are associated with fish oil and eicosapentaenoic acid (EPA); in fact, the human body is able to convert SDA to EPA. With a 20% composition of SDA in soybean oil, just one acre of soybeans would provide as much potential EPA as is present in 10,000 3-ounce servings of salmon.

Obviously, fish-oil sources are not a sustainable solution for the entire world. They are not available in the appropriate abundance in many parts of the world, and we would have a sustainability issue trying to get this much from fish. On the other hand to obtain

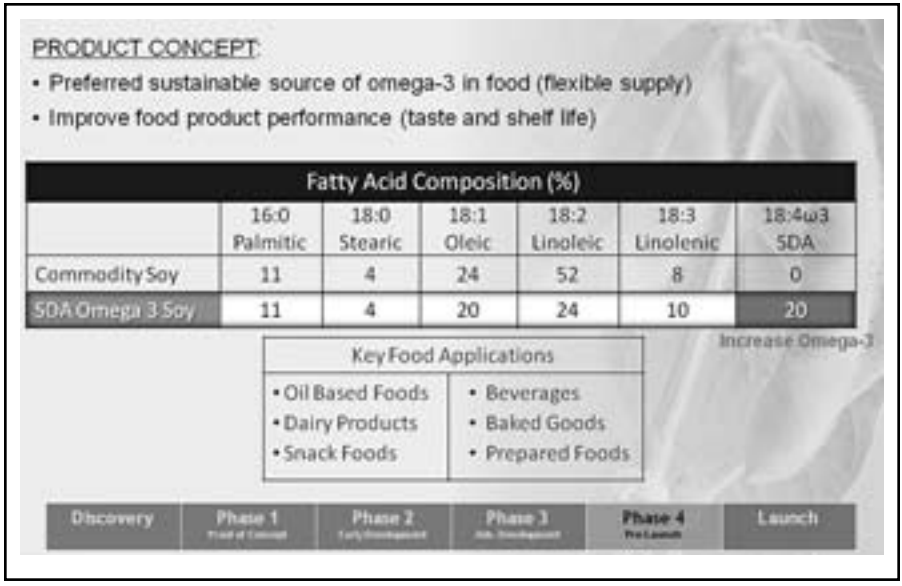

Figure 5. SDA soybean oil would provide a sustainable source of omega-3.

sufficient omega-3 fatty acids from soybean—with approximately 80 million acres grown in the United States alone—is very achievable. We have formulated this soybean omega-3 oil into various food products—yogurt, salad dressing, snack bars, smoothies, *etc*.—and the flavor properties are indistinguishable from currently used oils. This is an exciting opportunity for us to contribute to what is a major dietary limitation affecting human health.

Studies have demonstrated that SDA oil formulated into human diets results over the course of just 12 weeks in increased blood EPA, comparable to EPA formulated into the diet, which does not occur with commodity soy (Fig. 6).

Vegetable Innovation

Onion

About 5 years ago, Monsanto bought into the vegetable seed business by purchasing Seminis, with the primary objectives of increasing crop productivity, yield, reducing need for inputs, and breeding in natural disease resistance. At the same time we had the opportunity to provide vegetables improved in terms of the consumer sensory experience, realizing that helping consumers find it easy and desirable to eat more vegetables would be a positive contribution to their health.

We've launched a couple of products. The Evermild onion is a long-day storage variety that has the same mild properties of short-day onions that are available only seasonally, such as the Vidalia onion from the United States and the Peruvian sweet onion, which is available in the winter. The Evermild provides the same consumer benefit, but it is a

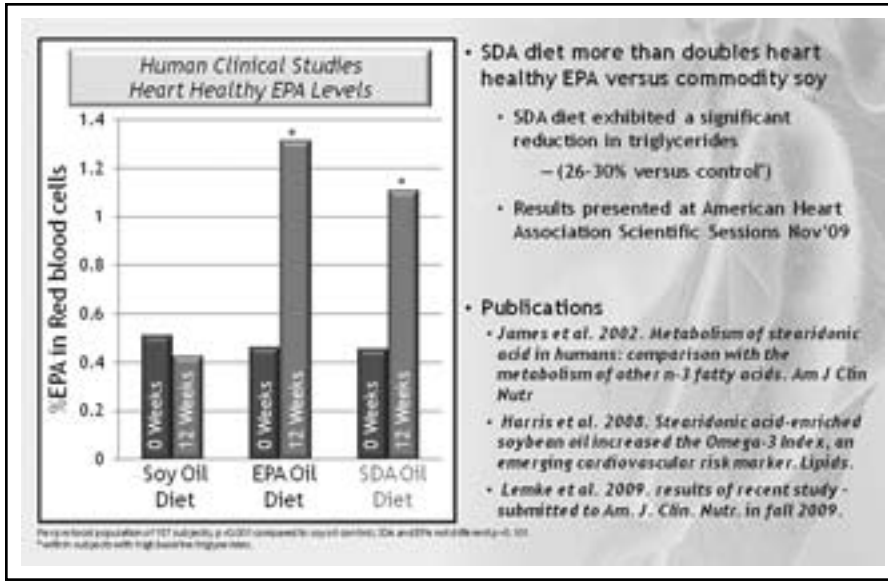

Figure 6. SDA omega-3 increases heart-healthy EPA in humans.

long-day storage onion available throughout the year. Bella Verde is an innovative new broccoli with an elongated stalk. Recently launched in Europe, it produces nutritious tender side-shoots with improved consumer appeal.

Tomato

By moving into this vegetable space, we acquired an array of elite diversity in crop species. Figure 7 illustrates diversity in tomatoes that are consumed around the world, representing all kinds of opportunities to use native genes to enhance quality, sensory properties and nutrition. Similar opportunities exist for our other major crops, peppers and onions; it's a tremendously useful toolbox for plant breeders developing improved products for growers and for consumers.

Figure 8 provides examples of innovations in our vegetable pipeline that are designed for consumer appeal. A seedless tomato in the upper left-hand panel combines cytoplasmic sterility with parthenocarpy, the ability of fruit to develop without pollination. We've developed a tomato that is completely seedless and delicious. Importantly, lacking seeds, it helps people with diverticulitis to avoid digestive distress. A great-tasting orange mini-tomato, a grape tomato, is shown in the upper right-hand panel; very high in natural sugars with a great acid balance, it is absolutely delightful to eat. People who generally don't like tomatoes do like this one, like the grower's son who is sneaking some from the greenhouse in Holland. In the lower left-hand panel is an all-flesh tomato. Slicing tomatoes that are used in sandwich shops, *etc.*, are often processed in central distribution centers, for safety reasons and shipped to sandwich vendors. In the process of being shipped and handled, they can lose 5% to 10% of the juice and, with it, much of the nutrition. Our

all-flesh tomato—2 to 3 years from launch—doesn't have juicy locules so that, after slicing, the moisture and nutrition are conserved during distribution. Some of our customers are excited about this prospect, which will help tomatoes be delivered more often to sand-

Figure 7. Tapping into diversity in elite germplasm.

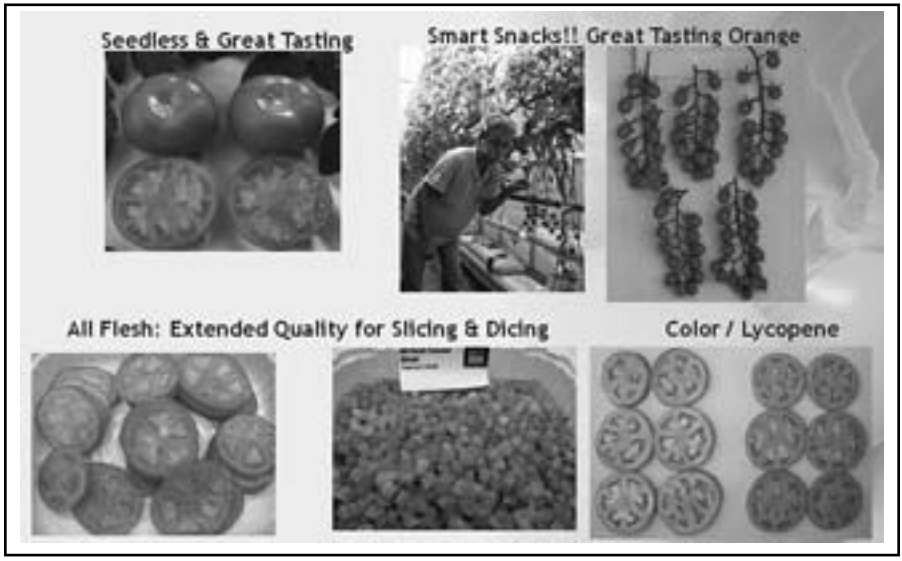

Figure 8. Sensory appeal critical for driving consumption: flavor, texture, color (nutrition) and convenience.

wich and fast-food businesses. And we have improvements in color and other nutritional components of tomato. In the lower-right hand panel, increased lycopene deepens the red color, which consumers find desirable aesthetically and nutritionally.

Lettuce

We have an innovation in lettuce that has been launched in Europe and which we are working on for the United States. It's a cross between the iceberg and Romaine lettuces that has the crispiness and texture and processing capability of an iceberg with nutritional benefits more comparable to the Romaine. It is more attractive when shredded and processed. Our studies on nutritional composition show that our "CRC" lettuce, represented in Figure 9 by the variety Rugby in the top panel, is a good source of vitamins A and C, unlike iceberg; it's more like Romaine in vitamin content. When we take it to consumer taste panels, we find that those who like Romaine like it equally to Romaine and Romaine dislikers—a significant portion of the population—like it equally to iceberg, and much better than Romaine. We think we have hit the sweet spot of doing something that improves nutrition while improving consumer appeal.

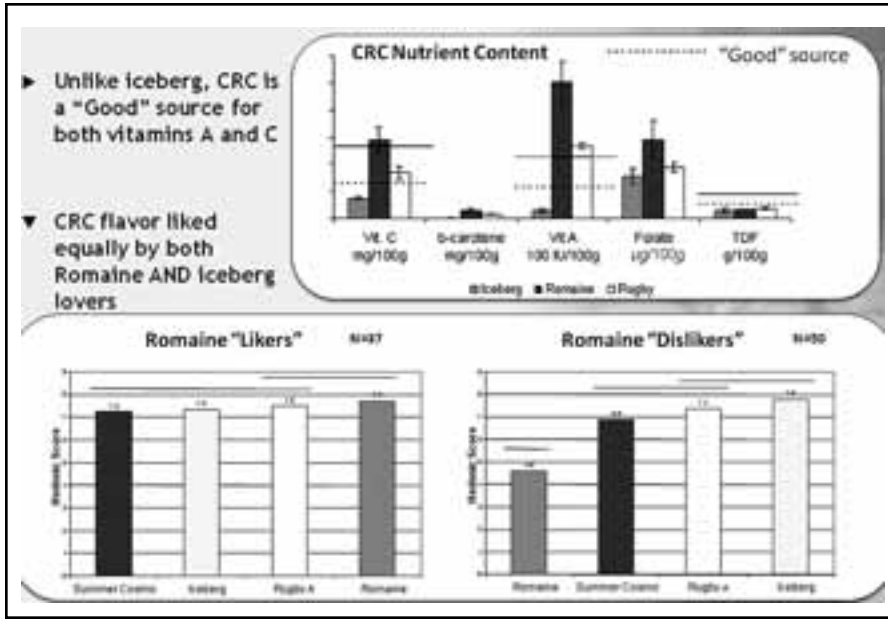

Figure 9. CRC lettuce provides nutrition and flavor.

Broccoli

For a number of years, we've been working in collaboration with scientists at the John Innes Institute and others in Europe to improve the nutritional content of broccoli through marker-assisted breeding. A relative of broccoli that grows in the hills of Sicily and is used locally in their salads, *etc.*, has a higher content of 4-methylsulfinybutyl glucosinolate

(MSB), which is obtained in the human diet only through intake of broccoli. In humans MSB is converted to sulforaphane, which enhances the body's own enzyme systems that preserve the activity of vitamins A, C and E, which are natural antioxidants that help to remove free radicals and environmental pollutants. We have introduced three genes to broccoli through marker-assisted breeding (Fig. 10). The panel on the left demonstrates that, over widely different environments, two- to three-fold increases in MSB have been achieved. The upper-right section shows that consumer panels indicated that this broccoli is just as desirable to eat, whether consumed raw or cooked. By increasing the levels, we have found that the MSB is rapidly converted into much higher levels of sulforaphane in human blood, which are conserved for many hours after consumption.

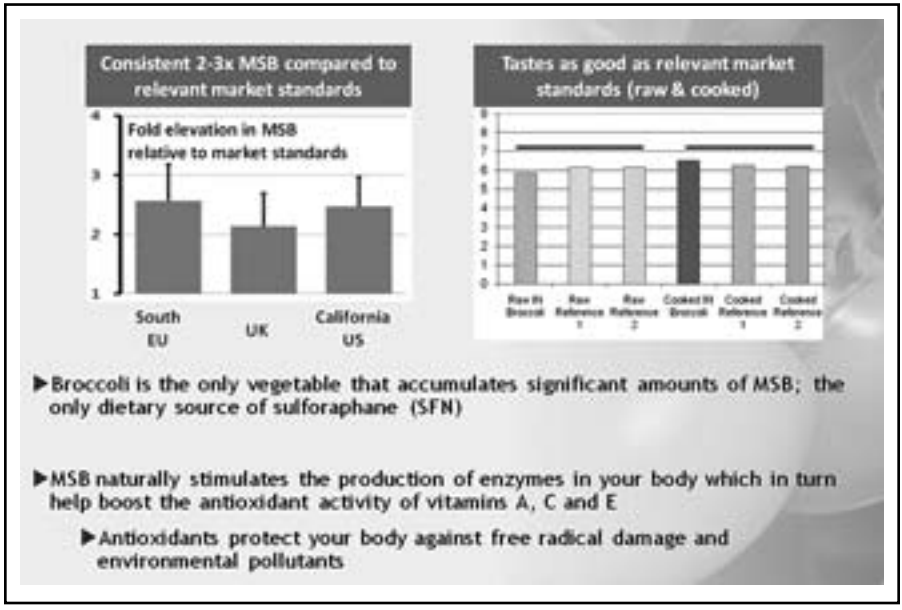

Figure 10. Broccoli with improved nutrition, developed through marker-assisted breeding.

As these examples illustrate, we are focusing on traits that we can deliver through seed and agricultural inputs that add benefits throughout the chain. Besides being beneficial for consumers, they have to be beneficial for growers, and for retailers, for produce and food companies. We have to share the benefits across the chain in order to get support in launching these products. We are working with regulators to validate the credibility of the nutritional improvements and we are working with consumers to make sure that the benefits are perceivable.

Biotechnology of Fruits and Vegetables

The wide perception is that biotech traits are not available in vegetables. In fact, some have been available for 15 years, virus-resistant squash for example. *Bt* sweet corn has been in the marketplace for nearly as long, and, of course, over 10 years ago, Cornell and the

USDA launched virus-resistant papaya, which saved the papaya industry of Hawaii. Other products are currently being worked on—whether by public or private institutions—in potato, tomato and fruit trees (Fig. 11).

A lot of the activity in biotechnology of foods is occurring in Asia. Figure 12 provides examples of a number of attributes that are being worked on by local and regional private interests as well as by government agencies, covering insect resistance, improved quality, virus resistance in eggplant, tomato and the brassicas.

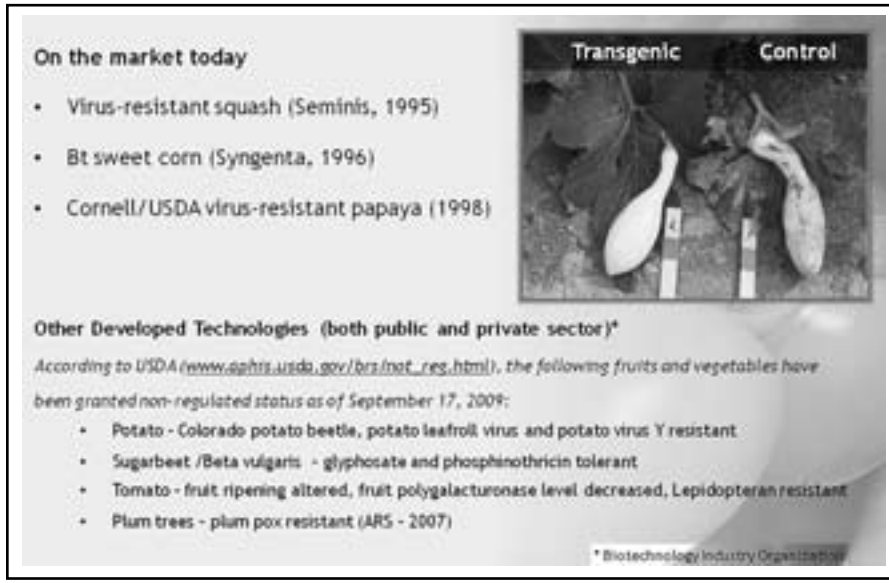

Figure 11. Biotechnology in the fruit and vegetable industries.

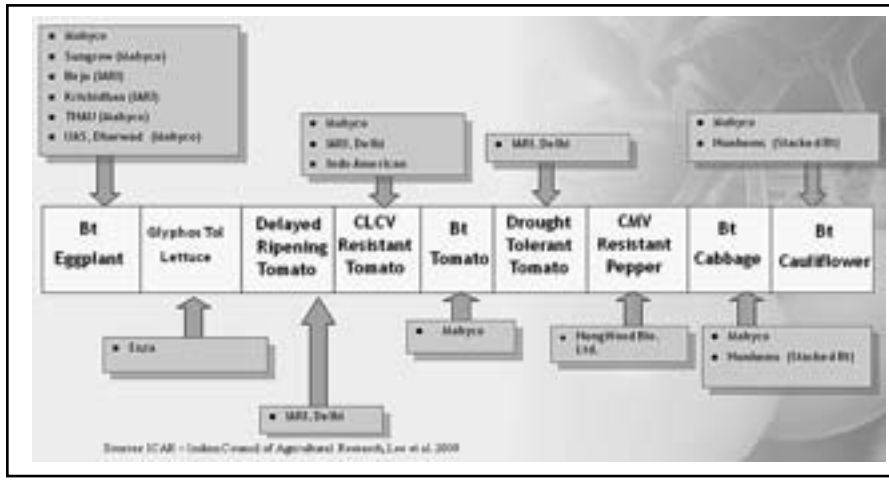

Figure 12. Biotechnology projects in Asia.

We are preparing to launch improved *Bt* sweet corn by 2012, initially targeted toward the fresh market, which is primarily where the competitive product from Syngenta has been used (Fig. 11). The market size in the United States is miniscule versus that of field corn—250,000 acres of sweet corn versus 90 million acres of field corn. It is designed to provide in-plant resistance to pests as well as herbicide tolerance, which is the same technology we launched in field corn some time ago. It's equivalent to our Genuity® VT Triple Pro™ which is widely established in field corn as providing great grower benefits. In sweet corn it will provide additional benefit because much sweet corn is produced in the southeast—in environments with intensive insect pressure—and shipped north to markets for much of the off season. Figure 13 shows results of a study that we conducted last fall in Florida, Georgia and Mississippi. The lower left-hand panel provides the numbers of marketable ears per plot from this *Bt* sweet corn, hybrid 'Passion,' as well as from the equivalent hybrid but without the biotech innovation; in the absence of any insecticide application, we completely failed to produce marketable ears. In the State of Florida, insecticide applications are recommended to begin before silking and continue at 2-day intervals all the way through product harvest, amounting to ten to twelve applications. In our trials, even with that level of insecticide application, we were producing only four to five marketable ears per plot. Therefore, this allows us to greatly reduce insecticide application in sweet-corn production and provide a better-quality, better-looking product to the consumer. There are other pests that this *Bt* doesn't control so, at this point, we are not advocating complete elimination of insecticide applications, but we are confident we can greatly reduce it, perhaps even more than the 50% that we now recommend.

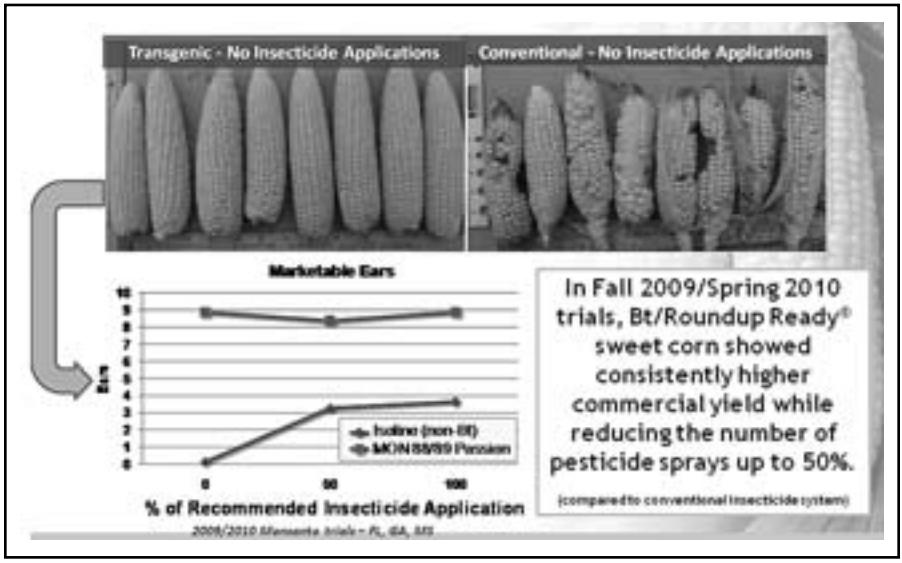

Figure 13. Sweet corn hybrid 'Passion' with the addition of Monsanto's Genuity® Triple Pro™ technology requires less pesticide to produce marketable ears.

There are many things that a company like ours can do in terms of providing agricultural inputs to help in human sustainability. Many issues are associated with today's diet. The majority of the US population has inadequate intake of a whole number of essential nutrients. Our calorie-rich diet is leading to problems with obesity, blood cholesterol, and type-2 diabetes. In fact 1% of the US GDP is spent in intensive care units. We have an opportunity—through increasing the attractiveness to consumers of our products and the internal composition of our products—to help address some of these issues.

Marlin Edwards joined Seminis, a subsidiary of Monsanto, in 2005 as the vice president of global research. Most recently he has led breeding technology at Monsanto where he developed the world's foremost high-throughput genotyping lab. This has allowed as much as 35% of Monsanto's plant breeding programs to be based on genetic marker-enabled selections.

Dr. Edwards has been involved in multiple aspects of plant breeding and agricultural biotechnology since he completed his post-doctoral research at North Carolina State University, where he conducted pioneering research into the application of molecular markers in plant breeding in the mid-1980s. He has experience in breeding field corn, sweet corn, peppers and cucumbers. He has a PhD in plant breeding and genetics, an MS in horticulture from the University of Wisconsin at Madison, and a BS in the Agriculture Honors Program from Kansas State University.

Mammalian Milk Genomics: Knowledge to Guide Diet and Health in the 21st Century

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The life sciences are struggling with the challenges of diet and health. Agriculture wrestles to become both more productive and more sustainable in the face of the world's population growing past 6 billion. At the same time, in the most affluent parts of the world, diet-related diseases are considered to be the major threat to public health. The problems are complex; how can agriculture become simultaneously more productive and sustainable while foods become simultaneously safer, more nourishing and more delightful to our quality of life? The Foods for Health Institute was established at UC Davis to promote research and development across the campus. The goal of the institute is to develop multi-disciplinary and multi-collaborative approaches to address these challenges and deliver on the bold promise to improve health and prevent disease with food-based solutions. Promising to prevent disease (defined as not to cure disease or reverse the damage accumulated by disease, but to pre-emptively prevent disease from occurring) is indeed provocative. How can science address such an attractive yet seemingly insurmountable goal? One critical question for science and for food is at the core of the problem: what do we target to improve health in ways that ultimately reduce the risks of all diseases?

Preventing disease is a far-reaching goal. If healthcare approaches are truly preventative, then they act on individuals before diseases develop—any disease. If a food or food ingredient is developed to reduce the risk of one disease, but in so doing also increases the risk of any other disease, consumers aren't healthier. The current strategy for treating diseases is built on a mature scientific foundation. Laboratory bench breakthroughs identify the causes of disease which become targets for diagnostic development to identify those afflicted with the disease. The same targets become the objects of high-throughput screening programs to identify candidate chemicals that could act to reverse disease, which in turn leads to their evaluation, testing and validation as small-molecule drugs. These pharmaceuticals are subsequently rolled out into a regulated, world-wide pharmaceutical industry and prescribed by trained clinical professionals as curative solutions to disease. Yet, if the goal is to prevent disease, then we cannot rely on diseases to define the scientific

targets on which to act. What are the targets for prevention? What mechanism do we act upon? What ingredients, when regularly ingested, are capable of acting on these targets and achieving this beneficial goal of overall prevention?

Evolutionary Basis for Discovering Metabolic Targets for Improving Health

Determining the targets for improving health is the fundamental problem of prevention. What are the targets, mechanisms of action and ingredients that we can discover that would make healthy people healthier? The good news is, an arsenal of "omic" technologies is at our disposal to approach this problem. The global scientific enterprise of genomics has sequenced various life forms. Science has now built this knowledge as a magnificent public resource; the entire genomic sequences of hundreds of viruses and bacteria, dozens of plants and animals and, of course, of *Homo sapiens* have been elucidated (Karolchik *et al.*, 2003; Pruitt *et al.*, 2006; Liolios *et al.*, 2008). What can genomics tell us about diet and health? An animal's genome is its blueprint of evolution and the basis of each organism's multiple solutions to its Darwinian pressures (Gould, 2002). Understanding Darwinian pressures can reveal the basis for genetic outcomes. Plants exposed to a dry environment develop molecular strategies for water conservation. Animals exposed to predators develop strategies for camouflage, protection or escape. To understand how animals have developed mechanisms of diet and prevention, we need a genomic model in which the Darwinian pressure was for nourishment and prevention. This basic scientific logic has been used previously in fields from pharmaceuticals to building construction. For example, the genomics of plants are mined to identify candidate drugs (Oksman-Caldentey and Inzé, 2004). Pharmaceutical companies have purchased the genetic rights to specific rainforests, reasoning that the jungle is full of candidate drugs (Mendelsohn and Balick, 1995). Analyzing from the context of Darwinian pressure, it is clear that plants evolved in part to the threat of predation. Since they cannot run away, their defence has been to become chemical factories of selective toxicity (Xie and Lou, 2009). The secondary metabolism of plants is an ingenious result of this pressure. Yet, our goal is not treatments for disease, but food-based solutions to achieve health.

What could possibly have emerged from millennia of evolution under the constant Darwinian pressures to be nourishing, protective, and to act on targets that improve the overall health of healthy animals? Milk. Lactation is the remarkable biological invention of mammals as the sole source of nourishment for post-natal infants.

Discovering the Darwinian Pressure of Milk as a Model for Foods for Health

Through evolutionary experimentation, mammals have spent the last 120 million years developing "the most efficient, effective and adaptable means of postnatal nutrient provision that has ever arisen among vertebrates—lactation" (Blackburn, 1993). Milk and lactation are an appropriate model to guide scientific discovery for foods for health. Lactation is appropriate for a wider range of activities than simply the chemicals in milk. The mammary epithelial cell is, in turn, itself a marvel of engineering: a bioreactor that

synthesizes bioactive components and guides the self-assembly of supra-molecular structures (German *et al.*, 2002). The constant Darwinian pressure on lactation has been to deliver a complete, absorbable ensemble of chemicals and structures that, when ingested, acts upon metabolic and physiologic targets that promote the competitive success of healthy mammals (Ward and German, 2004). This Darwinian pressure has led to the elaboration of complex food in milk that not only delivers nutrients as complex supra-molecular structures (*i.e.* milk-fat globules, casein), but includes immune-modulatory, toxin-binding and growth factors and antimicrobial peptides and proteins that act within the intestine and beyond to promote health, growth and protection of the neonate. Furthermore, safety and efficacy of milk has been rigorously tested during these same millions of years of evolution. Thus, unlike pharmaceutical research that must in every case ask: is it healthy? With milk, the question researchers need to ask is, "How does milk mechanistically elicit its health effects?"

Shifting the Paradigm for R&D: Disease Treatment to Prevention

Traditional drug development requires up to 20 years from candidate drug discovery to market, with greater than 90% of drugs failing during human trials (Eliopoulos *et al.*, 2008). The entire process from target discovery to successful intervention typically takes 30 to 50 years. As a direct response to the length of time and poor success rate in which basic bench science is transformed into a breakthrough with clinical utility, the field of translational science under the NIH was initiated as a new multi-disciplinary field in which the stated objective is to bring science to practice (Zerhouni, 2007). Yet, the current model of bringing science to practice is for the scientific discovery of pharmaceutical solutions to disease. This serial process requires the identification of pathways that are affected and their causal mechanisms—whether pathogens, toxins or enzymes. These causal mechanisms become the target for pharmaceutical solutions. With *in-vitro* screening, thousands of molecules are tested for their ability to act upon the target. Subsequently, successful hits move to drug-development pipelines where their safety in animals and humans is tested and their efficacy is tested against the target and then the disease. Finally, the small molecule found to act on the target is tested for efficacy, safety, and commercialization (Tonkens, 2005). The process of bringing scientific discovery to practice requires a quarter of a century. To speed up this process, key steps in this system will have to be accelerated. Yet, what part of translation of drugs should we skip: the efficacy or the safety?

If the translation of drugs for targeting disease requires decades of testing, how long would it take to discover, test, validate and bring to practice the prevention of disease by foods? A major challenge to prevention is actually in the time to translation. Prevention means that disease is prevented in healthy people. Do we wait an additional 50 years to assess the effectiveness in preventing disease by a food? Fortunately, evolution has used 120 million years for testing the efficacy AND safety of milk. For preventing disease with foods, research on milk at the Foods for Health Institute has led to the adoption of a different translational model (Figure 1). Unlike use of serial development for discovering disease targets, health can be translated using parallel research and development. Based

on the basic evolutionary principle in which lactation evolved under the relentless pressure to be nourishing, supportive and protective, once a molecule in milk is identified, it is understood that it is going to be valuable. It is only to be known how and in what population will it be effective. This confidence of efficacy suggests we can immediately start the process of developing industrial scale sources of the molecule, processing strategies, analytics and diagnostics of its presence and actions. Once populations that could benefit from consuming the molecule are identified and metabolic benefit is clinically assessed, ingredients and products are already scaled up for commercialization.

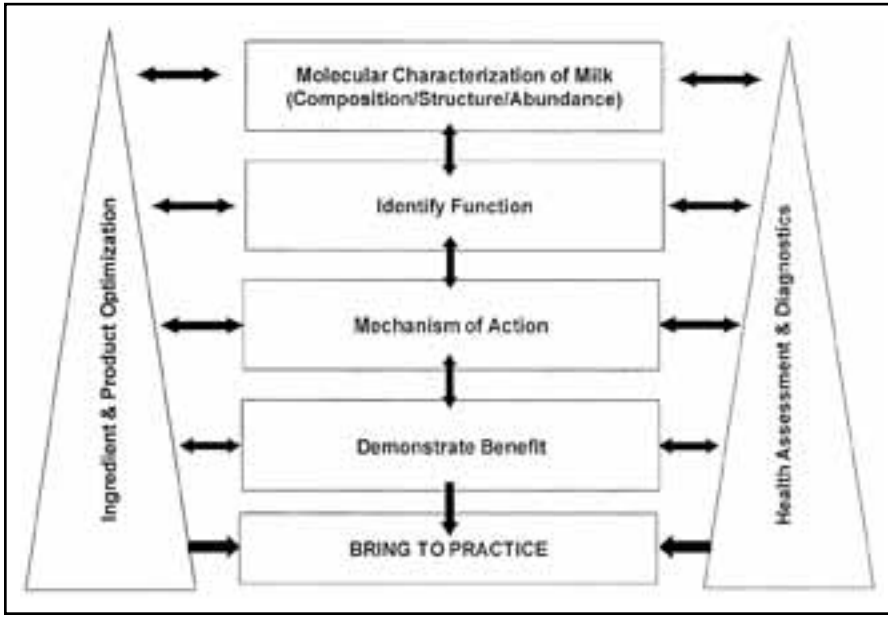

Figure 1. Parallel research and development for translating health.

Discovering the Mechanistic Targets of Milk Through Evolutionary Genomics

Identifying and annotating the milk genome is proving to be invaluable for the discovery of genes encoding molecules in human milk and their respective physiological targets. In efforts to provide a collaborative and interactive platform for researchers to accelerate the understanding of the biological processes underlying the mammalian milk genome, the International Milk Genomics Consortium (IMGC) was initiated in 2004. The IMGC has constructed a web-based portal as a public resource consisting of the genes of lactation and their annotation for the unique roles they play as molecules and structures for nourishment (www.milkgenomics.org). Research in this field extends across mammals and their varying lactation strategies, to provide insights into the diverse roles of milk (Bovine, 2009; Lemay *et al.*, 2009). IMGC has acquired lactation genomes across the entire evolution of mammals which permit the pursuit of a wide variety of scientific questions

about the origins, functions and distributions of lactation genes and their specific quality traits. For example, two animal species with contrasting lactation strategies have evolved in response to unique natural selective pressures: the black bear and the hooded seal. The black bear of the Northeastern United States and Canada gives birth during winter hibernation. The mother bear continues to hibernate for 2–3 months postpartum, during which time she does not exit the den to eat or drink despite nursing her cubs (Oftedal *et al.*, 2007). This example in which maternal stores solely support the first few months of lactation is a model for nutritional efficiency. At the other end of the spectrum is the hooded seal. This mammalian pup is born on an ice floe in the north Atlantic, in polar-bear country. The strategy for the neonate is to get off the ice floe and into the open sea quickly. During the 4 days of lactation, the mother seal transfers 26 kg of fat from her adipose stores and the pup gains 26 kg, of which three quarters is visceral fat. This most remarkable example of energy transfer in mammals supports the young seal through a post-weaning fasting period of 5–10 weeks (Oftedal *et al.*, 2007).

One over-arching question relates to the rate of evolution of lactation itself. Given the basic principle that mutations accumulate during evolution, the more identical the sequences are for a given protein, logic and prior experimentation have documented that the more important its sequence is to the survival of the organism. By taking such a quantitative perspective to evolution, lactation has been vital to the success of mammals. In Figure 2, the sequence identity of proteins expressed from genes in the entire genomes of seven mammals is distributed and compared with the proteins expressed by lactation genes of the same mammals. Most of the milk proteins are highly conserved across mammals, whereas a much smaller subset is highly divergent across mammals. There is less conservation among mammals for proteins of the liver, adipose, and brain than for lactation-related genes. This conservation throughout evolution emphasizes how important these genes have been to the survival of the species. Even evolution agrees that we have chosen the right model.

A Success Story for Foods For Health

Recall our model, the mother-infant pair. The mammalian mother actively dissolves her tissues to make milk. Everything in the milk is costly to the mother. If components found in milk do not enhance the survival of the infant, the cost to the mother would lead to its loss through evolution. However, if any component in milk, when consumed by the infant, provides it any competitive advantage over its genetic peers, it will be retained in evolution. This mother-infant pair is a Darwinian engine of nutrition. Considering this model, imagine to our surprise when we examined the various components in human milk and found that the third most abundant component class, at key stages of lactation more abundant than protein, were indigestible by the infant (Zivkovic *et al.*, 2010). How could this be?

Discovery

The presence of indigestible saccharides in milk led to a multi-disciplinary pursuit. Robert Ward, in Bruce German's laboratory, recognizing their paradoxical abundance, isolated these molecules from human milk and began to characterize their structures and func-

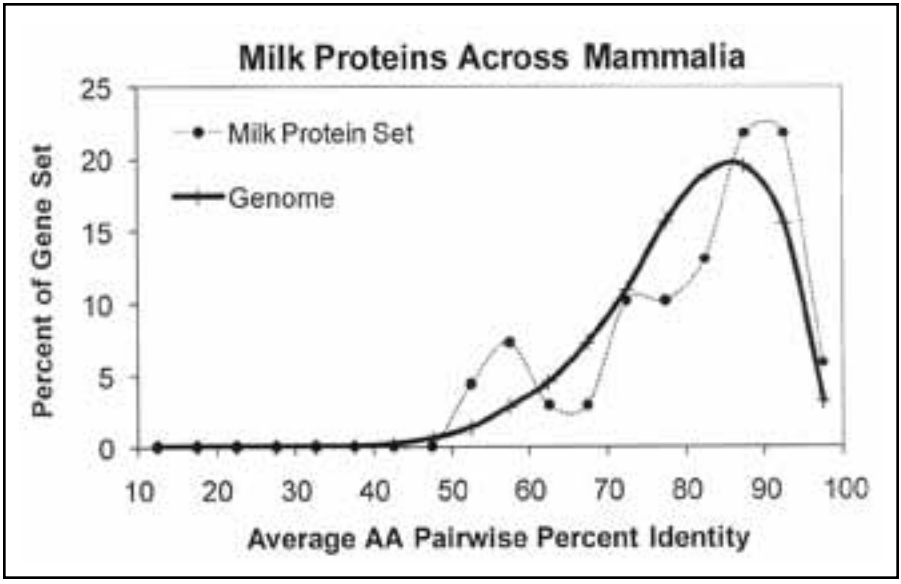

Figure 2. Distribution of proteins expressed by lactation-related and total genomes of seven mammals.

tions (Ward *et al*. 2007), although methods to characterize the chemical structures of these components were largely lacking. Their structural determination is one of the most complex problems for analytical chemistry. Carlito Lebrilla, a world leader in glycan analytics, and his team developed the tools to characterize the structures of the oligosaccharides in milk (Ninonuevo *et al.*, 2006, 2007, 2008; Tao *et al.*, 2009, 2010). If the infant cannot digest oligosaccharides, what are their functions? David Mills, a leading microbiologist specializing in the bacteria of the intestine, and his team characterized one component of the intestinal microbiota—*Bifidobacterium infantis*—which digested and thrived on oligosaccharides purified from human milk as their only carbon source (Sela *et al.*, 2008). This bacterial species was first isolated from the intestine of breast-fed infants. This is when the genius of milk became clear. Mothers are recruiting another life form: bacteria that protect their infants' health. These results have identified a unique target for foods; the intestinal microflora AND how to alter its population to derive a health benefit (Zivkovic *et al.*, 2010).

Translation

One advantage of doing research at the University of California at Davis is the breadth and depth of scientific and clinical programs across campus. Mark Underwood, the head of the Neonatology Unit at the UC Davis Medical Center has been pursuing intestinal health as a target of success and failure for premature infants. Mark and his colleagues are now investigating the use of human milk oligosaccharides and *Bifidobacterium infantis* to protect premature infants at increased risk of intestinal disease.

Commercialization

The final test of translational science is bringing it to practice for appropriate consumers. From the beginning of the project we have been simultaneously developing sources and technologies to produce this unique class of oligosaccharides as a food ingredient. Sources such as dairy process streams to decorated oligosaccharides, are all candidates that could achieve structure-function benefits of human-milk oligosaccharides. The UC Davis Center for Entrepreneurship is working in parallel to define business models for this ingredient class to enter the food marketplace. The goal is to translate health to those who would most immediately benefit from consuming such ingredients.

Conclusions

The challenges facing the life sciences and the entire agriculture enterprise are to deliver on the promise of prevention. The models established for small molecules as drugs developed by the pharmaceutical industry and delivered through the clinical profession as curative therapeutics are not appropriate for foods for prevention. This failure does not mean that we compromise the quality of science, the rigors of regulation nor the expectations for efficacy. New models that are capable of enhancing safety, efficacy and personal benefits from foods constitute the 21st century's most vivid opportunity to improve the human condition. The University of California, Davis, has assembled the multiple disciplines to respond to such an opportunity.

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During her PhD program, Smilowitz discovered metabolic phenotypes associated with changes in body composition in a large multi-center study, and designed and executed several clinical studies probing specific lipid metabolic pathways in the inflammation cascade. Her current research focuses on the development of assessment technologies for the identification of metabolic phenotypes in response to food-based solutions for ameliorating metabolic diseases and optimizing health and performance. Other research interests include elucidating structure-function relationships of lipoproteins and protective functions of skin and human milk. She is the project coordinator for the UC Davis Lactation Study, a large multi-disciplinary and multi-collaborative prospective clinical trial collecting well-annotated human milk samples from lactating mothers.

Dr. Smilowitz is the contact person at the FFHI for investigators interested in obtaining structural support and guidance for initiating clinical research designed to assess metabolic, performance and health responses to food.

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Opportunities for Biofortification of Cassava for Sub-Saharan Africa: The BioCassava Plus Program

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Cassava is an important staple crop in sub-Saharan Africa. Between 1970 and 2007, its production and acreage tripled across Africa and quadrupled in Nigeria, the continent's and the world's largest producer (FAO, 2008). Sub-Saharan Africa produced over 117 million tons of fresh roots of cassava in 2008, of which no less than 95% was consumed as food; the starch provides >25% of dietary energy for an estimated 200 million Africans (Dorosh, 2007). Frequent consumers of cassava are at greater risk for malnutrition—especially deficiencies in vitamin-A, iron, and zinc—than consumers of other diets, particularly those that are cereal-based (Gegios *et al.*, 2010). A nutrition survey in cassava-consuming areas of Nigeria and Kenya revealed inadequate intake of vitamin A in 83% and 41% and inadequate iron intake in 43% and 78% of pre-school-aged children, respectively (Gegios *et al.*, 2010). Vitamin-A deficiency causes a loss of 964,000 disability-adjusted life years (DALYs[1]) in Nigeria and 161,000 DALYs in Kenya annually; iron deficiency causes loss of 596,000 DALYs in Nigeria and 103,000 DALYs in Kenya (Fielder, 2009).

[1]A measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death.

Current efforts to combat micronutrient deficiencies in Africa include supplementation, through distribution of micronutrients to high-risk populations, addition to processed food and biofortification, *i.e.* the genetic improvement of nutrient content of crops via field-based breeding or genetic engineering. Supplementation requires tremendous effort to exceed 90% coverage and must be sustained for many years (Berti and Rowley 2001); few countries in Africa are able to run effective supplementation programs. Biofortification, on the other hand, can achieve 100% penetration and, although it requires a substantial initial investment in research and dissemination, it is self-sustaining. Cost per DALY saved for biofortification is 20% less compared to supplementation (Nestel et al., 2006).

BioCassava Plus (BC+) is a cassava-biofortification project at the Donald Danforth Center in St. Louis, MO, funded by the Bill and Melinda Gates Foundation. BC+ scientists are engineering cassava for increased accumulation of β-carotene, iron, and protein to provide minimum daily allowances of these essential nutrients as a means of ameliorating the burden of malnutrition that accompanies consumption of cassava as a staple food. Proof of concept for the enrichment of these nutrients has been demonstrated in the model cassava cultivar 60444, which, in greenhouse and confined field trials in Puerto Rico, contains up to 40 µg/g dry weight (DW) of β-carotene (provitamin A), 40 µg/g dry weight of iron, 10% protein storage roots, and reduced levels of anti-nutritional cyanogens.

Biofortification of Cassava

β-*carotene*

β-carotene enrichment of storage roots in cassava is conferred by two transgenes: the *Erwinia crtB* phytoene-synthase gene, and the *Arabidopsis* 1-deoxyxylulose-5-phosphate synthase (DXS) gene. The *crtB* transgene includes a 0.1-kb sequence for the plastid transit peptide for the Δ4-palmitoyl-acyl carrier protein desaturase from coriander. The phytoene synthase encoded by the *crtB* gene catalyzes the committed step in β-carotene synthesis using geranylgeranyl-diphosphate (GGDP) from the plastid isoprenoid pathway as its substrate. DXS catalyzes the first step in the plastid isoprenoid pathway. Increased expression of this enzyme is intended to enhance concentrations of GGDP for β-carotene synthesis and also to ensure sufficient amounts of GGDP to maintain vitamin-E production at or above wild-type levels. The *crtB* and *DXS* genes are each under the control of the *Solanum tuberosum* (potato) patatin promoter and flanked on their 3' ends by the 3' untranslated region (UTR) of the nopaline synthase (*nos*) gene from *Agrobacterium tumefaciens*. The selectable marker is the neomycin phosphotransferase II (nptII) from *E. coli* under control of the cauliflower mosaic virus 35S (CaMV 35S) promoter (with 2x enhancer). The nptII gene is flanked on its 3' end by the CaMV 35S 3' UTR.

Plants expressing the *crtB* and *DXS* genes were initially evaluated in four-inch pots under greenhouse conditions. Amounts of total carotenoids ranged from 30 to 60 µg/g DW in storage roots of the top lines. By comparison, amounts of total carotenoids in storage roots of control 60444 plants in these and subsequent greenhouse and field studies ranged from 1.5 to 2.5 µg/g DW. Subsequent evaluations were conducted of storage roots of plants growing in soil beds in the greenhouse and in confined field trials in Puerto Rico.

Concentrations of total carotenoids in roots from greenhouse beds typically ranged from 30 to 45 µg/g DW. Concentrations of carotenoids from the confined field studies ranged from 30 to 40 µg/g DW. Concentrations of vitamin E were not significantly different between storage roots from the top β-carotene lines and non-transformed controls. In the transformed lines, the relative amounts of all-trans-β-carotene, the most nutritionally efficacious form of carotenoid provitamin A, were 85 to 90% of the total carotenoid content. Relative amounts of trans-β-carotene in non-transformed controls were only 50 to 60% of the total carotenoid content. In collaboration with partners in Africa, BC+ has confined field trials of the β-carotene-enriched GM events (*i.e.* transformed plant lines) ongoing in Nigeria and another trial is planned for fall 2010 in Kenya.

In addition to the consumer benefit of improved nutrient levels, BC+ β-carotene-rich GM events also have producer benefits in terms of extended shelf-life. Five of the events with the highest amounts of total carotenoids could be stored for up to 28 days after harvest, whereas the wild-type recorded up to 80% spoilage after 7 days. Reduced shelf-life of cassava roots, a result of post-harvest physiological deterioration (PPD), is a major limitation to marketing of fresh roots. PPD begins 24 hours after harvest and can render the roots unpalatable and unmarketable within 72 hours. Short shelf-life affects cassava value-added chains because it increases losses during processing and limits access to markets distant from production sites. Longer shelf-life was correlated with total carotenoid content ($r^2 = 0.80$) in the GM events, which is consistent with previous studies indicating that high levels of carotenoids in the roots (> 8 ppm fresh weight basis) delay PPD (Sanchez *et al.*, 2005).

Nutrient retention during food preparation was also evaluated in three transgenic lines expressing higher levels of β-carotene. In three common Nigerian food preparations—*gari*, *fufu* and boiled—retention of provitamin A ranged from 82% to 37%, equal to, or better than, that seen in the wild-type 60444 variety. Values for *in vitro* bioavailability of provitamin A, as measured by uptake into micelles of Caco human intestinal cells, were similar for the transgenic and wild-type sources, *i.e.* 21% and 23%, respectively.

Iron

Increased iron content was achieved by the expression of the *FEA1* gene, from *Chlamydomonas reinhardtii*, in cassava storage roots. The FEA1 protein is an iron-specific metal transporter. It transfers iron efficiently at very low concentrations or at high pHs at which iron is largely insoluble. It does not transport toxic heavy metals unlike all other known metal transporters in plants. As with the β-carotene trait, *FEA1* expression was driven by the patatin promoter and *nos* terminator. Seven GM events were tested in the greenhouse and in confined field trials in Puerto Rico; iron content in the GM events ranged from 30 to 40 µg/g DW in storage roots compared to 10 µg/g dry weight in the wild type. Real-time PCR analyses strongly suggest that the additional iron is stored as a ferritin complex in the transgenic plants.

The morphology, including branching and flowering, of transgenic plants was identical to that of wild-type plants in Puerto Rico.

Protein

Increased protein content in cassava was achieved by the expression of sporazein, a storage fusion protein consisting of a 180-bp fragment of β-zein from maize, the sporamin gene from sweet potato and a 506-bp fragment of β-zein. Sporazein is a nutritionally balanced protein of 49.6 kD in which the zein components drive accumulation of the product to form protein bodies within the endoplasmic reticulum. As with the other two traits, the patatin promoter and nos terminator drive sporazein accumulation in cassava storage roots.

Seven GM events expressing sporazein were tested in the greenhouse, in soil beds, and in confined field trials in Puerto Rico. Total protein content of storage roots harvested ranged from 9 to 11% DW across all seven transgenic lines studied. The morphology and growth habit of these transgenic plants have shown no significant differences to non-transgenic controls in all three locations tested to date. No changes in expression of trait accumulation have been observed over the 18 months during which these plants have been tested in the greenhouse and field. As protein bodies are water-insoluble, water soaking overnight at room temperature resulted in 94% retention of the total protein content of the cassava roots. Boiling for 30 min resulted in 95% retention of the total protein content.

It is well known from other plant systems that the direction of reduced nitrogen to the synthesis of new proteins may come at the expense of nitrogen allocation to essential proteins required for metabolism. Thus, elevating expression of storage proteins in cassava may impair the growth or biochemical properties of roots. To address this concern, we have over-expressed a vacuolar targeted linamarase, an enzyme that breaks down linamarine, a cyanogenic glucoside found in cassava leaves, stems, and roots. This has been shown to increase the pool sizes of free amino acids in cassava.

Product Development of Nutrient-Enriched Cassava for Africa

BC+ has achieved nutrient enrichment of cassava such that if a 5-year-old child consumes 100 g/day of roots from the β-carotene, iron, or protein-rich GM events, (s)he will obtain 100% of the minimum daily allowance (MDA) of these nutrients. BC+ has, therefore, embarked on the expression of genes for the aforementioned nutritional traits in farmer-preferred cassava varieties from Nigeria and Kenya, its two target countries. Genetic transformations at the Donald Danforth Plant Science Center (DDPSC) have successfully generated transgenic lines of Oko-Iyawo, the most popular Nigerian variety of cassava currently grown on 22 to 24% of total acreage (about 4 million hectares) in that country, and the Kenyan cultivar Serere.

Based on *ex-ante* impact studies for nutrient deficiency in Kenya and Nigeria, a β-carotene- and iron-enriched Oko-Iyawo for Nigeria, and a β-carotene-, iron- and protein-enriched, and virus-resistant, Serere for Kenya were selected as first products. Oko-Iyawo is resistant to cassava mosaic disease (CMD), which is of viral origin and is the principal production constraint of cassava in Africa, whereas Serere is susceptible to CMD and needs to be engineered for resistance. Product development is divided into several stages, namely:

- generation of transgenic events,
- greenhouse characterization and testing,
- field testing,
- selection of a lead event,
- food and environmental safety assessments in a regulatory field trial,
- biosafety approval for commercial release,
- on-farm trials, and finally
- variety release and dissemination.

Lead Event Selection

A commercial quality construct that is codon-optimized without extraneous genetic elements, will be created for the *crtB, DXS, FEAI* genes (β-carotene and iron traits) and transformed into friable embryogenic callus derived from Oko-Iyawo. Six hundred transgenic plants will be regenerated and screened for events that possess a single copy of the construct, no vector backbone sequences and good RNA expression. Events, an estimated 125, that meet these criteria will be planted in the greenhouse and roots evaluated for β-carotene and iron contents. Events that meet the set targets of 40 μg/g DW for the two traits will be transferred to confined trials in Puerto Rico and Nigeria for trait assessment under field conditions. This will be followed by two cycles of replicated confined field trials at three locations to select a lead event and a back-up for regulatory trials. A similar procedure will be followed for the Kenyan product, with the exception that the gene construct will contain sporazein and RNAi for CMD and cassava brown streak disease (CBSD), a viral disease of cassava that is specific to East Africa.

Biosafety Regulatory Activities

Cultivation and consumption of cassava expressing these genes will require the granting of approval from regulatory bodies in Nigeria, based upon food and environmental safety assessments of each novel gene/protein that confers the targets traits. A safety assessment is required for each event intended for commercial release. *DXS*, *crtB*, *FEA1*, sporazein, and *npt* II proteins will be purified, characterized, and assessed for potential toxicity in acute (single dose) oral gavage studies with mice. Allergenicity of the *DXS, crtB*, and *FEA1* proteins will be assessed in accordance with international guidelines. This is a 'weight of evidence' assessment that includes the source of the gene, documented dietary exposure to the protein, any amino-acid sequence homology to known allergens, and protein stability upon incubation in simulated gastric fluid.

The purified proteins will also be used to develop Western blot and enzyme-linked immunosorbent assays for detection of the proteins in plant material. As the *DXS* and *crtB* proteins are enzymes and will be present at higher levels than what are typical in cassava, regulatory authorities will likely require information on substrate specificity. Evidence from the peer-reviewed literature on known substrate specificity for these enzymes will be sought.

A key consideration of regulators is assessment of any unintended effects that result from elevated biosynthesis of metabolites in the carotenoid biosynthetic pathway. Unintended effects are traditionally addressed in the safety assessment by performing extensive nutrient-composition and agronomic performance analyses. Compositional analyses of starch quantity and quality, fatty acids, total and free amino acids, minerals, vitamins, cyanogenic glucosides and phytates will be conducted. Protocols for the compositional and agronomic regulatory field trials—a final field trial conducted on a lead event to generate agronomic performance, food and environmental safety information—will be in accordance with international guidelines.

Reaching End-Users

Agricultural development in Africa is replete with examples of well intended scientific advances that have had limited impact because they were not sustainably adopted by producers and consumers. Fortunately, there are also excellent examples of widespread successful adoption of new varieties. The strategy to reach end-users should avoid the mistakes of the former and build on the successes of the latter, while taking into account the special issues associated with transgenic varieties. Many failures have resulted from a narrow focus on preferred production characteristics. A critical aspect important for reaching end-users is seed production and distribution. In Africa, the vast majority of cassava stakes for planting is generated from current plants by the farmer or obtained from neighbors; the private sector has little interest in this crop. However, non-government organizations (NGOs) involved in development activities and some national agricultural systems now have good experience with dissemination of new varieties. BC+ will partner with organizations that have the best linkages to large numbers of farmers. Tissue culture and an inexpensive two-node multiplication system for rapid and massive propagation will be used to bulk up foundation seed for distribution to large NGOs and government agencies.

Cost-effective strategies for farmer adoption and consumer acceptance of β-carotene and iron-rich cassava entail a marketing and promotion plan. For example, *gari* is the most important food staple of the rural and urban poor and the *gari* market chains have extensive coverage; over 70% of cassava grown in Nigeria is used for *gari* production. A great advantage is that the deep yellow color of high-β-carotene and -iron cassava is similar to a yellow *gari* product, made by addition of palm oil, already accepted by consumers. Although *gari* processing tends to lead to a depletion of β-carotene and iron, levels of nutrient enrichment achieved in BC+ ensure that sufficient amounts of these nutrients remain to meet minimum daily allowances based on the average quantity consumed and bioavailability.

Anti-GMO NGOs may be expected to mount campaigns in opposition to dissemination and adoption of β-carotene- and iron-enriched cassava. Opposition can be overcome through demonstration of the benefits to consumers (improved nutritional quality) and to producers/processors (extended shelf life of storage roots). Other elements for countering such opposition include: adhering strictly to bio-safety protocols and regulatory requirements; being transparent by engaging key stakeholders in constant dialogue to communicate progress and building confidence that the process is being properly and

responsibly run. Other efforts include publication of studies to address the issues of safety and product quality, and setting up local product-development committees to design and implement communication and issue-management strategies.

Socio-Economic Impact

An *ex-ante* socio-economic impact of BC+ was commissioned by the Bill and Melinda Gates Foundation and conducted by Harvest Plus, a biofortification initiative of the Consultative Group on International Agricultural Research. The study established a baseline of DALYs lost, estimated the cost of development and rate of adoption of BC+ products, and presented a comprehensive economic impact analysis of BC+ products (Fiedler, 2009). This resultant cost-effectiveness analysis was expressed in terms of cost per DALY saved, a benefit-cost ratio, and an internal rate of return. A cost per DALY saved of less than $248 is considered "very cost-effective" (Berti and Rowley 2001); a benefit-cost ratio greater than 1.0 is considered an attractive investment, and the higher the internal rate of return the better.

The cost of developing and disseminating a BC+ product is estimated at $41.35 million over 30 years, broken down into four phases of $13.48 million (basic research, applied research, capacity building), $8.49 million (applied research, product development, regulatory approval, capacity building), $16.35 million (regulatory approval, release promotion, technology diffusion), and $3.02 million (promotion, technology diffusion, monitoring and supervision, maintenance) (Fiedler, 2009). Although these costs are high, they are justified when considering the DALYs lost due to micronutrient deficiencies: each year losses of DALYs due to deficiencies in vitamin-A, zinc, and iron amass to 2.3 million in Nigeria and 337,000 in Kenya. The study revealed that BC+ cassava varieties will be readily adopted by African farmers, achieving adoption rates of 20% in Nigeria and more than that in Kenya. The higher rate in Kenya is based on the incentive for adoption based on viral resistance. This, in turn, will lead to consumption rates of 67% in Nigeria and 14% in Kenya. Well over half of these consumers live in rural areas.

Accounting for these production and consumption rates and noting that the new cassava varieties have increased levels of iron (457%) and β-carotene (3,000%) when compared to wild types, the DALYs saved were projected at 617,000 in Nigeria and 47,000 in Kenya. These numbers were then used to calculate the cost-effectiveness of the project, incorporating pessimistic and optimistic parameters. For the pessimistic model, the cost per DALY saved is $57, the benefit-cost ratio is 18, and the internal rate of return is 24%. In the optimistic model, the results are $33, 31, and 32%, respectively (Fiedler, 2009). In either model, the study suggests that biofortification is a cost-effective approach to reducing this region's micronutrient deficiencies and the corresponding health problems.

In Conclusion

Biofortification appears relatively more cost-effective than other interventions, particularly in regions where deficiency is widespread. Fortification can achieve a near 100% coverage rate, penetrating rural areas and high-risk population groups and has a potentially high socio-economic impact.

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Martin Fregene is a plant geneticist and molecular breeder with more than 18 years of experience in genetics and breeding of cassava. In addition to developing the first molecular genetic map of cassava and initiating the first cassava molecular-breeding program, he is an authority on the utilization and molecular phylogeny of wild *Manihot*.

Dr. Fregene began his career at the International Institute of Tropical Agriculture (IITA), Ibadan, Nigeria, in 1991 as a cassava breeder, where he received a Rockefeller Foundation postdoctoral fellowship on genetic mapping that took him to the International Center for Tropical Agriculture (CIAT), Cali, Colombia. At CIAT, he developed a molecular genetic map of cassava. From 1996 until 1997 he was an associate scientist at CIAT working on tagging of genes controlling early yield, and resistance to diseases and pests in cassava. From 1999, he served as senior scientist and cassava geneticist at CIAT and for nine years led a program to develop CMD-resistant neo-tropical gene pools and to broaden the genetic base of cassava with genes from wild relatives.

In 2008, he joined the Biocassava Plus (BC+) project at the Donald Danforth Plant Science Center, St. Louis, MO, as product development manager. In March 2010, he was designated director of BC+.

Fregene received his BS, MS and PhD degrees from the University of Ibadan.

Food for Health Successes and Prospects

Q&A

Moderator: Alan B. Bennett
University of California
Davis, California

Alan Bennett: Martin, you addressed market challenges. Marlin and Jennifer talked about a pipeline—things that are coming through very promising. So, you told us a lot about meeting technical challenges, but what about market challenges—bifidobacteria were mentioned. Can both of you address what you think of the ability of the market to embrace health and nutrition traits.

Jennifer Smilowitz: The *Bifidobacterium infantis* and oligosaccharide combination is more of a medical food approach than something available to everyone at this point. One thing that will be an issue is making claims on prevention, like on food products, and that's not where we are going. We are trying to discover molecular targets, using milk, for health, and the bifido and oligosaccharide combination is just one example. Another business idea is to basically reconstitute HDLs that can bind pathogenic bacteria, but also are still functional HDLs. Now, not all HDLs are the same. Some are actually dysfunctional and some are more functional, and so this could be more of a therapeutic or theranostic approach. But the idea is to use milk, which is the food, in this endeavor.

Marlin Edwards: I should emphasize that all the projects I presented with respect to nutritional or sensory enhancement in vegetables are produced using conventional plant breeding. We use modern technology as a diagnostic tool—molecular markers to understand the native genetics behind these traits, but they are delivered entirely through conventional breeding. So, we don't expect complications in launching those. With respect to the soybean-oil enhancements, of course there is a tradition in this country of acceptance of biotech projects in soybean oil and we are very hopefully that the public will embrace these products as they will have direct consumer benefits.

Bennett: A short follow-up for you, Martin. Your timelines are long and when you are talking about disability adjusted life years that's got to be a frustration. Two questions: Is there any way to accelerate these timelines? And does the Bill and Melinda Gates Foundation have a long-term commitment? Will they see this through to the end?

Martin Fregene: On the timeline, I was asked the same question by my president: "This is too long. I want to see it happen in two years." The truth is, if you are going to give farmers something reliable, you need to test for at least three years, so maybe you could reduce it to about five total, but that is about the minimum. Not less than five. One year to create the event, one year to greenhouse test and then 3 years of field testing. And then on long-term commitment—yes, they are committed over the long haul.

Bennett: And while I have the microphone, I have a quick technical question for you. I'm intrigued by the sporazein trait and the ability to produce protein bodies. What implications does that trait have for nitrogen fertilizer, for example?

Fregene: It's interesting that cassava has tons of nitrogen in the leaves. We aren't taking more out of the soil; we are deploying what is already in the plant—in the leaves and also in the roots—and redeploying it into storage proteins. So far, we haven't seen an effect in terms of lower yields. We haven't seen a penalty. But, again, it's early days so things may change. If we find a need for lots of nitrogen fertilizer, that would be a killer.

Audience member: A question for Jennifer, following up from what Alan was asking. You said you are taking more of a functional-food approach toward regulatory or safety tests and so on, but you talked about genetically engineering bacteria, so doesn't that raise a lot of flags? Martin, for example, had a 10-year program to try to get it through regulatory fences. Can you comment on that?

Smilowitz: We are not going to genetically engineer any plants or other commodities. We identify the molecular targets in milk and see where else we can find them. For example, human-milk oligosaccharides are also found in bovine milk, which we drink. And they are found in whey streams which are used as a by-product. We are enriching those. In terms of safety and efficacy we are using milk, which is pretty safe, right? We aren't having any issues using this product with neonates.

Audience member: Okay, but how are you enriching them?

Smilowitz: By engineering. With the Hilmar Cheese Company, we are using specially engineered pores to enrich them.

Robert Wager (Vancouver Island University): My question is for Martin. First off, congratulations on fabulous work. It must be very difficult to do biotechnology with all the constraints put on you in Africa. It's tremendous what I saw today. Where are the

field trials of the stacked cassava being done and, secondly, what's your opinion on the news that Kenya this week will finally push forward their biosafety regulations through parliament and how that relates to the difficulties of doing biotech work in most of the countries of Africa?

Fregene: The field trials for stacked products right now are in Puerto Rico, and they are yet to be tested in Nigeria. In Nigeria we still have single-trait events, β-carotene, with iron going to the field. On the question of the legislative and regulatory environment for doing this kind of work, you are right, the whole environment for biotech in Africa is still very premature, very primordial. But Kenya, as a matter of fact, has passed a biosafety law. Right now, they are going through the process of translating that law into a framework of laws that can be implemented. So the Kenyans actually do have a biosafety law. They, South Africa, Egypt and Burkina Faso are about the only ones. The Nigerians are in the process of passing the law, but the toughest part is translating that law into regulations and rules that can actually be used in practice. The Kenyans are now pushing ahead with that. It has taken them more than a year already, but, hopefully, things will improve. The selling point here that is good to mention is that we are looking at these not just as food but also as nutrition products. So when you talk about medicine, people are willing to go the extra mile and do something a little bit more risky than when you are talking about just food. This is also being sold as a nutritional product, and hopefully that will open the doors a little bit wider.

Tom Tomich (University of California-Davis): I'm interested in methods for risk assessment. In her banquet presentation, Dr. McGloughlin effectively put on the table that significant risks result from inaction, from doing nothing. That needs to be considered. But in terms of innovative technologies, there are production risks, which I think we have pretty good methods for, but then there are environmental risks and health risks, with which the methods are much more problematic. And then, getting back to Alan's question, there are also market risks about acceptance. So, my question for each on the panel is, "What do you view as the best practice in integrated risk assessment in your area and, how do you actually frame how those different elements fit together?"

Smilowitz: For integrated risk assessment, we are implementing clinical trials. And we are doing extensive tests with high through-put analyses to make sure we are actually capturing all of the metabolites, to assess which are decreased and which are increased. We are using food as our model. I mentioned earlier that we are using engineering technology to enhance, let's say, oligosaccharides in bovine milk, but it's really through filtration. We're not inserting genes and we're not adding any chemicals; via filtration we are augmenting what is already found in nature. We are not interfering with Mother Nature, and if we can show that with these clinical trials—feeding trials and many are already going on—we don't feel like we are going to have too many constraints. Now the issue is whether consumers will be interested in these products. We're not there yet in terms of market research, but we are working on that.

Edwards: We are increasing natural dietary components of vegetables. Of course we are concerned about and do studies to make sure that we are not increasing them beyond levels that consumers would otherwise get with other diets that are prevalent here or elsewhere in the world. So, there are those kinds of precautions. With respect to the modified oils I talked about, we already have GRAS certification because the oil composition is similar to others in the marketplace. We are already free to use those other oils for the kinds of food-formulation processes that were described, but we work carefully with regulatory and government agents and experts in the field to do the feeding formulations and whatever is necessary to certify health effects.

Fregene: For BioCassava Plus, of the food-related, environmental and trade risks, trade is easiest to deal with. There is almost no trade in cassava between Nigeria and other countries that might turn down GM crops. From the outset we make bioinformatic assessments for potential allergenicity related to the genes we are working with and we also do food toxicity tests—you purify the proteins and you feed them to rats and things like that. We also do environmental assessments. We are working hard to contain all the potential risk, but, as we go along, additional ones will show up. No doubt about that. The good thing is to have an issues-management plan in place to address all of the risks that shows that you have a rational, safe system. That way you build confidence and, hopefully, eliminate apprehension.

Concepcion Mendoza (University of California Cooperative Extension): Martin, yours is a novel approach to solving nutritional problems in developing countries. It's a huge effort with a lot of investment. Have you done any sensory tests for consumer acceptability of these new products, especially using traditional food-preparation methods?

Fregene: That's a very relevant question. As a matter of fact it will be done, but further down the road. We still don't have a lead event selected. We don't have a product that is going out. Our model variety is different from the farmer-preferred variety. Before we jump through that hoop, we will have to have something acceptable to farmers. It's in our product-development master document to do taste, food-processing and preparation tests to make sure that what we are producing will be acceptable, but right now we haven't done it.

Betty Burri (Western Human Nutrition Research Center): Martin, are the high β-carotene varieties of cassava also low in cyanogens?

Fregene: The variety we picked is low in cyanide. But, ordinarily, people process it into *gari*, which gets rid of a lot of the cyanide.

Stanislaus Dundon (California State University): One of the socially desirable aspects of cassava is that the soil doesn't have to be particularly fertile. The crop, as long as it stays in the ground, is like a storehouse. Its short shelf life means that it has to be eaten locally

and that's good because that's where the hungry people are. However, the financial world is interested in a competitive source of cheap starch to ship around the world. I suspect that, all of a sudden, that crappy land may become valuable and local farmers will lose control of it, meaning that the local people will lose control of that food source. Do you have any mechanism for preventing this side effect?

Fregene: I really haven't thought about that, but I can give you my take on land, at least in Kenya and Nigeria. The areas in which we are working in western Kenya and southern Nigeria are heavily populated. The average land size per farmer household is approximately an acre. It's really small. It would be hard for government or an investor from Dubai to buy that kind of land. It would create a social catastrophe; where are you going to move all those people to? So, where we are working, this is of lesser concern. Where you have large tracts of land, less heavily populated, the danger of having that land taken away from them by large investors is there.

Jozef Kokini (University of Illinois): Marlin, I am very impressed with the work that is going on at Monsanto. This is the second time that I have seen this presentation and it is really spectacular. It's wonderful to see that genomics is actually leading to new attributes beyond *Bt* corn. My first question is about the value of these advances to the farmer. I can see, for example, how, in the case of fruits and vegetables, improved quality might lead to value in the marketplace, but I'm just wondering if that would happen also in the case of a commodity like soybean. Will the farmer be able to get a premium, if you will, for improved fatty acid characteristics? And similarly to a previous question, before you launch these in the marketplace are you doing the range of consumer tests and sensory evaluations to determine if their properties are similar to or better than those already available?

Edwards: In terms of the sensory properties of the products from the oil, obviously this is critical. We are starting some of the initial work in house, but a lot of it will be done by food-company partners who have already expressed interest in those ingredients. Clearly, those criteria will have to be satisfied in order for those products to go to market, but our experience so far has been extremely positive. With respect to agronomic properties and benefits to growers—Flavr-Savr was mentioned earlier, and one of the challenges with Flavr-Savr was that it was launched in a product that was completely inadequate for the production region. One of the mantras of our business is that products we launch have equal or superior agronomic and production properties, as well as the benefits from our traits. We don't expect our traits to have enough value to carry them forward if they compromise agricultural productivity and farmer profitability. It's clear that some of these traits will require some channeling in the marketplace in order to get them into product streams where the oils will deliver benefit. There likely will be additional cost for the growers and we recognize that we have to work through the whole value chain to set up an incentive system so that all the players in the process come out equal or advantaged. We've been able to do this in the past and it takes a lot of work, but that is clearly the model to ensure success.

Kokini: Do you see a two-tier pricing system emerging? Today a soybean is a soybean and it sells on a cost per bushel basis. Do you see soybean with improved fatty acid characteristics to be worth more per bushel than a standard soybean?

Edwards: We certainly hope so. From their usefulness in the human diet, clearly they will be worth more. We are working on traits that we hope will provide benefits that will create a pull from consumers through food companies, *et cetera*. That added value might exist at the consumer level, and it might exist at the food-company level in terms of formulation. There are several places where that added value might manifest. We have to work with all the partners to establish a distribution process where everyone shares, or these don't go forward.

Audience Member: I also have a question about this new healthier soybean oil. How will the price compare to the soybean oil that we are producing today. How will that price compare to today's olive oil? In my view, the new oil is probably comparable to some of the olive oils of lower quality.

Edwards: With respect to the lower saturated fats, indeed the composition is comparable to other oils. With respect to that enriched in omega-3 fatty acid, I don't think it is comparable to any oil in the market. I'm sure that the value addition has been determined. Unfortunately I have to confess that I am not close to that, so I don't know what the analyses today say; but, I will tell you that these products are very expensive to launch. We will spend tens of millions of dollars in regulatory costs to launch these products. We need to make sure they actually meet needs and create value in the marketplace. The value in the marketplace determines the price, but I don't know the specifics, I'm sorry.

Ashley Burns (Clemson University): I'm a PhD student, here as part of the *Student Voice* program. My question is also related to the soybean issue. Have any of these products been tested on livestock? Has any work been done using these in feed? The high-oleic acid probably would not be beneficial to dairy producers due to associated milk-fat depression, but, has anything been done to alter fatty acid composition of our meat animals?

Edwards: Again, I'm sorry that I don't know the answer to that. In the process of launching these, we do feeding studies with a range of organisms, so I'm sure those kinds of studies can be done. However, given that there is considerable expense in launching these and we are actually formulating them for improvements in the human diet, I don't suppose that benefits from feeding to livestock are a primary consideration in our evaluations.

Functional Foods For Health: Negotiation and Implications

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If functional foods are to provide one of the solutions to the problems of dietary health that we currently face, consumers will need to incorporate them into their lives, making sense of them in relation to existing beliefs and values. Therefore, we must understand not only the scientific means of producing foods with additional health benefits, but also the relationship between functional foods and existing understandings of food and health. More research is needed in this area, particularly in the United States where very little scholarly (as opposed to market) research has been conducted to examine the cultural dynamics of functional foods. Here I present some preliminary findings based on my analyses of the intersections between functional foods and beliefs about dietary health among American consumers.

The term "functional" is typically used to refer to foods that provide health benefits "that go beyond basic nutrition" (Clydesdale, 2004; Hasler and Brown, 2009) This definition is quite broad and very inclusive, generating questions and confusion: "Aren't all foods functional?" "What is the difference between a functional food and an ordinary food?" "Do blueberries and cholesterol-lowering spreads really belong in the same nutritional category?" Therefore, my remarks identify and focus on a specific subset of functional foods; those that have had their nutritional profile engineered or enhanced in order to promote health or aid in disease prevention. These products are novel enough to require a particularly deliberate process of negotiation as consumers integrate them into existing practices and try to understand them in light of established beliefs and values. I will also argue that it is important to distinguish "nutritionally engineered" or "functionally enhanced" products from those inherently endowed with nutritional properties now recognized as conferring important health benefits, which we may call "intrinsically functional" and which may or may not also be "functionally marketed."

[1]The categories I distinguish here are influenced by those proposed by Scrinis (2008) and Leighton (2002).

Drivers

Many social and demographic factors contribute simultaneously to growing consumer interest in functional foods and growing interest among manufacturers in innovating and marketing products with enhanced functional benefits. Hasler (2000) has identified several of these: the aging of the population in concert with rising healthcare costs generating interest among baby boomers in using food as a means of preventing the chronic diseases of aging; technological advances such as those in biotechnology and nutritional genomics that have (and will) make new benefits possible; a changing regulatory context that, since the 1990s, has allowed the kind of health claims that distinguish functional foods; and scientific research documenting the health benefits of specific foods or food components that back up these claims. These factors describe some of the environing conditions that create the possibility for functional foods to play a role in improving the dietary health of the population.

Negotiation

The process of changing food habits takes place on two levels. Structural changes such as the technological, regulatory and economic alterations described above as "drivers" define the widest possible constraints within which change can occur on the more intimate level of daily life. It is on this intimate level of the lived conditions of consumption that people incorporate new items, made possible by structural changes, into their daily rituals and invest them with meaning (Mintz, 1996). Although the drivers allow functional foods to exist, the specific ways in which they are used and the meanings that become attached to them are worked out through a process of negotiation that is shaped in part by already established understandings about food and health. In her analysis of how middle-aged health-oriented Finns view functional foods, Mari Niva (2007) describes the process that takes place on this intimate level as one of "contextualization." She notes that consumers use "existing cultural categories to make sense of the new phenomenon and to find a place for the new products in everyday life." The structural changes allowing for the possibility of functional foods to address dietary problems and improve population health are clearly in motion, but we know too little about the process of negotiation through which consumers may, or may not, make sense of these products, incorporate them into their daily rituals and invest them with meaning.

Food, Health and Pleasure

Among existing understandings about food and health that play roles in how functional foods are negotiated and invested with meaning by consumers, the "health-pleasure paradox" is particularly significant (Biltekoff, 2010). This is the long-standing idea that "good" foods taste bad and good-tasting foods are "bad for us." Mark Twain (1897) expressed this paradox beautifully in *Following the Equator*: "The only way to keep your health is to eat what you don't want, drink what you don't like, and do what you'd rather not." The sentiment endures because it expresses beliefs about the meaning of health that are prevalent in Western, individualist cultures. We see health through the lens of our social and cultural values, imbuing the pursuit and accomplishment of health (and dietary health

in particular) with many of the same qualities that have historically been considered essential to mature subjectivity and good citizenship: autonomy, willpower and self-restraint (Crawford, 1984). To the extent that we see health as an accomplishment that is achieved through the exercise of the thinking self over bodily desires, we also understand health as anathema to carnal pleasure and associate healthy practices with self-denial.

One of the allures of functional enhancement is that it has the capacity to remake "bad food" as "good for us" and, perhaps, engineer a solution to the health-pleasure paradox. By combining the hedonics of a sinful treat with the nutrient profile of a "good food," products like Vitamuffins™ and Super Donuts® seem to make it finally possible for Americans to indulge their way to health. While these products may indeed offer both pleasure and health, they are negotiated within the context of the health-pleasure paradox and understood by consumers in ways that clearly distinguish the pleasures that they offer from muffins and donuts that have not been enhanced with fiber, vitamins or essential fatty acids and packaged in calorie-controlled portions. The pleasure of the functional treat is what Coveney and Bunton (2003) call "disciplined pleasure"…"reasoned, reasonable and safe," rather than risky or unplanned, and consistent with, rather than opposed to, the self-restraining dictates of health. This is not the reckless pleasure of a "sinfully" delicious dessert, but a studied attempt to achieve a balance between enjoyment and responsibility that is simply inconsistent with the experience associated with unrestrained—and therefore often guilt-inducing—gustatory pleasures. A fan of Deep Chocolate Vitalicious® VitaTops is quoted in the "Tastymonials™" section of the company Website[2] raving about the *disciplined* pleasures that the product affords: "When I eat the chocolate ones I feel like I am cheating on my diet when in fact I am eating something really healthy…I thank you for helping me start my day off with something that looks and tastes sinful but is great for me." Not surprisingly, in her study of Finnish consumers, Niva (2007) found that "functional foods had no place in indulgence. They were excluded since, by definition, they encompass a planned controlled health orientation…" Because the experience of disciplined pleasure is defined against indulgence, it also brings with it the pleasure of moral superiority over those whose unregulated pleasures are taken as a sign of irresponsibility, indifference and immorality (Niva, 2007). Product innovation that aims to use functional enhancement to align eating habits with healthy outcomes should attempt to better understand, motivate and capitalize on the existing drive for disciplined pleasures while bearing in mind the ways in which it is distinct from the pleasure of indulgence.

The Whole-Diet Approach to Nutrition

Functional foods are also negotiated and contextualized in relation to existing consumer understandings about what constitutes a healthy diet. But the appeal of functional foods—with its emphasis on single nutrients and the value of specific foods—conflicts with fundamental tenets of dietary health that have been promoted in the United States for over

[2]http://www.vitalicious.com/testimonials.html, retrieved May 16, 2010.

a century. Since the emergence of the science of nutrition in the late nineteenth century, dietary advice has focused on communicating the basic fact that foods are composed of nutrients and that certain foods are, therefore, nutritionally similar despite their apparent differences. Early twentieth-century dietary reformers sought to teach the urban poor that the protein in a cheap cut of tough meat is the same as that in the most expensive steak, and that the real value of food comes not from its cost but from its nutritional content. These ideas were popularized in a campaign during World War I that promoted the idea that beloved but scarce foods could be replaced by abundant yet unfamiliar ones at no nutritional cost. During World War II, the food-group approach to dietary health was introduced and Americans learned that eating right meant choosing at least one food from each of seven groups every day (Levenstein, 1988, 1993).

The idea that certain kinds of foods share nutritional qualities with others and that a good diet is varied and balanced remained central to dietary advice throughout the post-war period. As the nutrition and health communities shifted their focus from preventing vitamin-deficiency diseases to managing the chronic diseases of middle age, dietary advice became increasingly focused on warning people to avoid or reduce consumption of potentially harmful foods (sodium, cholesterol, fat, *etc*.). The USDA Food Pyramid's hierarchical structure conveyed the notion that some foods are better eaten in abundance and others in moderation, but remained focused on the dietary totality. In the context of this new dietary paradigm, which Warren Belasco has termed "Negative Nutrition," the food industry—concerned about the potential for negative impact on sales—played a major role in shaping an ongoing "no good foods or bad foods" approach to dietary advice that emphasized the importance of the whole diet rather than the role of specific foods within it (Belasco, 1989; Nestle, 2002)

Some observers have claimed that the emergence of functional foods represents a shift from a "food negatives" paradigm to a more positive approach to dietary health that entails seeking out functional benefits in food (Hasler, 2000; Leighton, 2002). While consumers are clearly interested in using foods to enhance health in new ways, the emphasis on the nutritional distinctiveness of particular foods and the particular value of specific micro-nutrients conflicts with traditional nutritional ideals. Although individual functional-food products may appeal to consumers seeking particular benefits, the general concept of functional foods may confuse consumers and be difficult to integrate into existing understandings of dietary health. In her analysis of lay perspectives on functional foods, Lotte Holm (2003) pointed to two related dangers. She noted that the "detail oriented and fragmented" messages of functional foods are similar to food-safety messages that have historically generated "confusion, uncertainty and ambivalence." She also noted that by introducing elements of one group into foods from another (vitamins in candy, for example), functional foods disturb the logic of food groupings and may, therefore, be "counter-productive to the nutritional health of populations."

The Nature of Healthy Food

As the products of scientific innovation and industrial processing, functionally enhanced foods promise healthfulness but conflict with understanding held by many consumers

that healthy foods are those that are the most "natural." In interviews with consumers in five European cities, Holm *et al.* found that healthy eating means avoiding additives, and that eating "pure" foods (homemade from raw ingredients and containing few additives) was understood to provide protection against the dangers of "modern foods" (Holm, 2003). Niva's subjects described healthy food as "pure," "natural," and "unprocessed" and felt that "foods enriched or fortified with healthy ingredients, even if they were extracted from nature, cannot attain the original balance and perfection of unprocessed foods" (Niva, 2007). Researchers report that while American consumers are receptive to the idea that some foods are naturally functional, they are skeptical of functionally engineered foods that emerge from labs and factories. In their 2007 telephone poll of 682 people, the Hartman Group found that when consumers are looking for health promotion and disease prevention they choose fresh and "real" foods (vegetables, fruits, vegetable juice, water, whole grains, fruit juice, fresh seafood, soy products, dairy products) over fortified or enhanced foods (Demeritt, 2008).

The association of "naturalness" with healthfulness may seem irrational to those who are using technologies to improve the nutritional profile (and safety) of foods through processing, but it is consistent with long-standing beliefs associating health with a simpler, more rural past in which people lived closer to nature. The historian Rachel Lauden argues that the idea that food was better and healthier in the pre-industrial past is based on a distorted view of history. She reminds us that, for our ancestors, "Natural was something quite nasty" and describes a not-so-distant past in which natural not only tasted bad, but was also unreliable and often indigestible. Processed and preserved foods were healthier, tasted better and freed those who were not members of the aristocracy (in some cases up to 95% of the population) from unending agricultural and domestic toil (Lauden, 2001). Nonetheless, the idea that pre-modern foods were more pure, healthy and wholesome, and that contemporary eaters should avoid the dangers of processed foods by eating as much as possible like our great-great-grandmothers did, clearly has traction, as evidenced by the popularity of Michael Pollan's work advising exactly this (Pollan, 2007, 2008). In fact, longing for a past seen as simpler, more natural, and healthier is a historically consistent companion to our ongoing quest for progress through innovation and technology. There is evidence that even Plato longed for a more wholesome past, a lost Golden Age that included whole meal ground at home (McCance and Widdowson, 1956). Foods offering nutritionally engineered functional benefits may appeal to our love of science, innovation and progress, but they also push up against these deeply held beliefs about the dangers of technology and the reassuring purity of those foods that are as close to nature as possible.

Because the distinction between processed and "natural" foods is one that many consumers find important when choosing a healthy diet, it may be counterproductive to continue to include intrinsically (or naturally) functional foods (such as blueberries and almonds) and functionally enhanced foods in the same broad category of "functional foods." Gyorgy Scrinis (2008) argues that the inclusion of whole or unmodified foods in the category of functional foods is a sleight of hand that extends the "aura of healthfulness attached to whole foods across to the 'functional' processed foods" and undermines

the "processed / unprocessed distinction as a basis for evaluating the healthfulness of foods." The Hartman Group has found that consumers do not use or understand the term "functional foods" in the same way that those in the food industry do; for lay people, the notion of functionality is integrally related to the natural health-giving properties in food. They suggest that opportunity lies in offering products that mediate between the poles of naturally functional and artificially engineered foods (Demeritt, 2008). Those who are developing and promoting functional foods can better address consumers in their contexts by adopting terminology and practices that recognize the meaningfulness of the distinction between intrinsically and enhanced functional foods while striving to find the optimal and acceptable intersection between them.

The Politics of Health

Understanding existing beliefs about food and health can improve our ability to design and promote functionally enhanced foods that make sense to consumers, but if our aim is a healthier future then we should also consider broader historical contexts and implications. Hasler (2000) describes the emergence of functional foods as a radically new approach to diet among consumers that began in the last decade of the twentieth century. But the changes she observes—consumers increasingly using food as a means to pursue optimal health and wellness—are part of a larger set of changes in the culture and politics of health in the United States that have been underway since the 1970s. Though they involve increased effort among individuals to control and mitigate health risks through their eating habits, it is not clear that these changes have been, broadly speaking, "good for us."

Functional foods as a product category and a health practice emerge from and participate in the establishment of a particular set of understandings around health that began in the 1970s. Around that time, the American public became increasingly concerned about health and safety in the context of growing awareness of environmental / occupational health hazards (carcinogens in food, air pollution, environmental degradation) and lifestyle hazards (smoking, high cholesterol). Political and corporate resistance to health-related regulations combined with a growing professional and public emphasis on individual health promotion led to the emergence of what Robert Crawford (2006) calls "the new health consciousness." He describes this as an "ideological formation that defined problems of health and their solutions principally, although not exclusively, as matters within the boundaries of personal control."

For the middle class in particular, the pursuit of health has become a major focus of attention, activity and concern. Understood as an outcome of individual effort and calculation, health also is an increasingly significant marker of self-control and responsibility. Crawford (2006) warns that, as the tasks related to maintaining personal health proliferate, awareness of the social aspects of health recede, leaving "little room for responsibility beyond the quest for personal well-being."

Functional foods are an artifact of this new health consciousness, one of many strategies that twenty-first-century Americans can use to manage an ever-increasing sense of health hazards and to pursue health through individual effort and calculation. Functional foods

play a role in increasing the required breadth of health knowledge (by introducing terms such as plant sterols and omega-3s into the public lexicon, for example) and add new tasks to an already extensive list of responsibilities. In doing so, they may participate in the foreclosure of our ability to see beyond individual responsibility and the marketplace of goods as a source of health and to recognize and act proactively in regard to the social factors that shape and impede health. While the aim of functional foods is to promote health, they also add to an ever-increasing sense of health risk; "Am I getting enough antioxidants?" was not an issue that most people worried about before products bearing antioxidant health claims hit the shelves. What Crawford (2006) calls the "anxiety / control spiral" (the more we seek to control risk, the more we know about risk, the more anxious we become about risk) may drive people to buy functional foods, but it may at the same time undermine a sense of security that is also an important aspect of well being.

An expansive view of the future of dietary health will include functional foods, but not to the detriment of social, political and legislative remedies that address the structural determinants of health. A better understanding of the ways that consumers negotiate functional foods on the intimate level of consumption in the context of existing values and beliefs about food and health is crucial to offering solutions in the marketplace. But we should not lose sight of the aspects of health that lie beyond consumption and beyond the reach of individual control, those environing social conditions that set the widest possible constraints for dietary health and its pursuit.

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Dr. Biltekoff's scholarship focuses on the values and beliefs that shape eating habits. Her research investigates the cultural aspects of dietary health; how our definitions of a good diet have changed over the course of the last century; what it means to "eat right"; and the historical relationship between dietary and social ideals.

In a book she is exploring the cultural politics of dietary advice from the late nineteenth century to the present.

The mandate of her cross-college appointment is to develop the intersection between UC-Davis's established strengths in the science of food and drink and their emerging strengths in the social and cultural analyses of food and eating. She teaches courses on food and culture, including *Eating America*, *Food and Health in the United States*, *Rethinking Obesity*, and *New Food Product Ideas*. Biltekoff is co-director of the University of California's Multi-Campus Research Group on Food and the Body and she serves on the board of directors of the Association for the Study of Food and Society.

Farm2School: *Giving Children a Healthy Choice for Lunch*

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Farm2School, a direct link between local farms and schools, has three objectives:

- Encouraging children to eat more fruits and vegetables—not functional foods, but fruits and vegetables straight from the farm.
- We want children to understand where their food comes from.
- We want to make our local farms sustainable, especially economically, but also in terms of the environment.

Farm2School is part of the local-food and whole-food movements, in the same family as farmers' markets—which are burgeoning—and as CSAs (community-supported agriculture, *i.e.* groups of people in a community who commit to buying and eating produce from a particular farm). CSA members pay up-front and, essentially, own a part of the farm, which provides financial sustainability to the farmer. CSAs are also part of the local-food movement and are burgeoning; in 1990, there were just sixty in the United States, and now there are more than 12,500. There were fewer than ten *Farm2School* programs in 1997, and now there are more than 2,000, gaining traction in various communities because of alignment of the interests of farmers, schools, government, students, and the public at large. They address a grass-roots consensus on health promotion by eating better and how to sustain elements of the community.

The *Farm2School* program that I'm involved with in southern California is called "Old Grove Orange." We grow citrus, a crop that covered much of southern California a century ago. However, southern California has been almost completely developed since then, and just a few pockets of agriculture are left. Southern California's economy and its urban infrastructure were developed on the basis of the citrus industry, which is now, all but gone. There's much resident emotion about this change, much of which has occurred within our generation.

Old Grove Orange

Old Grove Orange started three years ago, with one farm, mine—I grow oranges, mandarins, grapefruit, and kiwi fruit—and with one school district. Now, it comprises twenty-three local growers—producing oranges, mandarins, kiwis and strawberries—and twenty-five school districts. We also have four apple growers, two peach growers, and two grape growers, who help feed a half a million children within those twenty-five school districts.

Local Means Fresh

A fundamental aspect of *Farm2School* is that "local" means fresh. Since we're local, we can literally pick and deliver to schools in one day. When we pick strawberries, we have them at the school the same day. When we pick oranges, we have them at schools the next day. Essentially, we are delivering new experiences to environments that are used to chicken nuggets. We are providing a backyard food experience, with a remarkably improved level of taste that children respond to.

Fresh Means No Chemicals

Another important aspect is that "fresh" means no preservative chemicals. Since we can deliver produce in a day or two, application of preservatives is unnecessary. I used to run a Sunkist packing house in which oranges were treated to ensure a shelf life of six to eight weeks. Sunkist put the fruit through a hydrochloric acid pressure wash, then a boric-acid bath, followed by fungicide treatment and a wax coating. The orange that was exported to China was treated the same as the orange eaten by a child in the same neighborhood of the orange grove. For local consumption, we can pick and deliver so quickly that preservative application is unnecessary.

The third thing is that we're competitive with big global suppliers, primarily because we are local. We don't need the $7 million packing-house process. We don't need all that chemistry. We don't need the attendant management of effluent. In fact, we can pack citrus for half the price compared with highly mechanized packing houses; therefore, we can be price-competitive to the school district. Being price competitive along with the other advantages we bring, basically makes our clients' decision for them.

Local Means Mission

Lunch Ladies with a Higher Calling

The other thing about local is, it means "mission." As mentioned, our now-metropolitan area used to be covered with citrus groves, which are almost all gone. Residual sentiment plays into the concepts expressed by Drs. Biltekoff[1] and Shimek[2] about "we want to go back," and "we want something that's whole and pure and not processed." These emotions elicit buy-in from the community as a whole about moving from a commodity fruit-and-vegetable or the "Chicken-McNugget" model for schools into getting local produce into

[1]Pages 99–106.
[2]Pages 115–120.

local schools. We have found that lunch ladies who tolerate grim "Chicken-McNugget" working conditions have a higher calling. At Old Grove Orange, we bus in the lunch ladies for a "you pick" day on the farm and they take away with them all the fruit they can carry. Consequently, they realize that some local farms are left, and there's something that they can do about their "Tater-Tot" existence. These ladies influence choices that children make at school. They encourage the consumption of the locally grown fruits and vegetables.

Linking Food to Farm and Health

"Local" also means, in terms of mission, that we help children make connections between the fruit in their diet and the environment around them. One of the educational components that we deliver to our schools is called "Citrus History in a Box." Every third-grade classroom gets a citrus carton full of oranges, picked from 100-year-old trees. Southern California is where the fresh-pack navel-orange business started in the late 1800s and some of the original trees have survived. The older the navel-orange tree, the sweeter the fruit, and so we deliver an excellent taste experience. Also in the box of oranges, we provide aerial imagery, showing what the land on which the school was built looked like sixty to a hundred years ago, *i.e.* carpeted with citrus groves. This makes a deep impression; not only do the children eat fruit from trees that were planted when their grandparents were young, they also see what their neighborhoods looked like back then. It brings home the relationship between the food that they're eating, their supermarket and the surrounding neighborhood.

Parents Invested in Green Space, Heritage Preservation and Health

A key mission element is parents who understand that, "If our children eat this produce, the local growers will be able to maintain the open space, and preserve their heritage. Of course there's a health aspect also, born of feeling, "Oh great, it's not just Tater Tots it's also whole food. It's also natural products." They relate to that.

Figure 1 shows the seals of five cities in southern California. Each includes citrus fruit and/or groves, revealing the essence of these communities at the time of their establishment. Dozens more could be included. Practically every single city seal in southern California has an orange on it, whereas not a single one of them has a grove left.

Happy Farmers

Another fundamental element is that "local" means happy farmers. Growers who belong to Old Grove Orange receive substantially better returns than when selling on the commodity market. In fact, our growers are all "refugees" from the global distribution network. At the very least, we match the return a grower would get on the global market. In 2010, we paid more than four times the global rate. Clearly, the pairing between schools and farmers is truly beneficial to both sides.

Farm2School provides price predictability and stability. When linked to a global commodity market, the price changes from day to day and from week to week. We tell our member growers what price we can meet or exceed for the coming season, and we've never varied from those projections. They appreciate that. Also, our customers, the schools, like

Figure 1. Southern Californian city seals.

that as well; otherwise, they have no idea what they will pay for their produce until after the fact. Because, as farmers, we're not tied into a global market, we can decide what the local prices will be in conjunction with the school. There could be a freeze in Florida or a drought in Australia, but that price won't change, which is something that's appreciated on both sides. It's another win-win.

Most of the Farm2School growers have tried farmers' markets and CSAs, which are labor-intensive and relatively small in scale. In a school district, one person may make decisions for 30,000 children. Having convinced one person, you have 30,000 new consumers. That's attractive. A school district as a customer is like six supermarkets selling your product.

Another thing that farmers like is satisfaction gained from their community role. When selling into the global market, they never knew their customers. Their fruit would be hauled away and they don't know what happened to it. There is community satisfaction, and satisfaction for growers with the fact that their fruit is going to children in their local area. It's an experience that binds communities.

Icing on the Cake

Needy Children

The majority of the school districts in southern California provide free or reduced-price lunches to 60% to 80% of the children; the families are so poor that the government either pays for or subsidizes the meals. From a local foods and whole-foods point of

view, farmers' markets and CSAs are laudable, but they sell to elite, well-to-do customers. It is gratifying that Farm2School makes elite food available to the poorest people in the community, and on a massive scale. A half a million children are now eating fancy farmers' market fruit—the same as is sold in elite communities like Santa Monica and Palm Springs.

Needy Adults

There's a lot of waste with agriculture. We throw away about a third of what we grow in the United States because it's not big enough or it's too big or it has undesirable marks on it. In commercial agriculture, these leftovers are ploughed into the ground. Such oranges usually go to a juice plant or to a cattle farm. We donate them to the needy; we donated 93 tons of oranges in 2009 and 196 tons the year before. If you see a needy person carrying an orange in southern California, it's almost 90% likely that it came from Old Grove Orange. And that is also something to which our community responds well. Having fruit and vegetable farms in an urban area can help solve the problem of hunger, especially.

Carbon Footprint

Another source of pride stems from our belief that we provide negative carbon-footprint food. Since our farms are collocated with our customers, we travel negligible mileage to deliver our unprocessed food to the school districts. Furthermore, our groves are in the same air basin as our customers, and so we have forty or fifty thousand trees sequestering carbon. On one hand, much of the food eaten by our customers is shipped over long distances, some of it frozen and thus is energy intensive; on the other hand it's reassuring to eat food in the knowledge that, the more you eat, the better it is for the environment.

A Parting Shot

Science and technology have produced a consensus that we need to promote consumption of fruits and vegetables by our children, and one of the ways to achieve that is to gauge community understanding. What are the factors—besides the food itself—that can rally a community to make this a priority for their children? I'm sure that a different set of factors prevails in each community, but we feel that, around Redlands in the southern California area of Inland Empire, we've found those factors, because we are doing well as demonstrated by our win-win relationship.

Robert Knight was born in Redlands, CA, and raised in an orange grove. As a restless teenager, the grove was the last place he wanted to be, and, upon graduation from high school, he headed to New York City. After spending the bulk of 20-odd years overseas, working as a telecom exec with AT&T and Lucent, ironically he returned to the Inland Empire to manage his family's citrus business and raise his own pair of restless teenagers amidst an orange grove. Proud to be a fourth-generation orange grower—but shocked by how quickly Inland Empire groves are disappearing—Knight founded the Inland Orange Conservancy, a group dedicated to saving groves and building an orange-loving community.

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Putting People First: Designing for Healthy Product Choices

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I will discuss putting people first and meeting their unmet needs and desires, when designing healthy choices in foods and beverages. Consumers have a broad range of options when it comes to food, which may even be overwhelming. Also, it is possible to be overmessaged about health. People are being inundated about health from an array of sources. It's coming from the food industry as part of the packaging, and through advertizing. It's coming from the government and from food experts. It's coming from bloggers and advocates expressing strong views about food. It's even coming from retailers. Several retailers in the United States are working with experts developing systems to tag foods with stars or point values to express nutritional values and guide people on what to choose. Consumers are being inundated with messages about food and health.

Food science, agriculture and nutrition have created healthy dietary options over the years. But these options are almost lost in the sea of choice. Furthermore, science can take people only so far. As an analogy, science has given us the diving board and the pool, but many people prefer to sit at the water's edge. Ultimately, consumers choose what to eat and inducing people to make healthy food choices is a complex problem. On the other hand, at IDEO we like exploring complex problems. Many drivers influence why people choose what to eat.

The question under consideration—as we design new healthy food products, services and experiences—is, "How do we help people to want to use the diving board?" It's not just about product creation, but about understanding how a product fits into people's lives so that they will embrace it.

Human-Centered Design Process

At IDEO we use a "human-centered" process, to uncover latent consumer needs and desires and design meaningful solutions to meet them. We start with insights about people, gained by spending time with them in context, *i.e.* in their homes, in their workplaces, at school, and with their colleagues or their friends. We try to walk in their shoes, to understand what's going on in their lives, and thus glean insights about their desires and

their needs. We then look to the business world, for example, to discover opportunities, and use science and technology to design solutions.

When we visit people in their homes, we start by observing them and listening to what they say. Much of the process of observation entails listening. We try to build empathy, to understand what they are thinking and how they are feeling. Establishing empathy is core to understanding the extent to which their actions are consistent with their beliefs. And sometimes they are totally inconsistent. In discussing food, we are commonly told that their eating habits are healthy, with details provided. On the other hand, when we tour the kitchen, we discover that the healthy choices that they had mentioned aren't actually in the pantry or fridge. However, we defer judgment and try to discover why their thoughts and feelings fail to match what they are saying and doing. Clearly, these people have aspirations that they're unable to meet. Such situations are great opportunities for design.

Further to establishing empathy and deferring judgment, a project that we worked on at IDEO with the Centers for Disease Control was focused on helping "tweens" eat more fruits and vegetables. Our objective was to understand the motivations, contexts and drivers involved and to develop solutions. Accordingly, we spent time in various places around the country, including Atlanta, Georgia, where we met Madison who was eight years old at the time. We used flash cards showing fruits and vegetables to initiate conversation about diet, and it quickly became clear that she was unfamiliar with the items illustrated. We then asked what she'd had to eat that day. Breakfast at school comprised French toast sticks with syrup, and for lunch she'd had chicken nuggets and French fries. Her mother had three children in addition to Madison and by dinner time she was exhausted and, that evening, served pizza from the freezer. Madison hadn't recognized some of the fruits and vegetables, because they weren't foods that she was eating on a regular basis. Furthermore, her mother didn't know what Madison had eaten for breakfast or lunch. She hadn't packed that lunch and wasn't with her at school when she ate it. Again, this could be an occasion for passing judgment, but we regarded it as an opportunity to design for the situation. Were there time or financial constraints? Or was convenience the chief issue? All of those factors played a role.

We have work on varied projects, talking to people about healthy food and lifestyle. I will share a few patterns and themes that we are seeing.

Healthy Choices

Choosing healthy food is more than selecting particular products, just as eating isn't merely about being hungry. There's certainly a physical aspect to being hungry and to eating, and sometimes it's simply about calories; however, other factors impinge, such as the social element, particularly the community that develops through sharing food, *e.g.* around the dinner table and at parties. There's a mental element also. Mindless munching may occur mid-afternoon at work, to provide mental stimulation rather than satisfaction of hunger. And there's an emotional element, such as when a parent and child make a dish together—cookies or some other comfort food—providing opportunities for nurturing and bonding.

We are seeing an evolution in what is defined as a healthy food. People are realizing that it's more than what's on the nutrition label (although they don't always understand what they read there). Consumers look for familiar, recognizable ingredients, and are skeptical if the list of constituents is long. They like to have a sense of how a product is made. And packaging plays a role. Consumers like transparency, being able to see directly what they are purchasing. We are hearing that packaging that's compostable or otherwise eco-friendly, has positive "healthy" implications.

Information Sources

New trusted guides are emerging as sources of information on healthy foods. With the Internet and its inherent accessibility, people are having their voices heard, with a much more widespread reach than before—from food bloggers to product reviewers to people who simply wish to express a point of view on food—and people are listening. And traditional channels continue, including books by Michael Pollan and Marion Nestle, who also have blogs and post their opinions on the Internet, thus reaching wider audiences. Whether or not you agree with their advice or points of view, it's undeniable that they influence people's thinking and decision-making.

With these convenient modes of communication, some positive messages are resonating. People actually do know what's good for them in some senses, *e.g.* that baked is better than fried. However, even with that knowledge, they may not choose the healthiest options, and we see significant tension between what we call the "impulsive" and the "considered" sides. The impulsive side is about spontaneous, short-term gratification, whereas the considered side is about long-term implications, possibly involving planning. We know that many people with healthy lifestyles are planners, often deciding meals for the week in advance and shopping accordingly rather than shopping spontaneously. This is a thought-provoking area for us: How do we design to accommodate the impulsive side? Can we induce people to keep long-term aspirations in mind or can we design healthy choices that cater to spontaneity, rather than trying to convert people to being planners?

At IDEO, we work across many industries—not just food and beverages—and we've been looking at difficult choices across those industries, such as stopping smoking and introducing new medicines and behavioral-change regimes. We have developed six principles of change by design that provide useful guides as we consider products, experiences and technologies for healthier choices.

Six Principles

Use Judo

The first principle is "use judo," the martial art that employs the momentum of your opponent. From the point of view that motivations don't change but habits do, we try to manipulate motivation to alter habit. For example at IDEO, trash cans for collection of recycled material are integrated with trash cans for non-recycled material. The larger receptacle is for recycled items. This builds off the common behavior of people tossing trash under the desks, but encourages thought in the process to maximize recycling.

Joy Not Fear

The second principle is "joy not fear." It's common knowledge that fear can jumpstart change. For example, a heart attack or other serious medical event may instigate rapid alteration of behavior for the better, but often only on a temporary basis. How can we help people sustain an improved lifestyle?

Pie Ranch is a wonderful organization in Pescadero, California. It's a ranch and farm where they grow fruits and vegetables and raise livestock, and provide a youth-education program. We spent time talking to three teenage participants in the program who were struggling with obesity. Devon lived in an unsafe neighborhood in San Francisco, so he spent a lot of his time inside playing videogames for entertainment. On a daily basis, he made the difficult choice not to engage in the violence and the crime that was around him, but to stay indoors. His participation in the Pie Ranch program gave him the joy of healthy eating, helping him to ignore the negative aspects of his life: "The people there are nice to you. It's like a welcoming environment, which is healthy, with actually organic food straight from the farm. I love it there. That place is like a Disneyland…" He had lost thirty pounds since joining the program. This is an example of promoting the joy of healthy eating instead of emphasizing negative long-term effects of obesity.

Removing Choice

Sometimes, removing choice can help people to make behavioral changes, including healthy decisions. An analogous program is one that Bank of America calls *Keep the Change*; each time a debit card is used, the amount is rounded up to the nearest dollar and deposited in a savings account. Some consumers who aspired to save money but didn't, have been influenced by *Keep the Change* to balance their checkbooks to follow the accumulation of their savings. This is similar to consumers who aspire to eat healthy but fail to do so. Thus, an opportunity to elicit change is presented, where no change is actually necessary, and tension over choice is removed when people naturally achieve their aspirations in the long run.

Show, Don't Tell

When asking people to change their behavior, to make healthy decisions, offering feedback is critical, otherwise how are they to know that they are doing the right thing? As an example of this principle, we worked with Ford Motor Company during the development of one of their hybrid electric vehicles to help buyers get the best battery performance and optimal fuel efficiency. Rather than telling drivers, "This is how you do it," we built into the dashboard indicators that provide real-time feedback on whether they are doing the right things. A tutorial is also built in to encourage experimentation.

Finding Moments that Matter

How can we give people exactly what they need at the right time and place? *Healthy Choice Fresh Mixers* provide an example of a product that we at IDEO have worked on. It's a dry pasta on the bottom with a sauce on top; the consumer adds water, boils it in a microwave oven, drains it and mixes in the sauce. It's designed to be consumed away from home, *e.g.*

at work for lunch. Part of the objective is to provide a "cooking moment"—even within a busy schedule—about which people can feel good and see as healthy. It's interesting how science, technology, policy, and design can give people just what they need at the right time and place, and in the right amount.

Build a Crowd

And the last principle comes from the television show "Jamie Oliver's Food Revolution." Oliver, a British chef, came to Huntington, West Virginia, one of the most obese communities in the United States with the objective of starting a food revolution. On the reality show, he engaged a thousand people in the town, cooked a recipe with each and took a picture of each person with her/his dish. Considering that each of us is influenced by our environment and our culture, how do we build a crowd? How do we build momentum behind behavioral changes?

The following is an exchange that took place on one of Oliver's shows:

Oliver: Wow! I love working with kids. Elementary school is where it's at. You know, this is where you mold kids. We're going to do a little test. Right! Who knows what this is? [Holding up four tomatoes.]

Child: Potatoes?

Oliver: Potato? So you think that these are potatoes. They're not potatoes, though. Do you know what it is? No? Who knows what tomato ketchup is? Yeah—that's what it's made out of.

Child: Tomato?

Oliver, voice over: The test I did with the kids today was shocking.

Oliver: Do you know what that is? [A beet.]

Child: Broccoli?

Oliver: Do you know what this is, Honey? [A beet.]

Child: Celery?

Oliver: No.

Child: Onion?

Oliver, voice over: Immediately you get a really clear sense of "Do the kids know about where food comes from?"

Oliver: Who knows what that is? [An eggplant.]

Child: A pear.

Oliver: No. I'll give you the first word—egg.

Child: Eggshell!

Oliver: I've got another one here guys. What do you think this is? [A potato.]

Child: I don't know.

Oliver, voice over: We're talking about basic stuff. Even a potato—no idea. Most of them—no idea.

Oliver: Okay, our last question. What is this?

Children in unison: Chicken McNuggets!

Oliver: You all knew that. You're too good. Okay, what's this?

Children in unison: Pizza!

This is reminiscent of our conversation with Madison in Atlanta, Georgia. After Oliver's exchange with the schoolchildren, the teacher took it upon herself to bring fruits and vegetables to the class as object lessons. Other teachers followed suit in other communities and then there were emails, and comments on the Internet. And so, a crowd was built in that community that sparked a national movement.

Jamie Oliver won the TED Prize[1], and, accordingly, he had an open call out to people to join his food revolution to offer their time, talent and services, everyone from Web designers, marketing experts, to people that have a left-over Winnebago that they will donate to someone who wants to drive around the country and teach kids. We are working with Oliver to encourage this food revolution, to move it beyond him, to connect people with passion and dedication to maintain the food revolution and spread it across the nation.

In Closing

I'll close with a few questions. At the end of an IDEO project, we usually have some interesting solutions, and often more questions.

- How might we support existing healthy behaviors through science and through policy?
- What if we foster the joy of eating healthy rather than the fear of eating poorly?
- How might science and technology provide meaningful feedback to consumers?
- How might consumers' needs and desires, latent or not, play a role in creating new policy and in developing new technology?

[1]Technology, Entertainment, Design. It started in 1984 as a conference bringing together people from those three worlds. Since then it has broadened in scope. The TED Conference, held annually in the spring, is the heart of TED. More than a thousand people attend. The event sells out a year in advance, and the content has expanded to include science, business, the arts and global issues. The TED Prize is designed to leverage the TED community's exceptional array of talent and resources. It is awarded annually to an exceptional individual who receives $100,000 and, "One Wish to Change the World." After several months of preparation, (s)he unveils her/his wish at an award ceremony during the TED Conference. These wishes have led to collaborative initiatives with far-reaching impact.

As food science innovator and technical build guide, **Lauren Shimek** brings a passion for food, technical expertise, and food-science knowledge to food and beverage projects at IDEO.

Prior to joining IDEO, she developed breakthrough technologies and new food products at General Mills. She has worked in many food categories, *e.g.* snacks, bakeries and foodservice, and meals, including *Progresso 50% Reduced Sodium* soups in which she led product development from concept to market. At IDEO, since 2006, Dr Shimek has worked on projects that span the aisles of the supermarket, from beverages to frozen foods to shelf-stable meals.

She holds a PhD in food science and a BS degree in biochemistry from the University of California at Davis. A self-professed foodie, she brings a personal enthusiasm for food and food culture to IDEO via her monthly *Eater's Digest* newsletter and blog at www.foodspiration.com. She is also actively involved with the Institute of Food Technologists (IFT), serving as advisor for the national IFT Student Association.

Choosing Foods For Health

Q&A

Moderator: Tom Tomich
University of California
Davis, California

Tom Tomich: Bob Knight mentioned community and the food movement, and just a week ago in the *New York Review of Books*—not *Western Orchardist* or *California Agriculture*, this was the *New York Review of Books*—there was an interesting piece titled "The Food Movement Rising" about agriculture, food, nutrition and health. No points for guessing the author's name. He's from the school of journalism just down the road, at our sister campus, UC Berkeley. It's Michael Pollan. To set up the discussion, I want to share a quote from that piece and then turn to our panelists for their impressions and then also get your comments and impressions and questions for the panelists. I urge you to look at the whole article because there's actually quite a bit of nuance to this quote that I won't do justice to: "The healthcare crisis probably cannot be addressed without addressing the catastrophe of the American diet, and that diet is the direct, even if unintended, result of the way that our agriculture and food industry has been organized." He's talking about just the United States; this isn't a global perspective. Now, I want the panelists to step back, to use this observation. My questions to each of you are: "Do you see the emergence of a food movement?" and, if so, "What is the role of science and specifically food science *vis-à-vis* that movement?" And if you want to take it even further, "What would be the implications of the food movement for biotechnology? How do you see those aligning? Misaligning? Partially aligning?" Who would like to go first? Bob is stepping up. You already referred to the food movement, so how do you see the relationship between that movement on the demand side and science on the supply side?

Robert Knight: Certainly there's the local food movement—having survived as a farmer on the basis of that local food movement for about the last 30 years. Yeah, there is a local food movement, but is there a role for science and technology in that food movement? There is so much of a role for science and technology just for agriculture. And the local food movement is a small segment of agriculture, but it is a valid segment. So, definitely there is a role for science and technology.

Tomich: Do you see potential alignment, or not so much, between the functional-foods biotechnology we are talking about and the kinds of preferences that that food movement represents?

Knight: In my particular instance what people really connect to is being able to see the farm, have visibility into it, know they have transparent access to it, know that it is local. Whether the product is historical like the orange or some other product that is new and wonderful through food technology, doesn't matter so much, as long as they know who is growing it and where it is and that it's part of the community.

Tomich: Thanks. Lauren do you want to have a go at all or part of that?

Lauren Shimek: I think that there's a food movement beyond just the local food movement, for two reasons: one is because we go across the country and we talk to a lot of consumers in various regions across income levels and we hear a lot of the same things. People have similar concerns. They have new definitions of healthy. They are looking at food in new ways, more critical ways. At the consumer level there is a heightened awareness. But also, there's an interesting movement going on right now at the system level relevant to the quote—looking at the healthcare system, looking at the agriculture system, the industry and looking at the government—Michelle Obama's comments on obesity and food for example, and the symbolic garden at the White House. There's Jamie Oliver, and The Child and Nutrition Bill may funnel more money to school lunches. There's a lot of dialog. Discussion is coming up from the bottom and coming down from the top, which is key. As a food scientist, I think there is absolutely a role for science in this movement. I see food scientists as problem solvers. We've had amazing challenges in our history, when food wasn't abundant and choice was limited. Food science met those challenges, maybe in some cases too well. Now we have abundance of food, and we have an obesity crisis. We have a lot of choice in the marketplace. I'd love to see the food-science community rise to this new challenge and put that same energy and excitement and knowledge to solving those new problems. But, it's about acknowledging what's going on now and how it's different from what was going on 10, 20, 30, 50 years ago.

Charlotte Biltekoff: I'll echo what the other panelists said, and yes there is a food movement. I think we can all see it from the food network, to whole foods, to my field, to food study. There is a growing interest in food and there's politics around looking for change around food and alternative food systems. But, I think it is increasingly difficult to talk about American culture and the population in unified terms. If we think about the changes just in, say, television from the three networks to the hundreds of channels available on cable—we are an increasingly niche-fragmented society and it is important to keep in mind that various interests are pulling us in many different directions. Living in Berkeley leads me to see the world through a certain lens and think that a food revolution is everywhere, when in fact it's really not. We have a very diverse and fragmented food culture that is likely to become increasingly so. But, to address the question of science

on a slightly different level, some of my colleagues—my colleague, Warren Belasco in particular—has recognized two alternative futures for food. He has studied the history of the future of food and shown that, historically, we have talked about the future of food in dichotomist terms. We have talked about a technological fix that involves solving the problems through science and technology and an alternative anthropological fix, where we change our values, we change our culture and how we live in order to solve the problem by, say, using fewer resources, eating more simply, that kind of thing. But the likely scenario is that we meet somewhere in the middle. And, as Belasco says, it may be that the solutions to our problems in food and health will come from technology, but they will have to look very much like somebody's grandmother made them. A real or imagined grandmother, right? I think there will have to be some kind of meeting in the middle where these values—the technological fix and the anthropological fix—find a complementary solution.

Tomich: Thank you all. I want to open it now for audience questions and comments on choosing foods for health.

Robert Wager (Vancouver Island University): Bob, I am very impressed with what you are doing. I had never heard of this before and it's fabulous. However my questions are more to the other people on the panel. When I grew up in the 1960s and '70s, marketing was really about sexy, or new, or new and improved, and today it has moved toward fear sales marketing. About 10 years ago there was a *Nature* editorial that said scientists no longer have the luxury of staying in their labs and communicating only with their peers. Society needs scientists to speak up. I believe that's very true, and, keeping in mind the saying that the public must know that you care before they will ever care what you know, what is your advice to the scientists here?

Shimek: It's an interesting question in terms of the dialog between the scientific community and consumers and the role of the media. Also interesting is the comment that scientists should show that they care. In the human-centered design process, empathy and mutual respect are important. My message to the scientific community would be to think broadly about the implications of what you are working on. As a scientist myself, there were times in my life when I made scientific decisions and didn't necessarily think about their impact on products going into the marketplace, how they might shape that landscape. As a scientist, what seem like small decisions may add up across the community, and the things that I put into products that went onto supermarket shelves may actually have changed the landscape. I encourage you to think about that bigger picture, to step back from the moment of the technology or the ingredient and think about potential impact on consumers and the landscape as a whole.

Biltekoff: Understanding the context within which consumers choose foods is important to gaining a sense of empathy for the number of choices that people are making, the amount of variety they face and the uncertainty that results from conflicting informa-

tion about what is good to eat. The ethos of caring and connecting through empathy with consumers is a way to reassure people in a very uncertain marketplace and to take seriously their anxiety over food choices even if those concerns seem irrational from a scientific perspective.

Knight: It's hard to imagine a lunch lady in a cafeteria getting excited about delivering a chicken nugget with some extra functional-food additive. This isn't just a scientific issue, although scientists have a role in delivering new developments and how they are couched.

Tomich: Our land-grant history—many of us are from public universities—goes back to a nineteenth-century notion that it's not just about science, but it's about responsive science that actually listens to the needs of our population. What's different now is that most of the population, the vast majority, are not directly involved in agricultural production so that listening and engagement is now an infinitely more complicated process. But I think we can get really good at it.

Amanda Martin (University of Minnesota): I'm with the *Student Voice* program. When I go to the store I try to get the most calories for my dollar. With VitaMuffins and other 100-calorie packs, we are spending more money to get fewer calories. Are functional foods suitable only for a certain demographic or are they applicable to all socioeconomic strata?

Shimek: You bring up an interesting point about cost, and that your need may be different from that of someone who is struggling to obtain an abundance of food and calories. Cost is a huge driver for why people make their food decisions. In terms of the application of functional foods, I think that people here would agree that they span many demographics. However, it is more interesting to think about the specific needs of the groups you are discussing and how we tailor healthy food choices to meet those people's needs and address those drivers. Cost is a hugely debated issue when it comes to healthy foods.

Biltekoff: Some critics raise the question of whether or not it is ethical to commodify healthfulness, and, if healthy food and health in general are a public good, is it ethical to invest so much in commodities—as a way of providing health—resulting in added value and added cost.

Barbara Schneeman (US Food and Drug Administration): I was intrigued by the comments, particularly from the first two speakers, that "fresh" is linked with healthfulness of a food choice. Even with shipping and handling, food, including processed foods, is often more nutritious because nutrient content has been stabilized. The dietary guidelines point out that fresh as well as processed kinds of foods can help consumers meet the recommendations. From the research that you do in terms of consumer perception, I wonder

if that's a bridgeable gap? Is that connection with fresh so inherent that trying to create the understanding of the role that certain types of processed foods can play is something that consumers would reject? So, that's one thing I would be interested in comments on. And I felt it would be worthwhile commenting on a project that was done many years ago. It was actually initiated by the California Dairy Council and the American Institute of Wine and Food. Julia Child was a major driver in the program, and it was an attempt to bring together culinary experts with nutrition experts for dialog on how we make sure we are moving together. The group eventually developed a motto that "in matters of taste consider health and in matters of health consider taste." I don't know if any activity is still related to that, but it speaks to the fact that tension between culinary and nutritional aspects has been there for a long time. How do we bridge that gap?

Tomich: It's for the foodies on the panel.

Biltekoff: There's a really important role for history in helping people to understand the value of food processing. I said in my talk that I think that the sense of a more wholesome, rural past will always be with us and that nostalgia will always be a competing push against innovation and technology. But, that said, I do think that much of our food culture today is operating around a romantic view of the past. Our job as historians is, of course, to trace historical change to help people understand the kind of contribution that something as simple as, say, industrially produced tortillas, may have had in freeing people up to do things with their lives other than pat tortillas all morning. Food studies is a growing academic field in which we teach things like food history. Having a more realistic view of the history of food and food processing would go a long way.

Shimek: Processed foods are often criticized and under fire and yet there is a renaissance around canning and you can find wonderful boutique jam and jelly places in Berkeley and elsewhere, celebrating the craft of canning, which most of us are probably fairly removed from. So, there really is a role for processing and partly for seasonal reasons. If you are going to completely fresh then certain things are going to be out of season and the purpose of some of those original technologies was to have food throughout the year that would retain nutrients and flavor. So, there is a role there. The other piece, Barbara, you bring up is that with fresh comes the need to cook and prepare the food, yet there is loss of cooking skills and increasing ignorance of basic food preparation. That's part of Jamie Oliver's campaign—teaching people basic cooking skills. I love the idea of everyone eating fresh, but there's the seasonal issue and there's the issue of our food culture and the knowledge that comes with that. An interesting food culture exists in the Bay area. You have a slow-food movement and a fast-food movement on the other side and I believe that a third option exists somewhere in the middle, where it's not about eating all fresh all the time and it's not about eating all processed all the time. It's actually learning from both of those groups that have a point of view and figuring out what's realistic and what's a new possibility in the middle.

Tomich: I was struck in this session by how dichotomist the attributes are: fresh, processed, natural, artificial, tastes great, less filling. It's not the decision process that Carl Keen[1] was talking about when we think about comprehensive assessment of benefits and risks. I don't know how we juggle those.

Audience member: A question for Bob Knight: to what extent do you think that it is possible to bring back the orange groves to California? When you started your talk, I thought, "Okay, this is a great story." But I was looking at it as an agricultural history of the Golden State, but when you finished your talk you said maybe this is not only a sustainable business but also a profitable business. Do you think you are getting close to that on a wider scale? Is this a good example of how to integrate local agriculture in large metropolitan areas with huge numbers of possible consumers like LA and the Bay area?

Knight: Indeed it is a sustainable business. It is a profitable business. But it isn't going to take over California and that's because of real estate values. The growers left in southern California are mostly family growers. It's a lifestyle choice. They have inherited that land. It would be extremely difficult for someone new to move in and buy land and make it a profitable business. The good news is that what's left we have a really good chance of being able to sustain as a jewel in our communities for years to come, but to increase that farm acreage—actually take out parking lots—that's something I don't expect to happen.

Bhimanagouda Patil (Texas A&M University): A significant challenge for plant breeders in this country, particularly western fruit breeders, is the development of fruits or vegetables that taste good. Scientific data indicate that fruits and vegetables that are bitter or tasteless contain higher levels of potentially bioactive compounds. When they are manipulated to make them tasty there is the possibility of losing compounds that are good for health. In a hundred years we might want the old varieties for their health benefits. We developed a very mild onion and we have a mild pepper for American consumers. On the other hand, foreign visitors ask, "Why did you change this very good pepper to a mild one? We need the hot pepper."

Shimek: That again brings up preparation, especially when it comes to vegetables, many of which require cooking. It's pretty easy to wreck a vegetable. We've spent a lot of time with moms and kids and the struggle over vegetables—trying to find ways to make them attractive for children, and preparation is an interesting area to explore. It's not just about the vegetable on its own, but how might we pair it with things that people can relate to that can still be healthy. How might we use those culinary tools, spices and herbs that aren't going to take away from the health quality. Preparation is key, and we are actually experiencing what you are talking about right now with vegetables currently in the marketplace. If people don't know how to prepare it, they shy away from the vegetable in question or may dislike it from having experienced a poorly prepared dish.

[1]Pages 17–28.

Biltekoff: What if it's really true that in order to be healthy we have to eat what we don't like? Part of what is at issue here is diversity of taste—what we consider tasty, right? We see some positive trends towards more complex and bolder flavor profiles in the market. That bodes well for increasing acceptance of a variety of intensity levels and profiles as tasty. Bob Knight's program speaks to the question of taste education in a sense—exposing children to a wide array of different tastes. There is some natural aversion to bitterness at certain ages, but I do think there is a role for early education to play in making sure that a diversity of taste is experienced.

Michael Kahn (Washington State University): Yesterday we talked a lot about research and innovation, and the thing that struck me about the example that Lauren gave about the vegetables in the schools was that the teachers responded by bringing in vegetables and educating the kids. Obviously, that was something that might have occurred to them before you did the experiment you did, but they clearly were making the assumption that these children knew about vegetables. Ronald Reagan was right, ketchup is a vegetable. They recognized ketchup, but they don't recognize vegetables. Is this a problem where we know the information we need to deliver? Functionally or non-functionally, a lot of the information goes back to pyramids. It goes back to proteins and vitamins and things like that. We know that, but we are not delivering it very well. This gets back to the comment about niches. A lot of the niches for those children clearly don't include tomatoes.

Biltekoff: We may be delivering these foods into inhospitable contexts, basically. Delivery may not be the right metaphor. As a cultural historian and a cultural critic sometimes it becomes overwhelming because it is impossible to separate the question of why we can't get people to eat right from larger social and political issues. And frankly, one of those is poverty and the massive increase in income disparity that has occurred over the last several decades. Much of what we are talking about here are low-income and highly stressed communities where people are working insane hours trying to keep up with rising real estate costs, costs of medical care and child care, *et cetera*—living in a landscape that is basically inhospitable to healthy food preparation and consumption. We in this room are not going to solve those larger problems, but I do think we have to keep in mind the relationship between the question why can't we get people to eat right and the larger stressors on people's lives that make making the right choices nearly impossible most of the time.

Shimek: There are some other interesting cultural pieces, of which I'm sure Charlotte knows a lot more. When I was in high school, all of the home-economics labs were turned into computer labs. So the home-ec nutrition program disappeared in favor of technology. As we outsource more and more of our food preparation and our cooking, those traditions are being lost. It's interesting to examine the younger generation and important to understand the technology they are exposed to and the value that society now places on time and convenience, very different from even just 10 years ago.

Knight: Looking specifically at schools in the districts that we serve in southern California, as I mentioned, 60 per cent to 80 per cent of the school meals are free or reduced, which means that, in these districts, children are being fed by their schools. They are getting their breakfast at school. They are getting their lunch at school. And schools will even give them backpacks to take home to feed them on weekends, in some cases. And so, schools are incredibly important in urban areas like metropolitan Los Angeles because they are the ones that are determining taste. Many are unaware that they don't cook in schools anymore. They open boxes, they microwave things, but they don't wash dishes. Everything is disposable. And so, when I saw that video[2], I wasn't surprised at all that those children didn't know what a tomato was because if they are getting all their food from the school, they never see a tomato there. That's why it's important to find a solution to get those fruits and vegetables visible in schools. We are creating those kids' tastes for a lifetime, and *Farm2School* is a good mechanism for that.

[2]Pages 119–120.

Food-Labeling: Where Science, Health and Policy Meet

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I used this title for my presentation recognizing that most members of the audience have an academic focus. I hope to encourage thought, by pointing out where universities really do play a role. The Food and Drug Administration (FDA) is a science-based agency and so the scientific expertise that universities can bring to bear on many of these issues is very important to decision making. Diversity of expertise is important.

I am located at the Center for Food Safety and Applied Nutrition and will focus on nutritional aspects, describing the legal basis for the actions that we take—how my office uses its legal authority. I'll finish with a description of our current activities and priorities.

FDA's Legal Authority

Our legal authority is founded in three laws. The Federal Food, Drug, and Cosmetic Act, as amended, is the primary law that governs what we do. Everyone has great ideas about what FDA could do, but, in fact, our legal authority to regulate comes from the Federal Food, Drug, and Cosmetic Act, the Fair Packaging and Labeling Act, and the Public Health Service Act. The purpose of labeling is to inform the consumer at the point of purchase about the basic nature of the food, its ingredients, its nutritional attributes and other material or essential information, including warnings or clarifications. Identification of certain allergens is now mandatory in food labeling. The small print that is usually hard to read is often the mandatory part of food labeling. It has to be on the principal display panel or what's defined as the information panel. Other labeling—the

information that is typically most prominent—is usually voluntary and presented at the manufacturer's discretion, *i.e.* claims, marketing statements, and promotions. It is important to remember that all labeling—whatever is on the product or stated on a related Website about the product—must be truthful and not misleading. Figure 1 lists the items that are considered mandatory elements for labeling in the United States. Canada's laws are similar, and Canada and the United States are unusual in that nutrition information is mandatory in our labeling. Europe is going through a process to develop mandatory nutrition labeling.

Figure 1. Mandatory label requirements for foods, including sdietary supplements.

Biotechnology

A noteworthy item that relates to biotechnology issues is the concept of material fact information; any information that reveals facts in light of representations already on the label or any consequences of the use of the product have to be included on the label. If biotechnology changes the product in a manner that is considered a material fact, you have to give consumers that material fact, *i.e.* not the biotech piece, but what is different about that product in terms of its composition or use.

Nutrition Labeling

In 1990, the Nutrition Labeling and Education Act (NLEA) was enacted, making nutrition information mandatory on most packaged foods, and the regulations specified a format. It was no longer left to the manufacturer's discretion on how the information was presented.

It shifted emphasis toward the macronutrients that are associated with chronic disease risk and allowed for nutrient-content and health claims. The NLEA provides consumers with information to help them select foods for healthier diets. It eliminated confusion about nutrient-content claims, ensuring that when a claim is made, consumers can rely on that information. It also protects consumers from unfounded claims by developing a process by which health claims are authorized. It also encourages product innovation through the marketing of nutritionally improved foods. For example, there was a major effort to get rid of *trans*-fat before its mandatory labeling went into effect.

The public-health justification for enacting the NLEA included a surgeon general's *Report on Nutrition and Health*, a National Academy of Sciences report, *Diet and Health*, and *Dietary Guidelines for Americans* jointly from the Department of Health and Human Services (DHHS) and the Department of Agriculture (USDA), which made specific recommendations on how to improve health. Items to be listed on the "Nutrition Facts" label are shown in Figure 2.

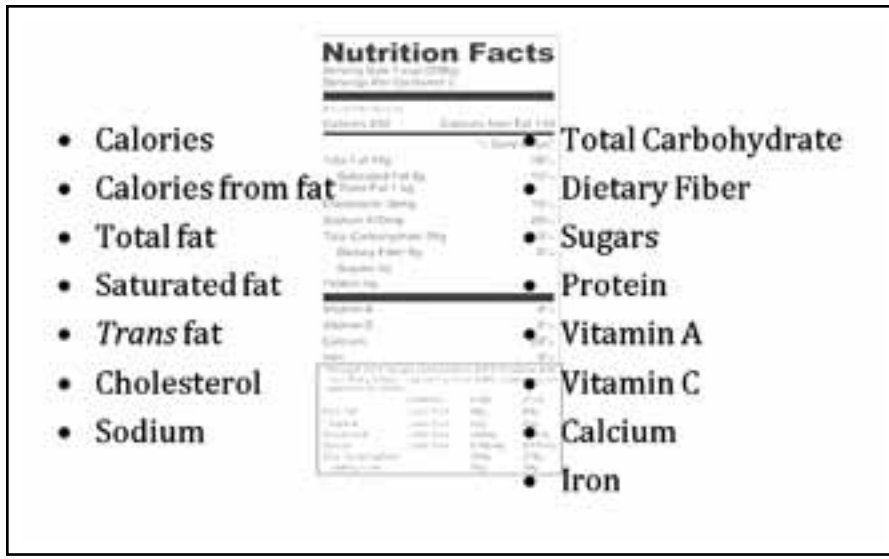

Figure 2. Items to be quantified on the "Nutrition Facts" label.

There are cases where some nutrients need not be listed, but the details of those regulations are beyond the scope of this presentation.

The Nutrition Facts label was designed with education in mind. Several formats were consumer-tested, which led to the inclusion of the concept of "daily value," to provide consumers with an easy means of judging whether a product is high or low in a nutrient, as part of planning their diets. The NLEA contains education as part of its core, so it was important that the Nutrition Facts be useful in education.

ANPRM

An advanced notice of proposed rule-making (ANPRM) lists the agency's questions and requests information in order to engage in a rule-making process. Three of these have been published in recent years, seeking input on possible revision of the Nutrition Facts. One was on the display of calorie information on the food label. Another was on serving size, particularly for products that can be reasonably consumed in one eating occasion; most of us are familiar with how we've gone from 12-ounce to 20-ounce sodas, exemplifying a need to reexamine serving size. And the third was major from a scientific perspective—revision of reference values and what the mandatory nutrients will be. This was driven particularly by the Dietary Reference Intake reports from the National Academy of Sciences, providing new scientific information for revising our reference values. The 2005 dietary guidelines will apply until the 2010 process is completed.

Public-Health Context

In addition to considering scientific information, the public-health context is important. For example, prevalence of childhood and adolescent obesity has increased significantly since the late 1970s. Sodium intake is another critical issue. Less than 25% of the US population consumes 2,400 mg or less of sodium daily, most of which originates in processed foods. Another particularly relevant dimension involves those food groups whose consumption is encouraged. Looking at fruit consumption, we are not doing too badly in terms of the percentage of the population meeting the recommendations (Fig. 3), whereas for vegetables we barely make it off the baseline, in terms of the percentage of the population meeting those recommendations. Also for whole grains, very few people meet the recommendations (Fig. 3).

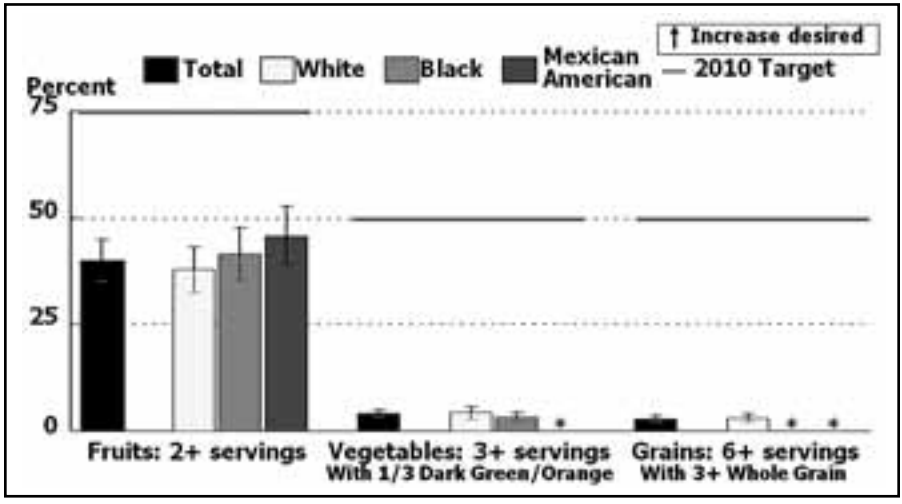

Figure 3. Fractions of the US population consuming indicated servings of fruits, vegetable and grains, 2003–2004 (source National Health and Nutrition Examination Survey, CDC).

Label Details

Serving size is at the top of the Nutrition-Facts label (Fig. 4). Do we have the right numbers? Are we displaying calorie information appropriately? Many questions have been raised about calories from fat and whether this item is needed. Do we need to improve the presentation format? We've had comments about the footnote, which many don't understand. Is there a better use for that space?

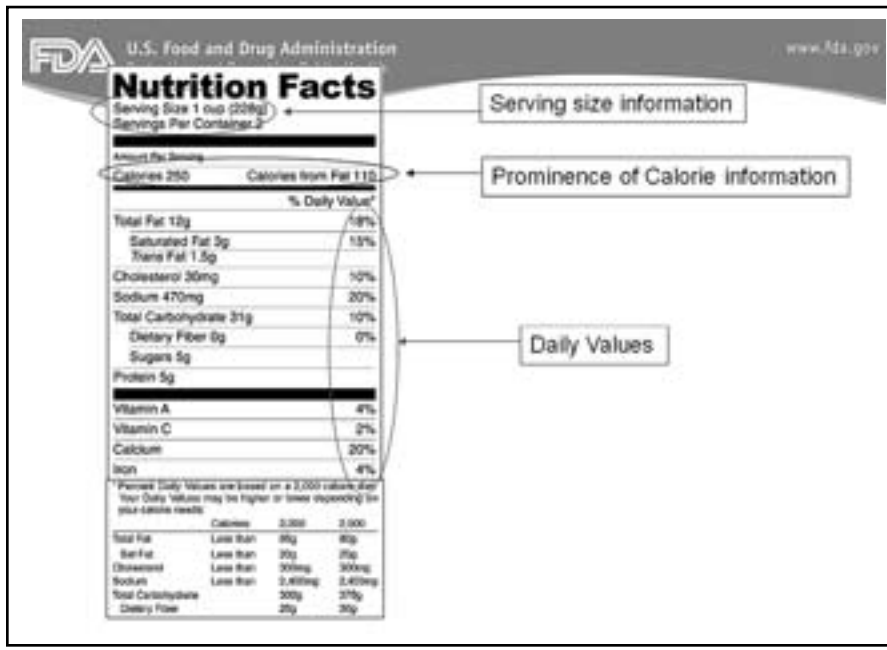

Figure 4. The Nutrition-Facts label.

Voluntary Information

From mandatory information on the Nutrition Facts label under the aegis of NLEA, I want to shift to voluntary information. Four general categories of claims can be used in nutrition labeling. Dietary-guidance and nutrition-support statements are not pre-approved by the agency. It's the manufacturer's responsibility to substantiate any such claims, and to make sure they are truthful and not misleading. A dietary-guidance statement is a general message that refers to categories of food, *e.g.* "Fruits and vegetables are part of a healthy diet," or "The food-guide pyramid recommends so many servings of vegetables," or similar statements. We are in the process of examining dietary-guidance statements: should the agency be setting parameters dictating when dietary-guidance statements can be used on food products? Nutrition-support statements include structure-function claims about maintaining health and function or structure of the body. For example, "Calcium builds strong bones" is a structure-function claim. Again, in the United States, we do not pre-approve or review those. They are the manufacturer's responsibility to be truthful and not misleading.

Claims that need to be reviewed by the agency before they can be used are of two types:

- nutrient-content claims that refer to a nutrient level in a product, and
- health claims that characterize the relationship between a food or food component and reduced risk of disease or a health-related condition.

Nutrient-Content Claims

Figure 5 gives examples of "expressed nutrient-content claims" stating that a component is non-existent or low or a good source or an excellent source. They may be comparative claims, stating that a food has more of a nutrient than another or it has less of nutrient, and particular types of percentage claims are used for dietary supplements. One of the challenges is making sure that we have the best tools and techniques for measuring nutrient content. The defined terminology, shown in Figure 5, helps the consumer understand, for example, that, if something is described as an "excellent" source, it has a specific meaning.

Type of claim	Criteria	Synonyms	Comments
"Good" source	At least 10% of RDI or DRV (i.e. DV)	provides, contains etc.	Cannot use without an established DV.
"High" source	At least 20% of the RDI or DRV (i.e. DV)	excellent, etc.	
Free or low	Grams or mg per RACC or labeled serving based on nutrient	Zero, without, insignificant; little, small amount etc.	See regulations for additional terms and criteria.
Reduced	At least 25% less per RACC than an appropriate reference food	Less, fewer etc.	

Terms: RDI=Reference Daily Intake, DRV=Daily Reference Value; DV=Daily Value
RACC=Reference Amount Customarily Consumed

Figure 5. Examples of expressed claims.

Nutrient-content claims are not possible for many compounds, including some bioactives, because reference values are unavailable. We don't know what constitutes a recommended amount, so it's not feasible to state when a food is a good or excellent source. Most regulations that apply to nutrient-content claims are only for nutrient or dietary substances that have a daily value (Fig. 6). We don't have that for antioxidants in general or for carotenoids, for example. Again, that's a challenge to science.

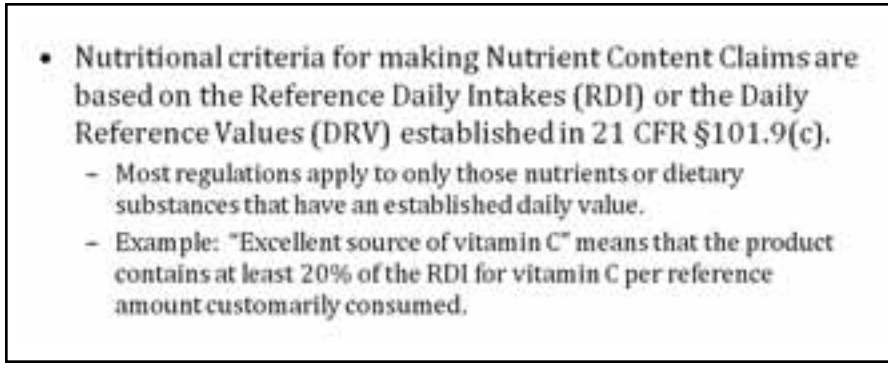

Figure 6. Basis for nutritional-content claims.

There are also "implied" nutrient-content claims, which suggest that a nutrient is present or absent, or equivalent to the level in another product (Fig. 7). FDA has defined when the term "healthy" may be used, in terms of minimum fat, saturated fat, sodium, cholesterol and certain beneficial nutrients, providing context for the consumer (Fig. 8).

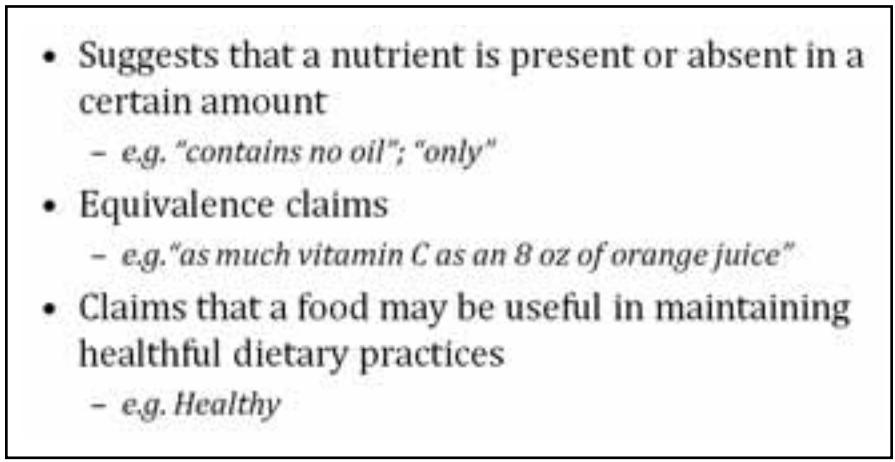

Figure 7. Implied nutrient-content claims.

Health Claims

Health claims are science-based statements of disease-risk reduction from foods and dietary supplements without being regulated as drugs. Before NLEA, the agency would have to approach such a declaration as a drug claim. Critically important is *reduction in the risk* of a certain type of disease; it's not about prevention, mitigation, treating or curing a disease. A key element of a health claim is that the food or supplement has to contain a specific substance. Also, the disease or health-related condition has to be defined.

	Individual Food* (RACC is ≥ 30 g)	Seafood/Game Meat	Main Dish/Meal Product
Total Fat	3 g or less /RACC (low)	Less than 5 g per RACC & 100g	3 g or less/100g & no more than 30% of calories (low)
Saturated Fat	1 g or less/RACC & 15% or less calories (low)	Less than 2 g per RACC and 100g	1 g or less/100 g & <10% of calories (low)
Sodium	480 mg or less/RACC & /labeled serving	480 mg or less/RACC & /labeled serving*	600 mg or less per labeled serving
Cholesterol	60 mg or less/RACC & /labeled serving	Less than 95 mg/RACC & 100g	90 mg or less per labeled serving
Beneficial Nutrients	At least 10% RDI or DRV per RACC for one or more of vitamins A, C, iron, calcium, protein, or fiber‡		Main dish: 2 nutrients; Meal: 3 nutrients

*For foods with a RACC of 30 g or less or 2 tablespoons or less, the criteria refer to the amount per 50 g of food.
‡Except raw fruits and vegetables, frozen or canned single ingredient/mixture fruits and vegs, except that ingredients whose addition does not change the nutrient profile of the fruit or veg may be added; enriched cereal-grain products that conform to a standard of identity.
RACC = Reference amount customarily consumed, which is the basis of serving size on food labels.

Figure 8. Criteria for the use of "healthy."

We've had some discussion about using biomarkers to estimate risk. Studies that require clinical outcomes—heart disease, cancer, *etc*.—are costly, therefore biomarkers offer a useful tool to show when risk has been reduced. We have five biomarkers that are validated surrogate endpoints of disease:

- LDL cholesterol or plasma cholesterol reduction for cardiovascular disease,
- blood-sugar levels or insulin resistance for diabetes,
- mild cognitive impairment for dementia.
- polyps for colon and rectal cancers, and
- bone-mineral density for osteoporosis.

An Institute of Medicine (IOM) project, funded by FDA, has the objective of developing a framework for elucidating more biomarkers to serve as surrogate endpoints of chronic disease. Few such tools are applicable to cancer, for example, therefore it's difficult to develop health claims in this area.

Three approaches are available for obtaining a health claim (Fig. 9). NLEA claims are based on significant scientific agreement. We authorize these through rulemaking, which means the agency stands behind the claim and makes it available through federal regulation. The agency developed qualified health claims as a result of a set of court cases that the agency lost, particularly with dietary supplements. These claims characterize the quality and strength of the scientific evidence because they are not based on significant scientific agreement; we do them only through enforcement discretion, not through

Figure 9. Health claims in food labeling.

rulemaking. Thirdly, an authoritative statement from a branch of the government or the National Academy of Sciences can be the basis of a health claim.

Significant scientific agreement implies consistent relevant evidence from well designed studies, whereas a qualified health claim is based more on emerging evidence, for which we use several types of qualifiers. Certain qualified claims are categorized as "highly unlikely" or "uncertain."

On our website, a final guidance document, titled "The Evidence-Based Review System for the Scientific Evaluation of Health Claims," details the steps the agency goes through to review the scientific evidence that is submitted with a petition. This would be a valuable aid for graduate students when designing their research, especially if they are working on something that eventually might relate to a health claim. Figure 10 provides a schematic representation of the process.

All relevant information must be submitted, not just favorable studies. We examine all of these, keeping in mind our guidance outlines for what kinds of information cannot be used for a scientific decision: review articles, meta analyses, book chapters, abstracts, animal and *in vitro* studies, non-identification of the substance or the disease, *etc.* (Fig. 10). We also identify fatal flaws within any of the studies, such as if there is no control, relevant statistics are lacking, or they have key confounders that are not controlled for. Often we receive observational data without any intake validation, and studies that are conducted on malnourished populations; again we set those aside because they are not useful in the decision-making process. Having accumulated data that are useful to us, we go through an evaluation to determine whether or not they constitute credible evidence for the claim, because some will support the claim and some will not support it. If there is no credible evidence, then we deny the petition. If there is some credible evidence we

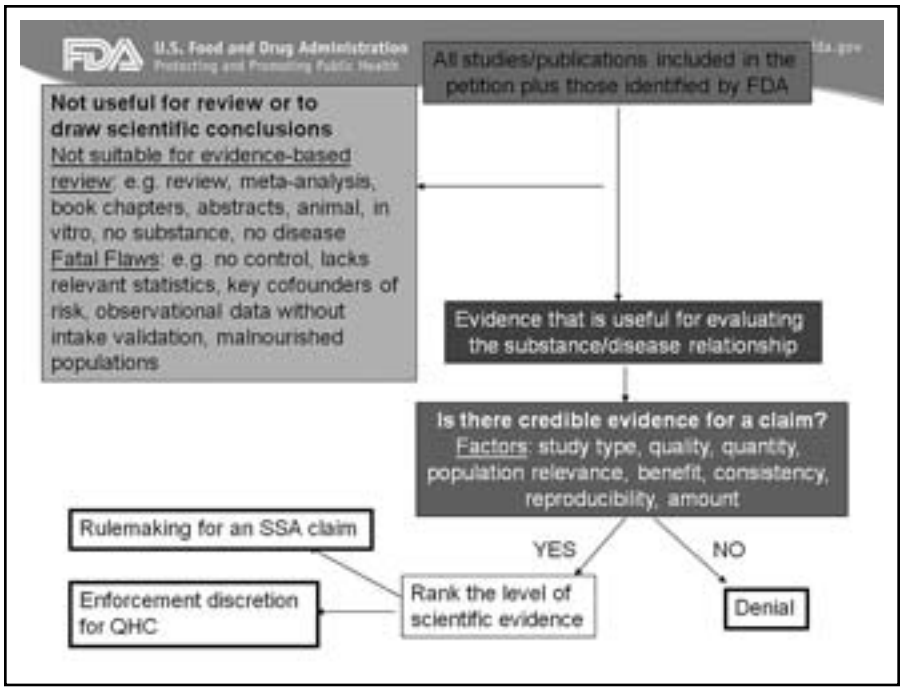

Figure 10. The evidence-based review system.

rank the level of scientific credibility, and then proceed with rulemaking for a significant scientific agreement (SSA) claim, or enforcement discretion for a qualified health claim (QHC). Many people think we use different evaluation processes for these two claims, which isn't so. The strength of the scientific evidence determines the outcome.

Regulation Development

As indicated, we implement the Federal Food, Drug and Cosmetic Act, which is amended routinely. The two primary ways in which we implement the Act are by adding to the Code of Federal Regulations (CFR) and by publishing guidance documents. These go through a notice-and-comment process, which can take time.

A rulemaking process may be initiated several different ways. A judicial decision may be involved. I mentioned that, for updating Nutrition Facts, we started with an advanced notice of proposed rulemaking, asking questions. It then can become a proposed rule to which comment is invited, and eventually we get to a final rule. Many factors have to be considered, requiring a multi-disciplinary approach. The background material provides scientific justification. Also, does the government have an interest from a public-health or other perspective in proceeding with the regulation? What are the petitions? What are the grounds for taking action? Does the FDA have the legal authority? How is the law interpreted to justify proceeding? There is also a First-Amendment consideration.

Labeling is deemed as speech, since we may be either compelling speech or suppressing speech, requiring a First Amendment analysis. Also, there has to be a regulatory-impact analysis, which is where economists contribute. We have to do a cost-benefit analysis on any rule under consideration, and the Office of Management and Budget (OMB) would like to see that the benefit outweighs the cost; if that is not clear from the analysis, then it's difficult to make progress in rulemaking.

There is plenty of opportunity for scientific input. For example, on the nutrition side, we rely heavily on reports from the National Academy of Sciences, and peer-reviewed scientific literature. We often engage with consultants either through advisory committees or public meetings, and experts may be consulted individually on a particular topic. The *Federal Register* describes everything, including notices, that we want comment on. A docket is opened, to which we solicit comments. Several dockets have been open recently; one on front-of-pack labeling and one on menu labeling, for example. These provide opportunities for the scientific community to give us comments. Most important are independent evaluations of scientific information that we need to consider. It's nice to be offered opinion; however, opinion is never in short supply, so we look for the scientific evidence that is relevant. Once we are finished within FDA, several other layers of review are required within the government before something is published.

Current Priorities

A major area of interest right now is addressing labeling on the principal display panel, also referred to as front-of-pack labeling. Under this initiative, we have taken several enforcement actions. In early 2010, we issued seventeen warning letters identifying claims on the front of food packages that are inconsistent with regulations and which we think are misleading to consumers. We have stated publicly that we are working on regulations regarding dietary-guidance statements to ensure that they are helpful to consumers in choosing diets consistent with the dietary guidelines. We are conducting consumer research on various front-of-pack labeling systems, to better understand how consumers use and comprehend those labels. And we have stated publicly that the agency intends to develop guidance on a government-sponsored approach to front-of-pack labeling, for which the research component will be critically important. And the Institute of Medicine of the National Academy of Sciences has a study on front-of-pack labeling underway.

Two other areas of high intensity are menu and vending-machine labeling. We are evaluating a National Academy report on strategies to reduce sodium intake in the United States with a view to formulating a pathway forward for the agency. With respect to menu and vending-machine labeling, a directive tucked away in the many pages of the Patient Protection and Affordable Care Act is the requirement that chain restaurants and similar retail establishments with twenty or more locations disclose nutrient-content information for standard menu items, including specifically that calories should be listed on menus, menu boards and food on display. It also requires certain-sized vending-machine operators to disclose certain nutrient-content information, particularly calories, on items. The statute provides us with only 12 months to develop a regulation for these requirements of the statute.

In Summary

At FDA, science, policy and human behavior come together. Ultimately, our goal is to make sure that consumers have safe and nutritious food.

Barbara Schneeman is director of the Office of Nutrition, Labeling, and Dietary Supplements in the Center for Food Safety and Applied Nutrition at the Food and Drug Administration (FDA). She oversees the development of policy and regulations for dietary supplements, nutrition labeling and food standards, infant formula and medical foods, and serves as the US delegate to two Codex committees. From 1976 to 2007, she was professor of nutrition at the University of California-Davis, and served in several administrative roles, including chair of the Department of Nutrition and dean of the College of Agricultural and Environmental Sciences.

She received her BS degree from the University of California-Davis, a PhD from the University of California-Berkeley, and postdoctoral training in gastrointestinal physiology at Children's Hospital in Oakland, CA.

Dr. Schneeman is a fellow of the American Association for the Advancement of Science, and is the recipient of the Carl Fellers Award from the Institute of Food Technology, the FDA Commissioner's Special Citation and the Harvey W. Wiley Medal, the Samuel Cate Prescott Award for research, the Future Leader Award, and several honorary lectureships. She is widely published and is recognized for her research contributions in the areas of gastrointestinal function, dietary fiber, lipid metabolism and food-based dietary guidelines.

The Science Behind the Claims and Why the Product that Bears a Claim Needs to be "Healthy"

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My focus is on what science is needed for a health claim or a nutrient-content claim, and Barbara Schneeman has paved the way for me[1] by describing these claims, which I will briefly review. I'll discuss the requirements for a product to carry a health claim or a nutrient-content claim. It's not enough to get the health claim, you must have a product that can carry that health claim. I'll talk about FDA's nutrient profiling—I'm calling it "nutrient profiling" although it can be called other things—and then segue into nutrient profiling for point-of-purchase systems. Point-of-purchase systems are little checkmarks, stars or smiley faces on packaging, directing consumers to healthy products. I'll talk about what these mean and the future direction in that area.

Health Claims

A health claim is an expressed or implied statement in labeling about the relationship of a food substance to a disease or health-related condition. Where many people—individuals and manufacturers—go wrong is, instead of looking at decreased *risk* of disease, they think in terms of treating, mitigating or curing disease, which categorizes the active agent as a drug. Also, and very importantly for both health claims and nutrient-content claims, they must have pre-market approval from FDA. Makers who place health claims on their products without prior approval receive warning letters from FDA (*e.g.* Fig. 1).

[1]Pages 133–144.

Figure 1. Misbranded foods that led to receipt of warning letters from FDA.

A warning was issued for Pollock baby fillets, on which the label stated that they help to prevent heart attacks (Fig. 1). If this were an approved health claim, the label could state that the risk of heart attack was decreased but not that heart attack was prevented. The letter from FDA stated that this would categorize the product as a drug, subject to other regulatory strictures. Packaging on a herbal supplement claimed "constipation relief" or "restoring regularity." You can't have constipation and mitigate it with a health claim, you must decrease the risk of it occurring in the first place. Diamond of California claimed that their shelled walnuts' content of omega-3 fatty acids "inhibits the tumor growth that is promoted by the acids found in other fats," which defined the product as a drug; furthermore, it would be a new drug requiring an approved new-drug application. To make matters worse, Diamond also claimed that "studies have also shown that omega-3s may lower the risk of stroke." Although "lowering the risk" was consistent with a health claim, no such health claim had been applied for. You can't make up a health claim saying that risk is decreased. Their claim that the walnuts contain omega-3 at 2.5 g per serving may seem innocuous; however, next to that statement were four little hearts, making an apparent connection between that amount of omega-3 in the product and heart disease.

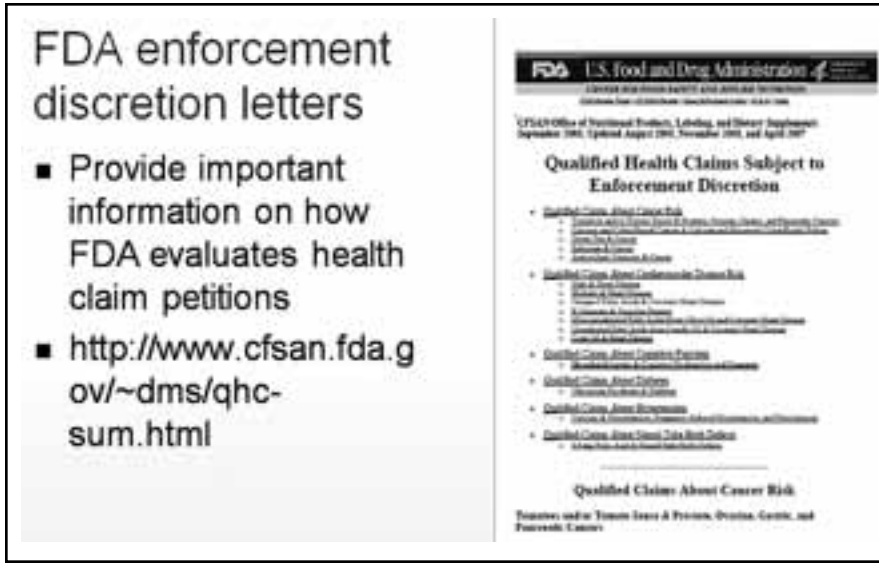

Figure 2. Enforcement discretion letters.

The FDA warning letter cautioned that "the heart symbols adjacent to this statement make this an implied health claim."

Figure 2 shows, in brief, guidance for industry issued in 2007[2]. This and the 2009 version[2] are required reading for anyone who wants to be a principal investigator on a study that may in the future be used for submission of a health claim. It clarifies pitfalls to be avoided when preparing and applying for a health claim. The company representative sends a dossier to FDA describing studies the results of which support the health claim. When FDA starts the review, any animal and/or *in-vitro* studies, review articles, and meta analyses—with a few exceptions—are set aside and major consideration is given to human studies on non-diseased populations. The animal, *etc*., studies can be used as background information, but they are not considered directly for the actual health claim. Substance X must reduce the risk of disease Y, with substance X and disease Y both defined and characterized.

Let's say that we want to make the statement that eating fish decreases the risk of heart disease. We would have to cite studies that had people eating fish and the endpoint would have to be decreased risk of heart disease or any one of the acceptable markers for heart disease. Alternatively, let's say that we want to claim that consuming omega-3 fatty acids decreases the risk of coronary heart disease. Instead of fish studies, we would use omega-3-supplement studies. Or let's say we wanted to make a similar claim for docosahexaenoic acid (DHA) or eicosapentaenoic acid (EPA), then we would have to show the results of the presence of DHA or EPA in the diet.

[2]An updated version, issued in 2009, is available at http://www.cfsan.fda.gov/guidance.html.

Substance X and disease Y have to be measurable and—very importantly—validated surrogate endpoints are necessary. For a heart disease, an endpoint would be LDL cholesterol, total cholesterol or blood pressure, which are accepted biomarkers. The results of a study will be discounted unless the data apply to an *accepted* biomarker

The submitted data are characterized as either intervention trials or observational studies. With the former, the single most important type of intervention study is a randomized clinical trial; the subjects of the trial and the information obtained must be able to be extrapolated to the population that is the subject of the health claim. Some observational studies are more important and receive higher levels of consideration because they entail less potential for bias. Long-term cohort studies rank higher than retrospective or cross-sectional studies. Within a prospective cohort study, some type of measurement other than a food-frequency questionnaire—*e.g.* blood levels of a certain omega-3 fatty acid—would give the quality of that study a higher rating. Studies are completely eliminated from consideration if they are deemed to be seriously flawed. For example, if the subjects already had cancer, a decreased risk of cancer would be meaningless and the results of the study would be unacceptable. On the other hand, some factors are on a continuum, such as blood pressure. You might make the case that people with moderately elevated blood pressure constitute a non-diseased population, since a lot of people over a certain age do have elevated blood pressure. The same may be said regarding obesity in view of the fact that two thirds of the US population are overweight or obese. It's another continuum, and, again, you would have to make a case for it. If there is no appropriate control group or the control group is dissimilar from the intervention group, the study would be considered as seriously flawed and eliminated from consideration. Similarly, elimination would occur if the effects obtained do not result clearly from the substance of interest. For example, an effect obtained from eating spinach cannot be deemed to be due to the lutein content of the spinach.

On completion of this process, the remaining studies are rated as "high," "moderate" or "low" in quality. Then the "surviving" studies—those that still count—are considered and the quality and quantity of the evidence are appraised along with their relevance to the US population. From the overall consistency of the entire body of data, FDA deduces the strength of the science showing that the food or nutrient or substance decreases the risk of the disease. The stronger the relationship, the better the science, the fewer the qualifications required on the eventual label. FDA sends an enforcement discretion letter, which describes how the health-claim petition was evaluated. Enforcement discretion letters are also available on the FDA's Website and they make for useful reading (Fig. 2).

Case Study: Enhanced Omega-3 Eggs

A producer of hens' eggs petitioned FDA for a health claim that daily consumption of one egg containing 660 mg of omega-3 fatty acids (balanced 1:1 with omega-6 fatty acids) reduces the risk of heart disease and sudden fatal heart attack (Fig. 3). They submitted seventy-four peer-reviewed publications, of which twenty-eight were on nonhuman subjects; therefore, we actually considered forty-six. Step 2 focused on the substance, *i.e.* the egg with the specific fatty acid composition. Of eighteen intervention trials described,

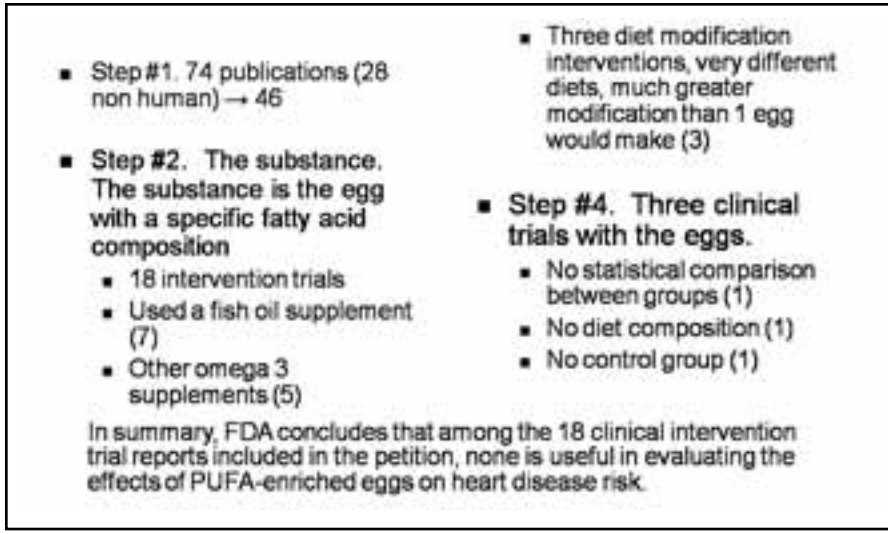

Figure 3. Case study: enhanced omega-3 eggs.

seven were eliminated because fish-oil supplement, not the egg, was used. Other omega-3 supplements were used in five of the eighteen trials, so they were eliminated from further discussion. Only six studies were left to provide evidence between intake of the substance and decreased risk of the disease. Three of those had such strong diet modifications in the intervention group—much more than the consumption of one egg—that they were very different from the control group. Those were eliminated. We were down to three clinical trials with the eggs, of which one showed no statistical comparisons, one provided no diet composition and one had no control group. In spite of the work and expense involved on the part of the company in making the submission, FDA concluded that none of the eighteen clinical-intervention trial reports in the petition was useful in evaluating the effects of polyunsaturated fatty acid-enriched eggs on risk of heart disease. The claim was denied and the last sentence in the letter of denial was: "Even if there were credible evidence for the proposed claims, polyunsaturated fatty acid-enriched eggs would be disqualified from bearing a health claim because of their cholesterol content." One would have thought that the producer would have anticipated this response and saved the not-insubstantial sum of money, time and effort involved in attempting to procure the health claim.

Nutrient-Content Claims

Dietary Fiber

The health-claim process is long and rigorous, and, unless the scientific basis of the claim is strong, a qualified health claim—which you probably wouldn't want on your product—may result. Therefore, people are turning to other types of claims, including nutrient-content claims. A daily value has to be quoted in order to obtain a nutrient-content claim. A content of 10% of the daily value of a nutrient in a serving is a "good"

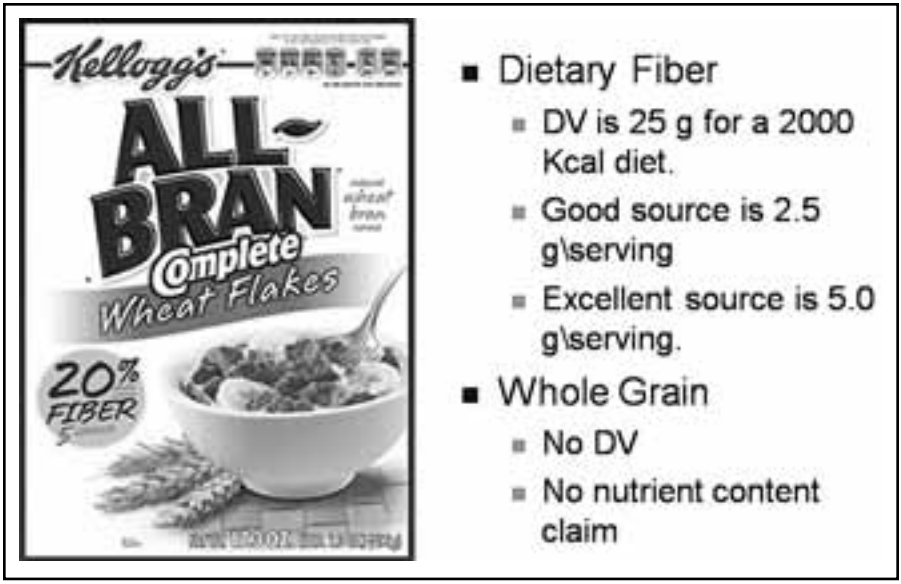

Figure 4. Nutrient-content claims: dietary fiber and whole grain

source, and 20% of the daily value is an "excellent source." For dietary fiber in a cereal (Fig. 4), the daily value is 25 g for a 2,000-calorie diet; therefore, 2.5 g of fiber per serving would be a "good" source and 5 g would be an "excellent" source. However, fiber cannot be interpreted in terms of whole grain (which we attempted to do in the 2005 Dietary Guidelines to encourage people to eat more whole grains, because they generally contain more fiber than refined grains). Contrary to popular belief, there simply isn't a daily value for a whole grain.

Isoflavones

A somewhat similar situation prevails for soy isoflavones, for which Figure 5 summarizes a warning letter. The product label stated that the applicable soy product was "very high" in isoflavones, whereas the warning letter stated that FDA authorizes claims of "high" and a "good source," but does not authorize claims of "very high." The letter went on to state that, in any case, there is no daily value intake for isoflavone because it isn't a nutrient, and so a nutrient-content claim is meaningless. Other similar cases are described on the FDA website.

Requirements for a Product to Carry a Claim

From FDA's perspective, if a food product carries a health claim or nutrient-content claim it has to be below a certain bar for "nutrients to limit" and it has to be above a certain bar for at least one key "nutrient to encourage" (Fig. 6). Also, there has to be at least a minimum effective amount of the beneficial ingredient in the food for it to carry the claim. If it's above the disqualifying levels for "nutrients to limit," it can't carry a health

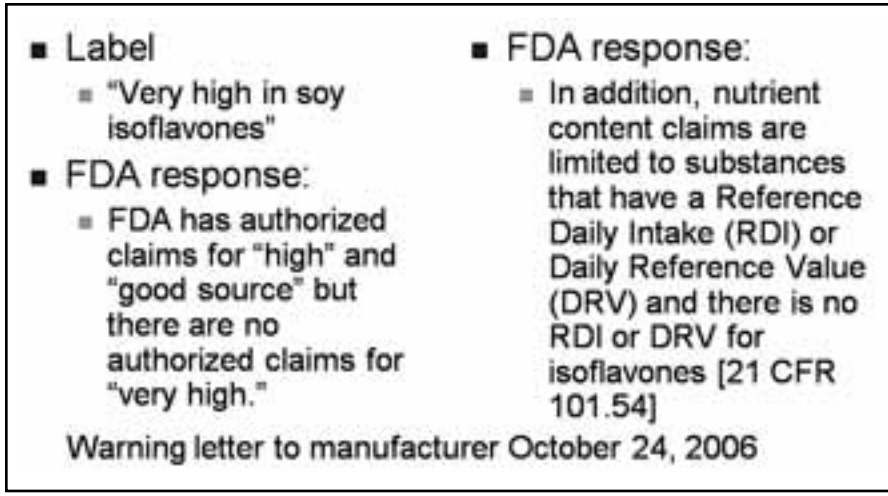

Figure 5. FDA response to a nutrient-content claim.

claim. If it's a nutrient-content claim and it's above this, it can still get a nutrient-content claim, but it has to disclose on the front of the package, right next to what it is saying in terms of a "good" or an "excellent" source. Let's say it's too high in saturated fat, it has to refer to the back panel or to the Nutrition Facts panel for the amount of fat, to bring it to people's attention.

P-O-P Nutrient Profiling Systems

Point-of-purchase nutrient-profiling systems are useful if they direct shoppers to healthier products. If they are easy to understand, they can be particularly beneficial for those

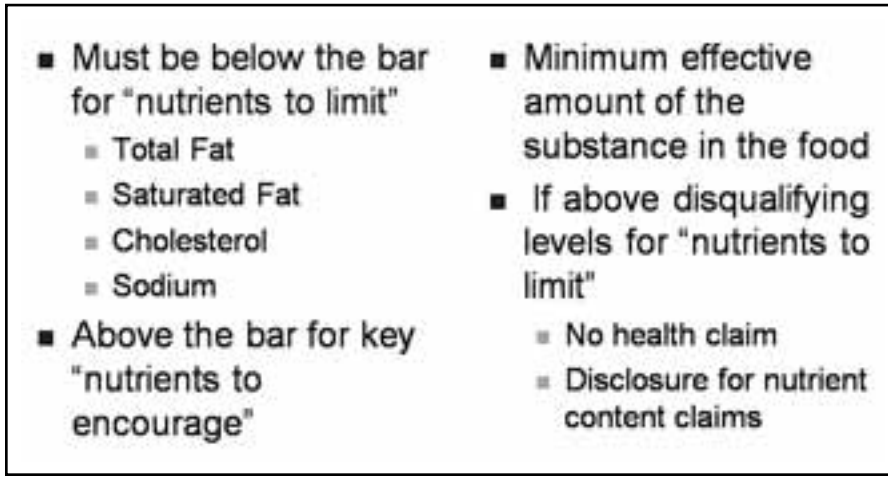

Figure 6. Requirements for foods bearing claims (FDA's nutrient profiling).

who do not have a lot of time for food shopping, circumventing the need to consult the Nutrition Facts panel or do calculations to make comparisons.

Discretionary Calories

By visiting the Website mypyramid.gov, we can find out our calorie allotments for the day, *i.e.* how many calories can one take in without gaining or losing weight. If we take the number needed in terms of energy intake and subtract from that the calories required to obtain needed nutrients from foods, the difference is our discretionary calories. That can be a glass of wine, a dessert, or full-sugar soda, for example—however you wish to spend them because you've already spent your calories on the foods and the nutrients that you need without exceeding your energy requirement.

The issue here is, how many discretionary calories do we actually have to spend? When the USDA provides the number of servings that we should have for our energy level, gender and age, those numbers are based on the item in each food group that is lowest in fat, added sugar, and sodium. For example, in the dairy category, a recommendation of three glasses of milk a day means three glasses of non-fat milk—not 1% or 2%, and certainly not ice cream, and not even low-fat yogurt. Three glasses of 1% milk would mean using discretionary calories.

Two thirds of adults in the United States are either overweight or obese, therefore they have no discretionary calories and should be eating less than their calorie allotments so that they lose weight. Many others are not meeting their nutrient requirements because they are not choosing the most nutrient-dense foods. For example, most of the dietary fiber we get from vegetables in the United States is from French fried potatoes, which is not to imply that this a good source of fiber. Similarly, our greatest sources of grain fiber are hot-dog and hamburger buns. Again, these are not great sources of dietary fiber, but we eat a lot of them and they contain some fiber. These examples show how we are wasting some of our calories by not picking the most nutrient-dense foods and they illustrate the potential utility of point-of-purchase nutrition-profiling systems.

A major criticism, however, is that there are multiple point-of-purchase nutrition-profiling systems with multiple nutrition criteria, resulting in consumer confusion rather than helping to solve the problem. It's generally agreed that a unified system is needed to cut through the clutter, and FDA has taken action with workshops and consumer-research projects. They are supporting an Institute of Medicine panel to evaluate different systems. They've held a press conference and sent a letter to manufacturers seeking input on what they are looking for and, if there is to be a unified system, what it should be. Information is expected to be available by the end of 2010.

In Summary

The evaluation of health claims is a rigorous, science-based process. Products that carry health or nutrient-content claims must meet nutrient-profiling requirements. There's a reason for not directing people to good substances that are in bad vehicles—we cannot afford to waste calories on non-nutrient-dense foods. Consequently, FDA and the Institute of Medicine are evaluating nutrient-profiling systems for point-of-purchase labeling. Results should be available by December, 2010.

Joanne Lupton is a distinguished professor, regent's professor and university faculty fellow at Texas A&M University, and holder of the William W. Allen Endowed Chair in Human Nutrition. She chaired the Macronutrients Panel for the Dietary Reference Intakes, Food and Nutrition Board of the National Academy of Sciences, which determined intake values for protein, carbohydrates, fats, fiber and energy, and she also chaired the National Academy panel to determine the definition of dietary fiber. She was a member of the 2005 Dietary Guidelines Committee.

Dr. Lupton is a member of the Institute of Medicine and a lifetime associate of the National Academy of Sciences, and is past president of the American Society for Nutrition. Her research has focused on the effects of diet on colon physiology and colon cancer with a particular focus on dietary fiber and n-3 fatty acids. She translates basic research on diet and colon physiology to science-based public policy, and has consulted with individuals in Japan, South Korea, China, Taiwan and elsewhere on the definition of dietary fiber and on establishing dietary-guidance systems in those countries.

Her undergraduate degree is from Mt. Holyoke College and her PhD in nutrition is from the University of California-Davis.

The EU Regulation on Nutrition and Health Claims: Current and Future Trends

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When considering how to promote health by linking agriculture, food and nutrition, it makes perfect sense to have a closer look at existing legislation in the area of nutrition and health claims made on food products. This is particularly important because what industry is allowed to say about the impact on health of the foods it sells is an essential element in a number of areas, such as consumer awareness, consumer education, product research and development, and research-funding opportunities. After all, why would anyone invest considerable resources to do research, develop and market a particular food product that would be more nutritious or would help mitigate certain disease-risk factors, if the law were to prohibit any commercial communication on those health benefits?

When examining existing legislation on nutrition and health claims made on foods, it is also useful to consider the regulatory framework in the European Union (EU). There are three main reasons for that. Firstly, the EU is certainly one of the most regulated regions in the world, particularly in the food area, and it tries to "export"—or at least promote—its regulatory options to other regions and countries worldwide. Food legislation adopted in the EU tends to inspire regulators in other countries. Secondly, EU food laws, in general, tend to be more restrictive than in other regions. Thirdly, the EU legislation on nutrition and health claims was adopted recently and some of its provisions are still being developed, causing considerable controversy. Therefore, keeping an eye on the developments in the EU in terms of food claims will help promote understanding of what food manufacturers will be able to communicate to consumers in the EU as well as what new regulatory "tools" could potentially be replicated in other countries.

The EU Regulation on Nutrition and Health Claims [Regulation (EC) No 1924/2006], hereafter "the Regulation," has certainly been one of the most controversial pieces of legislation of the last decade in the area of EU food law. Its significant impact—current and future—on the food industry, particularly on functional foods and food supplements, has made its gradual implementation remarkably complex and contentious. In addition, some of its provisions, such as nutrient profiles, have raised such significant opposition from industry that its ongoing implementation has constantly been the subject of extensive press coverage, with a number of tough political and technical debates, since its adoption in December 2006.

Before the adoption of this legislation, various national legal frameworks regulated the use of nutrition and health claims across the EU. Some Member States had strict rules whereas others relied only on very general principles. In certain cases, the differences among national provisions were obstacles to the free movement of food products within the EU market. This situation also created significant distortions of competition on the market. This explains why the food industry itself was one of the main entities asking EU regulators to harmonize legislation in this area.

Scope and Objectives of the Regulation

The Regulation became applicable on July 1, 2007, across all twenty-seven EU Member States. In principle, the same rules are now applicable to all companies selling their products in the EU market, including imported products.

The Regulation applies to all nutrition and health claims made in all "commercial communications." These include not only claims made on product labels, but also claims made in advertising (television, radio, *etc.*), websites, promotional leaflets, on-shelf presentations, *etc*. Any communication on the nutritional or health benefits of a food product made on any commercial entity must comply with the provisions of the Regulation.

When proposing and adopting this legislation, the EU regulators intended to achieve three main objectives:

- To ensure a high level of protection for consumers. This would be achieved through measures aiming at ensuring that all claims are scientifically substantiated, and also through provisions intended to avoid the over-consumption of certain products due to the claims they would make.
- To facilitate consumer choice. A clear set of rules applying across the EU, with strict conditions and specific restrictions would allow consumers to make their purchases knowing that the claims made on the products they would buy are meaningful and scientifically justified.
- To ensure the effective functioning of the internal market. Similarly, the same rules applying to all twenty-seven national markets would lead to equal conditions of competition for the food industry while enabling the free movement of food products across the EU.

To achieve these objectives, the Regulation is based on two key principles:

- All nutrition and health claims must be approved at EU level.
- Certain foods will be prohibited from nutrition and/or health claims.

All Claims Must be Approved at EU Level

The Regulation defines two general types of claims—"nutrition claims" and "health claims"—which are approved through different authorization procedures. Nutrition claims are defined in the Regulation as "any claim suggesting that a food has particular beneficial nutritional properties due to the energy, nutrients, or other substances it contains, contains in reduced or increased proportions or does not contain." Health claims are defined as "any claim suggesting that a relationship exists between a food category, a food or one of its constituents and health."

The key principle laid down in the Regulation is that all nutrition or health claims must be approved at the EU level through the applicable procedures and be included in a positive list. Only the claims mentioned in the EU positive lists will be permitted in the EU.

Permitted Nutrition Claims

The Regulation itself includes, in its Annex, a positive list of the permitted nutrition claims (Table 1). Since January 19, 2010, these have been the only permitted nutrition claims in the EU market. All others are prohibited, including certain nutrition claims that have been widely used across the EU until recently, such as "high energy," "cholesterol free," "extra light," "*trans*-fat free" and "high in omega-6 fatty acids."

Table 1. List of permitted nutrition claims in the EU.

Low energy	Source of fiber
Energy reduced	High fiber
Energy free	Source of protein
Low fat	High protein
Fat free	Source of [name of vitamin(s)] and/or [name of mineral(s)]
Low saturated fat	High [name of vitamin(s)] and/or [name of mineral(s)]
Saturated-fat free	Contains [name of the nutrient or other substance]
Low sugar	Increased [name of the nutrient]
Sugar free	Reduced [name of the nutrient]
With no added sugars	Light/lite
Low sodium/salt	Naturally/natural (as a qualifier for other nutrition claim,
Very low sodium/salt	*e.g.* "naturally high in fibre")
Sodium free or salt free	

The Annex to the Regulation includes specific conditions of use that must be complied with in order for a food product to bear a particular nutrition claim. As an example, a claim that a food is "fat free" may be made only if the product contains no more than 0.5 g of fat per 100 g or 100 mL. Also, claims expressed as "X% fat free" are prohibited.

This positive list of permitted nutrition claims may be amended to take into account scientific and technological developments. A first amendment was adopted in February 2010 [Commission Regulation (EU) No 116/2010] with the addition of five more permitted nutrition claims on fatty acids: "source of omega-3 fatty acids"; "high in omega-3 fatty acids"; "high in mono-unsaturated fat"; "high in poly-unsaturated fat"; and "high in unsaturated fat."

As it stands, the Annex on nutrition claims is generally considered to be very restrictive. For example, claims relating to cholesterol ("cholesterol free," "low in cholesterol") are not included, although they were popular with certain consumers. Their inclusion in the positive list had been requested by industry and a number of Member States, but the regulators decided in the end not to authorize them because they were regarded as potentially misleading. It was feared that consumers did not understand the difference between dietary cholesterol and blood cholesterol, and the small impact the former has on the latter. Another example of a "popular" nutrition claim that has not been included in the positive list is "high energy." The fact that this claim, and any claim having the same meaning, is not authorized in the EU has considerable implications on sports foods, for example. A large number of product concepts, such as energy bars, energy gels and sports beverages have been severely affected by this decision.

Certainly, one of the most restrictive aspects of the Regulation, in relation to nutrition claims, is the very limited number of permitted comparative nutrition claims and the conditions applying to them. As it currently stands, the Regulation authorizes only four comparative nutrition claims: "energy-reduced," "increased [name of nutrient]," "reduced [name of nutrient]" and "light/lite." One of the conditions of use for these four claims is that there must be a difference in the content of the nutrient in question of at least 30% between the products being compared. This is clearly a challenge for food manufacturers carrying out reformulation programmes, as reducing the content of certain nutrients by 30% is difficult to achieve and, in certain cases—such as salt reduction—it may even lead to consumer rejection of the new recipe. This restrictive condition, particularly for reduction claims, is seen as a missed opportunity for EU regulators to give an incentive to industry to reformulate their products. By raising the bar too high, the regulators may have discouraged certain companies from improving their product recipes; why would a company reformulate its products at great cost if the law does not allow those efforts to be communicated to consumers? Are reductions in fat, saturated fat, salt or sugar of 15% or 20% really irrelevant?

Permitted Health Claims?

Contrary to the situation for nutrition claims, the Regulation itself does not include a positive list of permitted health claims. However, it lays down specific provisions requiring the establishment of such positive lists, as well as describing the corresponding

authorization procedures that must be followed to obtain authorization for different types of health claims.

The Regulation classifies health claims in three broad categories, to each of which different authorization procedures apply:

- Nutrient-function claims, which include all claims referring to the growth, development or the functions of the body (*e.g.* "calcium helps maintain strong teeth and bones"), as well as psychological and behavioral claims (*e.g.* "substance X helps improve concentration and memory"), and slimming and satiety claims *(e.g.* "substance Y helps you want to eat less/lose weight").
- Reduction-of-disease-risk claims, which "state, suggest or imply that the consumption of a food category, a food or one of its constituents significantly reduces a risk factor in the development of a human disease" (*e.g.* "substance Z has been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease").
- Claims referring to children's development and health. The Regulation itself does not provide a definition for this category of health claims. However, guidance on the implementation of the Regulation (Guidance on the Implementation of Regulation No 1924/2006, 2007) was adopted at a later stage, which clarified that this particular type of health claim would include: a) those solely referring to the development and health of children, and where the scientific substantiation is valid only for children, *i.e.* the scientific substantiation should result from studies conducted with children; b) those used on products intended exclusively for children, like follow-on formulae and cereal-based baby foods.

Obtaining authorization for health claims and their subsequent inclusion in a positive list is possible through two different authorization processes that are currently operational in parallel.

Process 1—The Authorization Procedure for Nutrient-Function Claims that were Submitted for Approval by January 2008

The Regulation established an authorization procedure for nutrient-function claims, whereby the Member States had to send to the European Commission, before the end of January 2008, their national lists of proposed health claims. These lists included the proposed conditions of use for each claim, the proposed wordings and lists of scientific references substantiating the claims. The Commission compiled these national lists and sent them to the European Food Safety Authority (EFSA) for a scientific evaluation, before establishing a Community list of permitted health claims. The Regulation clarifies that until this list is established, claims submitted for approval through this procedure will be allowed to remain on the market until a final decision is adopted on them.

The Commission was probably expecting a few hundred health claims to be tabled for adoption. However, the twenty-seven EU Member States submitted a total of 43,420. The process for collecting these claims differed from one country to another. For example,

one Member State submitted more than 10,000 claims, which had been proposed by its national food industry, whereas another Member State submitted only nine, which were the only ones that had officially been approved in the past by the national authorities. However, a considerable number of the claims submitted were essentially duplicates, as the same claims were often submitted by the same applicants in the different Member States where the claims were being used. With some time and effort, the Commission was able to reduce the list of proposed claims to 4,637, by removing duplicates and deleting entries that were incomplete or inappropriate.

EFSA is now evaluating the scientific basis for these 4,637 proposed health claims. Because the number of claims to be assessed remains quite high, EFSA will publish the results of its assessment in several batches. To date, only two batches have been published, covering fewer than 1,000 claims (Table 2). However, they indicate what should be expected from future evaluations, and what types of claims are likely to be approved or rejected in the EU. Already, impact on the market is becoming clear, particularly for sectors such as probiotics, antioxidants and botanicals. The first EFSA evaluations were mostly negative (66% for the first batch, 98% for the second) with rejections of most claims submitted on probiotic bacteria/microorganisms, antioxidants, plant extracts/botanicals, and claims on carbohydrate glycemic index/response. The higher rate of positive evaluations in the first batch can be explained by the fact that these correspond essentially to claims for vitamins and minerals for which there has long been scientific consensus.

Table 2. EFSA evaluations of nutrient-function claims (to date)—Article 13.3.

	Batch number	
	1	2
Publication date	October 1, 2009	February 25, 2010
Number of claims processed	523	416
Substances involved	Vitamins & minerals Dietary fibers Fatty acids Probiotic bacteria Other (chewing gum, plant extracts, etc.)	Antioxidants Carbohydrates glycemic index/Response Probiotics/microorganisms Botanicals and herbals Substances linked to joints health Other (honey, stearic acid, guar gum, *etc*.)
Positive evaluations	33%	2%
Negative evaluations	66%	98%

Approximately 3,250 additional nutrient-function claims await evaluation. Based on these EFSA evaluations, the EU regulator will then need to officially approve or reject the proposed claims, and include the approved ones in a positive list. Due to the considerable number that remains to be evaluated, the authorization process is expected to take until 2012. Although it is difficult to predict how many claims are likely to be approved in the end, one can guess that, based on the current trend of the EFSA evaluations, the final list of permitted claims will comprise a few hundred rather than a few thousand. And some very popular claims currently on markets worldwide may not be included.

Process 2—The Authorization Procedures for Nutrient-Function Claims Submitted for Approval after January 2008, for Reduction of Disease-Risk Claims and for Claims referring to Children's Development and Health.

In addition to the authorization procedure described above, the Regulation provides the possibility of obtaining authorizations for other types of health claims on the basis of individual application dossiers, *i.e.* reduction of disease-risk claims and claims referring to children's development and health. This applies also to "new" nutrient-function claims that were not submitted via a Member State before the end of January 2008. These application dossiers will also be scientifically evaluated by EFSA, and the claims will subsequently be approved or rejected by the European Commission. Approximately 250 individual claim-application dossiers have been submitted so far (some of which have been withdrawn), of which eleven have been officially authorized (Tables 3a, b) and forty-five officially rejected. Approximately 170 additional applications currently await evaluation.

As is illustrated in Table 4, around 80% of the individual claim applications assessed by EFSA received a negative opinion. This confirms the strict evaluation standards being applied by EFSA to evaluate the scientific evidence being put forward by applicants to substantiate their proposed claims.

The outcomes so far of the two authorization processes mentioned above clearly illustrate that the scientific bases being tabled by applicants to justify their claims are not meeting the standards being applied by the EFSA to evaluate their quality. As EFSA is evaluating the evidence submitted in both processes using the same criteria, it is not surprising that recurring reasons are being given for negative evaluations in both processes. These are, essentially:

- weakness of the scientific evidence submitted, and
- insufficient characterization of the substance for which the claim is made.

A number of proposed claims were made for broad categories of foods ("dairy products," "fruits," "fruits and vegetables") which typically include many products with a range of nutritional compositions and impacts on health. For example, EFSA considers that it cannot approve claims relating to "dairy products" because this category includes many types of foods, from Camembert cheese to fat-free yoghurts. Also, the studies submitted were focused only on certain dairy products. In EFSA's terms, the substance—"dairy products"—is not sufficiently characterized to allow validation of the scientific evidence submitted.

TABLE 3A. HEALTH CLAIMS OFFICIALLY AUTHORIZED (TO JUNE 2010), BASED ON INDIVIDUAL APPLICATION DOSSIERS—ARTICLES 13.5 AND 14.

Health claims referring to the reduction of a risk factor in the development of a disease [Article 14(1)(a)]

Nutrient/substance/food	Claim	Conditions/restrictions of use
Plant sterols/plant stanol esters	Plant sterols and plant stanol esters have been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease.	Information to the consumer that the beneficial effect is obtained with a daily intake of 1.5–2.4 g plant sterols/stanols. Reference to the magnitude of the effect may be made only for foods within the following categories: yellow fat spreads, dairy products, mayonnaise and salad dressings. When referring to the magnitude of the effect, the entire range "7 to 10 %" and the duration to obtain the effect "in 2 to 3 weeks" must be communicated to the consumer.
Plant sterols: sterols extracted from plants, free or esterified with food-grade fatty acids.	Plant sterols have been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease.	Information to the consumer that the beneficial effect is obtained with a daily intake of at least 2 g plant sterols. Information to the consumer that the beneficial effect is obtained with a daily intake of 1.5–2.4 g plant sterols. Reference to the magnitude of the effect may be made only for foods within the following categories: yellow fat spreads, dairy products, mayonnaise and salad dressings. When referring to the magnitude of the effect, the entire range "7 to 10%" and the duration to obtain the effect "in 2 to 3 weeks" must be communicated to the consumer.
Plant stanol esters	Plant stanol esters have been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease.	Information to the consumer that the beneficial effect is obtained with a daily intake of 1.5–2.4 g plant stanols. Reference to the magnitude of the effect may be made only for foods within the following categories: yellow fat spreads, dairy products, mayonnaise and salad dressings. When referring to the magnitude of the effect, the entire range "7 to 10 %" and the duration to obtain the effect "in 2 to 3 weeks" must be communicated to the consumer.
Chewing gum sweetened with 100% xylitol	Chewing gum sweetened with 100% xylitol has been shown to reduce dental plaque. High content/level of dental plaque is a risk factor in the development of caries in children.	Information to the consumer that the beneficial effect is obtained with a consumption of 2–3g of chewing gum sweetened with 100% xylitol at least three times per day after the meals.

Table 3b. More health claims officially authorized (to June 2010), based on individual application dossiers—Articles 13.5 and 14.

Health claims referring to children's development and health [Article 14(1)(b)]		
Nutrient/substance/food	**Claim**	**Conditions/restrictions of use**
α-linolenic acid (ALA) & linoleic acid (LA), essential fatty acids	Essential fatty acids are needed for normal growth and development of children.	Information to the consumer that the beneficial effect is obtained with a daily intake of 2 g of α-linolenic acid (ALA) and a daily intake of 10 g of linoleic acid (LA).
Calcium and vitamin D	Calcium and vitamin D are needed for normal growth and development of bone in children.	The claim can be used only for food which is at least a source of calcium and vitamin D as referred to in the claim SOURCE OF [NAME OF VITAMIN(S)] AND/OR [NAME OF MINERAL(S)] as listed in the Annex to Regulation 1924/2006.
Calcium	Calcium is needed for normal growth and development of bone in children.	The claim can be used only for food which is at least a source of calcium as referred to in the claim SOURCE OF [NAME OF VITAMIN/S] AND/OR [NAME OF MINERAL/S] as listed in the Annex to Regulation 1924/2006.
Vitamin D	Vitamin D is needed for normal growth and development of bone in children.	The claim can be used only for food which is at least a source of vitamin D as referred to in the claim SOURCE OF [NAME OF VITAMIN/S] AND/OR [NAME OF MINERAL/S] as listed in the Annex to Regulation 1924/2006.
Phosphorus	Phosphorus is needed for the normal growth and development of bone in children.	The claim can be used only for food which is at least a source of phosphorus as referred to in the claim SOURCE OF [NAME OF VITAMIN/S] AND/OR [NAME OF MINERAL/S] as listed in the Annex to Regulation 1924/2006.
Protein	Protein is needed for normal growth and development of bone in children.	The claim can be used only for food which is at least a source of protein as referred to in the claim SOURCE OF PROTEIN as listed in the Annex to Regulation 1924/2006.
Health claims based on newly developed scientific evidence [Article 13(5)]		
Water-soluble tomato concentrate (WSTC I and II)	Water-soluble tomato concentrate (WSTC) I and II helps maintain normal platelet aggregation, which contributes to healthy blood flow.	Information to the consumer that the beneficial effect is obtained with a daily consumption of 3 g WSTC I or 150 mg WSTC II in up to 250 mL of either fruit juices, flavored drinks or yogurt drinks (unless heavily pasteurized).

Table 4. EFSA evaluations of individual claims application dossiers (to June 2010).

Type of claim	Favorable	Favorable with limited conditions	Issues raised	Total
New functional claims (Article 13.5)	1	–	21	22
Reduction of disease risk claims (Article 14)	5	–	10	15
Claims referring to children's development and health (Article 14)	6	6	36	48
Total	12 (14%)	6 (7%)	67 (79%)	85 (100%)

Another key lesson learned in recent years is that companies tend to be overoptimistic about the quality of their research and the strength of their application dossiers. Most applications were negatively evaluated by EFSA because the scientific evidence submitted did not include human-intervention studies. It was hoped by many that EFSA could be persuaded to, in certain cases, refer to a grading of the available evidence to evaluate whether the data submitted supported the claims—"convincingly," "possibly," "probably," or "insufficiently"—but EFSA refuses to be persuaded and strictly applies its gold standard: human-intervention studies are a must to obtain a positive evaluation. Commission Regulation (EC) No 353/2008 clearly lays down, hierarchically, the levels of data that should ideally be included in an application dossier:

- Human data
  - — Human-intervention studies, randomized controlled studies, other randomized studies (non-controlled), controlled (non-randomized) studies, other intervention studies.
  - — Human observational studies, cohort studies, case-control studies, cross-sectional studies, other observational studies such as case reports.
  - — Other human studies dealing with the mechanisms by which the food could be responsible for the claimed effect, including the studies on bioavailability.
- Non-human data
  - — Animal data including studies of aspects related to absorption, distribution, metabolism, excretion of the food, mechanistic studies, and other studies.
  - — *Ex vivo* or *in vitro* data based on either human or animal biological samples related to mechanisms of action by which the food could be responsible for the claimed effect, and other non-human studies.

However, it is clear now that most of the studies mentioned above will be useful in an application dossier only if submitted as supporting evidence for well designed human-intervention studies, without which there is very little chance of success. There is no grading of the available evidence.

A good illustration of the strict evaluation criteria being used by EFSA is provided by its opinion on an application for a reduction-of-disease-risk claim on cranberry juice (European Food Safety Authority, 2009a). The proposed claim was: "[the product] helps reduce the risk of urinary tract infection in women by inhibiting the adhesion of certain bacteria in the urinary tract". EFSA concluded that the evidence submitted by the applicant was insufficient to establish a cause-effect relationship between the consumption of the product in question and the claimed effect. Although the application dossier contained a number of human studies, they were dismissed by EFSA for the following reasons:

- Six human studies were judged of limited relevance because the claim targeted healthy women (aged 16 and above), whereas the studies were carried out on unhealthy subjects (patients suffering from neurogenic bladder) and children.
- In an additional human study the daily dose of the active substance consumed was approximately six times higher than the use levels proposed for the claim.
- Although five other human-intervention studies were considered pertinent to the claimed effect, EFSA criticized the two key randomized, placebo-controlled trials. The first one for its short duration and lack of statistical power, the second one for the lack of adequate randomization and high drop-out rate.
- The other three pertinent human studies were also criticized by EFSA due to significant limitations, including the use of different cranberry formulations (matrixes) from that in the application, poor study design, as well as high drop-out rates in some of the studies.
- It is also noteworthy that EFSA did not consider meta-analyses and previous opinions by national food-safety authorities (on the same/similar claim) as relevant evidence.

Interestingly, although EFSA recognized a proven *in vitro* inhibitory effect on adhesion of *E. coli* to mucosal cells, it concluded nevertheless that the evidence submitted did not establish that the anti-adherence effects shown *in vitro* are predictive of the occurrence of a clinically relevant bacterial anti-adherence effect within the urinary tract under the conditions of use proposed for the claim. This claim was rejected by the European Commission in November 2009 (Commission Regulation (EC) No 1167/2009).

Based on the EFSA evaluations so far, as well as on EFSA's guidance for the preparation of claim-application dossiers (European Food Safety Authority, 2007, 2009b), one can list key criteria that potential applicants should use to assess the strength of their application dossier (EAS, 2010):

- Is the food or food constituent sufficiently characterized to the extent that it can be verified that the food or food constituent is the subject of the studies performed and therefore responsible for the claimed effect?

- Are the studies carried out with the food or food constituent that is the subject of the claimed effect?
- Are human studies available with appropriate outcome measures in relation to the claimed effect?
- Are the conditions under which the food or food constituent is tested in the human studies representative for the proposed conditions of use for the claim (level of intake, pattern of consumption, *etc*.)?
- Are the human studies or study group representative of the proposed target of the claim? Can the study results be extrapolated to the target population of the claim?
- Is a rationale available to explain how studies in animals or *in vitro* support the claimed effect in humans?

However, these criteria were "officially" disclosed only after a considerable number of applications had already been submitted (Processes 1 and 2 above). EFSA's evaluation criteria became clearer after its first detailed opinions had been published. For example, the level of characterization that EFSA requires for microorganisms (probiotics) was clearly stipulated only after EFSA had already evaluated (negatively) a considerable number of claims on probiotics.

Needless to say, the extremely high rate of negative claim evaluations by EFSA, and the expected subsequent rejection by the European Commission of the vast majority of the claims submitted for approval, were not greeted with joy by the food industry in the EU. Consequences for the food market will be considerable, particularly in the area of functional foods, food supplements and botanicals. Based on the EFSA evaluations so far, it is fair to say that the mass rejections of most claims on antioxidants, probiotic bacteria/microorganisms, botanicals/plant extracts, joint health and glycemic index/response are likely to lead to serious difficulties for those markets. It is essential that makers of functional foods and supplements be able to communicate the beneficial effects of their products on the body or health. Not being able to do so means the end of such product concepts. It could also mean that fewer funds will be available for research in those areas, particularly if companies feel that regulators are unlikely to allow any commercial communications for those substances. These EFSA evaluations could, therefore, be the beginning of the end for certain functional-food markets in the EU.

Certain Foods will be Prohibited from Claims

The first principle established by the Regulation is that all claims must be approved at the EU level. However obtaining the authorization for a particular health claim on a specific substance will not be enough to ensure its use with the food formulation or product concept of choice. A second obstacle needs to be taken into account to determine use of the permitted claim on a specific product: the nutrient profile.

Nutrient Profiling

When drafting its proposal for a regulation on nutrition and health claims, the European Commission feared that indiscriminate use of claims by food manufacturers could lead to

overconsumption of "certain" food products, which could potentially contribute to the rising levels of obesity and diet-related diseases. It was feared also that the use of claims on such less nutritionally balanced products could potentially "mislead consumers when trying to make healthy choices in the context of a balanced diet" (Regulation 1924/2006, Whereas 11). Therefore, as part of the objective of ensuring "a high level of protection for consumers," and with the aim of avoiding the overconsumption of "certain" foods and consumer confusion as to what a balanced diet really is, the EU regulators introduced the concept of nutrient profiles in the claims Regulation. Nutrient profiling will be used as a tool to determine which foods will be "healthy enough" for claims to be made and which foods will be considered "unhealthy" and therefore unsuitable for claims.

This concept has been one of the most controversial provisions of the Regulation, leading to numerous scientific debates, political negotiations and intense lobbying by the food industry as well as by health and consumer non-governmental organizations. The main criticism raised by industry, as well as by a considerable number of nutritionists, against nutrient profiling is that it does not make much sense to classify individual foods as "healthy/good" or "unhealthy/bad." It is acknowledged that the relevant factor in terms of obesity and diet-related diseases is whether the range of foods that is consumed over a certain period of time is sufficiently varied and balanced. This argument was also stressed by EFSA itself, which recognized in its 2008 scientific opinion on the establishment of nutrient profiles that "there is an inherent difficulty in seeking to apply to individual food products nutrient-intake recommendations that are established for the overall diet" (European Food Safety Authority, 2008).

As was requested by the Regulation, the Commission asked EFSA for scientific advice on the development of nutrient profiles. However, the EFSA advice remained very general, consisting essentially of a list of possible options on how profiles could potentially be developed, indicating also the respective advantages and disadvantages of each option. As a consequence, the profiles are being developed mostly on the basis of political negotiations between the Commission and the Member-States experts, rather than on the basis of purely scientific arguments. This explains why the establishment of the profiles has been such a difficult task, and why the Commission was not able to meet the January 2009 deadline required by the Regulation to establish the profiles.

The Commission tabled a first proposal in June 2008, and various texts were then successively discussed until March 2009, at which time the process was put on hold when the political discussions reached a dramatic point: on the one hand, Member-State experts were seriously unhappy with the Commission's proposals and were making too many requests for exemptions for specific products—considered to be of national interest!—and, on the other hand, various services within the Commission itself were unhappy with the proposals being tabled by the service in charge of the negotiations, essentially for legal and economic reasons. So far, the Commission has not tabled any new proposals.

Although the process that will lead to the establishment of nutrient profiles in the EU is currently on hold, the proposals that have been discussed already give a good impression of what they will look like in the end. The Commission is focusing on three key nutrients: saturated fat, sodium and sugars. Different thresholds would be established

for these nutrients. The profiles would consist of generic thresholds for foods in general, expressed per 100 g or 100 mL, as well as specific thresholds for certain food categories that play important roles in the diet (*e.g.* dairy products, cereal products, meat products). Certain foods could be exempted from having to comply with the profiles, such as fruits and vegetables, food supplements, and sugar-free chewing gum. Products containing higher levels of saturated fat, sodium and sugars than the applicable thresholds would be restricted or prohibited from nutrition and/or health claims.

As was already mentioned, the development of the nutrient profiles has been essentially a political process with difficult negotiations on various points, including:

- What food categories should benefit from adapted thresholds?
- How should these categories be defined?
- What thresholds should apply to these categories?
- What foods should be exempted from the need for profiles?

As EFSA was not asked to develop a profiling system or to propose possible nutrient thresholds for different food categories, this is being done by the Commission and the Member-State experts. Inevitably, these discussions became very political with different thresholds being proposed by different Member States without any apparent scientific justification. For example, in the discussions on the threshold that should be set for sugar in the category "non-alcoholic beverages," some Member States insisted on a level of 5 g, another proposed 8 g, and a few suggested 10 g, without providing any explanations whatsoever to justify why 5, 8 or 10 g would be most appropriate.

It is clear that the food industry is not a strong supporter of nutrient profiling for many reasons, among which is the serious risk that nutrient profiling could hinder innovation—particularly in the area of product reformulations—as it will represent a clear disincentive for the development of healthier products within certain food categories. It will simply not be possible to make any claims at all (not even "reduction" claims) due to the strict thresholds that are being considered. However, although many legal, technical and scientific reasons are being put forward by industry to oppose nutrient profiling, one of the key reasons explaining this opposition has nothing to do with the nutrition and health claims. The main fear is that if a European, harmonized nutrient-profiling system, which would be used to identify "healthy" and "unhealthy" foods, were to be agreed by the Commission and the twenty-seven Member States, it would then be very difficult to resist calls for further restrictions and discriminations against certain food products. Already a number of national and EU-wide campaigns are calling for restrictions, such as color-coded nutrition labelling ("traffic lights"), advertising restrictions and food taxation, that would be based on the future EU profiles.

Conclusion

Although not all of the key provisions of the EU claims Regulation have been implemented yet, it is already possible to see its future impact on the EU market for functional foods, as well as on other related areas of activity such as food and nutrition research. It

is now clear that the full implementation of the claims Regulation will lead to a drastic reduction in the number of nutrition and health claims being used on the EU market. As a result, and taking into account the recent evaluations by EFSA of some of the claim-applications dossiers, it is fair to say that a number of product concepts, some of which have been successful worldwide in past years, will be facing serious challenges. Certain segments of the functional-foods market will be forced to reconsider their product concepts, particularly in the areas of antioxidants, probiotics, low glycemic-index products, and herbal products. The implementation of the Regulation will also lead to considerably less flexibility for food manufacturers and marketers to communicate to consumers the beneficial nutritional and health properties of certain products. Such communications will also be increasingly more standardized and repetitive as companies will need to keep their messages as similar as possible to the approved claims which, in addition, are not necessarily consumer-friendly.

Science will be the determining factor for success. The quality of the scientific evidence submitted to substantiate an application for the authorization of a health claim will be the essential element that will determine whether the application—and the product concept that would use the claim in question—has any chance of being approved. However, it must be stressed that it is EFSA, and EFSA alone, that will ultimately decide whether the data submitted really establish a cause-effect relationship between the substance or food and the claimed benefit. This should be taken into account if one intends to carry out studies to demonstrate the beneficial properties of certain substances. It would be worthwhile taking a closer look at the criteria being applied by EFSA to evaluate claim-application files, particularly with regard to the importance given to well designed human-intervention studies. Finally, the potential future implementation of nutrient profiles is likely to have a devastating effect on a number of functional foods as associated nutrition and/or health claims will be prohibited. This will also have very concrete implications on funding opportunities for research, as no company will want to invest in research if none of its current and future products will be the subject of claims due to their nutritional composition. And, worryingly for industry, when such a tool that will help discriminate between "healthy" and "unhealthy" foods will be agreed at the EU level, the temptation for national and European regulators to use it for other restrictive purposes will be very real.

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He began his career at a Belgian public affairs/public relations consultancy, providing services to companies in various sectors including chemicals, food and biotechnology. He joined EAS in 2004, since when he has focused on food law, with particular reference to food labeling, claims, and nutrition and health policy.

Mr. da Silva provides companies with regulatory and strategic advice for the marketing of their products in Europe. He also advises international food companies on global regulatory and policy trends in the area of health and nutrition. He is a member of the European Food Law Association, has spoken at numerous international conferences and has authored several publications on food issues.

He has a degree in political science, a diploma in business administration as well as a master of arts in European political and administrative studies from the College of Europe.

Regulatory Framework for Food Health Claims

Q&A

Moderator: Carl L. Keen
University of California
Davis, California

Carl Keen: One of the things that was stressed in the latest IOM[1] biomarker report is the suggestion that all of the food claims today should be at about the same level of a standard pharmaceutical. Miguel, you touched upon this. The cost of that may be prohibitive. Is it reasonable to ask that of the food industry or do we have to find some way to tweak it? Is there a light at the end of the tunnel?

Barbara Schneeman: FDA's goal with the biomarker report had been to identify a better process to develop validated biomarkers. For diseases for which we don't have valid biomarkers—many of the cancers for example—the only clinical studies that are possible to ascertain decreased risk are long term. With suitable biomarkers that are surrogate endpoints of disease, shorter-term studies are possible. So the recommendations were a little bit confusing based on what FDA had hoped to get out of that report, but we are gleaning, we are looking through it and hoping that the scientific community may be able to identify ways that they can take biomarkers that are currently in use and validate them as surrogate endpoints or develop new biomarkers that might be used in that capacity.

Roger Wasson (Wasson and Associates): You've talked about the regulations and about the rating systems and the labels, but I wondered if you would each go outside your own area and comment about advertising, because even some of the groups that you have regulated are able to come together and say something about "heart healthy" or omega-3 or something else, on the Web, in advertising and public relations—technically disconnected from the label itself—and advance a conversation on some of these issues that are quasi-claim making, but are not necessarily clearly regulated.

[1]Institute of Medicine.

Joanne Lupton: Actually, I think it's the opposite right now. I'm actually surprised how the Federal Trade Commission, the FTC, is coming after people for advertising and Websites. If it's on the label and it's on the Website, it counts the same, and FDA can go after those individuals. That's coming under more scrutiny rather than less.

Schneeman: As Joanne mentioned, we have a guidance document on our Website pointing out when material on the Web can be considered labeling. For example, if a Website URL is provided on a food label then we can review anything on that Website as labeling. The most famous instance in the United States was the cherry juice case about cancer. We can also look at advertising as a way of understanding the manufacturer's intended use of the product. So, it's not that we are regulating the advertising, but if it gives us information in a situation in which we might need to take enforcement action, we can use it to help inform our process. As a segue from your question, FTC was instructed by Congress to convene a work group from CDC, FDA and USDA to develop a report on criteria for marketing foods to children and, in December of 2009, a workshop was held in Washington, DC, with a preliminary discussion of the criteria that the work group had been considering. FTC will publish a *Federal Register* notice with the proposed criteria, with the goal of receiving comment before it actually sends its report to Congress, which is due in July 2010. I know that this has been an area of interest in Europe as well. Children are a vulnerable group. Should we be taking more steps to manage what is marketed and promoted to children in terms of food choice?

Miguel da Silva: And, in the case of Europe, the claims regulation applies to all commercial communications, including Websites and advertising, as I said. For example, last year, I think it was the ASA, the Advertising Standards Authority, of the United Kingdom prohibited ads on television for some food companies because they were not complying with the claims regulation. So, that is already having an effect on advertising *per se* in the UK.

Rickey Yada (University of Guelph): We often talk about science-based policy. Should we be looking at policy-based science now?

Lupton: Actually there is definitely a role for both and what you heard from the panel here is how we use scientific evidence to support the development of a policy, specifically around claims. But, where we probably need the research to go in the other direction, keep in mind that the intent with nutrition labeling is to help consumers make better food choices, and research can be done to help us figure out whether we are achieving that goal. Are there ways that we should be improving our labeling? Certainly in the front-of-pack labeling arena, there is a lot of speculation that this is going to be a tool that helps consumers, particularly some consumer groups that aren't currently using Nutrition Facts. Research can help us understand behavior, so, as the policy evolves, you need research to understand the impact the policy is having.

da Silva: In Europe, we have clearer separation between the risk assessors and the risk managers. That's why, in my presentation, I explained that the European Food Safety Authority looks at the science, but it's really the Commission and the Member States that authorize or decline the claim. Now, they tend to follow EFSA advice, so if EFSA says that the claim is scientifically justified then the Commission and regulators will approve it. However, what we are seeing also is, in the case of nutrient profiles, EFSA gave an opinion on how profiles could be established, but now it's pure politics. No science is involved.

Amanda Martin (University of Minnesota): Even if you ban claims, you're not banning the food. Will it actually affect consumer choice? By taking away the "probiotic" claim will yogurt consumption rates go down?

da Silva: Yes, that is a problem. For a functional food, if they cannot make a claim, who will pay more to buy it? And that's particularly the case for antioxidants, for probiotics and for all food supplements. If you have a pill, but the label doesn't tell you what it does for you, then why would you buy it? So, it really has a serious impact. Of course, even if a claim is prohibited, your product can remain on the market, but, if you have developed it as a functional food delivering a health benefit, you will want to communicate that to the consumer. When claims for probiotics were being rejected, Dannon withdrew their dossier on Activia, so as not to have a public rejection on their dossier. They have stopped their claims, but are keeping the products on supermarket shelves because people, having been "educated," are familiar with the media messages. However, I wonder what will be the situation in a number of years, because to educate people you need to educate constantly as the consumer population evolves.

Schneeman: You raised an interesting point and it can play out in different ways. First of all, yogurt can be part of a healthful diet. If you are interested in consuming dairy products, that is certainly one way to do it. It's not surprising that consumers tend to think positive of a product like that. A company that chooses to go down that path has to weigh the risks to them. Because, on the one hand, they do gain a halo if it looks like their product has a health benefit. But then, having a negative message come out about that product could tarnish that halo. If consumers already believe it and let's say it's a placebo effect, then the tarnish may not impact them, but, in some cases, it can have a much more negative effect: why would I trust a company that has said something not supported by the science? It gets complicated in terms of the messaging and how consumers perceive it.

Alimentary Pharmabiotics: Common Ground for Academia with the Food and Pharmaceutical Industries

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"…remember that words are signals, counters. They are not immortal."
—Brian Friel (*Translations*)

The changing landscape for research and development in the pharmaceutical and food industries, coupled with changing societal attitudes and requirements, creates new challenges and opportunities for industry-academe collaborations. The case of alimentary pharmabiotics is a representative niche area with opportunities for both industrial sectors. Although manipulation of the gut microbiota in the treatment and prevention of several disorders has become a plausible strategy, a more intriguing prospect is the potential to "mine" diet-host-microbe interactions for functional food ingredients and for novel discovery.

Changing Landscapes

As the pharmaceutical industry faces increasing challenges in drug discovery, new models for research and development (R&D) are called for (Crommelin *et al.,* 2010; Shah *et al.*, 2010). The landscape today is dominated by declining output of new molecular entities, more outsourcing of R&D, partnerships and alliances, increasing emphasis on biologics over small molecules and a commercial imperative for agility and flexibility. At the same time, advances in understanding major disease processes promise to open the way for definition of subsets of patients at a molecular level, with genotyping replacing historic approaches to phenotyping diseases. This will tend to fragment the industry's mass markets into genotype segments and will undermine the old blockbuster model ("one-size-fits-all drug") with a new era of personalized medicine.

The degree to which this brave new world will prevail is likely to vary for different diseases, and will be influenced by societal attitudes toward the treatment and prevention of disease, in particular, depending on whether a pharmacological or non-pharmacological approach is favored (Crommelin *et al.* 2010). The pharma sector is likely to remain dominant in innovation and may engage with academia in pursuit of solutions for chronic inflammatory, infectious and neoplastic diseases. For other disorders, particularly where alternatives to drug treatment are desired, small companies, academia and publicly funded institutions are likely to take a leading position with declining involvement of big pharma. Examples of the latter may include the exploration of functional-food ingredients or the pursuit of remedies for heterogeneous "functional" disorders and for those euphemistically referred to as "lifestyle" disorders (Crommelin *et al.* 2010).

Against these changing scenarios, opportunities for the food industry, especially in the functional-food business, must be considered in light of greater regulatory constraints, more stringent requirements for claims on food products, and a modern society that is risk averse. Thus, the distinction between a functional-food ingredient and a drug becomes blurred. Furthermore, pressure to control prices and focus on niche markets will affect both the food and pharma industries.

Opportunities for industry-academe interactions in both the food and pharma sectors will flourish, provided an entrepreneurial approach to science is encouraged, and where academic institutions provide for greater flexibility and agility in adapting to change. The case of alimentary pharmabiotics, as an example of a common ground for the food and pharmaceutical industries to explore in collaboration with academia, is summarized below.

Alimentary Pharmabiotics

Despite major technologic and conceptual advances in biology, new drug development in gastroenterology appears to be in decline (Parsons and Garner, 1995; Caskey, 2007). While large fortunes have been expended by the pharmaceutical industry in synthetic-drug development, it is noteworthy that about half of the drugs approved by the Food and Drug Administration (FDA) in the United States in the past twenty-five years have been derived from natural living material in the wider environment (Newman and Cragg, 2007; Bernstein and Ludwig, 2008). Therefore, it seems logical and timely that the inner microenvironment of the alimentary tract might be another rich repository from which functional-food ingredients and new drugs can be mined (Shanahan *et al.*, 2009; Shanahan, 2010).

An alimentary "pharmabiotic" is the name that we have given to products derived from mining host-microbe interactions in the gut that have a proven health benefit. This encompassing neologism overcomes the limitations of restrictive definitions of probiotics, prebiotics, synbiotics and postbiotics. Thus, it embraces whole organisms, live or dead, components and metabolites thereof, and genetically modified organisms and the concept has the potential for translation to the marketplace by either the food or pharmaceutical industry. Representative examples of the potential for mining microbe-microbe interactions, host-microbe and diet-host-microbe interactions in the gut are summarized in Table 1.

Table 1. Opportunities for "mining" the gut microbiota for pharmabiotics.

Interaction	Pharmabiotic	Reference
Microbe-microbe	Exploration of bacteriocins against specific pathogens (*e.g. Clostridium difficile*)	Rea *et al.* (2007)
Host-microbe	Anti-inflammatory drugs from bacterial components or metabolites that modify mucosal inflammation (*e.g.* lipoteichoic acid, CpG DNA)	Grangette *et al.* (2005); Obermeier *et al.* (2003) Rachmilewitz *et al.* (2004)
Diet-host-microbe	Immunomodulatory drugs from bacterial cell-wall polysaccharides	Mazmanian *et al.* (2005, 2008)
	Analgesic activities (some but not all probiotics are beneficial in irritable bowel syndrome and visceral hyperalgesia)	Rousseaux *et al.* (2007)
	Manipulation of the microbiota may alter bioavailability of dietary calories	Bakhed *et al.* (2004)
	Interaction between the microbiota and dietary components may alter the composition of host adipose tissue.	Wall *et al.* (2009)

Whether pharmabiotics mined from the natural environment of the gut will be exploited by the food or the pharma sector will depend in part on whether a small molecular entity or a bacterial fragment is involved, the nature of the desired effect, and the clinical indication. The clearest delineation will be the treatment of established disease or biomarkers of early disease in the case of the pharmaceutical sector, whereas the food industry is more likely to focus on disease prevention as measured by reduction in a biomarker of risk. Opportunities for academic collaborations exist in both scenarios. To that end, academic research centres, such as the Alimentary Pharmabiotic Centre (http://www.ucc.ie/research/apc/), have espoused the virtues of hybrid science and hybrid scientists capable of working across the boundaries of traditional disciplines and at the food-pharma interface. These include scientists, clinicians, and clinician-scientists with the collective ability to bring scientific ideas from the laboratory through the clinic to the bedside and marketplace. Research in academic centers can be aligned to simultaneously suit the requirements of both the food and pharma industrial sectors while fostering an environment conducive to entrepreneurship and freshness of ideas. For those who doubt it can be done—it *can* be done because it *is* being done!

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Before returning to Ireland in 1993, he was associate professor of medicine with tenure at UCLA.

He has published over 300 peer-reviewed articles and several books. As well as being director of the APC, Dr. Shanahan is also a principal investigator in the Host Response core, with particular research interests in mucosal immunology, inflammatory bowel disease and most things that influence the human experience.

A National Network for Advanced Food and Materials

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I will discuss how we've tried to link food, health and agriculture in Canada, which has been a challenge. The Networks of Centers of Excellence (NCEs) was a program established by the Federal Government in 1989 with the goal of mobilizing Canada's research capability. The government realized that, because the country is so broad geographically, a mechanism was needed to link expertise and build critical mass in certain areas to "mobilize Canada's research talent in the academic, private and public sectors and apply it to developing the economy and improving the quality of life of Canadians." Funding comes from the federal granting agencies that are equivalent to the NIH and the NSF in the United States—the Canadian Institutes of Health Research and the Natural Sciences and Engineering Research Council—as well as from the Social Sciences and Humanities Research Council, and Industry Canada, which is a federal government department with the mandate of adding economic benefit to Canada.

The NCEs are now focused on four broad areas (Fig. 1). I contribute to the *Advanced Foods and Materials Network* (AFMNet) under the aegis of *Health, Human Development and Biotechnology.* Because of the success of those original networks, the federal government has launched other multidisciplinary, sector-driven programs with the underlying theme of doing transformative research (*e.g.* Fig. 2).

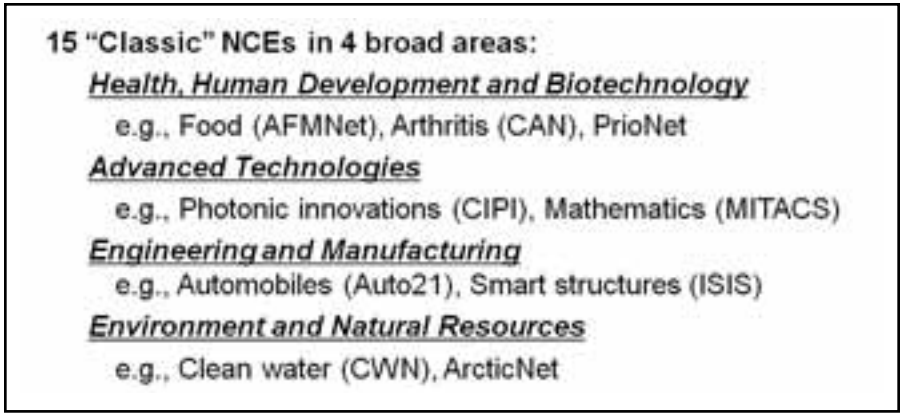

Figure 1. Networks of Centers of Excellence (NCEs):
Canada-wide networks linking universities, public and private sectors.

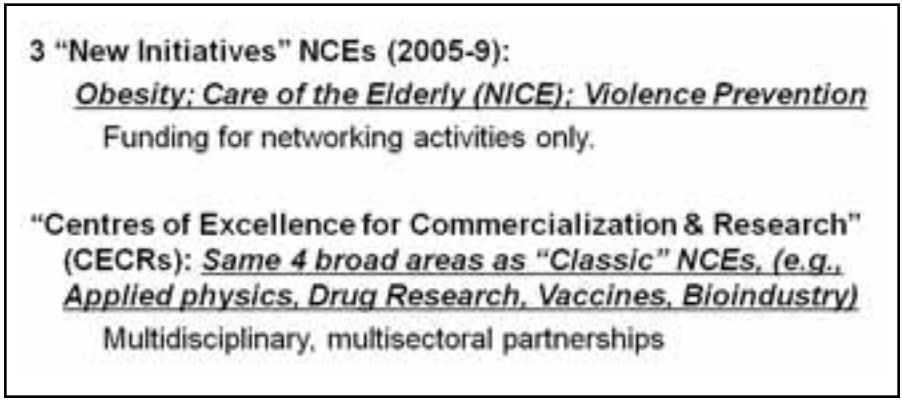

Figure 2. Other NCEs.

AFMNet

We submitted an application to the federal government for a multidisciplinary grant with the intent of bringing together researchers who traditionally hadn't worked together for a couple of days to develop a research project that was different from what we were already doing. Out of that process we received a million dollars to work on a project on biofilms, involving computer simulation, mathematical models, biochemistry, *etc*. This became one of the seeds for our network. Another contributory factor was a failed application; we applied to the provincial government for a broadly multidisciplinary grant, which, I believe, was ahead of its time. The application, written by food scientists and nutritionists, was reviewed by a medical panel whose view of food was simply something that you eat three times a day to satisfy requirements. At that time, there was a call for proposals by the

NCEs to build a program in food and health. Food was becoming increasingly important for the agricultural community in terms of how to add value; there was a surge of interest in functional foods and nutraceuticals; there was also a call for proposals involving social scientists. Our timing was good.

Also at that time, I was fortunate to sit on a Royal Society panel that looked at food biotechnology in Canada, the only food scientist on the panel of twelve, comprising ethicists, lawyers and ecologists. From that experience, I gained an appreciation of the importance of consumer and ethical issues, and the relevance of social science.

We submitted a successful application and began work in 2003. Networks of Centers of Excellence have a defined maximum lifetime of 14 years. We are in the process of finishing up our first 7 years and are applying for renewal. We get $5.6 million[1] a year from the program, which in some countries isn't a lot, but it helps leverage money, one of the intents of the network. It links academia, government, industry and not-for-profit organizations (Fig. 3). Seventy researchers are involved, at twenty-two Canadian universities. Our big claim to fame are the people involved, what we call "HQP" (highly qualified personnel), which includes students—undergraduate and graduate—post-docs and technical staff. We support 100 to 150 people and have forty-four industry partners. We have about $3.5 million dollars in cash or in-kind contributions as matching funds with the $5.6 million. Our federal and provincial governments are involved, as I said, as are some not-for-profits, and some foreign organizations are also involved. The whole intent is to build critical mass in specific areas.

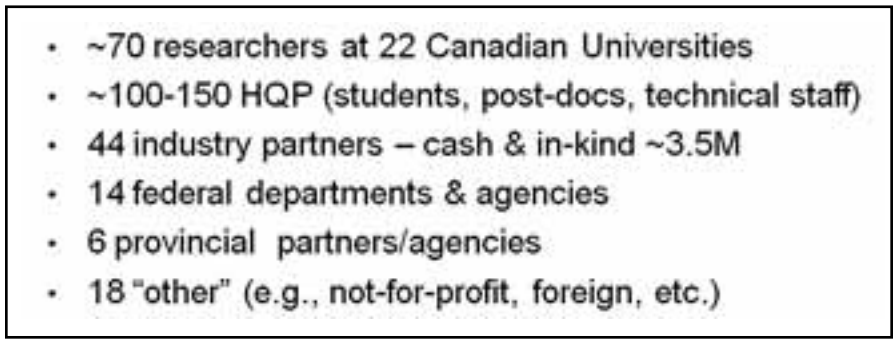

Figure 3. AFMNet NCE.

We started off with three interrelated topic areas, with the tag-line of "atom to application," *i.e.* using bench research to market commercially viable products or technologies (Fig. 4). We set up a topic specifically for social scientists—on regulation, policy and consumer health—with the rationale that if our products/technologies fail to meet regulatory approval then our research would have no tangible results. We engaged social scientists, ethicists and policy people from the outset in order to understand the challenges of getting over the regulatory hurdle.

[1]Dollar amounts in this chapter refer to Canadian currency.

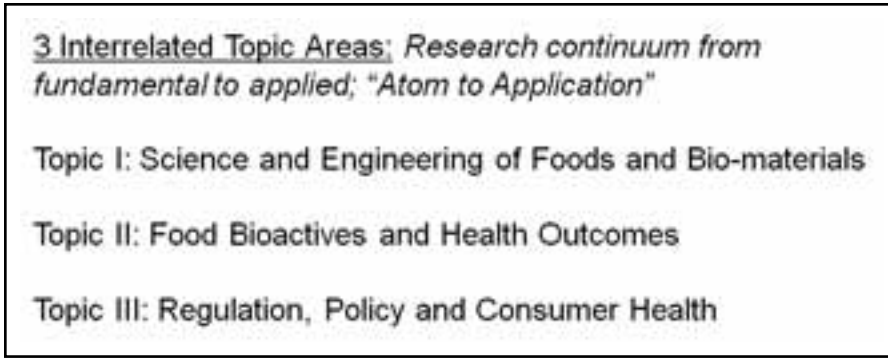

Figure 4. Original research programs.

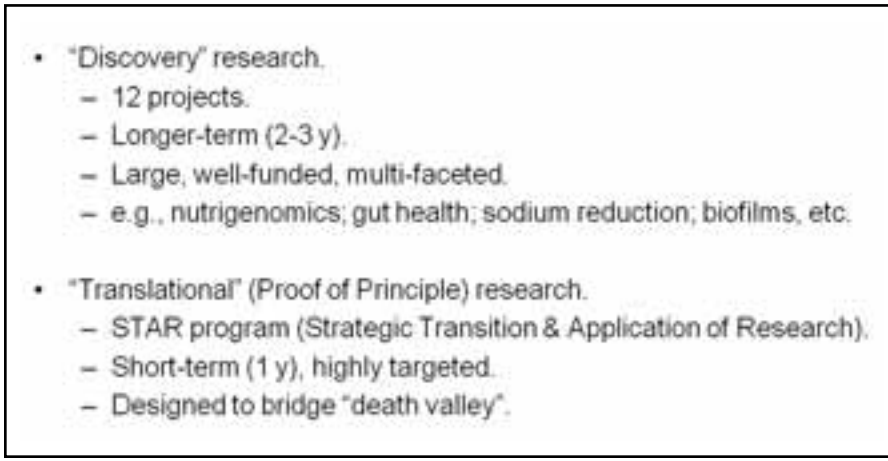

Figure 5. Research programs.

We have two major research programs (Fig. 5). "Discovery" projects have a 2–3 year lifetime, each with funding of ~$1 million dollars; current areas of focus are nutrigenomics, gut health, sodium reduction, biofilms, *etc*. The "Translational" program comprises Strategic Transition of Application of Research (STAR), which covers the proof-of-concept gap. Traditionally, funding agencies finance good fundamental science. On the other hand, industry often is looking for products or technologies to buy, whereas the developmental, proof-of-concept stage is unaddressed. It's a difficult area in Canada, as in other countries, for which we decided to provide funds.

Funding requirements are shown in Figure 6. Each project involves individuals from at least two disciplines—we encourage more—and two different organizations. Also required is a financial contribution from at least one partner who will be the receptor of the product potentially resulting for the research. As an example, a nutrigenomics project involving nano-encapsulation of folic acid fits these criteria: colleagues at seven institutions are collaborating, with funding from four partner companies.

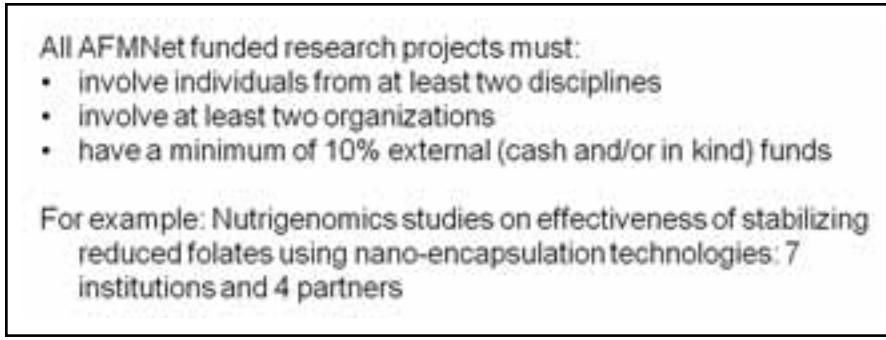

Figure 6. Funding requirements

Figure 7 lists some of our current projects, from polymorphisms to nutrigenomics, again biofilms, identification of bioactives, to sodium. Social scientists are involved in most of the projects, but we also have a specific social-science project, examining consumer issues. Led by a colleague of mine at the University of Guelph, Spencer Henson, they are monitoring 2,000 people in Guelph, who are demographically representative of the Canadian population. This consumer group is used to monitor progress and development in several of our projects. In the sodium project, for example, they were being used to determine what sort of platform consumers would be comfortable with.

Knowledge Transfer

Most university researchers are not interested in intellectual property (IP). They are passionate about doing research but, when it comes to protection of IP or commercialization issues, many will say, "Don't bother me with that. I need to get a paper out." Once a scientific discovery is announced at a conference or in a published article, it is publicly disclosed and companies will no longer be interested in developing it as a commercial entity. Another issue in Canada is that different universities have different IP policies. In some cases, the IP belongs to the university and sometimes the IP belongs to the individual researcher. At Guelph we just transitioned from university-owned to investigator-owned. We learned this lesson from the University of Waterloo, where the Blackberry originated. They returned IP back to their faculty, which has benefited the university in spades. Also, IP is valued differently by tenure and promotions committees at different institutions; how many published papers are equal to a patent?

One of the things we have done for our network is to introduce an educational program called R2B, *Research to Business*. A team of experts holds workshops—a venture capitalist, a scientist turned entrepreneur, an IP/patent lawyer, a financial expert, a person from the University-Industry Liaison Office, and a business development director—organizes workshops to educate our researchers and our HQP on these issues. Most interest is shown by our students and postdocs because they are more open to opportunities to take their research to the next step.

Do apolipoprotein E polymorphisms influence risk of cognitive decline by modulating omega-3 fatty acid metabolism?	Melanie Plourde Stephen Cunnane
Engineering the oil binding capacity and rheological properties of nanocrystalline fat networks structured using high shear fields under non-isothermal conditions	Gianfranco Mazzanti Alejandro Marangoni
Examining the impact of diet and the intestinal microbiome on gut health and general well-being	Brent Selinger Martin Kalmokoff
Nutrigenomic studies on the effectiveness of stabilizing reduced folates using nano-encapsulation technologies	David Kitts
Bacteria Biofilms and Foods: Nanotechnology-based strategies for the detection, characterization and remediation of bacterial contamination of foods and food processing surfaces	John Dutcher
Biopolymer based controlled release systems for biomedical applications	Wankei Wan
Creation of a new fish-peptide/n-3 PUFA-based functional food for the treatment of obesity and type 2 diabetes moving towards nutrigenomics-based personalized nutritional interventions	Andre Marette
Dietary peptide- and amino acid-based interventions to improve human gut health and immunity	Yoshinori Mine
Salt, science and society - a collaborative approach to salt reduction in processed foods	Derick Rousseau
The AFMNet Consumer Monitor: Tracking consumer attitudes towards new products for health and wellbeing in Canada	Spencer Henson
The traceability and authenticity of foods from analytical and consumer perspectives	Nicholas Low
Toronto nutrigenomics and health study	Ahmed El-Sohemy

Figure 7. Discovery projects—2009

STAR Program

The STAR program is basically proof-of-concept funding at up to $150,000 per year, to act as seed money (Fig. 8). Some of our STAR projects are listed in Figure 9. Bioactives and polysaccharides are going to be used as platforms, hopefully for nutrient delivery. Other projects cover shellfish poisoning on the east coast of Canada to value-added processing of wheat bran.

- Exploit research results and developments (IP) that promise to advance knowledge and technology transfer in emerging areas related to foods and bio–materials research by supporting Proof of Principle and Knowledge Mobilization projects which are of benefit and relevance to the social and economic health of Canada
- Funding up to $150,000/project (1 year) is available

Figure 8. Strategic Transition and Application of Research (STAR) Program.

Mine	Identification of bioactive peptides in egg yolk digests
Aluko	Antihypertensive properties of novel pea protein hydrolysate product
Nelson	Molecular and biological approaches for improved prediction and control of post harvest decay in pome fruit
Fudge	Manufacture of high performance renewable fibres from hagfish slime thread
Dutcher	Highly branched bacterial polysaccharides that assemble into nanospheres with unusual surface properties
Gill	Bacterial destruction of amnesic shellfish toxin
Guzman	Nutrigenomic approach to understanding cardioprotective mechanisms
Friel	Bioactives in human milk
Vasanthan	Value added processing of wheat bran

Figure 9. STAR Projects.

We also have a targeted program in which rapid infusions of $150,000 are available to quickly address emerging issues. Matching industrial funds of 20% are expected. The first request for proposals was for the development of a "DNA barcode" system for identification and authentication purposes. For example, work by the FDA and the Canadian Food Inspection Agency has revealed that 20% of tuna sold in Japanese restaurants is actually tilapia.

Business Model

Something that may be foreign to academics is our adoption of a business model, which is a combination of "blue sky"[2] and strategic research, using a highly consultative process to determine our theme areas. Early engagement of our public and policy researchers is critical. A request for quarterly reporting was very unpopular with researchers. However, we developed a relatively easy on-line system comprising ten questions, to provide a sense of how projects are progressing and, thus, facilitate success. And we can use it punitively, if we have to. We strongly encourage regular meetings with partners, with reports back to us. This system allows us to make early "go"/"no go" decisions. As in the business world, if failure is inevitable it is better to fail early because diligence is required on how we spend our money. Sustainability is also part of the business plan: can the network be maintained without the lifeline of funding from the government?

Governant Structure

I chair the research-management committee, which looks after the day to day operations (Fig. 10) and I report to a board of directors, comprising a variety of people including venture capitalists. An international scientific advisory board has been wonderful in providing insight into topical areas, including identification and authentication.

Figure 10. Network governance.

Improving Communications

Communications have been a subject for discussion at this conference. You can write an excellent grant to finance scientific research, but unless political elements are addressed, successful funding may be elusive. We took it upon ourselves to engage in an active outreach program through communication by producing a magazine, *ADVANCE*, which achieves several things. It engages journalism students in helping us to write about the research

[2]Research that has no immediately apparent commercial applications.

that we do as a network, and convey it to the public. I often say that one of my greatest challenges as a scientist is telling a class of grade-3 students what I do as a scientist, in language that they understand. Our intent with this magazine is similar. We send it to our members of parliament, our Senate members, our provincial partners, and all of our NGOs and researchers, with the intent of educating people on our activities, including helping our politicians understand what we are doing as a network.

We also work with a number of groups, including dieticians, the George Brown Chef School in Toronto, and healthcare providers. In conjunction with the George Brown School a 2–3-day workshop has been developed for family physicians and research chefs. The intent is for physicians to understand the components that contribute to food's nutritional quality and functionality because nutrition education is missing from many medical curricula.

We are working also with the Canadian Medical Association and have an insert in their magazine, *Health*. The mother of one of our scientists saw this magazine in her family doctor's office and reported, "Oh, I read about your research"; *Health* had replaced a 5-year-old *National Geographic* magazine in the waiting room. However, this was a tough nut to crack. The concept of using food as a preventative measure rather than as disease-treatment mechanism was something that the Canadian Medical Association apparently viewed as a challenge to future employment.

Figure 11. International Food Research Collaboration—objectives.

We launched the International Food Research Collaboration (Fig. 11) at the 2009 Institute of Food Technologists meeting. This fosters partnerships around the world, allowing access to information and sharing resources; it's a portal, providing access to the R&D community globally to find out who's doing what, strategic directions, potential synergies and, hopefully, reducing redundancies which otherwise are common. Wouldn't it be nice if we all collaborated, particularly in terms of research and training? Our initial members are in Australia, New Zealand, Greece and other countries in Europe, and Japan (Fig. 12). At a recent meeting in Paris, we talked to a number of potential partners and we are in discussions with a biocluster in Japan. We welcome other partners in this international endeavor.

Figure 12. International Food Research Collaboration—early members.

Strategic Directions

Food and health are our primary considerations as are nanoscale science and technology, traceability/authenticity, and the all-important regulatory aspects and consumer attitudes. Figure 13 illustrates how we view our organization, as a facilitator and a portal.

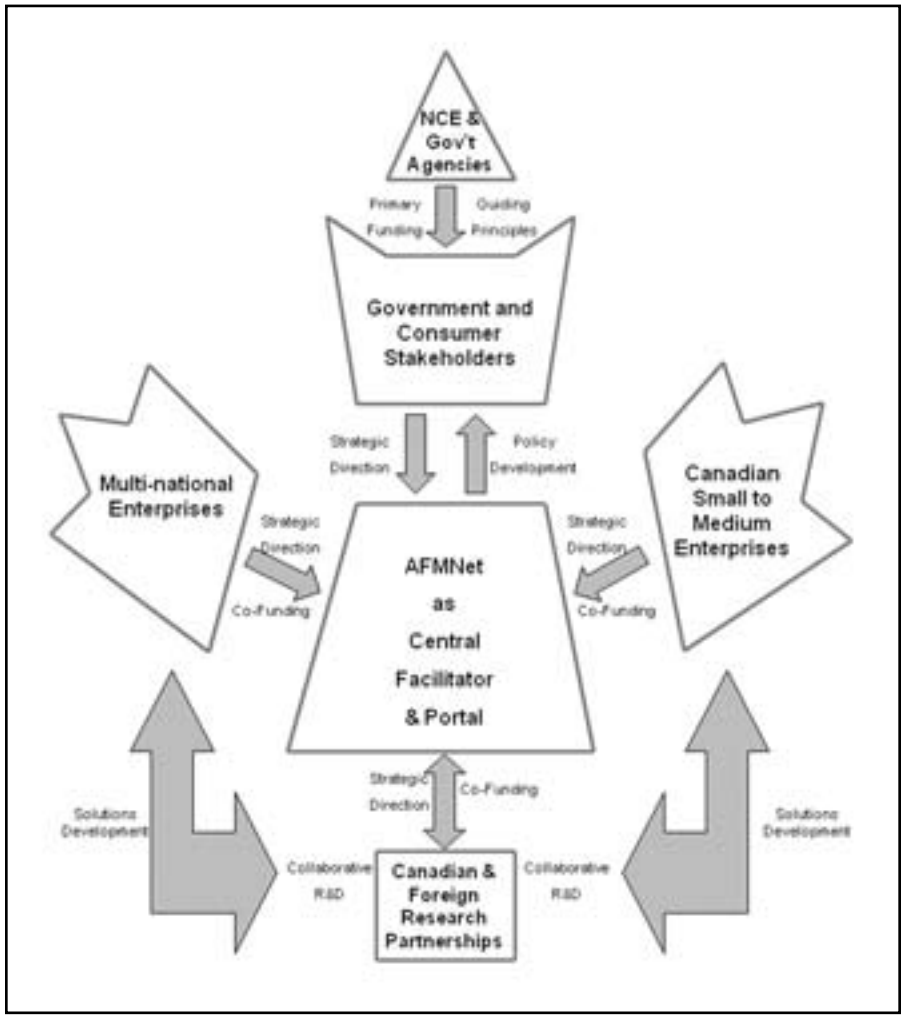

Figure 13. AFMNet's strategic role.

Rickey Yada received his PhD from the University of British Columbia in 1984. He has been a faculty member at the University of Guelph since that time, serving as chair of the Department of Food Science and as the assistant vice president for research in agri-food programs. He is a professor in the Department of Food Science, has a Canada Research Chair in food protein structure, and is the scientific director of the Advanced Foods and Materials Network.

Dr. Yada has served on numerous research awards panels and committees. Among other activities, he is on the Nanoscience Advisory Panel for IFT, is former president of the Canadian Institute of Food Science and Technology and the chair-elect for the Scientific Council of the International Union of Food Science and Technology. He was editor-in-chief of the *Food Research International Journal* from 1992 to 1998, is the North American editor for *Trends in Food Science and Technology* and serves on editorial boards for several other journals.

Yada has authored over 140 refereed publications and several book chapters. He is a fellow of the Canadian Institute of Food Science and Technology and of the International Academy of the International Union of Food Science and Technology.

Where Will Business Find the Next Best Food and Nutrition Innovations?

William Rosenzweig
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I am the managing director of Physic Ventures, one of a number of partners in a firm whose mission is to invest in keeping people healthy. I think we are the only venture-capital firm with a mission expressly focused on preventing disease and preventing the degradation of the environment rather than trying to fix something that is already broken. By no means will I be comprehensive in terms of where all nutrition innovations are coming from, but I want to frame how a venture-capital investor might think about this.

A venture-capital company manages other people's money. We have about $200 million under management, from a variety of institutional investors. Some are big pension funds. We have investment from two of the largest pension funds in the world, both of which are in California, as well as some of the world's largest corporations. We have, as major investors in our fund, two of the largest food and beverage companies in the world, with whom we have deep collaborative relationships in terms of using their expertise to gain insights into the market and into science and, in turn, they use our view of emerging technologies and entrepreneurship as a means of understanding market opportunities.

Physic Ventures

"Physic" comes from the Latin word meaning the science of healing. We got our name from the Chelsea Physic Garden in London, one of the most beautiful small protected gardens in the world which is now open to the public. It includes oncology, dermatology and rheumatology gardens, and is a beautiful reconnection to the roots of the science of food and medicine.

The Physic Ventures's thesis is built on the nexus of personal health and planetary health and the nexus of life science and lifestyle. Our investment landscape is rather unusual for a venture-capital firm because it includes sector-specific interests like information technology, biotechnology and semiconductors. Our linkage between personal health and planetary health also makes us unusual. One of our focus areas over the last couple of years has been the personalization of health, which brings in genomics, information technology and the management of very complex data relevant to the individual. Another of our themes is sustainable agriculture, as a subset of what we think of as sustainable living. We are interested in how technology comes to the consumer market. On our team is a person from Genentech, another from Cyron and a physicist and expert in nanotechnology from Lawrence Livermore National Lab. So we have expertise in the life sciences and material science, as well as in healthcare, healthcare delivery and consumer marketing.

Our insights for where innovations come from are gained in the midst of an ecosystem that includes industry, academia, government and others in the venture-capital community. At the heart of this are entrepreneurs; venture capitalists invest in entrepreneurs who have the magical transformative abilities to turn ideas into businesses using a combination of strategy, execution, persistence, patience, tenacity, vision of course, and—I have to say—luck. Any successful entrepreneur who doesn't admit that luck was involved is not providing full disclosure. But there are ways of increasing the chances of getting lucky, which is one of the functions of venture capitalists. They take a portfolio approach to investing. We see about a thousand investment opportunities a year in the "life science meets lifestyle" area. A lot of it is in the food and nutrition area, in which we make approximately four investments a year. Entrepreneurs should not be discouraged, but recognize that capital is constrained. Most people are very choosy about what they invest in, and venture-capitalist investors, in particular, have very specific ideas about what is an investable proposition. A number of the innovations I will discuss have not quite risen to the dynamic of having venture-capital-type characteristics, which tend to have ambitious returns on investment. Venture capitalists aspire to produce 25% to 40% returns on capital and tend to invest in companies that can scale up quickly and dramatically.

We are in the midst of a cultural upheaval, and our world view increasingly is that food equals health. For some of the large food companies, it's a new concept that they are being held up as accountable and responsible for health, rather than merely providing fun and calories, good taste and enjoyment. All of a sudden, it's about health. Furthermore, we are seeing convergence of the green movement, the sustainability movement, with the health movement with far-reaching implications. Venture capitalists and entrepreneurs always look for environments in which disruption is afoot. Where can we create a better mousetrap? Where can we create a model that is going to disrupt the incumbent leaders? The food industry is being chastised, criticized and held up as accountable—similarly to how the tobacco companies were—for the obesity epidemic. However, they are also on the offense, saying that they are concerned about these issues, while adjusting their portfolios. They are trying to transform their processes, their ingredients and, of course, they are spending a lot of money trying to reposition their identities.

About 5 years ago at a UC-Davis conference, I talked about functional food and food as medicine and, since then, that theme has cooled as an area for innovation and investment. We launched four functional-food companies four years ago in a rapid incubator process taking technologies out of universities like Davis, Brandeis and MIT, putting them in very tasty, convenient, healthy natural foods, and today, two of those four companies are thriving and two had to be closed. One that is thriving is Corazon Foods. It produces the world's first healthy potato and tortilla chips—delivering phytosterols in a snack-pack form—which licensed intellectual property and clinical studies from Brandeis. And the other one that's still in business is Attune Foods, which delivers probiotics through healthy food bars. The two that didn't make it were in the satiety space and the sleep space.

It has become clear to us that, with the regulatory environment and with the claims landscaping so ambiguous, even diligent companies that are doing the clinical studies are finding it difficult to gain differentiation in the marketplace. Also, the cultural ethos has shifted dramatically through voices like those of Michael Pollan and Marion Nestle who are talking about a "back to the land" movement. The idea of "more science in my food" has become a lot less desirable from a commercial perspective. Therefore, we have not made an investment in a functional food business or platform since about 2007. Part of that was the downturn in the economy, making it even more difficult for early-stage businesses to gain traction and get off the ground.

Innovation Themes

On the science front, chemistry is moving to the biological realm, as did pharmaceutical companies 10–15 years ago. Food companies are moving in this direction too. PepsiCo has a new chief scientific officer, a Mayo-Clinic-trained epidemiologist who had been head of global R&D at Takeda Pharmaceuticals, Mehmood Khan, who has been talking to me about shifting their entire R&D apparatus from a chemical processing basis to a biological basis requiring more understanding of metabolism, nutrigenomics, metagenomics, and personalization. Transparency is an important theme throughout the supply chain and throughout the consumer market. And we are seeing movement from innovations being product based to being integrated-service based or systems based. We've seen our investment practice move from investing in brand platforms to investing in integrated systems, at the core of which is behavioral science rather than biological science. With respect to linking food and health, there's a lot of interest in how to promote, incentivize, enforce, and sustain healthy behaviors that relate to food. Food is becoming connected to exercise, community, *etc*. I also want to talk about the movement that we are seeing towards local and artisanal food. Finally, my fifth theme will be food equity.

Biobased Approach

In the Physic Ventures portfolio, we have a company called Chromatin, which is a good example of a venture-backed intermediary. Scientists at Chromatin are working closely with UC-Davis. A recent publication in *Nature Biotechnology* was a collaborative effort involving Chromatin's CEO and Davis scientists. Chromatin is a venture-backed company.

It has raised a little over $15 million, providing an intermediary platform to rapidly commercialize technologies from academia by forming fast-moving partnerships with industry players for proof-of-concept and pilot-scale developments. Such companies are important because large institutions cannot be so flexible. This is a corollary to how biotech changed the pharmaceutical industry. It's now happening in agricultural biotechnology

Transparency

On the transparency side, GoodGuide provides information on the health, environmental and social attributes of products we consume. It was started by a scientist at UC Berkeley. We developed the business plan for this company in my social-venture development class at Berkeley. Physic led the series-B financing of this company. New Enterprise Associates (NEA) and Draper Fisher Jurvetson (DFJ) are co-investors. The iPhone has an application to scan the barcode of a product and bring up on the screen the GoodGuide health, environment and society ratings. The consumer can appraise the health attributes of a product being considered for purchase, as well as the environmental practices of the company and how they treat their workers. In 5–10 years, this kind of intermediate layer of information will become part of almost everyone's purchasing behavior. GoodGuide started by providing information like that found in *Consumer Reports*. Surprisingly, over the last year, the company has formed partnerships with Walmart, Safeway and Clorox—retailers and manufacturers that wish to disseminate this information for their own competitive purposes. Walmart is committed to a significant sustainability initiative and is using GoodGuide to manage the complex data set involved in making purchasing decisions that integrate health, social and environmental concerns.

There is also a lot of interest in transparency in the supply chain. FoodLogiQ provides traceability with a particular emphasis on local food and food safety. And Intuit is marketing a platform for small farmers in India to use their mobile devices to get market data so that, when they bring their crops to market, they can get real-time pricing information. This can be completely transformative by bringing transparency into the market for small, individual farmers equipping them with the information that they need to be competitive. This "disintermediates" what has often been a controlled environment and levels the playing field.

Integrated Services

Recently I went to the iTunes library on the Internet and found 3,547 "health and wellness" applications (apps) for the iPhone. The most popular was called "Lose It," a kind of calorie counter and personal diary. There are exercise logs as well. Before long, I will be able to choose the app that keeps track of how much I walk each day and link that to my food diary app and then connect that to my personal health record or my employer health system. All of this is coming. It will be transformative for personal behavior and have far-reaching impacts on the kinds of products people purchase.

Another example is an emerging company that we looked at, The Full Yield, which provides a behavioral system around fresh food. Similar to a Weight Watchers environment, it's run in a corporate or an employee health-plan program in conjunction with a food

retailer, encouraging people to eat fresher, healthier fruits and vegetables via convenient, prepared meals comprising nutritious, minimally refined ingredients. Dannon took an early stake in this company, which was co-founded by Gary Hirshberg, the CEO of Stonyfield Farm; it's an example of a product-based entrepreneur moving into a service business. Another company that we thought was interesting is Local Dirt. I view "local" as the new "natural." Companies are creating marketplaces for local produce using online platforms that help farmers connect with distributors, small markets and customers. Other themes in the local and artisanal area are urban farming, with greenhouses located in cities to minimize transportation, and, in "foody" cities, the explosion of high-quality street food. Entrepreneurship at its best, people are cooking food in their kitchens and selling it from trailers in the street, at fairs, *etc.*, for example, the Perierra Crêperie in Portland, Oregon.

The number of farmers' markets grew from 1,800 to 5,300 from 1994 to 2009, with a 13% increase between 2008 and 2009 alone. This has important implications for the food industry. Information technologies are available to underpin the disaggregation and the de-monopolization of the food-distribution network. However, progress will be uneven, percolating upwards initially only in certain markets.

Food Equity

Most of the companies in which I have been involved—Republic of Tea, Odwalla, Whole Foods Markets, Stonyfield Farm—have catered to a segment of the population that I call the "worried well," *i.e.* people with discretionary resources to enjoy premium items, including natural and organic high-quality foods regarded as premium. However, the theme is shifting—with more attention to underserved markets and the linkage of food to health, in particular to obesity and cardiovascular disease—to healthy food for a healthy population. Kristin Richmond and Kirsten Tobey, former students of mine at UC Berkeley's Haas School of Business, founded a company called Revolution Foods, which is growing dramatically. They serve over 40,000 healthful meals a week to students from kindergarten to high school. With a lot of will and chutzpah, they started a company that focused on a market being overlooked. They brought ingenuity and resourcefulness to a very exciting company.

A lot of work is going into figuring out how to return grocery stores to inner-city neighborhoods. Some funding is being aggregated from mainstream investors, foundation investors and community-development investors to replace convenience stores that offer little fresh food. Some interesting initiatives are also coming out of large food companies. I happen to know about one in the Chicago area, Food for Good, in which an intra-preneurial team in a well known food company is preparing to bring healthy food to an underserved population.

William Rosenzweig is co-founder and managing director at Physic Ventures. He focuses on creating and building early-stage opportunities that bring science to consumers in the areas of prevention, wellness and sustainable living. He also serves on the boards of directors of Attune Foods, EnergyHub, GoodGuide, and Pharmaca.

In 1990, Mr. Rosenzweig co-founded and served as president, CEO, and minister of progress of The Republic of Tea, an award-winning specialty tea company that is often credited with creating the premium tea category in the United States. In 1995, he was appointed as senior vice president of Odwalla, the nation's largest fresh-juice company where he directed the brand and strategy. He has served as faculty advisor to the Global Social Venture Competition and has been a visiting faculty member at London Business School and a guest lecturer at Stanford, Columbia, the University of California-Davis, the University of Southern California and the University of California-Los Angeles.

He has received awards for teaching from the Haas School of Business at Berkeley and from the London Business School, and has served as an advisor and consultant to the Rockefeller Foundation's ProVenEx Fund, an investment vehicle seeking "double bottom line returns" in for-profit businesses.

Food-for-Health Strategies and Programs

Q&A

Moderator: Kenneth Swartzel
North Carolina State University
Raleigh, North Carolina

Kenneth Swartzel: I'll follow Mark McLellan's lead with a question for all three of our panelists. I may receive three different answers since they come from different walks of life. What is the major barrier to commercialization in your world?

Rickey Yada: The challenge for us is defining the value proposition of wellness. We have a struggle convincing our governmental funding agencies to invest in food and health. We are lucky with our funding, but many of us realize that, on a political agenda, wellness is a long-term goal, whereas most politicians operate on a 2-, 3-, or 4-year cycle.

Will Rozenzweig: When we started our fund raising in 2007, we called our fund "Consumer Health Wellness and Sustainable Living" and when we went out to present that to institutional investors—the people who control very large sums of money—we got a lot of pushback on this term "wellness": What do you mean by that? Is it snake oil? Is it something that's sold on late-night TV commercials? We ended up taking that word out. Now, in the 3 or 4 years since, in the United States, our experience is that this word has been endorsed and is legitimate. So, there is hope. That Dean Ornish recently got Medicare to cover his cardiovascular program to prevent heart disease is interesting validation.

Fergus Shanahan[1]*:* My world is an academic world, and it's a small place. I would say that, in my world, the greatest barrier to commercialization is getting people to believe. My

[1]Dr. Shanahan left the discussion early to be interviewed on the conference by the media.

favorite word is "passion" and my second-favorite word "believe." It's getting people who see their world as quite small—getting them to believe they can actually do it and getting them to meet people like you and listen to some of these stories. There's such a buzz of achievement, fulfillment, accomplishment, and chutzpa when you pull off publishing a paper. But it's so much better when you translate the paper and actually make a difference somewhere—even if it's only to a small sector of the market—by getting something off the ground. So the greatest barrier is getting them to believe, even getting the people who run the universities to believe it can be done, and getting the people who coordinate the courses and educate our students to actually believe. That's the biggest barrier.

Rosenzweig: I'd say two things, one is with respect to citizens. I'm going to start using the word "citizen" instead of "consumer," because I think there is a problem with the word "consumer." It's antithetical to sustainability, so I'll use "citizen" today. I'm talking about people who buy things and then eat them. One of the barriers is that people don't really understand the true cost of producing what they buy and that many intangible externalities are part of those costs. We've been trained to think that food should be really cheap, which is a barrier to commercialization. We have to teach people to appreciate and reprioritize their spending to take care of the full system that is involved in producing healthy products. There was a debate this morning on the radio about methyl bromide vs. methyl iodide and neither one is very good for people or the planet. This relates to making big juicy strawberries. And somebody asked, "Why don't we just charge more for strawberries?" That's an interesting solution, and a barrier. The second barrier is the ambiguity in the regulatory environment. It's hard to navigate. It's hard to get people to invest significant sums of money when there's no clear pathway to being successful and to having their investment be protected from competitors who might not take the integrity part of what you are doing as seriously.

Robert Wager (Vancouver Island University): Dr. Shanahan, my wife is a clinical pharmacist and on a daily basis there are *Clostridium difficile* issues in her hospital. My question is, when do you think Thuricin might be a commercial product to give her another option to treat patients?

Shanahan: Realistically, you are probably talking 10 years. But it is conceivable—there's an outside chance—given that the organism that produces it is actually in the food chain, then that might be the most efficient way to deliver it. Beyond that, I can't say. There are lots of hurdles of which the regulatory aspect is only a small one, actually. There's the production side; will it be done by fermentation or will it be done by synthesis or isolation? Those are big hurdles. There's an outside chance that it could end up as a food—which would speed it up—but I doubt it.

James Seiber (University of California-Davis): Rickey, you mentioned the George Brown Chef School in Toronto, and you are from a food science department at Guelph and doing very good outreach in bridging and networking. Here at Davis, the Culinary Institute of

America is not very far away and we are working and growing our relationship there. What has worked in that interface between food science and culinary arts and what suggestions do you have for making that seemingly natural alliance grow and prosper?

Yada: I'll go back to one of the words that Dr. Shanahan used: "belief." People at George Brown believe that their research chefs and the students they train need to be better educated in nutritional science. Having willing participants—believers—on both sides may be the biggest hurdle that you face.

Betty Burri (Western Human Nutrition Research Center): We've heard a lot of good examples of how we're working with K through 12, but that's actually fairly late in life, nutritionally. Have you any comments on additional barriers or opportunities for the daycare-center age group or at the other extreme of life, in assisted-living homes?

Yada: One of the initiatives that we are helping to support is in the province of Quebec. They have undertaken a program to celebrate cultural diversity at a daycare center. It's very much the Jamie Oliver approach where they get young students to bring recipes from home and the class shares in the development of that food and at the end they celebrate by eating the foods from their classmates. When the reports come back from that group, the candidness of the students is surprising. They tell you exactly what they like and don't like at that level.

Rosenzweig: One of the opportunities that we are seeing results from increased willingness to form partnerships among collaborators. The women at Revolution Foods were successful at getting Whole Foods to work with them early as a supply-chain partner. To address your question, I think there are entrepreneurial opportunities for people with vision and belief to address those markets and I think the road forward is to knit together people who share that vision. We've looked a lot at the market that's being termed "aging in place" and certainly food is a big piece of it, but again it's moving toward an integrated systems dynamic. There's a lot of interesting technology with sensors to anticipate when people are going to fall and they are linking that back to, "If we can see when someone doesn't take their medication they are more likely to fall and if they are not taking their medication they may not be eating." My point is, there is a lot of monitoring and the sooner the food industry starts to think of itself as not a single point in a solution but as part of an overall lifestyle system, I think innovation will begin to accelerate.

Shanahan: If I might just put a plug in for the exploration of the microbiota at the extremes of life—I'd probably be shot by my colleagues if I didn't—but you are probably familiar with the Human Microbiome Project in the United States, which is essentially trying to define normal and the ranges of normal, and how diet and nutrition influence the composition of the microbes. If it's really going to make an impact, I actually think it would be at the extremes of life. At the very early stage in life at the time when we are colonizing our bodies and, therefore, influencing the "education" of the immune system

and probably risk factors for immuno-allergic diseases, the time to intervene is very early on—it's too late for us—and also at the other extreme of life, the elderly, when things start to break down. The Irish version of the Human Microbiome Project, called ELDERMET, is beginning to show that there is extreme diversity and instability in the microbiota of the elderly and what is particularly revealing is when the elderly go from living in the community to being institutionalized. You might think that's because of living in close contact with others, but I think it's almost certainly the influence of diet. Let's remember that food, nutrition, diet, is the single most important factor determining the microbiota. But, we have to understand "normal" first.

Bonnie Dixon (University of California-Davis): My question is for Will Rosenzwieg. I was particularly interested in the part of your talk dealing with Internet and IPhone applications for wellness. You said that one of the things you are watching for is a platform that will integrate all of these. Friends who work in the area of internet applications and information technology say that that integration can be quite a challenge. When a lot of websites are competing with each other—providing similar services—it can take a long time for integration to occur even though that's problematic for users. How do you see this developing with wellness applications?

Rosenzweig: My answer to this question is informed by a trip that I took to India not long ago. There you see lots of people with cell phones who don't have computers. Their cell phones are computers, and it's a remarkable example of skipping over an incumbent technology. The mobile environment is going to become rich for this sort of dynamic. When you think about food and behavior change, you are thinking about capturing information. There will be different ways to do that. You also want to give rewards or incentives for feedback. You want to set goals. You want to have feedback. If you pick a few key rules and you embed that in the platform, you create a fairly cohesive opportunity, once you agree on a language and a boundary for what you want to work on. We actually see this food, wellness, nutrition area being quite within grasp, and so, hopefully, we are going to make an investment very shortly in a company that will provide that platform. But it will be a mobile platform. It will be on an Android-based phone, not on a laptop.

Amanda Martin (University of Minnesota): Dr. Yada, you mentioned that we should be aware of intellectual property issues. At what stage is it important to start looking at that, considering that one might not be aware that one's research is heading in a direction where IP would eventually be important.

Yada: Tom Dowler, who is at this conference, was hired as our business analyst and one of his charges is to educate our HQP[2] on IP right from the get-go. We introduce them as early as possible to disclosure issues.

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[2]Highly qualified personnel, see page 187.

Rosenzweig: From a commercial perspective, if you are going to head in that direction, you want to get engaged in it as soon as possible. An excellent program here at UC-Davis is a graduate course for scientists in the business school. They do it over a semester and also have a "boot camp" where scientists receive training from venture investors and commercialization experts. IP is critical to ensure freedom to operate and exclude other people from doing what you want to do.

Martina Newell-McGloughlin (University of California-Davis): Will, I was pleasantly surprised to see that you are investing in Chromatin. I was shocked to see that you think there is hope for a recombinant DNA technology in agribusiness given so much push back from Europe. Clearly, you are, at least to some degree, hopeful and positive about this, and I'm wondering what convinced you that this was a worthwhile venture and if there is actually hope in Europe?

Rosenzweig: I think it's promising. Obviously it's a controversial area. A lot of our rationale for investing came from the thoughtfulness and the mindset of the scientists and the management team and where they were leading the company. Chromatin has been making good progress lately and is a great example for those thinking about being an entrepreneur. This company has already died five deaths and come back. There have been people who have abandoned it, people who have tried to take it over, investors who have left, and investors who have come in. But now it's starting to thrive, so patience and persistence are key.

Newell-McGloughlin: Well done to you for seeing that.

Rosalee Hellberg (Oregon State University): Dr. Yada, I am especially interested in your outreach program to physicians, educating them in food science. I'm working on a program in which we are educating healthcare providers on the benefits and risks of sea food. What kinds of communication strategies and materials have you found most useful for communicating with physicians?

Yada: As I said, the big challenge was getting some of the hierarchy at the Canadian Medical Association and our provincial medical association to appreciate the connection between food and health. We spent a number of hours talking to them, which resulted in that insert in the magazine to their members. Initially, we paid for a two-page insert and now we are on a gratis basis, so, I think they now appreciate the concept of food and health. As I said, the other thing that we are working on is the educational program for family physicians with research chefs and again, we're not sure what the upshot will be because there are believers and nonbelievers within the medical and chef communities. We are hoping that, initially, we will get the believers involved and they will act as messengers to others.

Rosenzweig: James Gordon, the director of the Center for Mind-Body Medicine in Washington, DC, offers a course to physicians on food. Their materials may be a good resource for you.

Swartzel: I would like to end this session by having our panelists comment on a topic that has come up in this conference: personal choice versus regulatory intervention. Would you care to make any comments relative to what you see as emerging, developing aspects? I know that's a tough question.

Yada: Ken, that's a real tough one but, as I often say to groups that I talk to, we need to empower our citizens with information so that they themselves can make healthy choices. There was a movement in the school-board system of Toronto to remove soda machines, which I spoke against because it would likely drive that market underground and students by other means would obtain "contraband" soda. At that time, I had a chat with John Krebs, who headed up the Food Standards Agency about the Jamie Oliver program, and he said, "Wonderful goals, but not very successful. When Jamie went into those schools to work with the kitchen ladies he didn't empower those kitchen ladies with knowledge. They were basically told what to cook and students refused to eat the meals. Money was passed through the fence for their buddies to supply them with 'contraband' food." So, again, it's all about empowering our citizens with good educational programs.

Rosenzweig: The hard part is that entrenched interests want to perpetuate themselves. These are large companies that have been selling products and doing very well over periods of time and their shareholders, their investors, expect them to keep growing. So, they end up in a dilemma; they are selling food products from which they make large profits but which are now known to be bad for people if used excessively. I'm all for empowerment. I also feel that money, energy and resources kept in the system to sustain incumbent activities slow down innovation. One of the reasons for the interesting innovation in this food-equity area is because there isn't a lot of money to be made there. Entrenched interests are not maintaining the *status quo*, and, as such, entrepreneurs have reprioritized their own values. A lot of people going to business school today aren't saying that the most important thing in life is to get rich. They are saying that the most important thing in life is to make the world a better place. That reprioritization of values has a very powerful impact on the innovation system. So, regulation can be helpful when shifting the interests of incumbents and also in leveling the playing field, but I don't think it's helpful in constraining people in terms of what's best for them.

PART IV–BANQUET PRESENTATION

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Plant Biotechnology: The Answer to your Nutrition Needs!

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At its most basic level, food is the source of nutrition to meet daily requirements but is now taking on an ever-greater role in the quest for health optimization. The latter focus is a luxury that is primarily the purview of an affluent society and has little relevance in many areas where mere survival is the driving force. From the basic-nutrition perspective, there is a clear dichotomy in demonstrated need between different regions and socioeconomic groups, the starkest being addressing injudicious consumption in the developed world and under-nourishment in less developed countries (LDCs). Both extremes suffer from forms of malnourishment, one through inadequate supply, the other, in many but not all instances, through inappropriate choices, the latter often influenced by economic considerations. From the food deserts of inner cities to the real barren wastelands of many regions, access to a healthy diet is a challenge. Dramatic increases in the occurrence of obesity, cardiovascular disease, diabetes, cancer and related ailments in developed countries are in sharp contrast to chronic under-nutrition and genuine malnutrition in many LDCs. Both problems require a modified food supply and the tools of biotechnology, while not the sole solution, do have a significant part to play.

Agriculture as a Tool

Worldwide, plant-based products comprise the vast majority of human food intake, irrespective of location or financial status (Mathers, 2006). In some cultures, either by design or default, plant-based nutrition comprises almost 100% of the diet. Given this, one can deduce that significant nutritional improvement can be achieved via modifications of staple crops. New and innovative techniques will be required to improve the efficiency of the global agriculture sector to ensure an ample supply of healthy food. To confound this situation, the inequity between the affluent and developing countries will continue to grow and only a handful of technologies are sufficiently scale-neutral to help with redressing this imbalance. In October 2009, the United Nations' Food and Agriculture Organization (FAO) determined that farming in developing countries needs $83 billion of annual investment for production to feed the world in 2050. The 2008 World Bank Development Report emphasized that, "Agriculture is a vital development tool for achieving the Millennium Development Goals that call for halving by 2015 the share of people suffering from extreme poverty and hunger" (World Bank, 2008). The Report notes that three out of every four people in developing countries live in rural areas and most of them depend directly or indirectly on agriculture for their livelihoods. It recognizes that overcoming abject poverty cannot be achieved in sub-Saharan Africa without a revolution in agricultural productivity for resource-poor farmers, many of whom are women.

The first generation of the products commercialized from one of those technologies, namely biotechnology, were crops focusing largely on input agronomic traits primarily in response to biotic stress. The coming generations of crop plants can be grouped into four broad areas. The present and future focus is on continuing improvement of agronomic traits such as yield and abiotic stress resistance in addition to the biotic stress tolerance of the present generation; crop plants as biomass feedstocks for biofuels and "bio-synthetics"; value-added output traits such as improved nutrition and food functionality; and plants as production factories for therapeutics and industrial products. Developing and commercializing plants with these improved traits involve overcoming a variety of technical, regulatory and perception challenges inherent in perceived and real challenges of complex modifications. Both the panoply of traditional plant-breeding tools and modern biotechnology-based techniques will be required to produce plants with the desired quality traits. Tables 1a–d present examples of crops that have already been genetically modified with macro- and micronutrient traits that may provide nutritional benefits.

The Food/Health Correlation

Although the correlative link between food and health, beyond meeting basic nutrition requirements, has been unequivocally proven only in a number of cases, a growing body of evidence indicates that food components can influence physiological processes at all stages of life. Nutrition intervention from a functionality perspective has a personal dimension. Determining individual response is at least as complex a challenge as the task of increasing or decreasing the amount of a specific protein, fatty acid, or other com-

TABLE 1A. EXAMPLES OF CROPS IN RESEARCH AND/OR DEVELOPMENT WITH NUTRITIONALLY IMPROVED TRAITS INTENDED TO PROVIDE HEALTH BENEFITS FOR CONSUMERS AND ANIMALS [1].

Trait	Crop (trait detail)	Reference
Protein and amino acids		
Protein quality and level	Bahiagrass (protein↑)	Luciani *et al.*, 2005
	Canola (amino acid composition)	Roesler *et al.*, 1997;
	Maize (amino acid composition; protein↑)	Cromwell *et al.*, 1967; O'Quinn *et al.*, 2000; Yang *et al.*, 2002; Young *et al.*, 2004
	Potato (amino acid composition; protein↑)	Yu and Ao 1997; Chakraborty *et al.*, 2000; Li et al., 2001; Atanassov *et al.*, 2004
	Rice (protein↑; amino acid)	Katsube *et al.*, 1999
	Soybean (amino acid balance)	Dinkins *et al.*, 2001; Rapp, 2002
	Sweet potato (protein↑)	Prakash *et al.*, 2000
	Wheat (protein↑)	Uauy *et al.*, 2006
Essential amino acids	Canola (lysine↑)	Falco *et al.*, 1995
	Lupin (methionine↑)	White *et al.* 2001
	Maize (lysine↑; methionine↑)	Lai and Messing, 2002;
	Potato (methionine↑)	Zeh *et al.*, 2001
	Sorghum (lysine↑)	Zhao *et al.*, 2003
	Soybean (lysine↑; tryptophan↑)	Falco *et al.*, 1995;
		Galili *et al.*, 2002

[1]Excludes protein/starch functionality, shelf life, taste/esthetics, fiber quality and allergen/toxin-reduction traits; modified from ILSI (2004a, b; 2008).

Table 1b. More examples of crops in research and/or development with nutritionally improved traits intended to provide health benefits for consumers and animals.

Trait	Crop (trait detail)	Reference
Oils and fatty acids		
	Canola (lauric acid↑; γ-linolenic acid↑; + ω-3 fatty acids; 8:0 and 10:0 fatty acids↑; lauric + myristic acid↑; oleic acid↑)	Dehesh et al., 1996; Roesler *et al.*, 1997; Del Vecchio, 1996; Froman and Ursin, 2002; James *et al.*, 2003; Ursin, 2003
	Cotton (oleic acid↑; oleic acid + stearic acid↑)	Chapman *et al.*, 2001; Liu *et al.*, 2002
	Linseed (+ ω-3 and -6 fatty acids)	Abbadi *et al.*, 2004
	Maize (oil↑)	Young *et al.*, 2004
	Oil palm (oleic acid↑ or stearic acid↑; oleic acid↑ + palmitic acid↓)	Jalani *et al.*, 1997; Parveez, 2003
	Rice (α-linolenic acid↑)	Anai *et al.*, 2003
	Soybean (oleic acid↑; γ-linolenic acid↑)	Reddy and Thomas 1996; Kinney and Knowlton 1998;
	Safflower (γ-linolenic acid GLA↑)	BNET, 2008

ponent of the plant itself (Brigelius-Flohe and Joost, 2006). There is also evidence that early food regimes can affect later life health; for example, some children who survived famine conditions in certain regions of Africa grew into adults battling obesity and related problems presumably due to the selective advantage of the thrifty gene in their early food-stressed environment becoming a hazard during more abundant times especially if later diets are calorie dense.

Functional-food components are of increasing interest in the prevention and/or treatment of a number of the leading causes of death including, but not limited to, cancer, diabetes, cardiovascular disease, and hypertension. Many food components are known to influence the expression of both structural genes and transcription factors in humans (Go *et al.*, 2005; Mazzatti *et al.*, 2008). Examples of these phytochemicals are listed in Tables 2a, b; the large diversity suggests that the potential impact of phytochemicals and functional foods on human and animal health is worth examining as targets of biotechnology efforts.

TABLE 1C. MORE EXAMPLES OF CROPS IN RESEARCH AND/OR DEVELOPMENT WITH NUTRITIONALLY IMPROVED TRAITS INTENDED TO PROVIDE HEALTH BENEFITS FOR CONSUMERS AND ANIMALS.

Trait	Crop (trait detail)	Reference
Carbohydrates		
Fructans	Chicory, (fructan↑; fructan modification)	Smeekens, 1997; Sprenger *et al.*, 1997; Sévenier *et al.*, 1998
	Maize (fructan↑)	Caimi *et al.*, 1996
	Potato (fructan↑)	Hellwege *et al.*, 1997
	Sugar beet (fructan↑)	Smeekens, 1997
Fructose, raffinose, stachyose	Soybean	Hartwig *et al.*, 1997
Inulin	Potato (inulin↑)	Hellwege *et al.*, 2000
Starch	Rice (amylase↑)	Chiang *et al.*, 2005; Schwall, 2000
Micronutrients and functional metabolites		
Vitamins and carotenoids	Canola (vitamin E↑)	Shintani and DellaPenna, 1998
	Maize (vitamin E↑; vitamin C↑)	Rocheford *et al.*, 2002; Cahoon *et al.*, 2003; Chen *et al.*, 2003
	Mustard (+β-carotene)	Shewmaker et al., 1999
	Potato (β-carotene and lutein↑)	Ducreux *et al.*, 2005
	Rice (+β-carotene)	Ye *et al.*, 2000
	Strawberry (vitamin C↑)	Agius *et al.*, 2003
	Tomato (folate↑; phytoene and β-carotene↑; lycopene↑; provitamin A↑)	Rosati, 2000; Fraser *et al.*, 2001; Mehta *et al.*, 2002; Díaz de la Garza *et al.*, 2004; Enfissi *et al.*, 2005; DellaPenna, 2007

Table 1d. More examples of crops in research and/or development with nutritionally improved traits intended to provide health benefits for consumers and animals.

Traits	Crop (trait detail)	Reference
Functional secondary metabolites	Apple (+stilbenes)	Szanowski *et al.*, 2003
	Alfalfa (+resveratrol)	Hipskind and Paiva, 2000
	Kiwi (+resveratrol)	Kobayashi *et al.*, 2000
	Maize (flavonoids↑)	Yu et al., 2000
	Potato (anthocyanin and alkaloid glycoside↓; solanine↓)	Lukaszewicz *et al.*, 2004
	Rice (flavonoids↑; +resveratrol)	Stark-Lorenzen, 1997; Shin *et al.*, 2006
	Soybean (flavonoids↑)	Yu *et al.*, 2003
	Tomato (+resveratrol; chlorogenic acid↑; flavonoids↑; stilbene↑anthocynanins↑)	Rosati, 2000; Muir *et al.*, 2001; Niggeweg *et al.*, 2004; Giovinazzo *et al.*, 2005; Gonzali *et al.*, 2009
	Wheat (caffeic and ferulic acids↑; +resveratrol)	UPI, 2002
Mineral availability		
	Alfalfa (phytase↑)	Austin-Phillips *et al.*, 1999
	Lettuce (iron↑)	Goto *et al.*, 2000
	Rice (iron↑)	Lucca *et al.*, 2002
	Maize(phytase↑, ferritin↑)	Drakakaki, 2005; AllBusiness, 2009
	Soybean (phytase↑)	Denbow *et al.*, 1998
	Wheat (phytase↑)	Brinch-Pedersen *et al.*, 2000, 2006

From a health perspective, plant components of dietary interest can be divided into four main categories, which can be further broken down into positive and negative attributes for human nutrition, macronutrients [proteins, carbohydrates, lipids (oils), and fiber], micronutrients (vitamins, minerals, phytochemicals), anti-nutrients (substances such as phytate that limit bioavailability of nutrients), allergens, intolerances and toxins.

Technological Challenges

There are approximately 25,000 metabolites (phytochemicals)—of the 200,000 or so produced by plants—with known effects in the human diet (Go *et al.*, 2005). Analysis of these metabolites (most specifically metabolomic analysis) is a valuable tool in gaining better understanding of what has occurred during crop domestication (lost and silenced traits) and in designing new paradigms for more targeted crop improvement that is better tailored to current needs (Hall *et al.*, 2008). In addition, with modern techniques, we have the potential to seek out, analyze and introgress traits of value that were limited in previous breeding strategies. Research to improve the nutritional quality of plants has historically been limited by a lack of basic knowledge of plant metabolism and the challenge of resolving complex interactions of thousands of metabolic pathways. A complementarity of techniques, both traditional and novel, is needed to metabolically engineer plants to produce desired quality traits. Metabolic engineering is generally defined as the redirection of one or more reactions (enzymatic and otherwise) to improve the production of existing compounds, produce new compounds or mediate the degradation of undesirable compounds. It involves the redirection of cellular activities by the modification of the enzymatic, transport, and/or regulatory functions of the cell. Significant progress has been made in recent years in the molecular dissection of many plant pathways and in the use of cloned genes to engineer plant metabolism.

Although progress in dissecting metabolic pathways and our ability to manipulate gene expression in genetically modified (GM) plants has progressed apace, attempts to use these tools to engineer plant metabolism have not quite kept pace. Since the success of this approach hinges on the ability to change host metabolism, its continued development will depend critically on a far more sophisticated knowledge of plant metabolism—especially the nuances of interconnected cellular networks—than currently exists. This complex interconnectivity is regularly demonstrated. Relatively minor genomic changes (point mutations, single-gene insertions) are regularly observed following metabolomic analysis, to lead to significant changes in biochemical composition (Bino *et al.*, 2005; Davidovich-Rikanati *et al.*, 2007; Long *et al.*, 2006). Giliberto *et al.* (2005) used a genetic modification approach to study the mechanism of light influence on antioxidant content (anthocyanin, lycopene) in the tomato cultivar Moneymaker. However, other, what on the surface would appear to be more significant, genetic changes unexpectedly yield little phenotypical effect (Schauer and Fernie, 2006).

Likewise, unexpected outcomes are often observed. For example, significant modifications made to primary Calvin-cycle enzymes (fructose-1,6-bisphosphatase and phosphoribulokinase) have little effect while modifications to minor enzymes (*e.g.* aldase, which catalyzes a reversible reaction) seemingly irrelevant to pathway flux, have major

TABLE 2A. EXAMPLES OF PLANT COMPONENTS WITH SUGGESTED FUNCTIONALITY.[a]

Class/components	Source[b]	Potential health benefit
Carotenoids		
α-carotene	Carrots	Neutralizes free radicals that may cause damage to cells.
β-carotene	Various fruits, vegetables	Neutralizes free radicals.
Lutein	Green vegetables	Contributes to maintenance of healthy vision.
Lycopene	Tomatoes and tomato products (ketchup, sauces)	May reduce risk of prostate cancer.
Zeaxanthin	Eggs, citrus, maize	Contributes to maintenance of healthy vision.
Dietary fiber		
Insoluble fiber	Wheat bran	May reduce risk of breast and/or colon cancer.
Beta glucan	Oats	May reduce risk of cardiovascular disease (CVD).
Soluble fiber	Psyllium	May reduce risk of CVD.
Whole grains	Cereal grains	May reduce risk of CVD.
Collagen hydrolysate	Gelatin	May help improve some symptoms associated with osteoarthritis.
Fatty Acids		
Omega-3 fatty acids - DHA/EPA	Tuna; fish and marine oils	May reduce risk of CVD and improve mental, visual functions.
Conjugated linoleic acid (CLA)	Cheese, meat products	May improve body composition, may decrease risk of certain cancers.
Gamma linolenic Acid	Borage, evening primrose	May reduce inflammation risk of cancer, CVD disease and improve body composition.
Flavonoids		
Anthocyanidins: cyanidin	Berries	Neutralize free radicals, may reduce risk of cancer.
Hydroxycinnamates	Wheat	Antioxidant-like activities, may reduce risk of degenerative diseases.
Flavanols: catechins, tannins	Tea (green, catechins), (black, tannins)	Neutralize free radicals, may reduce risk of cancer.
Flavanones	Citrus	Neutralize free radicals, may reduce risk of cancer.
Flavones: quercetin	Fruits/vegetables	Neutralize free radicals, may reduce risk of cancer.

[a]Not an all-inclusive list.

[b]US Food and Drug Administration approved health claim established for component; modified from ILSI (2004a, b).

Table 2b. More examples of plant components with suggested functionality.

Class/components	Source	Potential health benefit
Glucosinolates, indoles, isothiocyanates		
Sulphoraphane	Cruciferous vegetables (broccoli, kale), horseradish	Neutralizes free radicals, may reduce risk of cancer.
Phenolics		
Stilbenes-resveratrol,	Grapes	May reduce risk of degenerative diseases; heart disease; cancer. May have longevity effect.
Caffeic acid, ferulic acid	Fruits, vegetables, citrus	Antioxidant-like activities; may reduce risk of degenerative diseases; heart disease, eye disease.
Epicatechin	Cacao	Antioxidant-like activities; may reduce risk of degenerative diseases; heart disease.
Plant stanols/sterols		
Stanol/sterol ester	Maize, soy, wheat, wood oils	May reduce risk of coronary heart disease (CHD) by lowering blood cholesterol levels.
Prebiotics/probiotics		
Fructans, inulins, fructo-oligosaccharides (FOS)	Jerusalem artichokes, shallots, onion powder	May improve gastrointestinal health.
Lactobacillus	Yogurt, other dairy	May improve gastrointestinal health.
Saponins	Soybeans, soy foods, soy protein-containing foods	May lower LDL cholesterol; contains anti-cancer enzymes.
Soybean protein	Soybeans and soy-based foods	25 g/day may reduce risk of heart disease.
Phytoestrogens		
Isoflavones - daidzein, genistein	Soybeans and soy-based foods	May reduce menopause symptoms, such as hot flashes, reduce osteoporosis, CVD.
Lignans	Flax, rye, vegetables	May protect against heart disease and some cancers; may lower LDL cholesterol, cholesterol, total cholesterol, and triglycerides.
Sulfides/thiols		
Diallyl sulfide	Onions, garlic, olives, leeks, scallions	May lower LDL cholesterol, helps to maintain healthy immune system.
Allyl methyl trisulfide, dithiolthiones	Cruciferous vegetables	May lower LDL cholesterol, helps to maintain healthy immune system.
Tannins		
Proanthocyanidins	Cranberries, cranberry products, cocoa, chocolate, black tea	May improve urinary tract health. May reduce risk of CVD, and high blood pressure.

effects (Paul *et al.*, 1995; Hajirezaei *et al.*, 1994). These observations demonstrate that caution must be exercised when extrapolating individual enzyme kinetics to the control of flux in complex metabolic pathways. With evolving "omics" tools, a better understanding of global effects of metabolic engineering on metabolites, enzyme activities, and fluxes is beginning to be developed. Attempts to modify storage proteins or secondary metabolic pathways have also been more successful than have alterations of primary and intermediary metabolism (DellaPenna and Pogson, 2006). While offering many opportunities, this plasticity in metabolism complicates potential routes to the design of new, improved crop varieties. Regulatory oversight of engineered products has been designed to detect such unexpected outcomes in biotech crops and, as demonstrated by Chassy *et al.* (ILSI, 2004a, b, 2008), existing analytical and regulatory systems are adequate to address novel metabolic modifications in nutritionally improved crops.

A number of new approaches are being developed to counter some of the complex problems in metabolic engineering of pathways. Such approaches include use of RNA interference to modulate endogenous gene expression or the manipulation of transcription factors (TFs) that control networks of metabolism (Kinney, 1998; Bruce *et al.*, 2000; Butelli *et al.*, 2009, Gonzali *et al.*, 2009). For example, expression in tomato of two selected TFs involved in anthocyanin production in snapdragon (*Antirrhinum majus* L.) led to high levels of these flavonoids throughout the fruit tissues, which, as a consequence, were purple. They also stimulated genes involved in the side-chain modification of the anthocyanin pigments and genes possibly related to the final transport of these molecules into the vacuole, processes that are both necessary for the accumulation of anthocyanin (Gonzali *et al.*, 2009). Such expression experiments hold promise as an effective tool for the determination of transcriptional regulatory networks for important biochemical pathways. Gene expression can be modulated by numerous transcriptional and posttranscriptional processes. Correctly choreographing the many variables is the factor that makes metabolic engineering in plants so challenging.

In addition, there are several new technologies that can overcome the limitation of single-gene transfers and facilitate the concomitant transfer of multiple components of metabolic pathways. One example is multiple-transgene direct-DNA transfer, which simultaneously introduces all the components required for the expression of complex recombinant macromolecules into the plant genome as demonstrated by a number of reports, including those of Nicholson *et al.* (2005), who successfully delivered four transgenes that represent the components of a secretory antibody into rice, and of Carlson *et al.* (2007) who constructed a minichromosome vector that remains autonomous from the plant's chromosomes and stably replicates when introduced into maize cells. This work makes it possible to design minichromosomes that carry cassettes of genes, enhancing the ability to engineer plant processes such as the production of complex biochemicals. Christou and Kohli (2009) demonstrated that gene transfer using minimal cassettes is an efficient and rapid method for the production of transgenic plants stably expressing several different transgenes. Since no vector backbones are required, this prevents the integration of potentially recombinogenic sequences insuring stability across generations. They used combinatorial direct-DNA transformation to introduce

multi-complex metabolic pathways synthesizing β-carotene, vitamin C and folate. They achieved this by transferring five constructs controlled by various endosperm-specific promoters into white maize. Different enzyme combinations show distinct metabolic phenotypes resulting in a 169-fold increase in β-carotene, a five-fold increase vitamin C, and a doubling in folate production, effectively creating a multivitamin maize cultivar (Naqvi *et al.*, 2009). This system has an added advantage from a commercial perspective in that these methods circumvent problems with traditional approaches that not only limit the amount of sequences transferred, but may disrupt native genes or lead to poor expression of the transgene, thus reducing both the numbers of transgenic plants that must be screened and the subsequent breeding and introgression steps required to select a suitable commercial candidate.

As demonstrated, "omics"-based strategies for gene and metabolite discovery, coupled with high-throughput transformation processes and automated analytical and functionality assays, have accelerated the identification of product candidates. Identifying rate-limiting steps in synthesis could provide targets for modifying pathways for novel or customized traits. Targeted expression will be used to channel metabolic flow into new pathways, while gene-silencing tools will reduce or eliminate undesirable compounds or traits, or switch off genes to increase desirable products (Liu *et al.*, 2002; Herman *et al.*, 2003; Davies, 2007). In addition, molecular marker-based breeding strategies have already been used to accelerate the process of introgressing trait genes into high-yielding germplasm for commercialization. Tables 1a–d summarize the work done to date on specific applications in the categories listed above. The following sections briefly review some examples under those categories.

Macronutrients

Protein

The FAO estimates that 850 million people worldwide suffer from under-nutrition, of which insufficient protein in the diet is a significant contributing factor (FAO, 2004). Protein-energy malnutrition (PEM) is the most lethal form of malnutrition and affects every fourth child worldwide according to the WHO (2006). Most plants have a poor balance of essential amino acids relative to the needs of animals and humans. The cereals (maize, wheat, rice, *etc.*) tend to be low in lysine, whereas legumes (soybean, pea, *etc.*) are often deficient in the sulfur-rich amino acids, methionine and cysteine. Successful examples of improving amino acid balance to date include high-lysine maize (Eggeling *et al.*, 1998; O'Quinn *et al.*, 2000) canola and soybean (Falco *et al.*, 1995). Free lysine is significantly increased in high-lysine maize by the introduction of the dapA gene (cordapA) from *Corynebacterium glutamicum*, which encodes a form of dihydrodipicolinate synthase (cDHDPS) that is insensitive to lysine feedback inhibition. Consumption of foods made from these crops potentially can help to prevent malnutrition in developing countries, especially among children.

Another method of modifying storage-protein composition is to introduce heterologous or homologous genes that code for proteins containing elevated levels of the desired amino acid, such as sulfur-containing methionine and cysteine, or lysine. An interesting

solution to this is to create a completely artificial protein containing the optimum number of the essential amino acids—methionine, threonine, lysine, isoleucine and leucine—in a stable, helical conformation designed to resist proteases to prevent degradation. This has been achieved by a number of investigators, including a sweet potato modified with an artificial storage protein (ASP-1) gene (Prakash *et al.*, 2000). These transgenic plants exhibited two- and five-fold increases in the total protein contents in leaves and roots, respectively, over those of control plants. Significant increases in the levels of essential amino acids were also observed (Prakash *et al.*, 2000; ILSI, 2008). A key issue is to ensure that total amount and composition of storage proteins is not altered to the detriment of the development of the crop plant when attempting to improve amino-acid ratios (Rapp *et al.*, 2002).

Some novel indirect approaches have also been taken to improve protein content. Uauy *et al.* (2006) "rescued" an ancestral wheat allele that encodes a transcription factor (NAM-B1), which accelerates senescence and increases nutrient remobilization from leaves to developing grains (modern wheat varieties carry a nonfunctional allele.) Reduction in RNA levels of the multiple NAM homologs by RNA interference delayed senescence by more than 3 weeks and reduced wheat-grain protein, zinc, and iron contents by more than 30%. Young *et al.* (2004) used yet another approach to indirectly increase protein and oil content. They used a bacterial cytokinin-synthesizing isopentenyl transferase (IPT) enzyme, under the control of a self-limiting senescence-inducible promoter, to block the loss of the lower floret resulting in the production of just one kernel composed of a fused endosperm with two viable embryos. The presence of two embryos in a normal-sized kernel leads to displacement of endosperm growth, resulting in kernels with an increased ratio of embryo-to-endosperm content. The end result is maize with more protein and oil and less carbohydrate (Young *et al.*, 2004; ILSI, 2008).

Fiber and Carbohydrates

Fiber is a group of substances chemically similar to carbohydrates that non-ruminant animals, including humans, poorly metabolize for energy or other nutritional uses. Fiber provides bulk in the diet such that foods rich in fiber offer satiety without contributing significant calories. Current controversies aside, there is ample scientific evidence to show that prolonged intake of dietary fiber has various positive health benefits, especially the potential for reduced risk of colon and other types of cancer.

Recent microbiome twin studies by Jeff Gordon addressing the interrelationships between diet and gut microbial community structure/function indicated that differences in our gut microbial ecology affect our pre-disposition to obesity or malnutrition and that diet rather than applied probiotics was the single most important characterization of gut health (Turnbaugh *et al.*, 2009). These studies involved characterization of the gut microbiota/microbiome of twins, concordant or discordant for malnutrition, living in several developing countries, who were sampled just prior to, during and after treatment.

When such colonic bacteria (especially bifidobacteria) ferment dietary fiber or other unabsorbed carbohydrates, the products are short-chain saturated fatty acids. These short-chain fatty acids may enhance absorption of minerals such as iron, calcium, and zinc,

induce apoptosis—preventing colon cancer—and inhibit 3-hydroxy-3-methylglutaryl coenzyme-A reductase (HMG-CoAR), thus lowering low-density lipoprotein (LDL) production (German, 2005). Plants are effective at making both polymeric carbohydrates (*e.g.* starches and fructans), and individual sugars (*e.g.* sucrose and fructose). The biosynthesis of these compounds is sufficiently understood to allow the bioengineering of their properties and to engineer crops to produce polysaccharides not normally present. Polymeric carbohydrates such as fructans have been produced in sugar beet, and inulins and amylase (resistant starch) in potato (Hellwege *et al*. (2000) without adverse affects on growth or phenotype. A similar approach is being used to derive soybean varieties that contain some oligofructan components that selectively increase the population of beneficial species of bacteria in the intestines of humans and certain animals and inhibit growth of harmful ones (Bouhnik *et al*., 1999).

Novel Lipids

Genomics, specifically marker-assisted plant breeding, combined with recombinant DNA technology provide powerful means for modifying the composition of oilseeds to improve their nutritional value and provide the functional properties required for various food-oil applications. Genetic modification of oilseed crops can provide an abundant, relatively inexpensive source of dietary fatty acids with wide-ranging health benefits. Production of such lipids in vegetable oil provides a convenient mechanism to deliver healthier products to consumers without the requirement for significant dietary changes. Major alterations in the proportions of individual fatty acids have been achieved in a range of oilseeds using conventional selection, induced mutation and, more recently, post-transcriptional gene silencing. Examples of such modified oils include: low- and zero-saturated fat soybean and canola oils, canola oil containing medium chain fatty acids (MCFA) whose ergogenic potential may have application in LDCs, high stearic acid canola oil (for *trans* fatty acid-free products), high oleic acid (monounsaturated) soybean oil, and canola oil containing the polyunsaturated fatty acids (PUFA), λ-linolenic (GLA; 18:3 n-6) stearidonic acids (SDA; C18:4 n-3), very-long-chain fatty acids (Zou *et al*., 1997) and ω-three fatty acids (Yuan and Knauf, 1997). These modified oils are being marketed and many countries have a regulatory system in place for the pre-market safety review of novel foods produced through conventional technology.

Edible oils rich in monounsaturated fatty acids provide improved oil stability, flavor, and nutrition for human and animal consumption. High-oleic soybean oil is naturally more resistant to degradation by heat and oxidation, and so requires little or no post-refining processing (hydrogenation), depending on the intended application. Oleic acid (18:1), a monounsaturate, can provide more stability than the polyunsaturates, linoleic (18:2) and linolenic (18:3). Antisense inhibition of oleate desaturase expression in soybean resulted in oil that contained >80% oleic acid (23% is normal) and had a significant decrease in PUFA (Kinney and Knowlton, 1998). Dupont has introduced soybean oil composed of at least 80% oleic acid, and linolenic acid of about 3%, and over 20% less saturated fatty acids than commodity soybean oil. Monsanto's Vistive contains less than 3% linolenic acid, compared to 8% for traditional soybeans, resulting in more stable soybean oil and less need for hydrogenation.

A key function of α-linolenic acid (ALA) is as a substrate for the synthesis of longer-chain ω-3 fatty acids found in fish, eicosapentaenoic acid (EPA; C20:5n-3) and docosahexaenoic acid (DHA; C22:6n-3), which play an important role in the regulation of inflammatory immune reactions and blood pressure, brain development *in utero*, and, in early postnatal life, the development of cognitive function. Stearidonic acid, EPA, and DHA also possess anti-cancer properties (Christensen *et al.*, 1999; Smuts *et al.*, 2003; Reiffel and McDonald, 2006). Research indicates that the ratio of n-3 to n-6 fatty acids may be as important to health and nutrition as the absolute amounts present in the diet or in body tissues. Current western diets tend to be relatively high in n-6 fatty acids and relatively low in n-3 fatty acids. Production of a readily available source of long-chain-PUFA, specifically ω-3 fatty acids, delivered in widely consumed prepared foods could deliver much needed ω-3-fatty acids to large sectors of the population with skewed n-6: n-3 ratios. In plants, the microsomal ω-6 desaturase-catalyzed pathway is the primary route of production of polyunsaturated lipids. Ursin *et al.* (2000, 2003) has introduced the Δ-6 desaturase gene from a fungus (*Mortierella*) succeeding in producing ω-3 in canola. In a clinical study, James *et al.* (2003) observed that SDA was superior to ALA as a precursor by a factor of 3.6 in producing EPA, DHA and docosapentaenoic acid (DPA, C22:5n-3). Transgenic canola oil was obtained that contains >23% SDA, with an overall n-6: n-3 ratio of 0.5.

However, not all ω-6 FAs are created equal. Gamma linolenic acid (GLA, C18:3n-6) is an ω-6 fatty acid with health benefits that are similar and complementary to the benefits of ω-3 FAs including anti-inflammatory effects, improved skin health and weight-loss maintenance (Schirmer and Phinney, 2007). A Davis, CA, company, Arcadia, has engineered GLA safflower oil, with up to 40% GLA, essentially quadrupling the levels obtained in source plants such as evening primrose and borage (BNET, 2008). Structural lipids also have positive health benefits; for example, in addition to their effect in lowering cholesterol, membrane lipid phytosterols have been found to inhibit the proliferation of cancer cells by inducing apoptosis and G1/S cell-cycle arrest through the HMG-CoAR as noted above (Awad, 2000). In addition to this and the above, specialty oils may also be developed with further pharmaceutical and chemical feedstock applications in mind.

Micronutrients

Vitamins and Minerals

Micronutrient malnutrition, the so-called hidden hunger, affects more than half of the world's population, especially women and preschool children in developing countries (UN SCN, 2004). Even mild levels of micronutrient malnutrition may damage cognitive development and lower disease resistance in children, and increase incidence of childbirth mortality. The costs of these deficiencies, in terms of diminished quality of life and lives lost, are large (Pfeiffera and McClafferty, 2007). The clinical and epidemiological evidence is clear that select minerals (iron, calcium, selenium and iodine) and a limited number of vitamins (folate, vitamins E, B6 and A) play significant roles in maintenance of optimal health and are limiting in diets.

As with macronutrients, one way to ensure an adequate dietary intake of nutritionally beneficial phytochemicals is to adjust their levels in plant foods. Using various approaches including genomics, vitamin-E levels are being increased in several crops, including soybean, maize and canola, while rice varieties are being developed with the enhanced vitamin-A precursor, β-carotene, to address vitamin-A deficiency that leads to macular degeneration and impacts development. A similar method was used by Monsanto to produce β-carotene in canola and by Fauquet in cassava. The latter is being field tested in Nigeria. Ameliorating another major deficiency in LDCs, namely of minerals such as iron and zinc, has also been addressed. Iron is the most commonly deficient micronutrient in the human diet, affecting an estimated 1 to 2 billion people. Anemia, characterized by low hemoglobin, is the most widely recognized symptom of iron deficiency, but there are other serious problems such as impaired learning ability in children, increased susceptibility to infection, and reduced work capacity. Drakakaki *et al*. (2005) demonstrated endosperm-specific co-expression of recombinant soybean ferritin and *Aspergillus* phytase in maize which resulted in significant increases in the levels of bioavailable iron. A similar end was achieved with lettuce (Goto *et al*., 2000).

A rather interesting approach was taken by Connolly (2008) to increase the levels of calcium in crop plants by using a modified calcium/proton antiporter [known as short cation exchanger 1 (sCAX1)] to increase Ca transport into vacuoles. She also demonstrated that consumption of such Ca-fortified carrots results in enhanced Ca absorption. This demonstrates the potential of increasing plant-nutrient content through expression of a high-capacity transporter and illustrates the importance of demonstrating that the fortified nutrient is bioavailable. Other targets include folate-enriched tomatoes and isoflavonoids (DellaPenna, 2007; Yonekura-Sakakibara *et al*., 2007).

Micronutrients

Phytochemicals

Unlike for vitamins and minerals, the primary evidence for the health-promoting roles of phytochemicals comes from epidemiological studies, and the exact chemical identities of many active compounds have yet to be determined. However, for select groups of phytochemicals, such as non-provitamin-A carotenoids, glucosinolates, and phytoestrogens, the active compound or compounds have been identified and rigorously studied. Epidemiologic studies have suggested a potential benefit of the carotenoid lycopene in reducing the risk of prostate cancer, particularly the more lethal forms of this cancer. Five studies support a 30% to 40% reduction in risk associated with high tomato or lycopene consumption in the processed form in conjunction with lipid consumption, although other studies with raw tomatoes were not conclusive (Giovannucci, 2002). Since carotenoids are lipid soluble and cooking breaks down carotenoid-binding proteins, this is not an unexpected outcome. In a study by Mehta *et al*. (2002) to modify polyamines to retard tomato ripening, they found an unanticipated enrichment in lycopene with levels up by 2- to 3.5-fold compared to conventional tomatoes (Table 1c). This is a substantial enrichment, exceeding that so far achieved by conventional means. This approach may

work in other fruits and vegetables. Flavonoids, meanwhile, are soluble in water, and foods containing both water soluble and fat-dissolved antioxidants are considered to offer the best protection against disease. Anthocyanins offer protection against certain cancers, cardiovascular disease and age-related degenerative diseases. There is evidence that anthocyanins also have anti-inflammatory activity, promote visual acuity and hinder obesity and diabetes. Gonzali *et al*. (2009) and Butelli *et al*. (2008) used snapdragon-transcription factors to achieve high levels of expression of oxygen-scavenging anthocyanins in tomatoes. In a pilot test, the lifespan of cancer-susceptible mice was significantly extended when their diet was supplemented with purple tomatoes compared to supplementation with normal red tomatoes.

Other phytochemicals of interest include related polyphenolics such as resveratrol, which has been demonstrated to inhibit platelet aggregation and eicosanoid synthesis in addition to protecting the sirtuins, genes implicated in DNA modification and life extension; flavonoids, such as tomatoes expressing chalcone isomerase that show increased contents of the flavanols rutin and kaempferol glycoside; glucosinolates and their related products such as indole-3 carbinol (I3C); catechin and catechol; isoflavones, such as genistein and daidzein; anthocyanins; and some phytoalexins (Table 1d). A comprehensive list of phytochemicals is provided in Table 2. To reiterate: although a growing knowledge base indicates that elevated intakes of specific phytochemicals may reduce the risk of diseases, such as certain cancers, cardiovascular diseases, and chronic degenerative diseases associated with aging, further research and epidemiological studies are still required to prove definitive relationships.

Plants Fighting Back

Plants produce many defense strategies to protect themselves from predators. Many, such as resveratrol and glucosinolates, which are primarily pathogen-protective chemicals, also have demonstrated beneficial effects for human and animal health. Many, however, have the opposite effect. For example, phytate, a plant phosphate-storage compound, is considered an anti-nutrient as it strongly chelates iron, calcium, zinc and other divalent mineral ions, making them unavailable for uptake. Non-ruminant animals generally lack the phytase enzyme needed for digestion of phytate. Poultry and swine producers add processed phosphate to their feed rations to counter this. Excess phosphate is excreted into the environment resulting in water pollution. When low-phytate soybean meal is utilized along with low-phytate maize for animal feeds, the phosphate excretion in swine and poultry manure is halved. A number of groups have added heat-and acid-stable phytase from *Aspergillus fumigatus inter alia* to make the phosphate and liberated ions bioavailable in several crops (Potrykus, 1999). To promote the reabsorption of iron, a gene for a metallothionein-like protein has also been engineered. Low-phytate maize was commercialized in the United States in 1999 (Wehrspann, 1998). In November 2009, the Chinese company Origin Agritech announced the final approval of the world's first genetically modified phytase-expressing maize (AllBusiness, 2009). Research indicates that the protein in low-phytate soybean is also slightly more digestible than the protein in traditional soybean. In a poultry-feeding trial, better results were obtained using transgenic

plant material than with the commercially produced phytase supplement (Keshavarz, 2003). Poultry grew well on the engineered alfalfa diet without any inorganic phosphorus supplement, which shows that plants can be tailored to increase the bioavailability of this essential mineral. A similar effect was achieved in wheat by a Danish group, whose temperature-tolerant phytase resisted boiling (Brinch-Pedersen *et al.*, 2006)

Other anti-nutrients that are being examined as possible targets for reduction are trypsin inhibitors, lectins, and several heat-stable components found in soybean and other crops. Likewise, strategies are being employed to reduce or limit food allergens (albumins, globulins, *etc.*), malabsorption and food intolerances (gluten) and toxins (glycoalkaloids, cyanogenic glucosides, phytohemagglutinins) in crop plants and aesthetic undesirables such as caffeine (Ogita, 2003). Examples include changing the levels of expression of the thioredoxin gene to reduce the intolerance effects of wheat and other cereals (Buchanan *et al.*, 1997). Using RNAi to silence the major allergen in soybean (P34 a member of the papain superfamily of cysteine proteases) and rice (14–16 kDa allergenic proteins). Blood-serum tests indicate that p34-specific IgE antibodies could not be detected after consumption of gene-silenced beans (Helm *et al.*, 2000; Herman *et al.*, 2003).
Modern biotech approaches can be employed to down-regulate or even eliminate the genes involved in the metabolic pathways for the production, accumulation, and/or activation of toxins in plants. For example, the solanine content of potato has already been reduced substantially using an antisense approach, and efforts are underway to reduce the level of the other major potato glycoalkaloid, chaconine (McCue *et al.*, 2003). Work has also been done to reduce cyanogenic glycosides in cassava through expression of the cassava enzyme hydroxynitrile lyase in the roots (Siritunga and Sayre, 2003).

When "disarming" plants' natural defenses in this way, one must be aware of potentially increased susceptibility to pests, diseases and other stressors, therefore the recipient germplasm should have input traits to counter this.

Prospects for Crop Biotechnology

Improvement of crop-nutritional quality is a technical challenge hampered by a lack of basic knowledge of plant metabolism and the need to resolve the complexity of intersecting networks of thousands of metabolic pathways. With the tools now available through the field of genomics, proteomics, lipomics, glycobiomics, metabolomics and bioinformatics, we have the potential to study and manipulate genes and pathways at the metalevel, and simultaneously study the expression and interaction of transgenes on tens of thousands of endogenous genes. With these newly evolving tools, we are beginning to dissect the global effects of metabolic engineering on metabolites, enzyme activities and fluxes. For essential macro- and micronutrients that are limiting in various regional diets, the strategies for improvement are clear and concerns such as pleiotropic effects and safe upper limits are easily addressed. However, for many putative health-promoting phytochemicals, clear links with health benefits are yet to be demonstrated. In addition, one must be careful when extrapolating attributes from an individual substance acting independently to that substance acting within a complex milieu. However, if such links can be established, it will make it possible to identify the precise compound or compounds to target and which

crops to modify to achieve the greatest nutritional impact and health benefit. With rapidly emerging technologies, the increase in our understanding of, and ability to manipulate, plant metabolism during the coming decades should place plant researchers in the position of being able to modify the nutritional content of major and minor crops to improve many aspects of human and animal health and wellbeing.

However, the actual commercialization of such products may have little to do with technical limitations and more to do with external constraints, primarily the process of regulatory approval. The flagship of improved nutritional varieties, namely β-carotene-enhanced rice commonly referred to as "golden rice," despite being under consideration since the late nineties and subject to a barrage of risk assessments, is unlikely to be approved until 2012 at the earliest. Ingo Potrykus, the developer, says that an unreasonable amount of testing has been required without scientific justification. In a recent *Nature* article (Potrykus, 2010) he laid the blame solely at the door of the regulatory process, which he considers excessive, observing that unjustified and impractical legal requirements are stopping genetically engineered crops from saving millions from starvation and malnutrition.

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Dr. Newell-McLaughlin has published and edited numerous papers, articles, book chapters, and three books on biotechnology including her latest (with Edward Re), *The Evolution of Biotechnology: From Natufians to Nanotechnology*.

Her personal research experience has been in the areas of disease resistance in plants, scale-up systems for industrial and pharmaceutical production in microbes and microbiological mining. In 2003, the Council for Biotechnology named her one of the DNA Anniversary Year Faces of Innovation among such luminaries as Norman Borlaug, Ingo Potrykus, Barbara McClintock and Roger Beachy.

Q&A

Moderator: Alan B. Bennett
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Tom Tomich (University of California-Davis): Martina, you talked about the huge regulatory hurdles. Carl talked earlier about the notion of risk and benefit, and so my question has two parts. Who credibly do those risk/benefit balancing studies and how are they communicated to the public?

Martina Newell-McGloughlin: The regulations in this country are at least somewhat rational. The three main agencies that cover biotechnology are the ones you might expect. The USDA, where most of the deregulation process is gone through, was one of the first to determine that, in fact, they didn't have to introduce any new regulations—that those on the books were sufficient—but, that they would need to develop guidelines that allowed people to go through this process of determining if something had, or could reach, deregulation status, that is generally regarded as safe. The other agencies then are the EPA, looking at the environmental impact, and the FDA, where there is actually a voluntary consultation. You would be pretty stupid not to consult with them, so every company does.

Tomich: But my question wasn't who regulates. In order to look at the risk/benefit you would actually have to look at the agricultural, environmental and health—

Newell-McGloughlin: All they are looking at is the risk. There is no focus—and, in fact, that is one of the points I made here—there is no focus at all, anywhere, on the benefits.

Tomich: So in academia? Why doesn't somebody do it?

Newell-McGloughlin: It's not part of the process. We do it. Absolutely the benefit component is done. Nobody would be doing any of the work that I told you about because most of that is still sitting in the lab. It's all aspirational. One would hope that this will get through the deregulation process. But in some areas—Europe—it appears to be going backwards. There is such a focus on the precautionary principle that, in fact, it would probably be illegal, if you are going to interpret it to its fullest extent; it would be illegal to do anything for the first time. How ridiculous is that? So you are actually forced to depend on older, less-safe technologies. I'll give you an example from a personal heritage perspective. Growing up, we used to use a particular fungicide called bluestone, copper sulfate, to control late blight in potato. Now BASF has developed a potato with resistance to *Phytophthora infestans* by taking two genes from another potato, a solanaceous species in Mexico, and introducing them and getting complete resistance, and stable resistance—which is often hard with our genes—against late-blight disease. I thought they would be going with open arms in Ireland to get them. Instead they pulled out the plug, because they were told by certain groups that these were toxic. They failed under the precautionary principle. The alternative is using copper sulfate, which has organic approval because it is considered "natural." This is a complete false dichotomy, as Carl said earlier, this notion of natural and non-natural. The focus should be on good and efficacious versus non-good, or less good. With the precautionary principle, people are stuck, depending on older, less-safe, less-efficacious and—for sure—less sustainable production systems. So, when you are in that sort of situation and there is no focus on efficacy and benefits, it is really difficult to get past it.

Barbara Schneeman (US Food and Drug Administration): I just wanted to comment on the risk-benefit paradigm because—at least coming from the FDA perspective—to be on the market, foods have to be safe. They don't have to prove a benefit to be on the market and on the food side of FDA you actually, in fact, separate the risk-benefit construct, because, to be on the market, you have to be safe. You don't have to prove a benefit. It's really in drugs that you get into a risk-benefit balance. Now I think, Martina, you are trying to also address environmental benefits, but, at the end of the day, you still have to consider, "Is the food safe?"

Newell-McGloughlin: Yes. That's what I said, it's all risk in that respect. Now, of course, we could run ourselves into a real problem here if we are suggesting proving efficacy. Now you are up against drugs. You are now looking at $1 billion to $2 billion dollars to take it to market, if we are going to be looking at a pharmaceutical effect from a bioactive component. It's a very finely balanced line we need to walk here, because we don't want to have approval purely based on demonstrating efficacy.

Michael Jacobson (Center for Science in the Public Interest): Martina, on your last slide you listed a bunch of challenges. I would think a key challenge is finding something that consumers find useful, and I haven't seen anything that is anywhere near the pipeline. Monsanto has come to me and said, "Do you have ideas of something that might be use-

ful?" Until you get something obviously useful, like taste, consumers will say, "Why should we eat the genetically modified wheat or canola oil or whatever?" Do you have ideas?

Newell-McGloughlin: The short-chain fructans is a particular example there, where they actually taste sweet. Cynthia Kenyon, looking at genes that increase longevity, found most of them are actually sensate. Our primitive ancestors, the worms, *et cetera*, when sensing the environment, are actually responding to sugars. She has completely cut sugar from her diet and she looks good. The idea with the short-chain fructans is that you can, potentially, eliminate, high fructose corn syrup, sucrose and fructose from your diet.

Jacobson: How many years away do you think those are from market?

Newell-McGloughlin: That's the problem. It's sitting in Dr. Coop's lab because he knows that to get it through EU approval would be an enormous hurdle; the activation energy is so high, especially in Europe. Rather interestingly, on the animal side—since I talked about using plants as factories—the very first approval of using a genetically engineered animal to produce pharmaceuticals in its milk was given in Europe. There was a whole different view here, because, in fact, it was a pharmaceutical, an anti-thrombin agent at that point in time. It was a full year afterwards that the US approved it because, rather interestingly enough, the US was focusing on the health of the animal as well—this sounds counterintuitive—whereas Europe was looking at the safety and efficacy of the anti-thrombin drug itself, ATryn. But that's just an aside. The issue is the cost, the time, the enormous effort to get it through.

Michael Kahn (Washington State University): I've come to the conclusion that many people oppose GMOs less from the risk of the GMO itself than from the companies that are trying to put them out. We are in a situation now, which is ironic, where the Monsantos have figured that they can make enough money by pushing these things through the regulatory process, that they are willing to go ahead and do it, whereas, as you have indicated, small companies, and particularly producers of minor crop fruits and vegetables that we have been talking about as being nutritious here, are not going to be able to afford it. The whole market of those crops, in many cases, is less than what people are estimating for the certification. And so, instead of blocking monopolistic properties of Monsantos, the current regulatory situation is actually promoting them.

Newell-McGloughlin: For sure you could debate that and I absolutely agree, small commodities have a much harder row to hoe. The potato is a perfect example. Again it was produced by a big company, but, in fact, I heard from one individual who blithely told me, "We are not allowing that BASF product in here." No focus on the notion that you are going to reduce the actual amount of chemical used to control it. The big focus was that it was intellectual property owned by BASF. But the reason PIPRA exists actually is to focus on small commodity groups, which is a huge issue, of course, in California. We produce about 250 commodities. So it is much, much more difficult for us to go through

the process of deregulation because of the cost of the biosafety hurdle. But Monsanto will tell you they find it a total pain too. They were talking specifically about new abiotic-stress-resistant strains that they are bringing in, using transcription factor modifications. But they are back to square one with the USDA and EPA. Of course, needless to say, they have deeper pockets than we do in academia, so it's definitely an easier process for them than it is for us. And there have been very few products, in fact probably the only really strong product that has come out of academia is the ringspot-resistant papaya, from Dennis Gonsalves in Hawaii, and most of that work was done when he was at Cornell. There is no natural resistance against this virus, so it doesn't matter how good your marker-assisted selection process is. If the genes aren't in there you can't breed them in, no matter how much you try. So he took a copy of the coat protein from the virus, stuck it in there and it worked through the process that got the Nobel Prize, but not for him, called RNA interference, which confers protection against ring spot. In addition, it helps organic farmers, who grow rings of biotech crop around their non-engineered varieties to reduce the viral reservoir. However, back to your point, that was one of the few products that has gone through the process from an academic situation. All of the others have come from companies.

Alan McHughen (University of California-Riverside): Thank you Martina—enlightening and entertaining as usual. Just a quick comment on where are the products of benefit to consumers. If you ask consumers whether they would support a product, a food, a crop that could be developed with fewer pesticides, they would say, "Yeah, that is a good product. I'll support that and I'll even pay extra for it." So that is a benefit to consumers. They might not be aware of it directly. And, secondly, several recent economic studies, including one from our own National Research Council of the National Academies, have resulted in publication of economic analyses of the benefits of biotechnology to US agriculture, and determined there is a huge economic return that is not being captured exclusively by companies or even by farmers, but by society at large. And that means in practical terms you are paying less for your food because of agricultural biotechnology. That's something that consumers can relate to, but they are generally not aware of it.

McGloughlin: They're not aware of it. It's opaque to them.

PART V–THE STUDENT VOICE AT NABC 22

Student Voice Report[1]

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As *Student Voice at NABC 22* participants, we were asked to discuss our views in terms of what we got out of the conference, what we felt was missing, and some needs that we can address as young scientists. Our backgrounds included food science, nutrition, plant science, animal science, and applied economics.

Overall, our view of the meeting was very positive. We were inspired by many of the high-quality talks and discussion sessions. We identified key strengths and aspects that we especially appreciated:

- Incorporating a variety of speakers with diverse perspectives and opinions.
- Showcasing specific examples and case studies with potential applications. Such as the BioCassava-Plus program and the mammalian milk genome project.
- Addressing problems related to the diet in the United States and Canada as well as in developing countries.

[1]To increase graduate-student participation at NABC conferences, the *Student Voice at NABC* program was launched ahead of NABC 19. Feedback from those involved was positive, therefore the program was continued for NABC 20, 21 and 22. Grants of up to $750 are offered to graduate students at NABC-member institutions (one per non-host institution) to assist with travel and lodging expenses. In some cases, travel and lodging expenses were paid by the home university for a second student. Registration fees are waived for the SV participants. NABC-member institutions are listed on page v.

Student Voice delegates are expected to attend all of the plenary sessions as well as the breakout workshops then to meet as a group to identify current and emerging issues relevant to the conference subject matter. Information on the *Student Voice* at NABC 23 will be available in due course at http://nabc.cals.cornell.edu/studentvoice/.

[2]The *Student Voice* report was presented verbally at NABC 22 by Rosalee Hellberg. This report was assembled by Ms. Hellberg and Watchareeya Kuldamrong, with input from the other students.

- Referring to scientific studies and the use of specific details or data from these studies to support presentation points.
- Discourse that connected nutrition science and regulation policy.
- An overall excellent flow of the meeting.

As young scientists, we identified several messages and needs to address in the area of agriculture, food, and health, including:

- The importance of consumer education and awareness.
- Because human behaviour is very difficult to change, we will need to consider improving the quality of foods that are already a part of the consumers' diets in addition to promoting behavioural changes.
- The application of science, especially biotechnology, to address the need for healthy food among poverty-level populations.
- Development of solutions at the community level, such as *Farm2School* and the *Old Grove Orange Program*, are valid approach to incorporating healthy foods into children's diets.
- Clinical trials on the health benefits of specific foods must be conducted in order to obtain valid health claims.

Finally, we discussed suggestions that could be incorporated into future meetings:

- A greater emphasis on the potential solutions when discussing the problems associated with human health.
- An additional session focused on social science including:
    - — Linking healthful advances in biotechnology to consumer acceptance.
    - — How to address public perceptions of biotechnology.
    - — Consumer behaviour studies focused on incorporation of healthy foods into the diet.
    - — The effect of the media on consumer behavior.
- More information on agriculture, farming and the economics behind incorporating genetically engineered crops and biotechnological food products.
- More details on scientific studies, specific case studies, and examples rather than broad, all-inclusive talks.
- We would have liked more time to talk with the speakers either individually or in small groups. Perhaps, speakers could have either been available in designated areas after their talks or incorporated into the breakout-session discussions.
- A debate on the topics addressed, including ones with potential for controversy, would have been beneficial.

In conclusion, human health can be promoted by linking agriculture, food and nutrition; as Hippocrates once said, "Let food be thy medicine, thy medicine shall be thy food." NABC 22 was an enriching experience that has inspired us to ask questions and to work to find solutions that improve human health through science. We greatly thank the organizers for giving us this opportunity to attend.

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APPENDIX

Food and Agricultural Research: Innovation to Transform Human Health

- The role that food plays in human health is historic and broad. "Let your food be your remedy," attributed to Hippocrates 24 centuries ago, and "an apple a day keeps the doctor away" both encapsulate the food-health relationship.
- A 21st-century plan to make food and agriculture a full partner in human health is proposed. It builds on multiple seminal contributions to key treatment advances from research in food and agriculture, and expands low-cost approaches and quality-of-life benefits by mitigating diet-related diseases.
- A 10% reduction in healthcare costs would save over $200 billion every year.

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Providing an open forum for exploring issues in agricultural biotechnology

March 6, 2009

The National Agricultural Biotechnology Council (NABC), a consortium of over thirty major research and educational institutions in the United States and Canada, has developed *Food and Agricultural Research: Innovation to Transform Human Health*. This document proposes a 21st-century plan to make food and agriculture a full partner in improved human health. The proposal builds on multiple seminal contributions to key treatment advances from research in food and agriculture, including veterinary medicine and nutrition, and expands low economic-cost and quality-of-life benefits through mitigation of diet-related disease.

We are excited by this opportunity for food and agricultural research to expand its contributions to our human-health challenge. The track record and potential are succinctly stated and a plan of action outlined. A 10% reduction in healthcare costs would be equivalent to over $200 billion annually.

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Food and Agricultural Research: Innovation to Transform Human Health

Executive Summary

Delivery of healthcare is one of the most pressing social, economic, technical and political challenges of our time. Of the expenditure on healthcare in the United States—$2.2 trillion, 16% of the gross domestic product in 2007, and growing at more than twice the rate of inflation—diet-related chronic diseases, diabetes, heart disease, stroke, cancer, obesity and asthma, *etc*., account for about 75%. Emphasis has been on therapeutic and surgical treatments after disease development; prevention through food and diet has been under-utilized.

Research in food and agriculture has the potential to aid development of relatively low-cost, preventive solutions to these pressing healthcare issues. This *Food and Agricultural Research: Innovation to Transform Human Health* report provides justification and an action plan.

Research in food and agriculture, including nutrition and veterinary medicine, has an impressive record. Multiple seminal, innovative and transforming contributions have been made to the discovery, description, prevention and treatment of human disease including:

- Vaccines
- Antibiotics
- Biosourced Therapeutics
- Models
- Production Systems
- HIV
- Prion Diseases
- Small RNA Therapeutics
- Biopharma Therapeutics

Developments in biology, including molecular genetics, will provide the knowledge, tools, and opportunities to couple food and agriculture with new approaches to improving human health and containing costs.. These mainly preventive approaches include:

- Essential Nutrient
- Functional Foods
- Probiotics
- Toxin/Allergen Reduction
- Altering Diet
- Enhanced Flavor/Taste
- Nutrigenomics
- Food Safety
- Education/Communication

To expeditiously bring these benefits to human healthcare, we need a structure that integrates food and agricultural research as a full partner in the national health-research mission. Current national funding for research on food and agriculture must be expanded substantially to ensure timely delivery of preventive benefits. This investment is justifiable in terms of the cost savings that will result from disease prevention. A 10% cost reduction would save over $200 billion every year.

The new funding should be competitive and open to individuals and, in particular, to self-assembled groups possessing necessary skills, *e.g*. scientists, sociologists, economists, communicators/educators, marketers and regulators, from academe, government and industry. Examples of such structures exist. Each program will target specific objectives to improve health.

4

Introduction[1,2]

Preservation of human health is one of the most pressing social, economic, technical and political challenges of our time. $2.2 trillion—16% of the gross domestic product—were spent on US human healthcare in 2007. These costs are growing at an unsustainable rate of over twice that of inflation in the United States and Canada. Diet-related chronic diseases such as diabetes, heart disease, stroke, cancer, obesity and asthma account for about 75% of US expenditure[3]. Food and agricultural research must become full partners to provide the necessary knowledgebase and technology to aid development of proactive solutions to healthcare issues that are primarily preventive and relatively low cost rather than reactive therapeutic and surgical solutions that are costly in economic and quality-of-life terms.

Food and Agricultural Research: Innovation to Transform Human Health justifies greatly expanded investment in this area.

Food will continue to provide nutrition, but will also have a prominent role in the prevention of disease. This role for food and agricultural research is potentially huge, but is poorly recognized and underfunded. The objective of this white paper is to expand awareness and stimulate action so that human health will fully benefit from the projected major contributions from food and agriculture. The explosion in life-science knowledge and technology are creating novel opportunities for timely delivery of these benefits.

Major Seminal Contributions and Future Potential[4]

Research in food and agriculture, including nutrition and veterinary medicine, has an impressive record with many seminal contributions to the discovery, description, prevention and treatment of disease. Examples of transformative, innovative contributions, and future potentials, include:

Vaccines

Vaccines are one of the most efficacious and economical methods of preventing disease and may also be used as therapy. Here, agricultural research was seminal. Cowpox provided the first human vaccine as cross-protection against small pox, which led to its eradication. In fact, the word vaccine, which was first used to describe the use of a cowpox-related virus, Vaccinia, to protect against smallpox, is derived from the Latin word for cow (*vacca*). The FDA recently approved the first human vaccine against bird flu as a contingency against future outbreaks. Experimental vaccines produced by plants have been shown to lead to human immunity. Plant-produced vaccines have shown therapeutic potential for treating cancer; within mere weeks, tobacco plants genetically engineered with individual human-lymphoma antigens produced vaccines that were immunogenic.

Antibiotics

Agricultural research also provided the seminal advance for microbially-produced antibiotic therapy. Fleming discovered penicillin and showed that it was produced by a fungus commonly used in cheese making. However, it was not useful as a therapy until agricultural scientists selected fungal strains with higher productivity, and developed the fermentation system to produce clinically useful quantities for use in World War II. Other antibiotics are products of agricultural research.

Biosourced Therapeutics

Botanicals have been the source of over 25% of human therapeutic drugs. Aspirin for pain (and now cardiac-disease prevention) was originally isolated from willow bark; taxol for treating certain cancers was derived from the yew tree; the blood thinner coumadin was extracted from moldy sweet clover; and artemisinin from wormwood is a new cure for malaria, replacing quinine derived from cinchona bark. Therapeutics derived from animal sources include porcine insulin used to treat diabetes.

Chicken Dog, Pig & Plant Models

Chicken, dog, pig and, more recently, plant models have been useful in understanding and treating human diseases. Gene therapy to overcome retina-related blindness in dogs was a model for recent initial success in similar treatment of human blindness. Newborn pigs were used to understand how rotaviruses cause diarrhea and to develop oral vaccines against these devastating pathogens. Research using the model plant arabidopsis yielded discoveries with potential human-health benefits in the areas of, for example, inflammation and tumor suppression, macular degeneration, and arthritis.

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[1] The National Agricultural Biotechnology Council has already produced reports relating to food, agriculture and human health. Most relevant is NABC Report 14, *Integrating Agriculture, Medicine and Food for Future Health* (2002); others are NABC Report 2, *Agricultural Biotechnology: Food Safety and Nutritional Quality for the Consumer* (1990) and NABC Report 17, *Agricultural Biotechnology: Beyond Food and Energy to Health and the Environment* (2005).

[2] The proposal is relevant to the United States and Canada. Public agricultural research institutions in both countries are members of NABC.

[3] Centers for Disease Control and Prevention (2004). Chronic Disease Overview.

[4] Links to additional information are available at NABC's webpage http://nabc.cals.cornell.edu/.

Production Systems

Chicken eggs are broadly used in human vaccine production partly because, while they support growth of mammalian pathogens, the product carries no risk of disease from the presence of avian pathogens. Agricultural research has led to the use of baculoviruses that infect insects as production systems for therapeutics and vaccines, *e.g*. HPV[5] vaccine. These baculoviruses, grown using insect-cell lines, were initially developed to control insect infestations of crop plants.

HIV

Investigations of retroviruses in cats and chickens provided fundamental knowledge that jump-started understanding of HIV infection in the early 1980s.

Prion Diseases

Pioneering research on prion diseases like scrapie in sheep and mad-cow disease (bovine spongiform encephalopathy, BSE) in cattle provided the basis for understanding Creutzfeldt-Jakob disease (CJD) in humans.

Small-RNA Therapeutics & Diagnostics

Small RNAs control gene expression. Agricultural scientists made this seminal discovery by showing that they protect plants from viral infection. They are expected to have major impacts on cancer diagnosis and treatment, and treatments of cardiovascular and muscular diseases, diabetes, viral diseases, *etc*. A recent scientific article, "MicroRNAs make big impression in disease after disease,"[6] captures the potential. A 2006 Nobel Prize was awarded for this area of research.

Biopharma Therapeutics & Xenotransplants

Agricultural and veterinary-medicine research produced the first transgenic plants and animals. Both transgenic plants and animals are being used, mainly experimentally, to biomanufacture therapeutics and vaccines—"biopharma"—making it possible to rapidly scale up production of molecules that would otherwise be scarce or produced only by extraction from human tissues or blood. Absolute containment will be key so as to segregate pharma plants and animals from their food/feed counterparts. The Food and Drug Administration recently approved a plant-produced vaccine for animals and a human antithrombin produced in goat milk for humans with genetic deficiency. Bioengineered pigs may be a source of organs, such as livers, for xenotransplantation into humans.

[5] Human papilloma virus.

[6] Couzin, J. (2008) Science 319 1782–1784.

Other Landmark Contributions

Agriculture and veterinary medicine[7] have been pioneers in innovations relating to disease. Examples include the discovery of the first mammalian virus, the agent of foot and mouth disease. Rous sarcoma was the first cancer shown to be caused by a virus. Marek's disease of chickens was the first cancer treated with a vaccine. HPV[5] vaccine is now being broadly administered to women to reduce risk of cervical cancer. The first attenuated bacterium administered as a vaccine was for chicken cholera. Antibody-producing B-immune cells were discovered in bursa of chickens. Insect-transmitted diseases such as Texas fever contributed to the discovery that mosquitoes transmit malaria and yellow fever. Agricultural research developed DDT to stop transmission of insect-borne diseases. Male-sterile insects led to the eradication of the screwworm and its contamination of wounds, a technology that has been used throughout the world. The emergence of the SARS coronavirus from an animal host and its pandemic spread in 2003, and recent concerns with bird flu and swine flu, illustrate the connection between diseases circulating in mammalian and avian populations and the potential problems they create by moving to humans.

Agricultural research related to human health has been recognized with over fifteen Nobel prizes, many relevant to human health. For example in the 1960s, the structure of transfer RNAs was elucidated, providing one of the keys of the gene-to-protein sequence in living organisms; to recognize this historic event, the US Department of Agriculture recently renamed the laboratory where the work was done the Robert W. Holley Center for Agriculture and Health.

Most of the above examples benefit human health through disease treatment, while some, such as vaccines, are also preventive. The following examples are mainly preventive. Some, such as essential vitamins, amino acids, fatty acids and micronutrients, have a history of preventive benefits, but most of the others will require further research to realize such potential.

Essential Vitamins, Amino Acids, Fatty Acids & Micronutrients

Many earlier contributions of agricultural research were related to the discovery of essential vitamins, amino acids, minerals and fatty acids. For example, rickets was an important disease until the discovery that insufficient vitamin D is causal. Elucidation of this linkage, and the discovery in the 1920s that inclusion of irradiated milk in the diet could prevent the disease, resulted from agricultural

[7] National Research Council (2005) Critical Needs for Research in Veterinary Science. Washington, DC: The National Academies Press.

research. Today, increasing the intake of vitamin D is being evaluated for prevention/treatment of certain cancers and cardiovascular disease. The role of omega-3 fatty acids, derived from fish, flax and nut foods, is being recognized in neural and cardiovascular health and in child development. Research is in progress to modify the fatty acid composition of plant lipids in order to improve the healthfulness of their oils, *e.g*. making soybean oil more like canola or olive oil. Plant proteins often do not have a distribution of amino acids that is optimal for the human diet. Corn, with insufficient lysine, and soybean with too few sulfur-containing amino acids, are being modified to improve dietary balance. Vitamin A and its precursor β-carotene are necessary for normal vision. In some developing countries where rice is a major part of the diet, children become blind because of vitamin-A deficiency. Genetically improved generations of Golden Rice are being developed to contain enough β-carotene to prevent millions of cases of blindness. The HarvestPlus Cassava Alliance, with Gates Foundation and other support, seeks to increase the β-carotene and iron and zinc contents (biofortification) of this major food crop for tropical America and Africa. Foods containing vitamins and other bioactives at levels much greater than minimal nutritional requirements are *Functional Foods*, which are expected to prevent or slow chronic disease development as nutrient levels have protected against acute nutritional diseases.

Functional Foods

Vitamins and other phytochemicals are suggested to have functions in disease prevention beyond their value as nutrients. Examples are antioxidants, phenolic acids and polyphenols (anthocyanins, proanthocyanidins, flavonones, isoflavones, resveratrol—associated with red wine—and ellagic acid). Lycopene, glucosinolates and allyl sulphides have been reported to have beneficial protective and/or therapeutic effects on a variety of diseases. Evidence for the effectiveness of these compounds is based mostly on cell and animal studies. Human clinical data are needed to establish efficacy, such as has been generated for the cholesterol-reducing effects of β-glucans in oats and barley.

Probiotics

Probiotics are microbes that promote health. Genome sequences of gut-flora bacteria are providing understanding of the molecular bases of health-promoting benefits. Dietary priobiotics are being marketed on the basis of promotion and maintenance of human health, *e.g*. as yoghurts with clinically proven gastrointestinal benefits.

Elimination/Reduction of Food-Borne Toxins

Plants contain toxins, their natural protectants against mammalian and pest predation. Some such toxins are highly poisonous to humans, *e.g*. ricin in castor beans. Crops bioengineered for pest resistance have reduced levels of mold-produced aflatoxins. Some toxic compounds may cause chronic disease if consumed over long periods. Canadian researchers genetically modified oilseed rape, a mainly industrial crop, so as to reduce erucic acid and glucosinolates and produce canola, a major new food-oil source with desirable fatty acid composition. Elimination of plant toxins should make our foods more healthful, by reducing the diseases they cause.

Elimination/Reduction of Allergens

Many of our major foods—soybean, wheat, peanut, milk, eggs, shellfish, *etc*.—contain potent allergens that are intolerable or even lethal for some humans. Susceptibility to these allergens is due to a combination of genetics, age, history and, potentially, the gut microbiota. Some of these foods, *e.g*. rice, wheat, soybean and peanut, are being genetically modified to eliminate/reduce their allergens.

Altering Diet

Altering the diet will mean inclusion of more healthful foods. Ideally, these foods will be similar to traditional counterparts, and, in some cases, will be enhanced in desirable flavors and tastes. Current technology enables modification of food composition, increasing desirable and decreasing undesirable components. Examples of modified foods already in the marketplace include milk that is reduced in fat content (2%, 1% and skim) and free of lactose for consumers who are lactose intolerant. Recent elimination of trans fatty acids in processed foods has improved their healthfulness. Wheat products reduced in gluten content may lower the incidence of celiac-disease symptoms. Organically produced food is another example; a small but growing number of consumers perceive increased healthfulness based on altered production methods and are willing to seek out and pay a premium for food that meets the organic standard. Although organic foods have not been proven scientifically to be more healthful, the broad expansion of organic food sections in grocery stores suggests ready acceptance of foods differentiated by verifiable changes in composition and clinical evidence of contributions to improved health. Some of these foods will be directed to niche markets of individuals based on their genetics. An encouraging 2008 survey[8] found that 67% of Americans have made changes to improve their diet; however, achieving broad improvement in the healthfulness of the national diet will need major initiatives in communication and education.

[8] International Food Information Council (IFIC) (2008) 2008 Food & Health Survey: Consumer Attitudes Toward Food, Nutrition & Health. Washington, DC: IFIC.

Enhancement of Flavor & Taste

The food pyramid was developed to guide consumers in selecting foods with cumulative beneficial effects, *e.g*. those with less sugar and fat, and more fruits and vegetables. Considering the increasing rates of obesity, diabetes and other chronic diseases, less-healthy foods are winning the acceptance race versus more healthy foods. A major factor in this unfavourable situation is the dominant role of taste—less-healthy foods often have preferred taste. Taste and price have the greatest impacts on food-purchase decisions[8].

Improving taste and flavor should enhance acceptance and consumption of healthy foods. Different individuals detect flavors differently, based on their genes. For example, about 20% of the population do not like the taste of broccoli, which is recognized to provide human-health benefits. Human taste buds detect at least five tastes: sweet, salty, bitter, sour and umami (savory). Researchers are using receptors for the various tastes to develop GRAS[9] compounds, as alternatives or enhancers, to reduce intake of sugar, fat, salt, *etc*. These molecular approaches should provide powerful redirection of food selection with the potential to increase the consumption of healthier foods with protective benefits.

Genetic Modification

Many of the benefits described above will require genetic modification of the food source. Some will require "traditional" breeding as has been done over the years to most of our plant, animal and microbial food sources. For example, the conversion of rapeseed to canola used traditional plant breeding at the organismal level to produce the desired genetic modification. On the other hand, molecular genetic techniques were used to engineer microbial production of highly pure—98%—chymosin for manufacture of hard cheeses. The bioengineered product, FDA-approved in the early 1990s, has largely replaced crude chymosin (rennin, only 2% pure) obtained from calf stomachs. Crop plants, such as soybean and corn, genetically engineered with improved agronomic traits, are being commercialized in most of the world except Europe. Most of the soybean grown worldwide is bioengineered. For many of the projected health benefits, food crops and possibly animals will need to be modified using molecular genetics as well as traditional methods. Research investment is needed to develop the scientific base to evaluate these products and, in due course, to assure domestic and export markets that they are safe for consumption. These products must be as safe as their non-engineered parents; in addition, they will provide health benefits beyond those of their parents.

Nutrigenomics

Developments in biology and genomics will provide the opportunity to couple agriculture, food and nutrition with new approaches to improving human health (nutrigenomics[10]). A few individual human genomes have already been sequenced and major efforts are being focused on developing low-cost genomic sequencing for individuals. The information generated by these approaches will provide the bases for clinical trials that can link individual genotypes to outcomes, in contrast to the current "one size fits all" approach. In addition to genomics, an expanded use of other "omics," such as metabolomics, will provide more precise diagnostic and treatment directions. These innovations will lead to a greater ability to design prevention-and-treatment interventions that depend on implementing diet and lifestyle changes, initially at the group level and, in time, may be individualized.

Food Safety

Food safety, essential to human health, will be further improved by continued innovation. Microbial contamination of fruit and vegetable produce and animal and poultry products is the major cause of food poisoning. Improved diagnostics and traceability will reduce microbial-contamination problems. Irradiation is another option to minimize food-borne illnesses. Production practices, such as routine use of antibiotics in poultry and animal production, are being discontinued so as to diminish development of antibiotic resistance in microbes infecting humans, and to prolong efficacy of antibiotics. Animal vaccines were recently introduced to reduce shedding of toxic microbes during meat processing. Rapid-readout online tests of poultry, animal and vegetable products should identify unsafe foods before they enter the distribution chain. In addition, country-of-origin labelling will facilitate traceability.

Communication & Education

Disseminating the message of the necessity to eat more healthfully will need massive and continuous efforts in our educational institutions, but also aimed at adults. The potential benefits are compelling: improved longevity and quality of life, reduced chronic-disease rates and containment of national healthcare expenditures. Major reduction in smoking over the past 50 years provides a good analogy. Newsletters dealing with human nutrition are available from university and advocacy organizations—one of which has about a million subscribers[11]—documenting the interest in diet and health. A rating system using stars to identify the nutritional value of supermarket foods has been introduced and should facilitate consumer selection of healthy food.

[9] Generally regarded as safe.

[10] The National Academies Food and Nutrition Board (2007) Nutrigenomics and Beyond: Informing the Future—Workshop Summary. Washington DC: The National Academies Press.

[11] *Nutrition Action Newsletter*, published by the Center for Science in the Public Interest.

Action Plan

The following action plan is proposed for expeditious delivery of the benefits outlined above, to reduce the cost of healthcare and improve the quality of life.

- Research in food and agriculture, including nutrition and veterinary medicine, must become a full partner in the national mission to improve health. Our academic and government structures separate food and agriculture and human health. Colleges of agriculture and life sciences function separately from colleges of medicine and public health; the US Department of Agriculture is separate from the Department of Health and Human Services; governmental appropriations for agriculture are separate from those for human health. The proposed *One Health Initiative* is an encouraging step, seeking to unite veterinary and human medicine. Expansion is needed to unite food and agricultural research with health in both academe and government.
- Public funding for food and agricultural research, including nutrition and veterinary medicine, requires a log step increase, not redirection of existing funding, to provide the knowledge and technology for the disease-prevention opportunities outlined. The National Institute of Food and Agriculture (NIFA) initiative could be a canopy. The new USDA Agriculture and Food Research Initiative (AFRI) is a positive step; however, a much larger funding commitment is needed.
- Funding should be competitive and open to individuals, to generate new knowledge, and, in particular, to self-assembled groups from food, agriculture and health focussed on specific targets and possessing the necessary breadth of skills, *e.g*. scientists, economists, sociologists, clinicians, marketers, regulators and communicators/educators from academe, government and industry. Examples exist of such integrated programs in food, agriculture and human health[12]. Inclusion of academe, government and industry seeks to capture outstanding talent independent of sector location and, in the case of industry, couples the technology to its ultimate delivery.
- The targeted programs may include functional foods, probiotics, reduction/elimination of food-borne toxins, reduction/elimination of allergens, diet alteration, flavor and taste enhancement, nutrigenomics, food safety, communication/education, and others to be identified.
- An initial long-term commitment (*e.g*. 5 years) will be needed to attract the innovative individuals needed to assure the desired outcomes in these challenging programs.

In conclusion, food and agricultural research has an outstanding record of contributions to human health, many seminal, and this action plan should expand the established record and, in addition, provide important low-cost prevention of diet-based chronic diseases.

[12] Integrated food, agriculture and human health programs include the North Carolina Research Campus, the Linus Pauling Institute at Oregon State University, the functional foods component of the Agricultural Bioproducts Innovation Program at Agriculture and Agri-Food Canada, and the USDA's Human Research Centers, one of which is at a college of medicine.

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