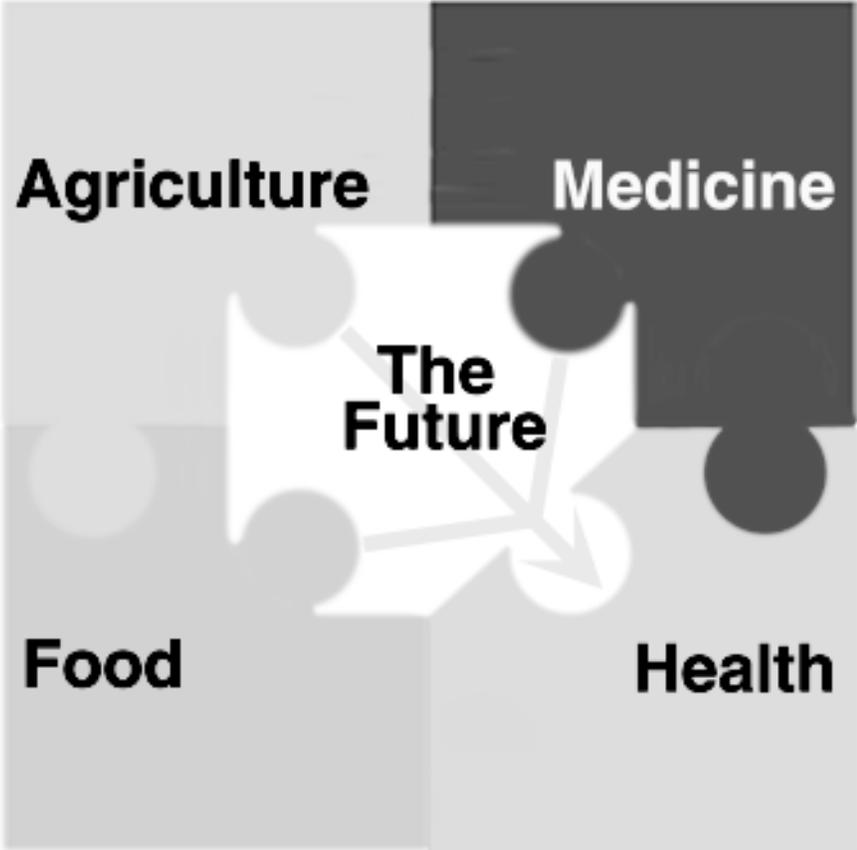


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NABC REPORT 14 ON *FOODS FOR HEALTH*



*Integrating Agriculture, Medicine  
and Food for Future Health*



## NATIONAL AGRICULTURAL BIOTECHNOLOGY COUNCIL REPORT

Links between agriculture and food and between medicine and health are well understood by society. The emerging roles of agricultural biotechnology in medicine, *e.g.* therapeutics and vaccines, and in food, *e.g.* nutraceuticals and functional foods, are described in this volume. In the future, human health will benefit from the integration of agriculture, food and medicine.

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NABC REPORT 14 ON *FOODS FOR HEALTH*

*Integrating Agriculture, Medicine  
and Food for Future Health*

*Edited by Allan Eaglesham, Carla Carlson, and Ralph W.F. Hardy*

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NABC REPORT 14 ON *FOODS FOR HEALTH*  
*Integrating Agriculture, Medicine and Food for Future Health*

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## NATIONAL AGRICULTURAL BIOTECHNOLOGY COUNCIL

*Providing an open forum  
for exploring issues in  
agricultural biotechnology*

The NABC, established in 1988, is a consortium of not-for-profit agricultural research, extension and educational institutions.

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NABC Report 6, *Agricultural Biotechnology & The Public Good* (1994)

NABC Report 8, *Agricultural Biotechnology: Novel Products and New Partnerships* (1996)

NABC Report 9, *Resource Management in Challenged Environments* (1997)

NABC Report 10, *Agricultural Biotechnology and Environmental Quality: Gene Escape and Pest Resistance* (1998)

NABC Report 12, *The Biobased Economy of the Twenty-First Century: Agriculture Expanding into Health, Energy, Chemicals, and Materials* (2000)

NABC Report 13, *Genetically Modified Food and the Consumer* (2001)

## ACKNOWLEDGMENTS

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The fourteenth annual meeting of the National Agricultural Biotechnology Council, *Foods for Health*, was convened May 19 to 21, 2002, at the University of Minnesota, Minneapolis-St. Paul. It was hosted by Charles C. Muscoplat, Vice President and Dean of the College of Agricultural, Food and Environmental Sciences, and Frank Cerra, Senior Vice President for Health Sciences, Academic Health Center. The outstanding success of the meeting was due to the careful planning and unflagging efforts of the conference organizer Carla Carlson, Chief of Staff, College of Agricultural, Food and Environmental Sciences, and the conference staff: Mary Buschette, John Byrnes, Sarah Hustoles and Karen Kotval (College of Agricultural, Food and Environmental Sciences), and Mary Kenyon, Mary Koppel and Sarah Youngerman (Academic Health Center).

Thanks are due to the Conference Advisory Committee for the excellent program: Bonnie Baskin (ViroMed, Inc.), Mark Becker (U MN School of Public Health), Tom Berquist (Mayo Clinic), Dan Burk (U MN Law School), Douglas C. Cameron (Cargill, Inc.), Stephen Hecht (U MN Cancer Center), Donald Hunninghake (U MN School of Pharmacy), Jeffrey Kahn (U MN Center for Bioethics), Vivek Kapur (U MN Biomedical Genomics Center), Kenneth Keller (U MN Humphrey Institute of Public Affairs), Jean Kinsey (U MN Department of Applied Economics), Sally Kohlstedt (U MN History of Science and Technology Program), Christopher B. Morton and Jan O'Donnell (Minnesota Food Association), Michael Osterholm (U MN Center for Infectious Disease Research and Policy), Ronald Phillips (U MN Department of Agronomy and Plant Genetics), Maggie Powers (Powers and Associates, Inc.), Mark Ritchie (Institute for Agriculture and Trade Policy), Sheri Schellhaass (Bell Institute of Health and Nutrition, General Mills, Inc.), Carroll Vance (US Department of Agriculture), and Warren Woessner (Schwegman, Lundberg, Woessner & Kluth, PA).

We are grateful also to Susanne Lipari (NABC) for many and varied organizational contributions, and to Raymond Wiiki for the design and skilled layout of this volume.

A contribution from Cargill, Inc., supported the attendance of students Ellen Gray (Tufts), Patrice Hanzel (Bethany Convent), Jennifer Schmidt (University of Delaware), and Sraddha Helfrich, Penny Kianian, Melissa Lee, Jennifer Nettleton, and Kara Slaughter (U MN).

Exhibitors who participated in the *Spotlight on Minnesota* session, an extension of *Foods for Health*, were: Bioenergy, Inc., Center for Spirituality and Healing (U MN), College of Agricultural, Food and Environmental Sciences (U MN), Institute of Agriculture and Trade Policy, Mayo Clinic, Minnesota Department of Agriculture, Minnesota Department of Trade and Economic Development, Minnesota Dietetic Association, Minnesota Rural Partners, and the University of Minnesota Cancer Center.

Finally, on behalf of NABC, we thank W. Randy Woodson for his leadership as Chair, 2001–2002.

Ralph W.F. Hardy  
*NABC President*

Allan Eaglesham  
*NABC Executive Director*

January 2003

## PREFACE

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As the National Agricultural Biotechnology Council (NABC) enters its fifteenth year of existence, the goals remain as stated in the preface of *NABC Report 1*:

*The Council, through sponsorship of meetings and workshops, and NABC Reports, strives to facilitate the development of policy recommendations for the safe and efficacious development and use of agricultural biotechnology products and processes for the benefit of society; to involve all interested and affected groups in a holistic, rather than disciplinary- or constituency-oriented evaluation of the potential impact of biotechnology on agriculture and development of policy alternatives; and to promote increased understanding of agriculture and biotechnology.*

The NABC has considered the following topics in open forum,

- sustainable agriculture (1989),
- food safety and nutritional quality (1990),
- societal aspects (1991),
- biotechnology of animals (1992),
- risk (1993),
- the public good (1994),
- discovery of, access to, and ownership of genes (1995),
- novel products and new partnerships (1996),
- challenged environments (1997),
- gene escape and pest resistance (1998),
- impacts of biotech and industrial consolidation on world food security and sustainability (1999),
- the biobased economy (2000), and
- genetically modified food and the consumer (2001),

thus providing the opportunity for stakeholders to come together to speak, to listen and learn.

The subject of the 2002 meeting, *Foods for Health*, was timely. The goal of the meeting—hosted by the University of Minnesota May 19–21, 2002—was to foster discussion, respectful of values and viewpoints, on the continuum of agriculture, food, nutrition, medicine and health and the integrated efforts that result in high-quality food and medicines, and in healthy people. Ideas were exchanged and understanding promoted on a broad range of issues, including:

- interrelationships among agriculture and medicine, food, and health,
- research potential of therapeutics from plants and improvements in food crops—through traditional and new gene-manipulation technologies—that may address human-health concerns,

- policy issues that affect regulation, institutional relationships and responsibilities, public/private funding for research, education and consumer information, and
- perspectives of consumers, producers, processors, researchers, clinicians, ethicists, policy analysts, and others.

With over 340 registrants, *Food for Health* had the highest attendance of all NABC meetings. Five countries and thirty-seven states were represented.

This report contains an overview of the 2002 meeting, summaries of workshop discussions and the keynote and plenary presentations. Transcripts of the Q&A sessions are provided. Included are eight presentations from the special session that was held in conjunction with *Foods for Health*, namely *Spotlight on Minnesota: Highlighting Innovation in Agriculture, Food and Medicine*.

On April 4, 2002, a Congressional Briefing, which focused on NABC's annual meeting in 2001 and the resultant report, *Genetically Modified Food and the Consumer*, was held in the Hart Senate Building on Capitol Hill. Presentations were made by Randy Woodson (NABC Chair 2001–2002) Steve Pueppke (University of Illinois, co-host of the meeting), and Ralph W.F. Hardy. Attendees included staffers from the offices of Senators Harkin and Lugar, and USDA personnel. Tony Van der haegen from the European Commission Delegation in Washington, DC (and a speaker at the NABC 2001 conference), contributed to the discussion. This volume will be disseminated at a similar Congressional Briefing planned for the spring of 2003, at which the outcomes of *Foods For Health* will be described and discussed.

The 2003 NABC annual meeting, *Biotechnology: Science and Society at a Crossroad*, hosted jointly by Washington State University and Oregon State University, will be held at the Seattle Westin Hotel, June 1–3 (<http://arc.cahe.wsu.edu/nabc>). Discussion topics will include:

- public perceptions of biotechnology,
- organic and sustainable agriculture and biotechnology,
- the safety of biotechnology—genes drifting into other crops,
- bringing biotechnology to bear on the problems of specialty crops,
- patenting and licensing—moving past the gridlock of intellectual property problems; material transfer agreements,
- biotechnology and international trade, and
- impact of biotechnology on rural communities.

Allan Eaglesham  
NABC Executive Director

Carla Carlson  
Chief of Staff  
College of Agricultural, Food  
and Environmental Sciences  
University of Minnesota

Ralph W.F. Hardy  
NABC President

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PART I  
CONFERENCE SUMMARY

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## ***Highlights of NABC 14: Foods for Health***

CARLA CARLSON  
*University of Minnesota,  
Minneapolis-St. Paul, MN*

More than 340 experts in agriculture, medicine, biotechnology, business, consumer health and policy from thirty-seven states and five countries convened at the *Foods for Health* conference in Minneapolis May 19–21, 2002. This annual conference marked a significant effort to expand the circle of discussion on agricultural biotechnology to include nutrition and healthcare professions. Participants explored the implications of better integrating medicine and food production to increase the health value of foods and the potential of therapeutics using plant-derived and technology-based enhancements.

The conference was hosted by the University of Minnesota's College of Agricultural, Food and Environmental Sciences and its Academic Health Center. Co-hosts Charles C. Muscoplat, Vice President and Dean of the College of Agricultural, Food and Environmental Sciences, and Frank Cerra, Senior Vice President for Health Sciences, highlighted integrated efforts at the University of Minnesota, including their partnership in the university's interdisciplinary Center for Plants and Human Health.

### **DIET AND HEALTH: CHALLENGES AND POTENTIALS**

Dual keynote addresses that described the challenges presented by diet-related disease and the opportunities at the intersection of agriculture and medicine set the stage for discussion at the conference. Shiriki Kumanyika, Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania School of Medicine, cited the increasing incidence of diet-related chronic diseases in the United States and worldwide, and provided data on direct costs to society. Charles Arntzen, founding director of the Arizona Biomedical Institute at Arizona State University, described the potential for addressing diet-related chronic disease through improvements in foods and in new therapeutics derived from agricultural and horticultural crop plants.

Kumanyika summarized the magnitude of the diet-related chronic disease problem as it affects the global population as well as individuals and their families. She noted that obesity and type-2 diabetes costs society in the United States \$50 billion per year (in 1995 dollars) in health services, loss of work, and other factors. Coronary heart disease carries a \$40 billion cost, with hypertension and osteoarthritis at about \$18 billion. In 1995, 13.9 million people in the United States had diabetes. Trends suggest that the number will increase to 21.9 million by 2025. India, the country with the highest rate of diabetes, will increase from 19.4 million affected in 1995 to 57.2 million by 2025.

Arntzen summarized the human timeline of crop improvement and applications of technology from the beginnings of crop domestication about 10,000 years ago to the present. He noted that early populations selected traits to reduce toxicity, reducing or removing glycoalkaloids in potatoes, for example. Over time, breeders selected traits that enhanced taste, nutritional quality, color, and storage. Recent technologies, including plant-tissue cultures and DNA transfer, allow more-specific improvement in traits. He emphasized that the “transition point” from agriculture to medicine has been reached. Researchers now are evaluating selection processes that could restore natural, beneficial, chemicals in plants such as cancer-preventing antioxidants, that have been lost through breeding over time. Arntzen concluded with a glimpse of the future of plant-based vaccines, referencing his own work in potato, that has resulted in three vaccines in stage-1 clinical trials: a hepatitis-B vaccine and two diarrhea vaccines. He emphasized that the production of plant-based vaccines will likely be more efficient and less expensive, and could be set up anywhere in the world—meeting critical disease-prevention needs in developing countries.

Kumanyika and Arntzen were followed by thirty-eight speakers and panelists who addressed the regulatory process, ethics and consumer demand, choice, and health and wellness trends. Other speakers more specifically detailed historical linkages between agriculture and medicine, botanicals as therapeutics, plant-produced antibodies, edible vaccines, functional foods and allergenicity. An additional fifty-two individuals served as facilitators and recorders for conference participants as they discussed key issues in fifteen concurrent workshop sessions<sup>1</sup>.

## **BIOTECHNOLOGY AS A TOOL**

This conference discussion positioned biotechnology squarely as a tool, not as a focal point or goal. Technology also featured in current and historical examples of food as a vehicle to deliver essential nutrition to consumers—from the emergence of nutrient-fortified breads of the mid-1900s to calcium-fortified orange juice. With land grant university agronomists seated amid dieticians and

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<sup>1</sup>See workshop summary article, page 26.

public health service epidemiologists, the goal was articulated as: achieving high-quality, enhanced foods and increased consumer understanding to help improve nutrition. Further, enhancements could contribute to a reduced incidence of diet-related chronic disease—with the long-term goal of disease prevention. The tools of biotechnology could lead to cheaper, more-effective and plentiful vaccines. They could support the development of medicinal components in food to simultaneously treat symptoms and provide nutrition. Biotechnology is already being used to generate pharmaceutical components in commodity and horticultural crops, such as corn and tomatoes.

The potential of the tools of biotech were discussed throughout the conference in terms of what ethicist Jeffrey Burkhardt, University of Florida, described as “the promise of biotechnology.” He said that biotechnology will provide benefits in the future only if scientific and legal successes are achieved, if consumers accept new developments, and if benefits are actually conferred. These developments cannot merely be a prediction; they must be a promise. This promise must be an ethical obligation to act and achieve benefits in the future.

Speakers collectively emphasized that the “promise of biotechnology” must be realistically extended to all concerned: the public, growers, food companies and health sector professionals. They also highlighted a shared responsibility for keeping such promises— throughout the food system and including regulators.

## FOCUS ON CONSUMERS

Speakers addressing consumer interests and demands emphasized that there is, in fact, no average consumer. Tastes, preferences, and cultural bases for food choices vary widely. In sum, although consumers are somewhat confused by the barrage of conflicting messages in the market place, they maintain interest in nutrition, food, and health, and desire understandable, useable, and credible information. In addition, it will be important for agricultural science to reorient its traditional view of the farmer as its client. Many voiced the need to direct research that is in step with the real client, the consumer. Specifically, Laurie Demeritt, the Hartman Group, discussed five factors driving the trend toward wellness among consumers:

- a generalized loss of control,
- transformative life experience,
- compressed sense of time,
- growing frustration with healthcare, and
- the aging population.

She noted that wellness lifestyle trends in the near term will include more emphasis on the economy than on the environment, and an increased focus on prevention as people continue to turn more to food as medicine and therapy.

## REGULATORY ASPECTS

Numerous speakers addressed the current regulatory framework, reflecting on examples from the first generation of biotech crops—and speculating on new guidelines that were published for public comment in September 2002 jointly from the Food and Drug Administration (FDA) and the United States Department of Agriculture (USDA). Gregory Jaffe, Center for Science in the Public Interest, noted that, to date, almost all commercialized genetically engineered crops have gone through the FDA's voluntary consultation process, in which safety data provided by companies are reviewed to ensure compliance with existing laws. He advocated a mandatory FDA process for the second generation of biotech foods (golden rice and high-lycopene tomato, for example) as well as a revamping of USDA's current system. Others noted that many companies will not move aggressively in development of new vaccines or enhanced foods until regulatory processes under discussion are clear. Speakers underscored the important relationship of consumer choice to confidence in the regulatory process and the validation of safety and efficacy of new products.

## EMPHASIS ON STUDENTS

NABC 14 placed a renewed emphasis on engaging students in shaping conference discussions and the future. The conference hosts awarded scholarships to eight students from the fields of medicine, public policy, and nutrition as well as from agricultural disciplines.

## INNOVATIONS IN MINNESOTA

At the close of the conference, local hosts sponsored a special session that highlighted innovation in agriculture, food and medicine in Minnesota. A panel discussion on safe and healthy foods included Kati Fritz-Jung of Schwan's Sales Enterprises, Inc., Hershell Ball of Michael Foods, Inc., Susan Crockett of the General Mills, Inc., Bell Institute of Health and Nutrition, and Steve Snyder of Cargill Health and Food Technologies. A panel on developments in medicine and health included Clarence Johnson of Bioenergy, Inc., Mark Bolander of the Mayo Clinic, and Gregory Plotnikoff and Gary Gardner of the University of Minnesota. Plotnikoff, associate professor of medicine, and Gardner, professor of horticultural science, are part of the university's interdisciplinary Center for Plants and Human Health.

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## Perspectives

LEA THOMPSON

NBC Dateline  
Washington, DC

**Shiriki Kumanyika**, professor of epidemiology and associate dean for health promotion and disease prevention, University of Pennsylvania School of Medicine, told us that the subject matter covered in *Foods for Health* has important implications for the general health of Americans. She made the point that vested interests are acceptable as long as they are in the public good and not based on the bottom line or on the next quarter's profitability. She reminded us that most people do not view food in terms of risk—they expect others to assess that for them.

Integration and harmony within the food industry are essential; there should be no disconnects anywhere in the process. There is a real need to share information, and environmental impacts must be considered.

Kumanyika provided an example of a top-down approach in the Finnish food industry that worked well in decreasing cardiovascular disease. We should consider this *modus operandi* in this country. We need to also consider our ability to forecast and track what is really happening versus what we think will happen. Calcium is now added to orange juice; does the typical consumer think of orange juice when thinking of calcium? The bottom line is that people must be provided with full information in easily understood terminology.

**Charles Arntzen**, founding director of the Arizona Biomedical Institute at Arizona State University, reminded us that the food industry has a history—that scholars and scientists have faced difficult decisions before, and, as a society, we have made good and bad choices in the past. One man's noxious weed may be another's cure for depression, and there can also be serious implications if we don't consider human behavior. We have seen a number of cases recently of serious complications involving mixtures of ingredients—with some combined on purpose and others inadvertently—because people did not know that if they took one medication it could have an adverse effect in conjunction with another.

Arntzen discussed the need for uniformity and standardization to reduce risks in the alternative health-care area, including the need for clinical trials. In his work with oral vaccines—although unexpected side effects have not been observed in clinical trials—there is need for continued vigilance and containment of genetically modified (GM) crops. Finally, he expressed concern that the greatest block to biotechnology in the future may be consumer perception; as someone who covers this area from a consumer perspective, I agree.

**Gregory Jaffe**, director of the Biotechnology Project at the Center for Science in the Public Interest (CSPI), advocated the need for a stronger regulatory system to ensure food safety and to promote public acceptance of GM food. There is great promise—more-nutritious foods, better pharmaceuticals, and plants producing antibodies and edible vaccines. But who will decide if these are safe—can federal agencies be relied upon? The present voluntary regulatory system does not require comprehensive scientific review. Jaffe believes that this is inadequate. Testing for safety is legally mandated in other countries; why not here in the United States? The process should be transparent so that consumers know what is going on. In addition, the CSPI advocates a ban on introducing known allergens into food products without full disclosure.

The bottom line for Jaffe and for many other consumer advocates is mandatory pre-market approval of GM foods. CSPI would also like to see case-by-case environmental assessment; they question how effective are the containment and segregation procedures now in place. He pointed out there was no public comment before current regulations were instituted and that USDA is doing little to enforce rules already on the books. The CSPI believes that the federal government is totally unprepared to deal with the explosion of GM foods soon to come.

**Jeffrey Burkhardt**, professor of agriculture and natural resource ethics and policy, University of Florida, reminded us that scientists will be judged in terms of benefits rendered to the human race. Will biotechnology be beneficial? In Burkhardt's opinion: "We don't know." Scientists believe that what they are doing is justifiable, yet cannot justify why that is. The bottom line is that biotechnology will provide benefits that are greater than the risks if—and it is a big if—it is scientific, if it is legal, and if consumers accept it. Scientists must not make promises that they may not be able to keep.

**Susan Borra**, president of the American Dietetic Association and vice president of the International Food Information Council, presented data showing that, if the food industry fails to keep its promises, consumers won't buy and great potential may be lost. Consumers already feel guilt about food. Borra showed that 50% are very concerned about food, 70% need help with diet, and 38% said they are modifying their diets. Clearly, they are paying attention. At the same time, 37% of those who know about GM foods expressed concern about

them. The good news is that those who know about GM foods are optimists. However, agricultural biotechnology means little to most people.

Consumers want more information, and I was glad to note that most get theirs from television. Here is a story from my own life from which I learned a lot. In 1981, I had just had a baby and was making regular visits to my pediatrician, who told me that he and his colleagues were seeing a rash of metabolic problems in young babies—Barter's Syndrome—considered very rare. My producers and I called children's hospitals and discovered an epidemic with no known cause. After in-depth interviews with many parents we were able to find a common denominator: all of the babies were on the same soy infant formula. Without adequate testing or even thinking the concept through, the company had removed all salt and sugar from its formula, believing it would be better for babies. Instead, it was causing brain damage and death. Congress acted quickly to regulate what must go into infant formula—but for dozens of families it was too late.

On a daily basis, I cover things that have gone wrong—often terribly wrong. I always ask the following questions of the people involved, whether they are lawyers trying to keep the company out of bankruptcy, company executives fighting for their professional lives, or those in the trenches who developed or saw the problems early.

- Why did you fight so hard when experts questioned what you were doing?
- Why did you resist making what you were doing public?
- What is wrong with letting people know what is in what they eat or what is implanted in their bodies or in their air?
- Why not give people a chance to be on your side by giving them enough information to understand.
- Why didn't you work as hard to find a fix as you did to cover up the problem?

Whether it's the developer or the engineer or the CEO, I always ask:

- Surely you never meant to harm people, so what happened?
- What allowed you to forget the big picture?
- How is it that you let your guard down?
- Why didn't you ask more questions?"

I wish all consumers could be as well informed as I am after moderating this session. Speaking on behalf of those consumers who don't have even an inkling of what's going on: foods for health is terribly important, but has to be meticulously challenged. We truly are on the cusp of a brave new world. There is a lot of money in all of this and many lives may be affected. It truly is the stuff of history; as your grand children and great grandchildren look back on the first half of the twenty-first century, let them read that scientists in this field did well by doing good.



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## ***Applying Agriculture To Medicine: Therapeutics And Treatment***

**RICK E. BORCHELT**

*Whitehead Institute for Biomedical Research  
Cambridge, MA*

Anthropologists speak of the concept “liminal space”—topographical boundaries, the shore between ocean and land, for example, cave entrances (neither underground nor aboveground), and mountaintops (between land and sky). To many aboriginal societies, these were places of cultural and social power, sites for ritual and religious observance.

There exists a similar conceptual liminal space in contemporary biotechnology—the boundary between medicine and agriculture. Historically, the distinction was not clear-cut: herbal medicine was one of the earliest drivers of sedentary agriculture, and agricultural trade in therapeutic products was an important part of commerce in both the East and West. In the recent past, beginning with the rise of established medicine during the Enlightenment, medicine and agriculture developed distinct cultures and methods. The barriers are wide and deep in present-day practice, and integration of the two fields remains a daunting task facing biotechnology.

**Irwin Goldman**, associate professor of horticulture at the University of Wisconsin, traced the development of these two cultures and their current uneasy coexistence. Paradoxically, he noted that the refinement of agricultural production methods had the unintended effect of severing the relationship between most of society and the soil; in the United States, the largely rural population of the turn of the twentieth century has been whittled down to fewer than 2% of the general population now living on farms with direct contact with food production. Food and dietary behaviors in the modern developed world are driven far more by cost and convenience than they are by perceived or presumed health benefit, despite a rich literature that suggests significant health functionality derives from a diet rich in whole foods and vegetables. Rather, the American public in particular seems to favor single-source dietary supplementation, a mode that also conforms with the one-disease-one-pill model of medical practice.

**Harry Preuss**, professor of physiology, medicine and pathology at the Georgetown University School of Medicine, is working to bring plant extracts and compounds back into contemporary usage for manifestations of aging, such as obesity, hypertension, insulin resistance, and prostate cancer. Dietary interventions and herbal supplements are surprisingly effective for many of these illnesses, according to Preuss, and such traditional components of folk medicine as oregano oil and garlic are as effective as commonly used antibiotics in reducing some infections. Preuss observed, however, that it is difficult to get his medical-school colleagues to take these “alternative” medicinals seriously, or to support basic research into understanding the biological effectiveness of plants or plant compounds pejoratively labeled “folk medicine.”

Clearly, the forefront of agriculture/medicine interactions is the use of plants to manufacture innovative medicinal products directly. **Mich Hein**, adjunct professor of cell biology at The Scripps Research Institute and president and director of Epicyte Pharmaceutical, Inc., described an emerging biopharmaceutical industry geared toward manufacture of human monoclonal antibodies using crop plants as factories, reducing the serious manufacturing bottleneck that often currently prevents mass-scale application of antibody therapeutics from meeting clinical needs. This medical market, already valued at \$4 billion a year, could be revolutionized with the kind of inexpensive production system that Hein envisions.

In addition to the philosophical barriers noted by Preuss, all panelists affirmed great difficulty in “fitting in” with either traditional agriculture or traditional medicine. One serious issue is the funding stream: few funding agencies have the flexibility or the structure that enables the broad multidisciplinary work that such an approach requires. Moreover, funding agencies tend to be conservative in their portfolio management, and program officers seldom are well enough cross-trained in related disciplines to see emerging collaborative opportunities.

For the foreseeable future, the best path of collaboration seems to be at the corporate level, which is capable of funding compatible projects in both agriculture and medicine, drawing in the requisite intellectual resources and technologies from both endeavors. To truly maximize the fertile intersection of these fields, however, will require a complete reassessment of federal funding mechanisms and traditional philanthropic support.

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## ***Applying Agriculture to Health: Food to Prevent Disease***

**MICHAEL D. FERNANDEZ**

*Pew Initiative on Food and Biotechnology  
Washington, DC*

More than 2,000 years ago, Hippocrates expressed the concept that food is medicine and medicine is food. Through the application of modern biotechnology to agriculture, that maxim is taking on a new reality. With new information from plant, animal, and human genomes, we may be able to specifically tailor newly “functional” foods to help prevent disease. Biotechnology may also allow us to reduce or eliminate conditions caused by consumption of some foods, such as allergies.

The concept of food as medicine may have seemed natural to Hippocrates, but for much of the last century the developed world saw an increasing separation of the two. With the advent of modern biotechnology, however, we may be at the beginning of an era where the differences between food and medicine are increasingly reduced. While this blending of categories presents new opportunities for disease prevention, it also presents challenges to scientists, healthcare providers, food and health communicators, and government regulators. Are we substituting one “magic bullet” approach for another? How much do we need to know before we can talk to the public about new benefits? If foods really are medicines, do we regulate them like drugs? Can we appropriately separate “medical” crops from their conventional counterparts? These and other questions were addressed by the panelists and audience.

**Clare Hasler**, assistant professor of nutrition and associate director of the Functional Foods for Health Program at the University of Illinois at Urbana-Champaign, defined functional foods as whole foods enhanced to provide health benefits beyond basic nutrition. For Dr. Hasler, enhancing the functionality of foods builds on the well established and growing body of

information that enhanced nutrition and dietary modification can dramatically reduce incidence of some diseases. The five-a-day campaign, for example, is based on evidence that dietary changes, including greater consumption of fruits and vegetables, can reduce cancer risk by 30 to 40%. New information—in particular, new genome-sequence information—may take this concept to a new level. Consumers could be in a position to choose specifically tailored functional foods to address their particular needs, or what Hasler calls “nutritional genomics.” She also described some of the factors that could impact these developments. For example, consumers appear increasingly likely to treat themselves before seeing a physician, suggesting that new functional foods could enter into a ready marketplace. Technological advances, the ability to add positive attributes and remove the negative, would also contribute to this vision. At the same time, she also noted that narrowing the gaps between dietary supplements, foods, drugs and herbal-fortified products will pose challenges for scientists and regulators. In the end, functional foods must be safe, their use must be supported by sound scientific evidence of benefit, and they must not be viewed as a “magic bullet.”

**Samuel Lehrer**, research professor of medicine at Tulane University, talked about a different kind of functionality in foods. His research focuses on understanding food allergies and using biotechnology to reduce allergenicity. Much attention has been focused on the possibility that modification of foods through recombinant DNA technology could unintentionally introduce new allergens into the food supply, and Lehrer described the steps that developers and regulators use to assess allergenicity of novel proteins. The bulk of his presentation, however, focused on his research to reduce allergenicity of foods. In particular he describes steps he has used to identify the major allergens in shrimp and to alter those proteins so that they no longer trigger an immune response in sensitive individuals. The work involves multiple steps—identifying the major allergenic proteins, mapping the regions or “epitopes” of the proteins responsible for triggering allergic reactions, identifying specific amino acid targets within those regions, and introducing specific genetic changes to reduce the allergenicity without sacrificing any essential functions of the protein. While it may not be possible to alter all of the allergenic proteins in some foods, and while much work is still needed to demonstrate the effectiveness of these altered proteins and to introduce them into commercially useful varieties, the work of Dr. Lehrer and others may open up a whole new range of foods for those who cannot consume them now.

**John Howard**, chief scientific officer of ProdiGene, described work at his company that would blur the distinction between food and medicine even further by producing human pharmaceuticals in food crops. The benefits of such an approach are abundantly clear. Producing biopharmaceutical molecules

synthetically, or purifying them from microbial fermentation systems, can be extremely difficult and expensive. Plants, on the other hand, especially food crops such as corn, are extremely efficient producers of large amounts of protein. This ability could be extremely important for the production of oral vaccines, for example, where large doses are typically required to elicit immunity. Corn plants also make their own natural storage containers—the kernels—in which the biological activity of proteins is maintained for extended periods of time. Furthermore, there exists a great deal of know-how and a ready infrastructure for processing corn into a variety of useful forms for delivering edible vaccines. This latter advantage, however, also points to one of the key challenges. For, as Dr. Howard pointed out, these are *not* commodity food crops. It will be imperative that systems for reliably segregating pharma crops from food crops will be in place to ensure that an appropriate level of separation is maintained. How that appropriate level is determined, though, will be a combination of market forces and science-based risk assessment. Even where a safety assessment suggests that a food “tolerance” could be safely established, the marketplace might ultimately respond to other signals, including the willingness of consumers to accept even trace amounts of a pharmaceutical compound in the food supply.



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## ***Towards Healthy People: Lifestyles and Choice***

**JEAN D. KINSEY**

*University of Minnesota  
Minneapolis-St. Paul, MN*

Eating healthfully and maintaining healthy bodies is a shared responsibility. Consumer-driven food systems are evolving in the face of abundant food and more self-care on the part of individuals. The idea that food can be your medicine is sinking into the consciousness of consumers as the possibility of choosing foods to prevent chronic and dread diseases becomes more widely known and more technically feasible.

Producing agricultural crops that are used directly as medicine is a relatively new phenomenon on American farms. It requires rigorous segregation of medicinal grains from all other grains, but it illustrates that such segregation can be done and will be done when the profit margins are high enough to pay for the equipment and effort. The commercial development of other crops that have attributes that help prevent diabetes or cancer is not far off, but consumer demand for eating these crops is not well established.

The introduction of new substances into people's lives starts with scientific discoveries, moves on to commercially viable products, and ends with consumer acceptance. The use of biotechnology to develop new foods and food-medicines is largely driven by science in the research stage. Consumers drive the commercialization and marketing stages by their knowledge, needs, and willingness to pay for new products.

There is a gap in consumer acceptance between bioengineered medicines and foods. Part of this can be explained by the trust people have in the parties who authenticate the new products. Medical doctors authenticate new medicines and verify their usefulness to consumers; they are trusted authorities. The food industry, in conjunction with state and federal agencies, authenticate most new foods through informative labels, testing for allergens and other harmful substances, and educational efforts. But there are lots of things about the plethora of new foods that no one seems to know, or test for, or monitor. Even with a rather high level of trust in "the government" to assure safe and wholesome food, consumers are skeptical when it comes to genetic modification. An explanation for this difference in acceptance between bio-engineered

medicines and food lies in the behavioral-economics literature. Numerous experiments have shown that consumers will pay considerable amounts of money to eliminate or reduce risks or pain, as in finding a new medicine for an ailment. They will pay very little and often a negative amount to increase their risk from the *status quo*, as in accepting foods with unproven authenticity.

Consumer behavior is hard to change. There is a large gap between education, perception, and adoption. **Laurie Demeritt** pointed out that consumers need to feel that they are in control. With time and activity commitments, they compress their information intake into seconds and their food intake into minutes per day. They often feel out of control of much of their lives, but selecting foods they want to eat is one form of control they still believe they can exercise. Having the right information helps them maintain that control. They do not want advice or education, they want information that allows them to make their own decisions. We know that social networks are powerful in transmitting information about the value of various foods, diets, and medicines. The core consumers, the “campaigners,” are very vocal and, therefore, influential in what others believe to be true about benefits or dangers of various types of diets. The food industry cannot afford to ignore the campaigners as a small minority since their influence outweighs their numbers. One of the great challenges to the food system as it creates and commercializes food for better health is that of providing information that develops trust among consumers.

**Linda Golodner** spoke about the importance of consumers taking voluntary risks as they navigate the supermarket and select foods and diets. Labeling is a critical tool for information for consumers, yet many are routinely confused about how to select food that is conducive to good health. They need to better understand food-processing technologies like radiation, organic, and what is implied, or not, by the marketing term “natural.” Like Laurie Demeritt she emphasized the importance of social relationships, of family and friends, in creating the belief structure so critical to people’s choice of food and diet. Largely unregulated dietary supplements and herbals put new demands on consumers to gather information themselves. She cautioned that consumers should remember that not all things natural are safe.

**William Horan** and his brother run a 4,000-acre farm in northwest Iowa where they engage in diversified crop production including the production of pharmaceutical corn. He explained how the use of biotech seed on his farm has saved his family hours of labor. Strict methods of segregation keep pharmaceutical corn isolated from crops meant for other purposes. A poignant story about a mother who wrote him a letter thanking him for helping to produce more abundant and lower priced medicine for her child who has a chronic disease foretells the future opportunities for this type of agricultural production.

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## ***Dinner and Luncheon Addresses***

**ALLAN EAGLESHAM**

*National Agricultural Biotechnology Council  
Ithaca, NY*

**Charles Muscoplat**, vice president for agricultural policy and dean of the College of Agricultural, Food and Environmental Sciences, University of Minnesota, stated that appropriate diet and lifestyle are twice as effective as pharmaceutical therapy in preventing adult-onset diabetes in certain high-risk populations. Diet and lifestyle also influence cardiovascular disease, cancer, and other major causes of mortality. Muscoplat provided a historical perspective of diet and health, coming up to date with a discussion of conjugated linoleic acids (CLAs): possibly the most potent cancer-fighting substances in the human diet. The milk from cows that graze on grass contains five-fold more CLAs than that from cows given alternative feeds. Plant and animal genomics will help improve our understanding of genes that encode antioxidants, vitamins, *etc.*, and how supplements and functional foods affect disease.

Concerns over genetically modified organisms were briefly summarized by **Anne Kapuscinski**, professor of fisheries and conservation biology, founding director of the Institute for Social, Economic and Ecological Sustainability, and extension specialist in biotechnology and aquaculture, University of Minnesota. She described the structure and efforts of the National Safety First Initiative, a diverse coalition that is addressing biosafety issues—to ensure that the promises of agricultural biotechnology will be realized—by drawing up cross-industry, publicly trusted standards for designing, producing, and monitoring biotech products. In the initial phase of operation, the Initiative will focus on crops that provide non-food products, encompassing pharmaceuticals to industrial materials, and food products from genetically modified fish and shellfish.

Twenty-first century biology will be increasingly multi-disciplinary and multi-dimensional, according to **Mary Clutter**, assistant director for biological sciences at the National Science Foundation. Whereas the biology of the twentieth century was mainly reductionist, new technologies and new disciplines will address questions from the atomic through the ecosystem to the planetary level. Clutter described six major challenges associated with twenty-first century biology. New partnerships will be needed to meet these challenges, including involvement of the public sector, state and local government as well as the national government, with significantly increased federal funding for research. She described interagency working groups at the federal level and international collaborative efforts that have already been productive in terms of elucidation of the genomes of *Arabidopsis* and *Oryza*.

**George McGovern**, ambassador to the Food and Agriculture Organization of the United Nations, Rome, Italy, described his contributions to the World Food Summit's resolution to halve the number of chronically hungry people in the world—from 800 million to 400 million—by 2015. He has proposed that the United Nations, with the United States in the lead, commit to providing a nutritious school meal to every child in the world. Not only is the hungry child lethargic when in class, many, particularly girls, never start school in the first place. In contrast, once the news is disseminated that a good meal is to be had just by showing up at school, parents ensure that girls are well as boys attend in increasing numbers: academic performance, athletic performance and health all improve dramatically. McGovern voiced approval of agricultural biotechnology as a means of increasing agricultural productivity—particularly in developing countries—thus helping to increase food production while preserving natural ecosystems.

PART II  
WORKSHOP REPORT

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Discussions on Treatment, Prevention and Consumer Choice	23
<i>Carla Carlson</i>	



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## **Discussions on Treatment, Prevention and Consumer Choice<sup>1</sup>**

CARLA CARLSON  
University of Minnesota  
Minneapolis-St. Paul, MN

Participants in the workshop sessions explored themes raised by the keynote speakers and in the Q&A sessions—there were three broad areas of discussion:

- Applying agriculture to medicine: therapeutics and treatment. Presentations on this theme included *Why Medicine Needs Agriculture*, *Botanicals as Therapeutics*, and *Supplementing the Immune System with Plant-Produced Antibodies*.
- Applying agriculture to health: food to prevent disease. Presentations included *Where do Functional Foods Fit in the Diet?*, *Can We Have Allergen-Free Food?*, and *The Role of Edible Vaccines*.
- Towards healthy people: lifestyles and choice. Presentations included *The Evolving Wellness Consumer*, *Delivering on the Promise of Safe and Healthy Foods*, and *Farmers as Consumers: Making Choices*.

The 340 conference attendees each chose one of the three workshop sessions for their 2½-hour exchange of knowledge and expertise. Notably, three quarters of the conference attendees chose to participate in the session on prevention, or applying agriculture to health, perhaps indicating a strong view to the future and endorsement of the benefits to society of further integrating agriculture and medicine. Of the fifteen workshops, eleven focused on prevention, two on therapeutics and treatment, and two on consumer choice. Lists of questions (Table 1) helped initiate and perpetuate discussion and the assistance of two facilitators and one recorder in each of the fifteen workshop sessions (Table 2) helped to focus the participants on key ideas and move them to conclusions.

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<sup>1</sup>Prepared from session reports provided by nineteen recorders (Table 2).

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TABLE I. WORKSHOP-SESSION QUESTIONS.

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### **Agriculture and Medicine: Therapeutics and Treatment**

- **Integration?** Hippocrates said food is medicine. Some suggest that since the 1500s, agriculture and medicine have diverged in key ways. Some suggest that the two have come together during the last 20 years. Is integration of the two desirable? If so, how can the agriculture/food production side and the health/medicine side better understand and work with each other? What innovative institutional relationships might be developed that would influence research, funding, education, public/private partnerships, others?
- **Technologies?** To date, modern technologies have been applied to medicine and agriculture. Biotechnologies have been applied to both. Papayas. Human insulin. *Bt* cotton. Herbicide-tolerant soybeans. Should research and application pause? Move forward? Be applied in medicine for treatment? In agriculture for nutrition, production? Neither? Both?
- **Botanical therapeutics?** Mushrooms, bee pollen, grape seeds, flower extracts. What opportunities can therapeutic botanicals and food derivatives provide? How does the public perceive natural products and their potential benefits? How do research and regulation address potentials and concerns?
- **Plant-produced antibodies?** Why are scientists pursuing the production of antibodies in plants? Would such a development have benefits to health? What about implications for the food supply? The environment? What kind of regulatory process would need to be in place? Who would grow antibody-producing crop plants? Where would they be grown?
- **Yield and value?** Some would say that agriculture is no longer a bushels-per-acre endeavor—it's value per acre. Is this true? Who would or should derive value from traditional or new crops? The farmer (small or large)? The developer? The processor? The general consumer? The patient?
- **Open question** to be defined by the group.

### **Foods to Prevent Disease**

- **Functional foods?** Breakfast cereals that reduce cholesterol. Increased lycopenes in your catsup. Vitamin D in milk. Soy. Can “functional foods” help prevent disease? What are the risks and benefits of designing fortified foods? What are the regulatory and safety issues? Are increased nutritional constituents in foods a public good?
- **Allergenicity?** Would foods developed via biotechnologies carry proteins that might induce allergic reactions? Would biotechnology applications result in hypoallergenic foods and improved allergen detection methods? How should research and policy be used to address these issues?
- **Edible vaccines?** Why are scientists pursuing research on edible vaccines? How would plants carrying disease-prevention constituents be segregated from the food supply? Would health professionals, consumers accept edible vaccines?
- **Prevention?** How can the incidence of diet-related chronic diseases be reduced given the complexities of consumer attitudes and behaviors; suppliers; health professionals; changing policies; the structural forces that influence eating patterns indirectly?
- **Responsiveness?** How can the agricultural and food systems be more responsive to what is known about diet-related chronic disease and prevention? Can agriculture produce to improve nutrition and health?
- **Open question** to be defined by the group.

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TABLE 1. WORKSHOP-SESSION QUESTIONS. (continued)

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### **Lifestyles and Consumer Choice**

- **Information?** Health claims. Advertisements. Who do consumers trust? The government and its regulatory process? Labels? Research institutions? Consumer organizations? How can consumers sort out messages on food, nutrition and health, nutrient content, genetically engineered foods and therapeutics, natural products, plant-derived treatments, child nutrition, and food preparation and handling?
- **Consumer preferences?** Are consumers voicing their preferences? Are their voices being heard? What does 'wellness' mean to consumers? Can nutrition, public health, medical professions and other public education organizations help ensure that nutrition, health and wellness become a way of life?
- **Rural lifestyles?** How might rural lifestyles be affected by local production of pharmaceutical crops or specialty crops such as high-glucosinolate crucifers (cabbage and broccoli, for example) or increased acres in organic crops or increased emphasis on local food systems? What are the scales and profitability potentials for small farmers and larger farmers across the country?
- **International collaborations?** Do developed countries have a role in addressing hunger, improved diets, eradication of disease and improved agriculture in developing countries? If so, what types of science and technology developments for the future should be in the portfolio?
- **Open question** to be defined by the group.

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**TABLE 2. WORKSHOP FACILITATORS AND RECORDERS.**

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**Facilitators**

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Mark Ascerno, <i>University of Minnesota</i>	Jean Kinsey, <i>University of Minnesota</i>
Susan Barefoot, <i>Clemson University</i>	Theodore Labuza, <i>University of Minnesota</i>
Dianne Bartels, <i>University of Minnesota</i>	Marshall Martin, <i>Purdue University</i>
Janet Bokemeier, <i>Michigan State University</i>	Helene Murray, <i>University of Minnesota</i>
William Brown, <i>University of Florida</i>	Darrell Nelson, <i>University of Nebraska</i>
Michael Burke, <i>Oregon State University</i>	Christopher Morton, <i>Minnesota Food Association</i>
G. Michael Chippendale, <i>University of Missouri</i>	James Orf, <i>University of Minnesota</i>
Gregory Cuomo, <i>University of Minnesota</i>	Frank Pflieger, <i>University of Minnesota</i>
Beverly Durgan, <i>University of Minnesota</i>	Maggie Powers, <i>Powers and Associates, Inc.</i>
Thane Dutson, <i>Oregon State University</i>	Steven Pueppke, <i>University of Illinois</i>
Walter Fehr, <i>Iowa State University</i>	Charles Scifres, <i>Texas A&amp;M University</i>
James Fischer, <i>Clemson University</i>	Philip Schwab, <i>U.S. Department of Agriculture</i>
Vincent Fritz, <i>University of Minnesota</i>	Steven Slack, <i>Ohio State University</i>
Burle Gengenbach, <i>University of Minnesota</i>	Catherine Solheim, <i>University of Minnesota</i>
Ian Gray, <i>Michigan State University</i>	Neal Van Alfen, <i>University of California-Davis</i>
Richard Jones, <i>University of Florida</i>	Joseph Warthesen, <i>University of Minnesota</i>
Catherine Jordan, <i>University of Minnesota</i>	Gregory Weidemann, <i>University of Arkansas</i>
Kevin Kephart, <i>South Dakota State University</i>	Randy Woodson, <i>Purdue University</i>

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**Recorders<sup>2</sup>**

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Mary Buschette, *College of Agricultural, Food and Environmental Sciences*  
 John Byrnes, *College of Agricultural, Food and Environmental Sciences*  
 Allison Campbell, *Academic Health Center*  
 Allan Eaglesham, *National Agricultural Biotechnology Council\**  
 Sarah Greening, *Minnesota Agricultural Experiment Station*  
 Alicia Hall, *Graduate Research Assistant, Department of Philosophy*  
 Brenda Hudson, *Academic Health Center*  
 Sarah Iverson, *College of Agricultural, Food and Environmental Sciences*  
 Jessica Krueger, *College of Agricultural, Food and Environmental Sciences*  
 Jane Leonard, *Minnesota Rural Partners\**  
 Suzanne Livingston, *College of Agricultural, Food and Environmental Sciences*  
 Shane Maefsky, *Undergraduate, College of Agricultural, Food and Environmental Sciences*  
 Ann Kirby McGill, *University Relations*  
 Jennifer Obst, *University of Minnesota Extension Service*  
 Susan Parry, *Graduate Research Assistant, Department of Philosophy*  
 Patrick Plonski, *College of Agricultural, Food and Environmental Sciences*  
 Anne Pylkas, *Undergraduate, College of Agricultural, Food and Environmental Sciences*  
 Cynthia Scott, *University Relations*  
 Kelly Sullivan, *College of Agricultural, Food and Environmental Sciences*

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<sup>2</sup>From the University of Minnesota unless indicated with an asterisk.

## APPLYING AGRICULTURE TO MEDICINE: THERAPEUTICS AND TREATMENT

These discussions were summarized for the plenary audience by Catherine Solheim, University of Minnesota, and Kevin Kephart, South Dakota State University.

*Integration* Participants foresaw the accrual of great benefit from the further integration of agriculture and medicine. They addressed integration on two broad levels: higher education and cross-sector collaboration. First, they recommended that medical schools and colleges of agriculture both need to enhance curricula, and the preparation of students, using nutrition as a focal point. Future physicians and other healthcare professionals need an expanded understanding of nutrition as a component of disease treatment, prevention, and healthfulness. Similarly, because agricultural colleges tend to adhere to traditional emphases on production of commodity crops and food, the integration of nutrition into their curricula would help orient students in terms of food consumption, consumer preferences, and other end-use outcomes. The importance of human-resource issues was noted, to address the best approaches for educating healthcare professionals and agriculturalists, also to ensure continuing education for practitioners to foster attentiveness to new interdisciplinary approaches. Participants highlighted the industry model of structuring teams to approach specific problems and suggested that higher-education institutions should encourage more interdisciplinary team approaches and address the faculty-reward system that can be a barrier to teamwork. They also noted that a nutrition emphasis in K–12 education would serve as an important foundation for all students, not only for those who pursue careers in food systems and healthcare.

Second, participants noted that funding will be the driver for better integration of agriculture and medicine. Cooperatives and alliances that connect the producer with the consumer in innovative partnerships can be a mechanism for integration. Also discussed were sources of funding and public/private partnerships that can give integration a boost; it was noted that, whether from federal or state agencies or private concerns, funding is seldom free of special interests. Technology was cited as a tool that can assist in building new relationships and effective virtual partnerships.

*Technology* In general, participants were of the opinion that science and technology—in almost all disciplines—advances at a rate beyond that of society's ability to comprehend complex developments and their ultimate ramifications. A government mandate by any country to “pause” development and application of biotechnology would merely cause research and development to shift to other more-supportive settings.

There is need for a holistic approach to discussion and application of biotechnology in order to accommodate varied values and societal perspectives and integrate not only agriculture and medicine but also the public-private sector relationships, the environment, and economics. The discussants noted the special importance of inclusive discussions that engage the public on the challenges of the intersection of technological advancement with the religious and spiritual beliefs of some groups.

*Botanical Therapeutics* Participants suggested that the body of data on the safety, efficacy and potential of a range of botanicals is currently insufficient perhaps because of inadequate public investment in this area. Discussion focused largely on regulatory frameworks and the need for improved consumer information and education.

*Plant-Produced Antibodies* Similarly, participants discussed regulatory aspects of using plants as “factories,” e.g. a corn plant genetically modified to synthesize an antibody for the treatment of cystic fibrosis. Some suggested zero tolerance for “escapes” or potential pollen drift. Others felt that zero tolerance is an impossible endpoint given detection methods and suggested that risk/benefit analyses should be instituted. A body such as the National Research Council might be tasked to develop a protocol that would inform producers and also set a framework for combined U.S. Department of Agriculture/Food and Drug Administration guidelines and future legislation.

*Yield and Value* The financial benefits from new pharmaceutical crops will likely accrue chiefly to industry, through grower contracts, and land-access and distribution restrictions. Participants were divided on the issue of whether biotechnology and “pharming” herald a revitalization of rural America. The production of new crops might benefit small numbers of growers, but will likely not be a boon to rural vitality unless value-added components are processed near production areas. Some emphasized that neither biotechnology nor agriculture itself will be major forces in rural revitalization. It was suggested that the value added by biotechnology for farmers should be measured as savings of time and by increased diversity in crop rotations due to herbicide tolerance.

#### **APPLYING AGRICULTURE TO MEDICINE: FOOD TO PREVENT DISEASE**

These discussions were summarized for the plenary audience by Steven G. Pueppke, University of Illinois, and Joseph Warthesen, University of Minnesota.

*Functional Foods* Participants agreed that indeed functional foods have the potential to help lower the risk of chronic disease, as can individual changes in

behavior relating to diet, exercise and other risk factors such as smoking. Moreover, in the absence of changes in behavior, functional foods may help address nutrition needs. However, it is difficult to second-guess consumers; they indicate a preference for healthy foods, but do not necessarily buy them. Participants suggested that consumers are somewhat complacent about the role of food in their lives, particularly when it comes to disease prevention. They do not necessarily see a problem that needs to be addressed—prevention of diet-related chronic disease—and, therefore, do not see a need for fortified foods.

Potential risks should be addressed as functional foods are developed, including the amount of nutrient added to a food or product and the recommended level of intake, as well as potential interactions with other foods or medications. These considerations are particularly significant for infants and children.

Consumer education and information must take a holistic approach. Consumers might misinterpret information about a fortified product without weighing other aspects such as caloric or sugar content. More consumer education is needed regarding nutritional synergisms, antagonisms, displacement and cross-reactions across the diet. The benefits of functional foods may be more visible in developing countries, but conflicts are possible where opinion leaders who are interested in directions for healthy foods have reservations about the role of biotechnology.

*Allergenicity* Participants highlighted applications of new technology as ways to improve detection of allergens and predict the protein characteristics that might lead to allergic responses. They noted that the development of new animal models for allergenicity might be helpful.

*Edible Vaccines* Edible vaccines may ultimately be the most highly visible benefit from biotechnology—a benefit that the consumer can directly see as relevant to daily life. A vaccine as a food product will be perceived as more attractive than injected inoculation, and significant benefits are possible particularly for developing countries. Public-education and information programs were recommended in anticipation of new products to ensure that safe, beneficial and life-saving vaccines are accepted by consumers rather than discounted due to misinformation or confusion.

Participants noted the need for safety measures, including physical separation of crops and staggered plantings. Also discussed were measures, such as geographic isolation of vaccine crops and contained environments, to ensure segregation.

*Prevention* The prevention of diet-related chronic disease is beyond the realm of science and technology in important ways. Prevention is linked to behavioral

psychology. A key recommendation was for improved integration across agriculture and medicine, certainly across institutions of higher education that focus on teaching, research, and outreach. Participants highlighted partnerships that should be fostered among universities and social service providers, across K–12 educational systems and with the participation of federal policy leadership. Connections need to draw upon capacity of national organizations, corporations and healthcare providers. Broad collaborative efforts may help avoid unintended consequences—messages to reduce dietary fat and consume new “fat-free” products, for example, resulted in over-consumption of carbohydrates and sugar.

*Responsiveness* The agricultural and food system can be most responsive to nutrition and health interests by understanding its customer. The traditional agricultural and food-system customer has been the farmer, who, in turn, sees the grain cooperative or the food-processing plant as his or her customer. It has been easy for the system to push improvements such as enhanced agronomic traits into the market place, because they were readily accepted by the customer. Now, however, the real customer—the consumer—has stepped forward with a growing voice. Consumers are describing their preferences, and articulating what they do not want. Now, the agricultural and food system finds the need to respond to a demand for food quality and variety that is very different from the traditional farmer awaiting a new production technology. The system, including institutions of higher education, must listen and understand consumer messages, by forming new partnerships and by including a wider range of views and perspectives.

Participants acknowledged the critical role of federal policy, noting that the current Farm Bill does not integrate—and perhaps highlights the chasm between—food production and diet and health. They also noted opportunities for addressing prevention through policy relating to school-lunch and food-stamp programs, for example. They posed the question of what agriculture and food production might look like if it were based on dietary guidelines and the USDA’s food pyramid. The role of the media was emphasized in terms of the need for comprehensive messages on food and health aimed at consumers.

## **TOWARDS HEALTHY PEOPLE: LIFESTYLES AND CHOICE**

These discussions were summarized for the plenary audience by Janet Bokemeier, Michigan State University, and Maggie Powers, Powers and Associates, Inc.

*Information* There is no monolithic consumer. Information on food and health must be accessible and appropriately tailored to a variety of audiences. There is an important distinction between the myriad sources of information on food,

nutrition, and health and the sources that consumers trust. Information for consumers could be improved by increased collaboration among physicians, nutritionists, agriculturalists, and healthcare organizations—but it should not be simply to add to information overload. Federal agencies and universities are regarded as relatively unbiased sources of information; however, leadership at the federal and state levels will be required to ensure high-quality, synthesized information that stands out to consumers.

*Consumer Preferences* There was general agreement that consumers are being offered a wider range of choices based on demand. However, the voices of only some consumers are being heard. Those of limited resources and of some ethnic and age groups may not be considered. It was suggested that, indeed, consumer preferences and demands are being met—for food that is fast, tasty and inexpensive—showing that such consumers have not linked food preferences to health preferences. However, demand attributes include not only convenience and price, but also health and environmental and social values as shown by the growing demand for organic foods and other new products.

*Rural Lifestyles* Participants in the consumer-choice workshops echoed those in the “applying agriculture to medicine” workshops: the introduction of pharmaceutical crops will do little to reverse the trends of consolidation in agriculture or to revitalize rural America. Overall acreage devoted to “pharm” crops will be minimal. Pharmaceutical crops might elevate farm income for small numbers of producers and increase demands for a better-educated workforce in some regions. Improved relations between farmers, retailers, and wholesalers might enlarge urban specialty markets (for local seasonal fruits and vegetables, for example), thereby creating more opportunities for sustainable growth in rural areas. Community Supported Agriculture (CSA), with individuals participating with local farms, and organic agriculture were identified as potential mechanisms for rural community revitalization. Participants’ views were mixed, however, on whether CSA and organic food production would increase to a level that could strengthen and support vibrant rural economies.

*International Collaboration* Developed countries have a responsibility to address hunger, improve diets, help eradicate disease and improve agriculture in developing countries. Participants specified that assistance should:

- help developing countries develop their own solutions to their own problems,
- engage the collaboration of a variety of in-country and international entities specific to an issue or problem, and
- focus on long-term objectives rather than short-term fixes.

In sum, participants in the consumer-choice workshops emphasized the importance of information. They stated that quality information will enable consumers to make choices that can enhance rural and urban lifestyles in the United States. Integrated research and improved information can also lead to international collaborations for improved health worldwide.

**PART III**  
**PERSPECTIVES**  

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## ***Diet-Related Chronic Diseases: Moving from Cause to Prevention***

**SHIRIKI KUMANYIKA**

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There is a need for better communication between people involved in public-health issues, of which I am one, and representatives of the food industry. My objective here is to initiate the kind of dialog that I feel is necessary on public-health nutrition issues and how they relate to agricultural biotechnology and food production.

By way of background, I will discuss the current disease burden in the United States and globally, and public-health objectives and approaches: as public-health workers, what are we trying to achieve with health and how does that relate to food? Then I will discuss how food technology makes our lives as public-health people better on one hand and makes it worse on the other. Some implications for the food supply are noteworthy, based on a presentation at a World Health Organization/Food and Agriculture Organization (WHO/FAO) Consultation on Diet, Nutrition, and Chronic Diseases, Geneva, Switzerland, in January 2002, in which I participated. And I will conclude with policy implications and research needs, from my perspective.

### **CURRENT DISEASE BURDEN**

An article by Michael McGinnis, formerly the Deputy Assistant Secretary for Health, and Bill Foege, who was at the Centers for Disease Control (CDC), Atlanta, and also was President of the American Public Health Association, is often cited to establish that most deaths are now related to modifiable “lifestyle” factors: tobacco, alcohol, diet, and other personal behaviors (McGinnis and Foege, 1993). This picture of chronic disease is increasingly applicable globally, as shown by the *Global Burden of Disease* report (Murray and Lopez, 1996), which was a topic of much discussion at the January 2002 WHO/FAO meeting. Heart disease is now the most prevalent ailment globally, *i.e.* for developing as well as for developed countries. Although communicable diseases remain important in developing countries, they kill fewer people than non-communi-

cable or chronic diseases. Even in regions where there are food shortages, and people continue to strive for survival, some are dying from heart disease and diabetes. It is projected that, by 2025, most of the people affected by chronic diseases will be outside the United States, *i.e.* in India, China, the Russian Federation, Japan, Pakistan, and Indonesia.

Attempts have been made to calculate how much of the United States healthcare budget is devoted to conditions such as obesity. In 1995 dollars, type-2 diabetes cost about \$50 billion, for example. Some 5 to 8% of the national health care budget is spent on obesity-related diseases—a huge fraction for one condition, and it is probably an underestimate. In Australia it is over 2%, and 4% in the Netherlands and France. In developing countries in which healthcare budgets are small, and where diabetes is emerging, as much as 25% of the healthcare budget is being spent treating complications like end-stage renal disease. In such countries, there is potential for overwhelming effects of chronic diseases. Therefore, there is need to deal with these conditions even where there is need to get food to the hungry.

The latest data, for 1999, from the CDC website, show continuing increasing trends in obesity, including children in the 6 to 11 and 12 to 18 age groups. It is to be expected that 5% would be above the ninety-fifth percentile standard; instead 14 or 15% are above it, and this does not include the children who are considered to be at risk of being overweight, *i.e.* up to 30% of some populations. Not only does childhood obesity often lead to adult obesity, it is associated with problems during childhood.

The burden is not evenly distributed by ethnicity and income status; 6-to 11-year-old black girls were no more obese than white girls in the 1950s, whereas they were more likely to be above the ninety-five percentile in 1994 data, and a similar trend is seen in Hispanic girls. There is more obesity and more chronic disease within some minority populations than in the general population. For death rates, the excess shows up primarily in African Americans. Deaths per 100,000 population for heart disease and cancer are higher for blacks, whereas other minority groups have lower rates than for the white population. This indicates ethnicity-linked protective factors. One of our goals, from a public-health perspective, is to elucidate and preserve the factors that contribute to lower death rates—to understand why these groups have not acquired all of the risk factors in these diseases, at least to the point of mortality.

For heart disease and cancer, similar patterns by ethnicity are seen for men and women. For diabetes, Asian Americans are the only group with rates lower than for whites. More years of potential life are lost from diabetes among American Indians, Hispanics, and blacks compared to whites.

Finally, on disease burden, there is considerable low birth weight in this country among black and Puerto Rican Americans, and the chronic-disease-risk profile now includes this factor. The concept is that something happens *in utero*

to compromise an adequate pattern of growth. Children are born small, and, although they may gain weight rapidly, epidemiologically they remain at higher risk for chronic diseases in adulthood. This was seen in the Dutch-famine and in other studies leading to the “Barker hypothesis” or the “fetal-origins-of-disease” hypothesis. We are still trying to elucidate the reasons why low birth-weight due to undernutrition during pregnancy results in a predisposition in certain communities to chronic diseases later in life.

### **PUBLIC HEALTH PERSPECTIVE ON DIET**

The task of the public-health worker is to prevent and control disease. Anything in the system that appears to cause or aggravate disease is a possible focus for intervention. We are also responsible for positioning these issues in the larger discussion: in my work, I am interested in engaging those whose work has effects on what people eat or how active they are, or on other aspects of their health, *e.g.* urban planners, bus route planners, bankers. The role of the public-health scientist is to show that everything in the system is connected: apparently unrelated activities can have unexpected repercussions in terms of adverse effects on the health of the population. We are trying harder to quantify relative impact in order to allot priority in terms of numbers of people affected as well as severity. We are advocating for an objective policy process, *i.e.* to prevent vested interests from unduly influencing the policy process. I was at the infamous release of dietary guidelines when Secretary Glickman had a pie thrown in his face; part of the concern thus expressed was that vested interests had been influential. The only vested interest entering the policy process should be that of protecting vulnerable populations. We need to be one step removed when we are setting policy.

How do we set dietary guidelines? We try to keep track of everything—what people eat and how it affects their health—*i.e.* the nutrition-monitoring system that is now endangered because of lack of funds. We try to track food and where it is eaten, we set nutrient requirements, measure health outcomes, monitor consumer behavior, *etc.* With the appropriate data, we can monitor downstream effects of various choices, both in terms of industry activity and in terms of consumer behavior. It is complicated, especially when teaching epidemiology students, because it involves not just what is eaten but also host-specific factors. Whether supplements are being taken and in what forms and whether a nutrient needs activation all influence what doses people are getting and the ultimate health effects. It becomes a complicated process also from the conceptual and causal-model points of view; our data are seldom precise, and we are never quite sure whether an apparent effect is real or not.

We are now using an outcomes-based approach for devising dietary guidelines. Formerly, the approach was to look at whether intake seemed to be low or high based on our best data, and then examine evidence linking the nutrient to a particular disease or other adverse effects associated with intake at

that level. If there were possible adverse effects then we would track them, and if we could confirm them then we would change the level in the food supply, increase it or decrease it to alleviate the risk. However, there are too many components in the food supply. Going nutrient by nutrient, even with just fifty items to track, rapidly becomes too ponderous. Therefore, as we obtain better data—in the United States and in other countries, and the WHO is now using this approach—we can start with disease outcomes. Heart disease, diabetes, obesity, cancer, osteoporosis, and bone and dental diseases were most recently addressed by the aforementioned WHO/FAO diet and disease consultation. We then look at how convincing is the evidence that appears to associate a disease with food intake. If it is convincing, if it is a definite public-health/nutrition issue, we make a recommendation to increase or decrease intake. If it is probable, a potential issue, and we are not quite sure—food changes are considered to be harmless compared to, say, drugs with which physiological effects are unknown—any recommendation to increase or decrease intake would not be made aggressively, but offered as advice. And then, if there is no evidence of a pattern, *e.g.* with coffee—although past studies have proven negative—there may still be a potential research issue. As long as consumers or scientists *think* that there is potential for harm, we keep studying it. And when something new comes on the market, even in the absence of apparent adverse effects it will be a potential research issue, but, without evidence of disease, no effort will be expended to affect intake.

As an aside: intake is likely to change. If one item is modified because of convincing evidence, then it will shift at least part, if not all, of the dietary pattern. Also, intake may change unexpectedly because of alterations in the food supply. Again, it is difficult to draw sound conclusions from such complexity.

The type of evidence we obtain contrasts with data that are generated in controlled experiments. We seek ecological validity for human populations rather than for small numbers of individuals in a laboratory setting. We glean ideas by comparing countries or by following people over time and by seeking patterns in retrospect in those afflicted with disease, having examined what they were eating. In clinical trials we investigate whether changing that component of the diet has the desired effect. Then larger-scale trials are conducted before we consider new policy; simultaneous studies in the lab examine mechanisms to elucidate what should be tested in the trials.

To decide whether an association is causal, however—because it is not laboratory based—we use logic, graded logic, to determine if we have consistent, unbiased, strong, coherent, repeated, predictive, and plausible evidence. Although such firm evidence is seldom obtained, areas of relative certainty exist. We assign importance to relative risk; we are most concerned about factors that have large effects on people with diseases, but small effects on a lot of people are also of great concern.

The World Cancer Research Fund Panel published a comprehensive coverage of studies that attempted to relate cancer to diet up to 1997, and the evidence rules that they used with slight modification were also those used in the WHO/FAO report referred to above. In the strongest category there is consistency, with strong laboratory support and evidence of a dose-response, *e.g.* the more fruit and vegetables you eat the better off you are compared to people who eat less or none. In the “probable” category, there is less consistency, possibly resulting from fewer studies, but there is strong mechanistic or laboratory support. Then there is the “possible” category, which is generally supportive but no firm conclusion is possible. Lastly, in the “insufficient” category are issues that have public appeal, but no supporting evidence; they may garner media coverage but there is no persuasive reason for formal study.

The following are common themes, and areas in which we feel secure: calorie intake should be controlled, correct energy balance maintains weight, fat and cholesterol should be limited, a variety of plant foods have positive effects, and moderation in intake of sugar and salt is important, as are adequate physical activity, alcohol in moderation and avoidance of smoking. A conference was convened in 1997 (*Preventive Nutrition: Pediatrics to Geriatrics* in Salt Lake City, Utah by the Nutrition Committee of the American Heart Association, with invitees from the American Cancer Society, Diabetes Association, Dietetic Association, National Institutes of Health, American Academy of Pediatrics, and the USDA Dietary Guidelines) to discuss targets for change in the American diet (Deckelbaum *et al.*, 1999). At first, some of the commonality that emerged was thought to be coincidental, but, as more data are obtained, a convergence is emerging in mechanisms causing various diseases once considered to be very different. For example, at the time the conference was held, insulin resistance was not known to be related to cancer, but much data now indicate a link. Inflammation was thought to be strictly of infectious or other origin, but now it is understood to be linked to the atherosclerotic pathway. And apoptosis related to cancer is now understood to be related also to diabetes and atherosclerosis. So, it could be that one set of physiological processes, variously expressed in individuals with different predispositions or different exposures, leads to different diseases.

What is wrong with this approach? First of all, it is essentially outside the agricultural sector. So new recommendations on dietary guidelines are made with no knowledge of implications for the food supply, which has global implications. This type of public-health approach should be taken in conjunction with people in the production sector. Also, this perspective on food is very different from that of the consumer. We look at food as a carrier of risk, whereas few people sit down at the table thinking they that they are partaking of risk factors, or in the supermarket feel a need to minimize risk factors as they shop for food. Our reductionist chemical perspective is difficult to communi-

cate to consumers. In large part, our approach still emphasizes individual diseases and is simplistic with respect to dietary interactions. Epidemiology is very bad at handling interactions: we need broad control in order to investigate one part, even though in nature it is impossible to control one component that is influenced by others. It is also non-experimental because that is the only means of investigating natural scenarios in human populations, therefore, we can never be sure about cause. And a long lag-time is necessary for definitive answers; suspicion over a new addition to the food supply is likely to require thirty or forty years before it is proven to be justified, or not.

### FOOD TECHNOLOGY

Food technologists are addressing many of these issues, but outside of the public-health sector. There are unlimited possibilities, which is problematical from a study-design point of view. When I assess diet I have no idea what I am looking for in the population, because the many new variables that are entering the food supply are changing our bases for risk assessment.

Furthermore—a pet peeve of mine—the health-based marketing of single foods is not really consonant with dietary guidance, because we are moving more towards patterns. The emphasis on health effects from single foods is making life more difficult, because consumers have the tendency to look for magic bullets, as some claims seem to promise.

### FOOD SUPPLY

From a food-supply perspective, let's consider the United Kingdom, where most people are not meeting dietary guidelines—*e.g.* very few, especially women, meet the guidelines for fat or fiber—and also consider that huge changes are taking place in countries like China because of the globalization of the food supply. A model developed by the International Obesity Task Force, the policy and advocacy arm of the International Society for the Study of Obesity (London) gives ideas on how links between global markets and development factors and advertising reach across national boundaries effect changes. It becomes very difficult to devise generally applicable methods to elicit change.

Prakash Shetti at the Food and Agriculture Organization, addressing the WHO/FAO consultation, posed the question of whether, in recommending 400 g of fruits and vegetables per day, anybody had multiplied the global population by 400 to see if enough fruits and vegetables are actually available? Can dietary guidelines be met without talking to producers? Also, he pointed out that 80% of fish imports are to Japan, the United States and the European Community; a third of the catches from developing countries enter international trade, supplying 50% of total exported fish. We may be creating a situation with dietary guidelines in which we take food from developing countries so that we can have the right amounts of fish and fruits and vegetables in affluent countries. These issues need careful consideration.

It is difficult to predict trends in consumer preferences. Even with intense advertising campaigns, it is hard to tell if consumers will accept something different in the diet. An analysis of national-survey data between 1965 and 1991 by Barry Popkin documented changes in whites and blacks for fiber products, pasta, *etc.* For example, blacks increased their high-fiber cereal consumption by 1,500%, whereas whites increased theirs by a smaller amount. In some cases, trends for blacks and whites were in opposite directions. When the food supply changes, we still cannot predict long-term effects.

### **POLICY AND RESEARCH ISSUES**

Top-down strategies are being discussed, making some people uneasy because they conflict with the free-market ethic. Finland, for example, has successfully instituted such a strategy, although it requires community involvement, including cooperation from people who resist regulation and who object to the government telling them what to do. Certainly, integration and harmonization of public-health strategies with the food industry are essential. Having drawn up dietary guidelines, integration of agricultural and public-health policies becomes necessary. However, when agricultural policy is being set, improvement in public health is not a chief objective; clearly, coordinated policy development is needed.

With the top-down approach, there is less reliance on consumer education than hitherto. In the Finnish example, high rates of cardiovascular disease were reversed by environmental changes, with taxation and other strategies that did not rely only on direct appeals to individuals to change their behavior. Technology played a key role in developing a locally adapted rapeseed oil. The concept of a cholesterol-lowering oil produced domestically gained popular acceptance. The reductions in chronic heart-disease rates over a 25-year period are well documented—not merely through improved treatment (as here in the US), but by significantly reducing new cases. Dr. Pekka Puska, who led this successful program in Finland, is now with the WHO leading a global effort to reduce rates of heart disease (Puskka, 2000).

What are the implications of agricultural biotechnology for dietary guidance? If the food supply changes as a result of genetic engineering, we need to blend those changes with dietary guidance. This morning, my orange-juice carton indicated a calcium content equal to that in milk. Nutrients that were here are now also there. This may be good, but how does it affect the food pyramid? We need to forecast trends and consumer reactions with which to match the guidelines. Clearly, we need to study not only what people are eating and what is in the food, but, especially, shifts in food intake and particularly in vulnerable populations.

And finally, regarding environmental issues: in fact, there is very little understanding of how to change the environment in a way that would be beneficial for both producers and consumers with respect to diet and health.

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## ***Technology Progression In Plants Used For Food and Medicine***

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Over the past 10,000 years, humans have affected crop evolution by selecting and growing plants for dietary and medicinal purposes. Creation of the crops that provide our present food supply has been a dynamic and rapid evolutionary process resulting from selection for palatability and for nutritional and health-related traits. Comparatively less effort has been devoted to improvement of therapeutic or pharmacological properties, although new technologies are making this much more feasible. The first section of this report will focus on New-World species of the *Solanaceae* (the potato/tomato/tobacco family) to illustrate selection processes we have used to create new foods, with some mention of the value of new DNA-based tools for future improvements. Secondly, I will discuss biotechnological tools now being used to convert wild plants to “cultured materials” that may provide superior pharmaceuticals such as anti-cancer agents. Lastly, the potential for using modern biotechnology is discussed as a means of creating “modern herbal medicines,” *e.g.* crops as sources of oral vaccines.

### **CROP DOMESTICATION—REMOVING TOXICITY**

Potato (*Solanum tuberosum*) and its relatives evolved in the central Andes of Peru and Bolivia. More than a hundred wild species of tuber-bearing *Solanum* can still be found in the mountains of South America. Chemical analyses show that these tubers contain many toxic chemicals, including glycoalkaloids (which give a bitter taste), saponins, phytohemagglutinins, proteinase inhibitors, sesquiterpene phytoalexins, and phenols. These chemicals provide protection against attack by fungi, bacteria, and insects, and certainly also deterred our ancestors from eating them because of with their bitter taste and toxicity. About 6,000 years ago, a strategy for converting toxic potatoes to a palatable foodstuff was developed, and is still reflected in customs of modern Andeans when they collect wild tubers and make tunta. Bitter-tasting potatoes are spread on the ground at high altitudes to freeze overnight, and then are

walked upon to fragment them. Lying in the dry mountain air and going through cycles of freezing and thawing results in a “freeze-dried” product that is then placed in a depression along a running stream. The flowing water leaches out over 90% of the toxins, leaving the tunta for consumption. (One is reminded of instant mashed potatoes, albeit with much less work involved in their preparation.)

It is likely that ancestral “farmers” tasted the potatoes they collected and preserved and replanted any that were less bitter. This early domestication led to preferred “varieties” that could be grown at lower altitudes, since they no longer needed the dry, cold mountain nights for freeze drying. Several thousand varieties of potatoes are grown today in the Andean region, of varied flavor and nutritional value; they represent the trial-and-error selection of many, many farming generations. By the late sixteenth century, early explorers of South America who had developed a taste for the domesticated potato brought some varieties to Europe, whence they were later transferred to North America and other parts of the world. Today, potato is the world’s fourth most important food crop (after wheat, maize, and rice); we can thank our American ancestors for the “genetic improvement” that made this possible.

Scientists interested in how foraging humans developed agricultural societies have documented other examples of crop domestication over the last 10,000 years. The introduction of new foods has also been studied, with examples of slow acceptance. For example, tomatoes, which are in the same family as potatoes and also originated in South America, have only recently been regarded as edible. In the nineteenth century, Europeans and Americans believed they were poisonous. (There was logic to this assumption; wild tomatoes contain highly toxic compounds, especially alkaloids, much like the American wild relative—black nightshade (*Solanum nigrum*)—which we still avoid due to its toxicity. Early introductions of tomato to Europe may have been for ornamental value related to pretty flowers and colorful fruit.) As recently as 1820, the state of New York forbade tomato consumption; the edict was changed when Colonel Robert Johnston announced that he would eat an entire bag of them outside the courthouse in Salem, New Jersey. It is reported that two thousand people turned up to watch him die, and a band played a funeral march while Johnston ate the lot and announced: “This luscious, scarlet apple will form the foundation of a great garden industry.” He was correct; genetic improvement of tomatoes has led to a multitude of sizes, shapes, colors, and tastes (Figure 1). Some of those known today as “heritage varieties” date back to selections from the early 1900s.

### UNINTENDED OUTCOMES OF TOXIN REMOVAL

The domestication of virtually all of the world’s major food crops has involved the selection of varieties that have lost their genetic capacity to make toxic chemicals. While this is clearly of advantage for human digestion, it leaves the



Figure 1. Genetic diversity in tomatoes is evident in fruit size, color, and shape. Biochemical variability is less obvious, especially with respect to secondary metabolites such as toxic alkaloids.

plants with a greatly reduced defensive capacity against pathogens and predators (fungi, bacteria, and insects). (Toxic chemicals are nature's pesticides; weeds, which often have a bitter taste due to the presence of these chemicals, generally resist disease and predation better than crops.) About 300 years after introduction into Europe, potatoes were attacked by late-blight disease (caused by the oomycete *Phytophthora infestans*) in the devastating Irish potato famine of 1845 and 1846. *Phytophthora* had probably been a pathogen on other species, but mutations allowed it to alter its host range to include potato, especially "chemically weakened" domesticated varieties.

Agricultural specialists have developed alternative chemical strategies to improve crop defenses against pathogens and predators. In the nineteenth century, various "pesticide" formulations were developed in attempts to protect

potatoes, grapes, and other crops. These included sprays containing copper or arsenic, or nicotine in tobacco juice. Nicotine, a toxic alkaloid, is similar in chemistry to compounds found in other members of the *Solanaceae*, including some in tomato and potato that have been “genetically reduced” during domestication. (It is ironic that we genetically removed “defense” molecules from some crops, and then sprayed them with analogous compounds to limit disease and insect predation!) In the twentieth century, improvements in chemical synthesis allowed the development of many new classes of pesticides. In spite of very sizable expenditures by farmers who continue to purchase pesticides to fight diseases and insects, pests are still the primary cause of yield losses. We now know that many commercial pesticides mimic, at least partially, the actions of the defense chemicals that were originally in our food crops, but have been lost during domestication. In recent decades, many agricultural scientists have pursued the selective genetic restoration of “defense chemicals” to our crops, but without their inclusion in harvested portions that are eaten. This is a complex process, but one that is greatly aided by modern genomics research that defines genes and genetic elements that regulate metabolic pathways. It can be anticipated that the combined tools of DNA-based, marker-assisted breeding and gene transfer will foster guided evolution for further improvements in crop quality and resistance to pests and pathogens.

The power of new techniques is already apparent in the results of efforts of crop breeders to modify domestic potatoes: genetically modified varieties are now commercially available. One of the first targets was insect resistance, since predation (especially by the Colorado potato beetle) is among the most important reasons for yield losses, and prevention sometimes requires several applications of insecticide. In addition, loss of harvested tubers to insect larvae is a significant problem in developing countries lacking adequate storage facilities. The strategy first used to create insect-resistant potatoes involved transfer of a gene from a bacterium that is pathogenic to insect larvae, but which is harmless to birds, fish, and mammals. The bacterium, *Bacillus thuringiensis*, produces an insecticidal protein in nature (the *Bt* protein). When an insect larva eats plant tissue containing the *Bt* protein, its digestive process is fatally interrupted. This approach offers reduction in crop losses and, in parallel, less use of chemical insecticides.

### SELECTION OF PLANTS FOR “VALUABLE TOXICITY”

In addition to developing food crops with reduced toxin content, our ancestors used a trial-and-error approach to identify plants for treatment or prevention of disease. Herbal extracts have been used for thousands of years and still comprise the primary medicinals used by nearly two thirds of the world’s population. About 30% of “western” medicines utilize plant products in their formulation or synthesis. Although our ancestors could not have described it in modern terms, we now know that they were selectively identifying plants or

plant parts that contain complex chemicals that can directly modulate human metabolism. With the advent of modern chemical analyses coupled with the emerging tools of DNA-based genomic characterization of plants, the search for new bioactive molecules is progressing rapidly.

One of the goals of cancer chemotherapy and prevention is the discovery of compounds that are relatively selective of tumor cells and, therefore, have little effect on healthy tissue. By extracting chemicals from many plant species and analyzing the mixtures for activity in cancer-cell assays, we discovered that certain triterpene saponins (called avicins) from the desert tree *Acacia victoriae* are selectively toxic to tumor cells at very low doses (Joshi *et al.*, in press). To extend this research to human clinical studies we developed a transformed “hairy-root” culture system as a reliable means of production of avicins (Figure 2). Culture conditions have been optimized for root biomass production, and we have identified putative triterpene “metabolic clusters” with enhanced activity against tumor cells. This system provides sufficient material for clinical trials, and also a means of correlating structure of individual triterpene glycosides with specific target activity in mammalian cells.



Figure 2. A “hairy root” culture established by genetic transformation of *Acacia victoriae* using *Agrobacterium rhizogenes* for gene transfer. These cultures have the advantage of immortal root growth in fermentation tanks, with uniform and predictable metabolic performance necessary for commercial pharmaceutical production.

To relate our studies of “avicins” to the broader picture of drug discovery, it is noteworthy that plants contain tens of thousands of complex chemicals, many of potential value as “yet to be discovered” biologically active molecules for use as pharmaceuticals or nutraceuticals. This is a very active area of discovery research in public-sector and industrial laboratories. As new prototype products are identified, the tools of agricultural biotechnology will increasingly be used to establish reliable and uniform sources of pharmaceutical supply.

### **NEXT GENERATION AGRICULTURAL BIOTECHNOLOGY PRODUCTS**

Over the last decade, my colleagues and I have adapted the tools of plant biotechnology to the area of vaccine technology. Our primary motivation came from the need for less expensive vaccines in the developing world and for technology to allow developing countries to rapidly expand in-country manufacture of vaccines. According to the World Health Organization, more than 5 million children in developing countries die each year from common infectious diseases, predominantly those that cause diarrhea and respiratory ailments. Although preventative medicine has progressed rapidly in the last decade as biotechnology has been applied to create new vaccines, the new products are comparatively expensive for developing countries. For this reason, a novel strategy has been developed for vaccine production using transgenic plants that contain genes derived from bacteria or viruses that are pathogenic to humans. The “transgene” causes the plant to produce a protein that is the “antigenic signature” of the disease. Using mice as a model, we have shown that consumption of transgenic plant samples as food triggered an oral immune response to the “signature” protein.

Research on plant-based vaccines has progressed to human clinical trials, three of which have been conducted in the United States. All were conducted after the Food and Drug Administration evaluated and approved the protocols. Vaccines to prevent diarrhea were chosen for two early studies since it causes approximately 2.5 million infant deaths annually, chiefly in the developing world. The human studies have now been completed—Phase I trials that verified the safety and efficacy of the approach (Figure 3).

To accomplish oral immunization of infants using transgenic food, it is necessary to select an appropriate crop that can be grown in developing countries, and which is eaten uncooked, to avoid destruction of the vaccine proteins by heat. Accordingly, efforts are underway to develop vaccine-synthesizing tomatoes and bananas. Current research is identifying ways to prepare a dry formulation of vaccine-containing tomato extract using common food processing technology, and to cause the appropriate proteins to accumulate in the banana fruit for infant vaccination with a food puree. In both cases, our objective is to develop agricultural and food-based technologies that can readily be adopted in developing countries.



Figure 3. Human clinical trials have been conducted to test the effectiveness of transgenic potatoes as oral vaccines. This volunteer, shown eating raw potato, was part of a successful vaccine trial; plant tissues were engineered to accumulate a specific protein normally produced by a bacterium that causes severe diarrhea. When the potato samples were eaten, the immune system of the volunteers responded by production of antibodies specific to the bacterial protein, thereby providing evidence for success of a “plant-derived oral vaccine.”

The use of transgenic plants to produce and deliver oral vaccines also has applicability as novel strategies for disease prevention in animals, thereby improving the safety of our food supply, and stability of animal production.

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## ***How to Approach the Regulatory Conundrum?***

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Today, farmers and the environment are benefiting from the first generation of genetically engineered (GE) crops. The biotechnology industry and academics trumpet the next generation of such crops in terms of greater nutritive value, and new sources of pharmaceuticals, antibodies, industrial enzymes, *etc.* If those crops are commercialized, is the current regulatory structure in the United States up to the task of ensuring that they are safe for humans and the environment? In this paper, I analyze the ability of the regulatory system to adequately regulate the next generation of products from agricultural biotechnology. Without additional legal authority and stronger oversight, the regulatory system cannot ensure that only GE crops that are safe for humans and the environment will be commercialized.

### **WHAT DOES THE FUTURE HOLD?**

Virtually every week there is media coverage of new applications for agricultural biotechnology. New genes are being added to crops to make food more nutritious. For example, in the past year, the press has reported on the following potential products:

- Two genes from daffodil and one from a bacterium have been inserted into rice. “Golden” rice produces beta-carotene, which the human body converts to vitamin A.
- At University of California at Davis, scientists have transformed rice with the gene for the human breast-milk protein lactoferrin, with the objective of fighting infections.
- In Australia, a gene for a protein present in cows’ milk has been inserted into calves to enable production of higher-protein, more nutritious milk.
- Researchers are increasing the anti-oxidant properties of tomatoes by engineering them to synthesize more lycopene and increased levels of lutein (known to help fight eye disease).

Progress is being made in inducing crops to serve as “factories” for biologically active molecules in a cost-efficient and renewable manner. For example:

- Prodigene has engineered corn to produce avidin and trypsin. Avidin, naturally found in egg whites, is used in medical and biochemical diagnostics. Trypsin is an industrial enzyme used in drug production.
- Epicyte is currently engineering plants to synthesize a topically applied antibody that prevents the transmission of herpes simplex virus.
- Hiridin, a human anticoagulant protein, produced in transgenic canola, is available commercially in Canada.
- Corn has been genetically engineered to make an antigenic protein from the surface of the human immunodeficiency virus (HIV), which causes AIDS. Tests in animals are in progress for immune responses after ingestion of the transformed corn. Bananas and carrots are also being engineered to produce vaccines.

Those potential products, and many others, provide hope that the next generation of GE crops—fruits, vegetables, and grains—will benefit consumers, both in developed and developing countries, as nutritious and healthful foods and as new sources of pharmaceutical and industrial molecules.

### **IS THE REGULATORY STRUCTURE UP TO THE TASK OF REGULATING NEW USES OF AGRICULTURAL BIOTECHNOLOGY?**

Currently, agricultural biotechnology is regulated to protect human health and the environment. Is the current federal regulatory system up to the task of thoroughly assessing how safe the next generation of GE crops will be for humans and the environment? A review of the regulatory system’s treatment of the first generation of GE crops reveals weaknesses and gaps in the current system and problems that will arise when regulating future crops. New statutory authority and stronger oversight are needed to ensure that only commercial products that are safe for humans and the environment will be marketed.<sup>1</sup>

### **ENSURING THAT GE CROPS ARE SAFE TO EAT**

Consumers want assurances that the foods they eat are safe. Thus, the Food and Drug Administration (FDA) should ensure the safety of biotech foods. The FDA’s current regulatory system, however, does not adequately ensure that only safe GE crops are marketed.

*Current Regulation of Biotech Foods* Currently, FDA does not formally approve any GE crops as safe to eat. The FDA has the authority to approve new food

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<sup>1</sup>Drugs and vaccines produced by the next generation of GE crops will be regulated similarly to their conventionally produced counterparts. Discussion of those regulatory issues is not included here.

additives, but says that the GE crops developed so far do not fall within that category. Instead, FDA has determined that GE crops are similar to conventionally bred crops and typically fall into the category of “generally recognized as safe” (GRAS) foods. FDA’s policy does allow a GE crop to be treated as a food additive requiring mandatory approval if that crop raises a food-safety concern. However, to date, FDA has not determined that any GE crop should be considered a food additive, and it is unclear if any future crop will be so considered. Both FDA and the biotech industry will strongly resist putting GE foods through the food-additive process, which is perceived as time-consuming and burdensome.

To oversee any potential food-safety concerns that might exist for a GE crop, FDA adopted a voluntary consultation process to review safety data provided by companies to ensure compliance with existing laws. In that process, the company provides summary information about the safety of its product to FDA, which, in turn, provides informal advice about the adequacy of the tests conducted by the company. In conducting its scientific safety assessment, the company provides information to show that the GE variety is “substantially equivalent”, *i.e.* as safe as its conventionally bred counterpart. To date, all commercialized GE crops have proceeded through the voluntary consultation process before marketing.

*Problems with FDA Current Biotechnology Policy* There are numerous problems with FDA’s current policy for GE crops. First, the consultation process is voluntary. There is no legal obligation requiring a company to provide a safety assessment to FDA and no consequences to the company that does not voluntarily consult. Second, the consultation process is developer-driven instead of FDA-driven. The biotechnology company decides what safety tests to conduct and what data to submit, because the company’s obligation is to satisfy itself that the product is safe rather than to prove safety to FDA. This process provides FDA with limited ability to require specific tests or mandate specific data. Third, FDA’s food-safety analysis is not comprehensive. Their guidance states that the consultation process is “not a comprehensive scientific review of the data generated by the developer.” Fourth, and most importantly, FDA does not determine if the product is safe. The voluntary consultation process culminates with FDA stating that it has “no further questions . . . at this time” rather than stating that the product is safe to eat.

Although no human-health problems with GE crops have been detected, the voluntary consultation process is not the most effective way to protect the consumer and engender confidence. In the coming years, the scientific safety issues raised by more-complex GE crops (nutritionally enhanced, engineered with new metabolic pathways) cannot be adequately assessed with the current industry-driven process.

*FDA's Proposed Mandatory Notification Rule* In January 2001, the FDA proposed regulations that would mandate notification before a GE food is marketed. Although that proposal improves upon the current process by mandating agency review and by increasing transparency, it does not change the agency's scientific review nor will it result in an official determination of safety. Under the mandatory notification, FDA still will not respond with an affirmation that the food is safe to eat. Also, if a developer markets a GE food without notifying FDA, FDA still must prove the food is adulterated before it can be removed from commerce.

*How Will the Current System Treat the Second Generation of Biotech Foods?*

If high-lycopene tomato makes its way to the marketplace, will FDA's current regulatory policy treat it any differently from the first generation of herbicide-resistant and pesticide-producing crops? The answer is no. It is unlikely that FDA will treat the second generation of GE crops as products that contain additives since the gene products in high-lycopene tomato or rice engineered to contain human breast-milk protein are already present in the normal human diet. Thus, the only food-safety assessment those products will receive is the less-than-comprehensive voluntary-consultation process. Those products will have to abide by the mandatory notification process, but only if FDA finalizes that proposed rule. The FDA has stated that it will not make a decision on its proposed rule before fiscal year 2003, and, if promulgated, no one knows what form the final rule will take.

*A Proposal for a Mandatory Approval Process* The FDA should establish a new mandatory approval process for GE crops, unrelated to the current food-additive process. It should promulgate regulations that establish testing and data requirements based on advice from a National Academy of Sciences panel charged with determining what scientific information is needed to assess food-safety concerns regarding such crops. The approval process should have time limits so that each application receives a determination within a reasonable interval. In addition, the mandatory approval process should ban any GE food with a new allergen as well as prohibit approvals for crops intended for animal feed but not human consumption. If new legislation is needed so that FDA can implement an approval process, Congress should pass such legislation.

A mandatory pre-market approval process at FDA for biotech foods would have numerous advantages over the current system. First, formal approval would provide an independent check on industry's safety determination. FDA would share responsibility for the safety determination and would help prevent food-safety mistakes. Second, it would eliminate the gap in the regulatory system that allows some biotech foods, but not others, to be marketed without pre-approval. Currently, transgenic animals require pre-market approval by FDA and pesticidal plants require pre-market approval by the Environmental

Protection Agency, yet non-pesticidal transgenic plants are subject only to FDA's voluntary consultation process. Third, a mandatory process need not be more burdensome to applicants than the current voluntary procedure. The industry states that it already conducts all reasonable and necessary tests to ensure safe products, so there is little likelihood that FDA would require significant new testing. Fourth, a mandatory approval process would make the regulatory system in the United States similar to those in Canada and Europe, where biotech foods must be affirmatively approved before marketing. Finally, a food-safety determination by FDA would go a long way to improving consumer confidence and public perception of the safety and acceptability of biotech foods. Consumers would be much more comfortable with FDA's determination that a food is safe to eat than with Monsanto or Dupont's in-house determination.

In conclusion, the benefits of a properly constructed mandatory approval process at FDA would be significant and the burden for industry need not be much greater than the current voluntary consultation process. It is unclear why industry is against a process that would provide an independent verification of a product's safety and thus sway the skeptical consumer. Therefore, producers of new GE crops should embrace sensible legislation to require a mandatory approval, such as Senator Durbin's Genetically Engineered Foods Act.

## ENVIRONMENTAL ISSUES SURROUNDING GE CROPS

The second major regulatory issue for new GE crops is ensuring that they do not adversely affect the environment. For the federal regulatory system to adequately carry out that function, the system must:

- ensure that all biotech products get a thorough environmental assessment by a competent government agency before release into the environment; and
- ensure that, if products are approved with conditions to manage possible environmental risks, those conditions are adhered to (through compliance assurance and enforcement measures).

Unfortunately, the current federal regulatory system for GE crops at the United States Department of Agriculture (USDA) falls short on both accounts.<sup>2</sup>

*The Current Regulatory System at USDA* Under the auspices of the Plant Pest Act, the USDA has established a regulatory system for genetically engineered plants that could become plant pests. Crops subject to those regulations include (1) any crop that is a listed plant pest, and (2) any crop that has introduced DNA from a listed plant pest or an organism whose plant-pest status is

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<sup>2</sup>The focus here is on the USDA regulatory process for biotech crops and not EPA's regulatory structure for plants engineered to contain a pesticide.

undetermined. For example, the regulations capture any variety that was genetically engineered using *Agrobacterium* DNA as a vector. The regulations do not include crops engineered using a gene gun, unless the inserted DNA comes from a listed plant pest or an organism whose plant-pest status is undetermined.

Any plant covered by USDA's regulation must submit to one of three oversight processes before release. The first is a notification, in which the applicant provides details about its proposed release and the USDA has thirty days to respond. The USDA has established criteria to determine which products are eligible for the notification process and guidelines that must be met to minimize environmental effects from the release. Notification is currently used to regulate virtually all of the field tests for GE crops under USDA's jurisdiction, and even for some crops that are grown commercially.

The second process is permitting, which requires a more detailed application and a longer review time at USDA before the release is authorized. Genetically engineered plants that must be permitted (instead of a notification) include crops producing pharmaceuticals and those that could affect non-target organisms. Permitting is not used as commonly as notification, although hundreds of permits have been issued since USDA began regulating GE crops.

The third process is a petition for non-regulated status. A petition is a request that USDA determine that there is no associated plant-pest risk and the crop no longer needs to be regulated. A petition for non-regulated status has been the primary pathway to commercialize GE crops. Before a petition is granted, USDA conducts an environmental assessment of the crop and seeks input through a formal public-comment period.

*Inadequacies in USDA's Current System* There are numerous inadequacies in USDA's current method of regulating GE crops. First, the regulatory system captures only GE crops that could become plant pests, whereas others, such as those made with the gene gun and corn DNA, do not require even a notification before release into the environment

Second, the USDA does not require a thorough environmental assessment before a regulated GE crop is released. Crops released through either the notification or the permitting process almost never receive an individual environmental assessment, yet some of those crops might have a significant impact on the environment. A recent report published by the National Research Council (NRC) stated that, "With few exceptions, the environmental risks that might accompany future novel plants cannot be predicted. Therefore, they should be evaluated on a case-by-case basis." Yet, notification and permitting do not evaluate environmental risks on a case-by-case basis since, in most cases, no environmental assessment is conducted.

Third, for those crops that do receive an environmental assessment from USDA (primarily for nonregulated status), those assessments are inadequate.

According to the NRC report: “Currently, APHIS’s<sup>3</sup> environmental assessments focus on the simplest ecological scale. . . . APHIS should include any impact on regional farming practice or systems in its deregulation assessments.” Thus, USDA’s environmental assessments do not address all relevant environmental concerns.

Fourth, it is unclear whether USDA has the legal authority to adequately address environmental issues that arise in an environmental assessment. USDA has regulatory authority to address plant-pest risks, but does not have authority to prevent a crop’s release if it may cause ecological damage unrelated to agriculture.

Fifth, most large-scale releases occur after the GE crop has obtained nonregulated status. Although the petition process for nonregulated status is transparent, open for public comment and involving an environmental assessment, the process results in a crop that is no longer regulated by USDA. That prevents USDA from requiring post-release monitoring for environmental effects and from addressing unforeseen environmental issues. Therefore, for the vast majority of crops, USDA has extremely limited ability to address environmental issues that might arise after commercialization.

Finally, the process at USDA involves no food-safety analysis of the crop before it is released into the environment. For open-pollinated crops such as corn, a release could result in the gene-product entering the food chain. USDA’s process makes no assessment of whether that gene product would be harmful to humans if it were to enter the food supply.

*Preventing Contamination of Other Crops and the Food Supply from Experimental GE Crops and/or GE Crops Producing Non-food Products* When the USDA regulates a GE plant under either the notification or the permitting process, one of its goals is “to minimize persistence in the environment and inadvertent mixing with . . . products which are used for food or feed.” This is accomplished, in part, by using containment and/or segregation procedures. Those procedures may limit contamination, but do not eliminate it, since eliminating all contamination is impossible.

The ability of the regulatory system to adequately contain GE plants that might harm the environment or humans is extremely important, whether it is a corn plant producing a pharmaceutical or a sunflower plant producing an industrial chemical. The USDA and FDA have stated they are working on guidelines that will address contamination issues surrounding pharmaceutical plants, but that guidance currently is not publicly available. Yet, numerous field trials and commercial planting of pharmaceutical crops have occurred without uniform standards to minimize contamination. Consumers would lose confidence in agricultural biotechnology and the safety of the food supply if

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<sup>3</sup>Animal and Plant Health Inspection Service, a branch of the USDA.

they found out that some food they are eating contained a pharmaceutical or industrial chemical that has not been found safe to ingest. Thus, strong regulatory structures that minimize contamination are important.

The first way to minimize the effects of GE crops on non-GE counterparts and the food supply is through containment to limit gene flow. Containment procedures include reproductive isolation measures, such as prescribed distances for planting GE crops in areas where non-GE crops of the same species are grown, planting guard rows between GE and non-GE crops, the use of lines that shed sterile pollen, harvesting prior to flowering, netting or bagging anthers prior to pollen shed, and the staggering of flowering times with respect to adjacent crops.

For example, the USDA recently sent a letter to companies planning on planting pharmaceutical corn crops in 2002, in which distance restrictions were set forth, ranging from 0.25 to 5 miles (the latter being the distance from seed corn) and planting times for the GE corn that are either 14 or 21 days before or after adjacent non-GE corn. The letter, however, contained no scientific justification for the distances or planting times chosen nor did it state how effective the restrictions would be in reducing contamination of non-GE crops. It is unclear whether those distances and planting times will reduce the chances of gene flow by 50%, 90%, or 99%. Thus, although reproductive isolation is necessary and needs to be established, there should be a public explanation as to why certain procedures are required and what is the expected benefit.

The second type of containment procedure that minimizes persistence of the GE crop in the environment is in post-harvest activities, which includes limiting the use of land for a period of time following the crop, monitoring the land and neighboring fields for volunteer plants of the GE crop, and destroying the crop after harvest using specific procedures. Those post-harvest restrictions are important to prevent GE crops from persisting in the environment after field trials or commercial plantings. It is unclear, however, how effective they are in preventing gene transfer.

In addition to containment procedures, segregation is usually employed to ensure that experimental GE crops and those producing non-food products do not mix with crops (both GE and conventional) that are grown for food. Segregation has generally involved dedicated machinery and vehicles to harvest, transport, and store certain GE crops.

Is segregation effective in preventing contamination? When farmers planted StarLink™ corn that had been approved only for feed use, Aventis (the developer) agreed that the crop would be segregated from corn used for human consumption. StarLink™, however, ended up in the food supply, either because no segregation system was actually in place or because it was ineffective. Many experts now question whether any segregation system can effectively separate one type of corn from another. Thus, it is an open question how effective segregation can be at eliminating contamination of the food supply. If properly

set up, segregation can minimize contamination, but may never be able to eliminate it.

*Enforcement* When a GE crop has been approved for release, frequently the approval sets forth conditions to minimize or eliminate environmental and/or food-safety risks. It is imperative that developers and growers comply with those conditions, and it is USDA's job to verify adherence. Is the USDA doing a good job enforcing its conditional approvals? The answer is no.

The USDA has conducted some inspections of field trials and commercial releases that have permits or submitted notifications, although the level of effort is small compared to the universe of GE crops. To date, there have been over 9,000 permitted releases or notifications for GE crops, of which only a very small fraction has been inspected by USDA. The inspections USDA has conducted have resulted in approximately sixty enforcement actions, primarily letters explaining improper conduct and requesting adherence to restrictions.

When the USDA does inspect a permitted release, however, it is unclear whether those inspections are as comprehensive as needed to safeguard the environment. In particular, the USDA does not check to see if the containment or segregation procedures are working. For example, inspectors do not check neighboring fields to see if pollen has drifted to non-GE crops. Neither do they test grains on the farm or on neighboring farms to ensure that the crop has been properly segregated. Thus, the USDA should not only inspect to see if the conditions imposed on a GE crop have been met; there is need to determine whether those conditions resulted in containment and segregation.

*Conclusions About USDA's Regulation of GE Crops* The USDA's regulations do not adequately protect the environment or humans from current GE crops and will not adequately protect the environment and humans from the next generation of crops, such as those producing pharmaceuticals. In particular, the USDA regulatory system has the following deficiencies:

- it does not capture all GE crops;
- it does not result in a thorough environmental assessment of all GE crops;
- it does not have a mechanism for the monitoring of environmental problems that might arise after a crop has obtained nonregulated status, nor a means of enforcement if a problem occurs; and
- it does not conduct inspections to determine the effectiveness of containment procedures to minimize gene flow from GE crops or of segregation requirements to minimize food contamination from certain GE crops.

Until those deficiencies are eliminated, the federal government will not be adequately ensuring that the only GE crops released are safe to humans and the environment.

## WHAT TO DO ABOUT GE CROPS THAT ARE NOT INTENDED TO BE FOOD BUT MIGHT END UP IN THE FOOD SUPPLY?

As discussed earlier, the next generation of biotech food crops will provide non-food products: pharmaceuticals, medical diagnostic proteins, *etc.* What would happen if those crops accidentally ended up in the food supply due to gene flow from pollen, contamination of seed stock, or a breakdown in an identity-preserved segregation system? Would they be safe to consume? Would they be safe to consume only at certain exposure levels? Is there any authority for FDA to review and approve those products as safe to eat in the event that they enter the food supply? Those are all questions that need to be addressed. Containment and segregation will not be 100% effective, so it is only a matter of time before one or more of the non-food GE crops enters the food chain.

The Federal Food Drug and Cosmetic Act (FFDCA) regulates everything that is intended to be used as food or feed. A pharmaceutical corn plant or a corn plant producing avidin, however, is not intended by the developer to be used as food or feed. Thus, such products are neither food additives, nor would they be subject to FDA's voluntary notification process (or their proposed mandatory notification rule). The FDA has limited authority over those products unless they show up in food. At that stage, the FDA could consider foods containing the pharmaceutical or industrial chemical as adulterated, and remove them from the market. The burden would be on FDA, however, to prove that they are adulterated.

The current system is not the best way to guarantee a safe food supply, when contamination by non-food GE crops is inevitable. A possible solution to this problem would be for the proposed mandatory FDA-approval process to apply to non-food GE crops. Under that approval system, FDA could set tolerances for non-food GE crops. Then, if that GE crop entered the food supply, eating the engineered substance would be safe as long as the amount was below the tolerance level. No consumer would need to fear that they were eating food containing unsafe substances. In addition, the rigor of the food-safety assessment conducted by FDA could be proportionate to the physical and biological confinement of the crop. If the pharmaceutical plant is grown in a location far from other corn plants, only a limited food-safety assessment might be required because the likelihood of contamination would be extremely small. On the other hand, if the pharmaceutical plant is grown in Iowa, a complete food-safety analysis might be warranted.

## CONCLUSION

Although agricultural biotechnology may allow us to produce more-nutritious foods and useful medical products, the current federal regulatory structure is not up to the task of guaranteeing that they are safe. With new legal authority and better regulations, a strong, but not stifling, system can be established that independently reviews products and approves those that are safe for consumers and the environment. Such a system is essential if consumers are to have confidence in biotechnology and accept its products in the marketplace.

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## ***Genetically Engineered “Foods for Health”: Are We Asking the Right (Ethical) Questions?***

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My purpose is to discuss the ethics of genetically engineered foods for health (GE foods for health, GE foods). Ethical questions about agricultural biotechnology in general, and about specific applications, such as biofuels and biomaterials, have been addressed in previous NABC meetings. These have included considerations of environmental safety, research ethics, and socioeconomic concerns such as power and control in the food system (e.g. Thompson, 2000; Comstock, 2001). I want to focus on a different kind—perhaps a different order—of questions associated with ethics and agricultural biotechnology. These concern the basic ethical legitimacy of GE foods for health. Simply put, are these GE foods ethically justifiable? The importance of this issue stems from the increasing human and financial resources that are being committed to research and development on GE foods. Yet, most people in the food biotechnology establishment have never asked whether this R&D is ethically justifiable in the first place. Indeed, most appear to *assume* that GE foods are ethically justifiable or legitimate. This assumption may not be legitimate, even if science generally is ethically justifiable and some other applications of biotechnology are also legitimate. If GE foods are ethically justifiable, the biotechnology establishment will have to accept the ethical responsibility to prove that they are. This, however, implies that some other questions, specifically concerning the ethical responsibilities of those in the biotechnology establishment, need to be addressed.

### **ETHICAL QUESTIONS**

Basic ethical questions are normative and critical. They ask for *justifications* for actions, for the principles or reasons why we should or should not do certain things. Ethical questions demand reflection on our principles and values, on the way we live our lives, and how we interact among ourselves as we go about our business. Critical ethical reflection should give us answers to the following questions:

1. Should we genetically engineer foods to produce health- and nutrition-enhancing traits?
2. Are we ethically justified in doing so?
3. And, most importantly, why are we ethically justified in this work—that is, on what principled basis?

There are two main kinds of ethical principles that can be employed to justify and critique actions and /or practices: *Consequentialist* and *Intentionalist*. Consequentialist ethical principles assess actions or practices in terms of their outcomes. Accordingly, good outcomes justify an action, bad outcomes condemn it. How “good” and “bad” are defined is, of course, critical, though most ethicists interpret good in terms of benefits and bad in terms of costs or risks. It is important to note that consequentialist ethics stand in contrast to intentionalist ethics (technically, *deontological* ethics). Intentionalist principles judge actions in terms of their consonance with a pre-determined set of duties or virtuous character traits. Intentionalist justifications undertake to show that people have followed or tried to follow what ethical principles demand. When people do their duty, they are justified; when they stray from acting on principle, they are wrong.

Before we can ask whether GE foods are ethically justifiable, we need to ask on what ethical basis science in general is to be judged. This is important, because science is usually regarded as ethically neutral. Science generates knowledge and technology, and it is only after the results of scientific practice are in the public arena that questions can be raised as to their ethical justifiability. But this is precisely the point. While the ethical neutrality of science may be a goal or ideal, in fact we judge science by its results or outcomes. Indeed, scientists appear to want their work to be judged by its fruits. There is some consensus among ethical analysts that the very nature of modern science—institutionalized, corporate, product-driven—demands that we focus on outcomes or products as a way of determining whether the scientific enterprise is ethically sound, since it is difficult, if not impossible, to discern intentions to be dutiful or virtuous. The ethical basis for judging science must, therefore, be a consequentialist ethical principle: science is justified when its outcomes are justifiable. Usually, this means when its consequences are beneficial. When science confers benefits that outweigh costs or override risks, it is considered to be engaged in justifiable practices. When it does not confer benefits, ethical questions remain (Burkhardt, 1992). As much as we may want science to conform to predetermined ethical principles or virtues such as the Golden Rule or the Hippocratic Oath, in fact we judge it by its results.

There is consensus among ethical analysts—echoed by many scientists and endorsed by the public—that science has *prima facie* ethical legitimacy. Science has produced knowledge and technologies whose benefits are clear and

outweigh any relevant costs or risks. Certainly, on occasion, science has generated outcomes of a less-than-clearly-beneficial nature. Overall, however, it has succeeded in an ethical sense. The importance of this ethical legitimacy cannot be overstated, because it confers on the larger scientific enterprise an ethical “high ground” from which scientists and research administrators can defend themselves from critics, and command resources and moral support from the public. Surveys have shown a general trust of university scientists and medical people, providing some support for this claim. This is because the public believes that science has justified itself through what it has delivered (NSF, 2000). For the past several years, researchers engaged in biotechnology have been making a bid for the same ethical justifiability and public credibility, which has met with less success. Ultimately, the outcome of this attempt will depend on benefits actually delivered.

Indeed, the question is whether a currently proposed set of products—GE foods for health—is ethically justifiable. According to consequentialism, actions are ethical only if they provide benefits that outweigh costs and minimize risks. Products that are the outcomes of those actions are legitimate only if they are truly beneficial. *Are* GE foods beneficial? The problem is, we cannot answer that question, since GE foods do not yet exist in a real-world context in which to judge their benefits.

We can, however, ask a similar question about GE products currently on the market and extrapolate an answer for foods for health. Consider two types of current GE products: in the medical arena, human insulin and in agriculture, *Bt* corn. Are these products ethically acceptable, meaning, are they beneficial? If so, the actions of those who researched, developed, commercialized and marketed them are (were) justifiable.

Regarding GE human insulin, I think the answer is yes. Genetic engineering has resulted in a product that serves a significant portion of the public, without risk or benefit to the rest of society, and with only minimal (if any) risk to the consumer. The benefits conferred far outweigh any risks. We might even make the case that once scientists knew how to engineer bacteria to produce human insulin, they were ethically obliged to do so.

*Bt* corn appears to be less unequivocal as to benefit/cost/risk assessment. This is not to say that it is ethically unacceptable. There are ongoing debates about environmental and economic risks, and questions as to farmers’ ability to sell *Bt* crops. This may be a situation in which differing parties to the debates have different understanding of what counts as a benefit and what counts as a cost or risk. The point is that a consequentialist ethical principle such as “provide benefits greater than risks” demands that “benefits greater than risks” must be proven unequivocally for the action or product under consideration to be ethically justified.

This points to an important concern regarding the ethics of GE foods for health. If consequentialist ethics demand actual benefit/risk/cost calculation in

order for an action to be justified, future products of genetic engineering cannot (yet) be subject to an ethical judgement. It would appear that we cannot answer the question, “Is research and development of GE foods for health ethically justifiable?” Yet, given the clearly positive connotation of the term “foods for health” and the clearly beneficial nature of the kinds of GE foods that have been proposed, biotechnologists, nutritionists, farmers, and many others want to answer that question with a resounding “Yes!” Despite hopes and visions of a hunger-free world and universal health, ethics demand that some principled reason be given for that answer. This reason can be found in what I refer to as the “Future Benefits” argument.

### THE FUTURE BENEFITS ARGUMENT

The vision and hopes associated with GE foods for health are occasionally framed in terms of slogans proclaiming “the promise of biotechnology.” There is actually a philosophically sophisticated and potentially powerful argument that underlies the slogan. This argument might provide an ethical justification for the actions of people in the agricultural and scientific communities who not only believe that pursuit of products such as the “foods for health” is ethically justifiable but that it is obligatory. In one form, the “Future Benefits” argument is as follows (Burkhardt, 2001):

1. Technologies intended to provide benefits in the future are ethically justifiable if they will provide benefits that outweigh risks/costs.
2. Agricultural biotechnology will provide benefits in the future that outweigh risks/costs.
3. Therefore, current agricultural biotechnology R&D is ethically justifiable.

Two things are initially worth noting. First, Premise 1 is a general principle that establishes conditions on ethical acceptability or justifiability. Second, Premise 1 is a consequentialist principle, concerned with the outcomes of (future) actions or, in this case, technology products. This is important because it means that ethical justifiability depends on benefits actually being conferred that outweigh risks or costs. It further means that the conclusion, *i.e.* that current research and product development is ethically acceptable, depends on those benefits actually being conferred. The onus is on what the second premise actually means.

In the way that it is stated, Premise 2 looks like a prediction, an answer to several of the “can” and “will” questions found in the conference program. This begs the question, “What will it take for Premise 2 to come true?”

Charles Arntzen (2002) noted several hurdles that must be overcome for the hope of medicine’s and agriculture’s merger to be fulfilled, and I will not dwell on them. Still, we must note that the first and foremost condition for functional foods to become a reality is that scientists succeed in their individual and collective enterprises. Crops must be transformed so that health and nutritional

properties can be added or enhanced, or allergenic properties eliminated. Beneficial traits must be introduced or enhanced in crops that people already consume or will readily adjust to consuming. There will have to be legal and institutional successes as well, as Gregory Jaffe (2002) has pointed out. The patent process will have to be successfully negotiated both domestically and internationally. Differences in the cultures that prevail in medical/health/nutritional research, agriculture, and agricultural research will have to be worked through. Corporations involved in everything from life-sciences research to marketing seed may have to adjust to the realities of dealing with perhaps numerous federal, regional, state/provincial or even local bodies such as health departments rather than just one or two federal government agencies. Ultimately, consumers will have to accept the new foods. Furthermore, the products must be such that their first consumer, the farmer, can easily adapt and grow the crops. For example, protein-enriched wheat that requires excessive inputs of, say, water or a grower's time, without there being a concomitant price increase, would never succeed.

GE foods for health will ultimately have to reach, and be accepted by, the ordinary consumer. This means that these foods will have to be compatible with consumers' tastes and preferences, lifestyles, and basic values. Most importantly, these foods will have to be available and affordable, or they will fail. Even if they are inexpensive, nutritious, delicious, allergen-free, disease-curing, *etc.*, possessing all of the health-positive characteristics we currently envision, if they fail in the marketplace they will fail to confer the benefits necessary to make their present development ethically justifiable. In other words, GE foods will actually have to be beneficial in order for them to be ethical. Will they be beneficial? Will they succeed at each step in the chain, from the laboratory, through regulatory assessment, through farmers' fields, to the dinner table? Although social scientists can offer some assurances about the future, most would concede that they can predict only broad social trends or patterns. Since science, law, agriculture, and economics are all human enterprises, predictions about the benefits of future foods for health are uncertain.

If we cannot reasonably predict that agricultural biotechnology will confer benefits in the future, the Future Benefits argument fails, leaving the conclusion without foundation. If biotechnology will not confer future benefits, then, in terms of consequentialist ethics, current research and development are not ethically justifiable.

Clearly, this conclusion contradicts what most of us believe about future foods for health and about current work being done to produce them. It certainly contradicts what most of us *hope* about them. The above conclusion suggests, however, that we might want to interpret the Future Benefits argument's Premise 2—agriculture biotechnology will provide benefits in the future—not as a prediction, but as a promise. There has certainly been enough *rhetoric* about the “Promise of Biotechnology.” Perhaps it is time to interpret

that “promise” not in terms of *potential*, but as an *ethical commitment*. As such, “agricultural biotechnology will provide benefits in the future” means that those who engage in it place themselves under an ethical obligation to guarantee, as far as it is within their power, that benefits are actually conferred sometime in the future. Since “agricultural biotechnology” means the whole food biotechnology establishment—all the individuals and institutions that surround the conceptualization, research, development, marketing, *etc.*—this also includes those in the medical/health/nutritional establishment engaged in this enterprise.

### THE PROMISE OF BIOTECHNOLOGY

The “Promise of Biotechnology,” so understood, immediately leads to another set of ethical questions, and to many scientific and social-political-economic questions that follow from them. Promises or commitments are only as good as the possibility of their being carried out. One question that immediately arises is thus: “What should one do to guarantee that benefits result from one’s work in this enterprise?” This may appear to be a scientific question—*e.g.*, “What will make this plant species exhibit this trait?”—and this is certainly relevant. More to the point, however, are questions that address social-political-economic concerns: “What future institutional or historical or economic conditions must be in place for the benefits of GE foods for health to be fully realized?” “What must we do to ensure, strengthen, or change institutions so that benefits are realized?” These questions follow from a prior commitment to help bring about the “promised” benefits of GE foods for health.

One standard argument used to justify the high prices of prescription drugs is the cost of producing them. These costs include everything from basic laboratory research to obtaining patents, to passing regulatory requirements concerning utility and safety, to marketing. People in poverty and those on fixed incomes might begrudge pharmaceutical companies the high costs of health-preserving and lifesaving medications. In a comparatively free-market context, however, it is not the pharmaceutical companies’ responsibilities to ensure affordability. Governments, employers, or individuals must shoulder the burden if everyone who needs medications is to receive them.

We have reached a situation in which conditions are ripe for the same thing to happen with food, especially new disease-fighting or nutrition-enhancing foods for health. Similar institutional R&D, patenting, regulatory and production costs will occur, and we must also include the farmer’s livelihood as an additional cost. If we are to fulfill our “promise of biotechnology,” it seems to be implied that we—whoever can affect such things—must attempt to make sure that legal-economic conditions exist so that the new foods are available and affordable, especially to those who need them most. Some may believe that asking this is outside the province of science. The response is that the Future Benefits argument is sound only insofar as the promises it entails are kept.

## CONCLUSION: KEEPING PROMISES

Recently, Norman Borlaug (2000) offered the argument that we *must* pursue agricultural biotechnology as a matter of humanitarian duty. Although his focus was not GE foods for health, he was referring to one problem that at least one “food for health”—golden rice—is meant to address: improved nutrition for the world’s ever-increasing population. It is hard to deny Borlaug’s assessment that agriculture will not be able to provide enough food without increasing the use of biotechnology. Nevertheless, what he and many others fail to acknowledge is that even if we were to produce enough food, poverty, economic underdevelopment, and unjust political regimes would prevent people who need it from growing and/or obtaining it. If the benefits of GE foods for health, or any other product of agricultural biotechnology, are to be made available to the starving populations of less-developed nations (and the poor in North America as well), political conditions must change. Therefore, it is appropriate and even imperative that we ask another ethical question: “How can we bring about international economic justice so that the results of our science can truly benefit humankind?” The social power of science—and of scientists worldwide—is such that many small efforts in this regard may yield large payoffs.

Jawaharlal Nehru (1960) wrote:

*It is science alone that can solve the problems of hunger and poverty, of insanitation and illiteracy, of superstition and deadening custom and tradition, of vast resources running to waste, of a rich country inhabited by starving people. Who indeed could afford to ignore science today? At every turn we seek its aid.*

The power of science, especially genetic engineering, and its capacity to solve human problems, seems to establish a *noblesse oblige* that we are not entitled to ignore or leave to others—or impersonal market forces—to carry out. If this appears to overstep the so-called ethical neutrality of science, the presumed ethical neutrality of those of us in the scientific establishment, so be it. If science—and now genetic engineering—wants to be judged positively by the fruits of its labors, we cannot simply cast the fruit on the market, or to the public, and expect that it will necessarily confer positive results. Rather, we must tend the fruit, and watch it and guide it, so that we can ultimately say that this work is indeed ethically justifiable.

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## ***Are We Listening to Consumers on Diet and Health?***

SUSAN BORRA

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I wish to include the consumer in our discussions: what are consumers' attitudes on nutrition, food and health, and what messages are they hearing on these subjects? Also, what are the implications for communicating information to the consumer in the future?

### **POPULAR VIEWS ON FOOD**

We went onto the streets of Chicago last summer and asked a variety of questions and videotaped responses. We asked consumers to tell us what they think of food, what are their favorite foods, what do they like about food? As they talked about foods they love they smiled and their eyes lit up.

- I like vanilla ice cream.
- Donuts. Yeah, I work in a courthouse and we love donuts.
- I love bread.
- I like oatmeal.
- I love pizza—I'm from New York. Pizza. Pizza. Pizza.
- I like spaghetti.
- Cream sauces and gravies.
- Shrimp. Shrimp. Shrimp. Shrimp.
- Desserts. Cake is good but cookies are even better.
- Etc.

Then we asked them to tell us what they think about nutrition.

- Oh, when I hear the word nutrition I think of flat, boring, no taste.
- Nutrition? No, nutrition usually gets in the way of good food.

## FOOD AS A SOURCE OF CONCERN

As a dietitian working in communications at the International Food Information Council (IFIC), I am involved in consumer research. We talk with consumers in formal focus groups, in one-on-one interviews, and in national research surveys. In 1998, talking with female food gatekeepers about fat in the diet, we learned that messages about controlling fat intake induce guilt, anger, worry, helplessness, and fearfulness—an array of strongly negative emotions associated with food.

In a survey published in May 2002 by the Food Marketing Institute (FMI), consumers were asked if they are concerned about the foods they eat. Fifty percent said that they were “very concerned,” 40% said “somewhat concerned,” and only 10% said “not at all concerned.” This question has been asked almost every year since 1983; the “very concerned” rating peaked at 64% in the early 90s and has declined over the past decade. Clearly, people are changing in how they think about dealing with nutrition. We don’t know whether this decline in concern means, “I’m not concerned because I think I’m eating more healthfully” or is because “I’m just tuning this stuff out due to information overload.” The FMI Trends Survey also tell us that 70% of consumers need help with their diet. Only about a third claimed that their diets are already healthy.

Consumers tell us that to eat healthfully, they must forego desserts, snacks and their other favorite foods—“If it tastes good it must be bad for me.” In a consumer survey by the American Dietetic Association (ADA) 2 years ago, 44% said that they really don’t try to eat a healthy diet because they are afraid they would have to give up their favorite foods. A third of those surveyed said that they are confused over conflicting information, and almost 40% said that it just takes too much time to be bothered with it all.

However they did feel that this is important: 80% of consumers told us that diet, nutrition and health are important to them, which may be something to build upon. When asked if they are doing everything they can to achieve a healthful diet, only about a third replied in the positive. Similarly for physical activity—they feel that is important, but need help to achieve their goals.

In ADA’s trend survey for 2002, we gauged attitudes towards food and nutrition. About a third said, “I’m already doing everything I can. I think I’m doing great.” This represented an increase of 10% over 2 years before. About 30% said, “I know I should be doing this but...” with a whole string of excuses behind the “but”: it takes too much time, it costs too much money, it doesn’t taste good, *etc.* As nutrition professionals, we must confront those barriers to achieving a healthy diet. About a third of respondent said, “Don’t bug me about this. I don’t want to hear it. I don’t want to see it. I don’t want to get near it.” As a dietetic professional, I usually say, “Let them do their thing. I’m not sure that I can change them. We might be able to change the environment around them.”

## NUTRITION COMMUNICATIONS AND GENETICALLY MODIFIED FOOD

How do we get consumers to say, “Maybe some day I can do better”? This is part of the goal of understanding nutrition communications. In the ADA survey, we asked aided questions: “Have you heard something or a lot about” a variety of subjects. For example, 87% knew that obesity is a problem and a national health issue. Eighty-one percent had heard of dietary supplements. Food radiation was known to smaller numbers and 40% said they had heard something about genetically modified foods. Of those who had heard “something,” 65% were concerned about overweight and obesity, 45% about food radiation, 40% about dietary supplements, and under 40% about genetically modified foods.

In research at IFIC, we asked consumers if they believe that biotechnology will provide benefits for them and their families within the next 5 years, and, for the most part, people do believe that biotechnology will bring benefits. When targeting specifically what those benefits might be, about a third said that biotech will help them in health and nutrition. Improved quality, taste or variety was also considered a likely benefit. Reduced use of chemicals and pesticides was perceived as a benefit as was improved safety.

We gauged the likelihood of their purchasing a genetically modified product if it tasted better or fresher. A little more than half were “likely,” but some were “not likely.” It depends on the value system: taste may do it for some people, and health may do it for other people. The information-knowledge base is important. We have seen data that show that education level affects how consumers understand information that is presented to them. Ability to trust who is giving the information and what is the source of the information is part of it. Overall perception of the safety of the food supply certainly impacts it.

Having conversations with consumers is fundamentally important. We have conducted numerous focus-group studies looking at consumer reactions to terms like “genetically modified organisms.” Consumers react negatively to such scary words, whereas “food biotechnology” is more acceptable in the context of conversation, and they then tend to relate to those products differently.

## FUNCTIONAL FOODS

Further aided questions in the ADA survey indicated almost 100% of people believe that certain foods can reduce the risk of disease or have other health benefits. Of those surveyed, 77% had heard about low-fat and over half said they had taken steps to increase their intake of low-fat foods. About half said that they had heard of the positive health effects of red wine, antioxidants, berries, and soy. It is interesting that fewer were drinking red wine than, say, including more berries in their diet. Awareness of folic acid, green tea and energy drinks were in the 40% range, then omega-3 was in 30s. Lycopene hadn’t made it onto the radar screen.

There is need for a definition of functional foods that makes sense to consumers. According to IFIC, they are foods that provide a health benefit beyond basic nutrition. In 1998, 53% of consumers said that they were eating at least one functional food, and in the year 2000 it was about 63%. Although consumers say they are overloaded with information, they also say that they want more and are interested in learning the health benefits of functional foods. We must find better ways to frame that communication. As a dietician I see this as an opportunity to talk more broadly about what are the good things about food. People are tired of hearing what is bad about foods, what is going to harm them. They really want to hear the good stories that are out there.

### INFORMATION SOURCES

Finally, where are people getting their information? The ADA trend survey showed that they get most of their information on food, nutrition and health from the mass media: mainly from television, less so from magazines, and less so from newspapers. Other studies suggest that physicians and medical people are also getting their information from these sources.

What do consumers perceive as good sources of such information? Some 90% of consumers expressed awareness of registered dietitians and 86% felt that RDs would be credible sources on obesity for example, which certainly makes sense. Over 50% felt that dietitians would be credible sources of information on dietary supplements, food radiation, and food biotechnology. Clearly, this represents a great opportunity—the more dietetic professionals involved in communicating through the mass media, the better will be the information received by consumers.

The ADA Website, [www.eatright.org](http://www.eatright.org), is an excellent resource for information on biotech and functional foods, as is IFIC's, [ific.org](http://ific.org).

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## Perspectives

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### Q&A

MODERATED BY

LEA THOMPSON

NBC Dateline  
Washington, DC

*Phyllis Johnson (USDA, Beltsville, MD):* We are moving into a third generation of genetically enhanced crops. We can control the part of the plant in which a gene is expressed so that an insecticidal protein is present in the leaves but not in the edible portion. Does that change the regulatory or the ethical context, and, if so, how?

*Gregory Jaffe:* On the regulatory angle, it is a positive step because you can control where the protein will show up. You may have different containment and segregation issues, but some of the same food-safety issues and some of the same regulatory issues still need to be addressed. Containment risks to the environment can be reduced, but I don't think they will be eliminated.

*Lea Thompson:* Greg, you said in your presentation that if there were to be mandated pre-market testing that the FDA would take control of that. Can you explain that to us? Even for animals?

*Jaffe:* The USDA will continue to deal with environmental crop-safety issues. The FDA has no expertise in agriculture and I don't think anyone would want to see that agency regulating agriculture and how crops are grown. The FDA has expertise in food issues and will continue to regulate food safety.

*Thompson:* So, would all pre-marketing be done by the FDA even if it dealt with animals?

*Jaffe:* If you were genetically engineering an animal and you were going to put that in the food, then yes, you would want approval by FDA that the product is safe to eat. Right now that is the case for animals, but not the case for crops.

*Audience member:* Lycopene is listed in about 400 articles, indicating that it is good for your health and particularly for prostate cancer. How can a commodity group use that as a sales tool, for citrus for example?

*Jeffrey Burkhardt:* This is one of these claims that you see in health food stores all the time when it may not have been substantiated by anybody that matters. If they want to claim that lycopene is going to solve prostate cancer then pass the ball to Greg. But let's see if it really does help prevent or deal with prostate cancer, and market it accordingly.

*Thompson:* Expect some reporter at your door asking for the clinical test results to prove it.

*Phil Berger (University of Idaho, Moscow, ID):* Mr. Jaffe, you are calling for an increase in regulations, some of which may be beneficial. But if you think about it, the only product currently in production that is deregulated that is not from a private sector source are papayas in Hawaii. Traditionally, the source of germplasm for our growers has been the agricultural experiment stations. We are very interested in producing crops generated through biotechnological processes. The reality is that we really cannot easily afford to deregulate these crops now, and with additional regulations you will basically lock out the traditional sources of germplasm for the United States and most of the world. So, my question is: under the different regulatory framework, how do you propose to pay for it?

*Jaffe:* Even though we seek a stronger regulatory framework, there are ways to address minor crops and ways to address research at universities and agricultural research stations. We need more publicly funded biotechnology research. Too much is being done by industry, which is where the products are coming from. We are losing a lot of the promise of biotechnology by not having more publicly funded research. There are ways to set up regulations to help with additional burden in terms of testing for food safety where original funding comes from the government. There are programs, for example, for pesticides under the IR4 program that allow pesticides for minor uses with funding for the testing. There are ways that you can set up mechanisms within a regulatory structure that can give incentives to those types of products and also help pay some of the costs if the public institution has no return on investment.

*Charles Arntzen:* The concern should also be for smaller companies. Increased regulatory hurdles are an entry-barrier. If new products are to enter the marketplace, we have to keep that factor in mind also.

*Jaffe:* To some extent what I am calling for is not necessarily a raising of the bar. Part of it is a public perception thing and part of it is a legal authority thing

for the agencies. They already have this deregulation and permitting processes and so forth. Part of it is actually making them work.

*Thompson:* Greg, aren't you saying that, indeed, many of the companies that are producing these products are already going through this process because they have to do it for other countries?

*Jaffe:* Right. That's what I am saying. Especially the food-safety aspects, where we are adding more in terms of data requirements. These companies are already doing huge numbers of food-safety studies. I am not sure more studies should be done, but I think that the FDA should be reviewing those.

*Arntzen:* I believe we already have a costly process in place. I am not saying that there is anything wrong with a costly process, but it is driving a few very large companies such as Monsanto, Dupont, and Dow to carry new products into the marketplace. And the strategy for those of us in the universities, or with small biotech companies has to be to partner with someone who has the global regulatory expertise, *etc.* Now, I really don't see us going back on that, but I also would not like to see us go any further in making it impossible for somebody out of an ag experiment station to introduce a new product that has real value for the consumer.

*Thompson:* This is an issue that everyone in this room cares about. Susan, I wonder if you could enlighten us about how important is this kind of premarket testing to the consumer. After all, if the consumer won't buy, you are wasting your time.

*Susan Borra:* I don't think consumers are aware of premarket testing. They have an assumption of safety. They feel that if something is on the market then it is safe. Until there's a challenge to that presumption, they probably won't think about it very much.

*Thompson:* Shiriki, any comment as to where consumers are on all this?

*Shiriki Kumanyika:* I was reflecting on my experience a few years ago on the Commission on Dietary Supplement Labels where we were trying to clarify what the regulations were and the different nutrition-support claims and health claims. Unfortunately, I agree with Sue. For example, I don't think that the disclaimer on the labels is noticed by consumers who have decided to use the supplement. There are just so many disclaimers, whatever is on the label is so much verbiage. If something comes down the pike that is the dietary version of "Phen-Fen"-type problems (phentermine-fenfluramine combination), I think we will be in big trouble, because a lot of people trust that it wouldn't be out there if it weren't safe, if it weren't good for you.

*Thompson:* So often all of this happens in a crisis mode, such as with StarLink™, and the more crises there are, the more people are going to be concerned and the more they are going to call for testing or regulation. It doesn't take much to turn the consumer around when there is a real problem. I see that all the time. I cover crises in the food area and have been stunned, frankly, to see how quickly consumer opinion can be turned—not that the consumer at this point would know whether there is something biotech in the food they are eating anyway. I think it is something that everyone needs to be concerned about, because, once again, if people won't buy it you are wasting your time.

*C.Y. Hu (Oregon State University, Corvallis, OR):* Jeff, you mentioned that biotechnology will provide benefits only if scientifically and legally successful and they garner consumer acceptance. I am wondering, as a scientist, shouldn't we consider legal and consumer aspects before we take on any project.

*Jeffrey Burkhardt:* Yes. I think that's right—your responsibility is to do what you do. But there is almost a relay-race mentality. The scientist does his thing, runs his leg, then hands it off to the research administrator or to the company developer, who hands it off to the marketer, who hands it off to the government regulator. Everyone is back there clapping hoping that the guy finally crosses the finish line with the baton. They have a stake in the final outcome. A stake, sometimes financial, and certainly a stake in terms of their participation in the development. Even if you are doing basic theoretical science, you have a stake and some degree of responsibility for the outcome. We have got either the “cast it to the wind and hope it flies” mentality or the “relay-race” mentality. Maybe more so for the research administrators than for the bench scientists, but we all need to do more conceptualizing of what we are about, or perhaps we should actually be watching and monitoring, to the extent that we can, products as they move from the laboratory or the research assistant's spot in the lab out to the market. We can't expect a first-year research scientist at a major state university to know everything there is to know about social responsibility of research scientists, but we can expect more than we do.

*Barbara Schneeman (University of California, Davis, CA):* The major thrust we have seen, using biotech for nutritional and health improvement, has been by adding the nutrient or bioactive compound to the food, in a sense making the product comply with the dietary guidelines. I would like to hear comments from the consumer perspective and the public-health perspective regarding the value of that kind of approach, versus other approaches, where biotech might be useful to help the consumer comply with dietary recommendations.

*Kumanyika:* I don't have an example in mind of an approach that would be based in the product that would help the consumer comply, unless you are talking about, say, a cookie that could make you stop eating it when you have had too much. One could go in that direction: things that lose their sensory properties at a certain point! A more coordinated approach may be needed among food technologists about products in general, rather than considering particular products. That is how we got into the problem with something as simple as lower fat but higher in calories. A coordinating panel could look at a grouping of foods and ingredients being added and consider how that meshes with what policymakers expect to be in that food—because if we did make big shifts we would need to adjust the dietary guidance. But, I can't think of ways in which you would work directly with the consumer, unless you are looking at appetite control.

*Borra:* Biotech may provide changes to the food supply that will be helpful for public health. However, macronutrient issues are now of greatest concern, for example the obesity issue in America.

*Schneeman:* In the case of golden rice, one or two nutrients are added to rice in a region of the world where the people obtain 75% of their energy from rice. The problem is probably just that—75% of the energy comes from rice, and adding two nutrients won't have a big impact. That's what I mean by the nutrient-focused approach—modifying the product rather than asking the question of what else needs to happen for the population to have a healthful diet?

*Arntzen:* The golden rice story is one that warrants discussion of what caused it to happen. As you'll recall, almost all the funding came from the Rockefeller Foundation after an intensive study by multidisciplinary groups who cared about nutrition and plant molecular biology and defining what was possible. The decision to put genes for carotene enhancement in rice was made with under-served populations of the world in mind. If you planned a similar product for the United States or Europe, you'd be laughed off—why would you bother doing it? You have to keep that in perspective.

I don't know why people focus on biotech. There are other technical approaches that don't involve genetics, *e.g.* DHA or omega-3 fatty acid supplementation of baby food. It took ten years of activity, eight years longer than it took in Europe, to get that supplementation in, even though there was abundant nutritional evidence that it was good for children to have DHA supplementation. Why did it come? Well, finally one company adopted it and the other infant-formula companies couldn't avoid it—they added so as not to be pushed out of the marketplace. Low-cholesterol eggs, produced by feeding chickens various things, were a non-event in the marketplace. And stanol esters

in Benecol<sup>®</sup> margarine—to lower cholesterol—hasn't had a significant impact on that segment of the marketplace. The problem in the United States is that we have an abundant supply of food with people interested in eating what they like, not necessarily what is good for them. And we have a whole bunch of claims out there. Probably the only successful area has been low-fat foods, because it was an opportunity for the food industry to make proprietary technical advancements and lower the fat content and substitute, usually, carbohydrate content in its place. It has been a good marketing niche. It doesn't take a lot of advertising and there is some proprietary advantage. Lycopene from Texas A&M requires a lot of education and there is no incentive for the food industry to invest money unless they can get a proprietary advantage. I would not focus on biotech. There are things we can do with biotechnology, but by and large there are so many other things we could do based upon other food-processing technologies that would be easier, faster, and cheaper. With respect to nutrition we have a tremendous opportunity in the developing world. The DOMI program—Diseases of the Most Impoverished—is funded by Bill Gates, and nutrition is popping up on their radar as something to focus on; they are considering all sorts of things, including biotechnology.

*Thompson:* Shiriki, one of the big things that has come to the marketplace in the past five years has been WOW<sup>®</sup> potato chips, which are marketed as being low fat. Are people buying them?

*Arntzen:* Why would someone eating potato chips care about a health claim? You're eating salted fat—

*Thompson:* But you can eat the whole bag—

*Arntzen:* I think the people who respond to health claims are the same people who belong to health clubs or they jog religiously, *etc.* They care about their health. And they don't eat potato chips. They eat tofu.

*Kumanyika:* I think a lot of people are using alternative foods that don't have the consequences associated with the regular form. I have no data on how much they are selling, but if they are on the shelf, I assume that they are selling. I have noticed, however, that, depending on where I shop some products are absent. There are neighborhoods in Philadelphia, where I live, where there is a high profile for WOW<sup>®</sup> and that type of product, and other neighborhoods where I go there are none in the store because the demand probably isn't there. There is an interaction between having some of these things available and the consumer creating demand. Sometimes people can afford only the generic choice and will be unable to buy something healthier because it is three times the price. There are interlocking aspects.

*Borra:* I understand that the no-fat potato chip has not survived in some marketplaces because it hasn't done well. For some reason, it didn't fill a consumer niche; perhaps the taste profile wasn't right. But your comment is interesting: "You can eat the whole bag." That's the issue—that should not have been the selling point.

*Maggie Powers (Powers and Associates, Inc., St. Paul, MN):* I own a health communications firm here, and I appreciate Sue's work with consumer messages, because I think that is what is ultimately going to get them to listen to us, to have a positive impact. Shiriki, do you have a comment based on the obesity information you provided, regarding children developing type-2 diabetes. Recently, in a school district in Pennsylvania, notices were given to children who were obese. I found that fascinating. It gets into policy issues. We give out notices concerning other diseases prevalent in school systems—my children bring home such notices—I am curious as to your thinking.

*Kumanyika:* Obesity is one of the chronic diseases that is much more socially than biomedically defined. Even though from a public-health point of view we can look at body-mass index and say your weight over height squared is such and such, consumers have different definitions. Parents, as the CDC is finding out, define obesity in their children in terms of how the children function psychologically and physically, not in terms of their weight for their height. So, we have some things to learn. We were asleep at the wheel and this was an epidemic before we noticed it. It will take a lot of social and cultural reflection and intervention to see how best to address it without stigmatizing the children or their parents. But, it is definitely something that we will have to address, which is why some of us favor environmental solutions, such as placing those kids in schools that have a physical ed class. Thus, without labeling anyone as obese, they find themselves in more active play and with a different school lunch.

*Audience Member:* Greg, some people would argue that food risks associated with the process of genetic engineering are dwarfed by other kinds of risks, such as bacterial-borne diseases and contaminants. If that is the case, how can we justify a presumed increased cost in the regulatory system associated with mandatory approval, and would those dollars be better spent in other ways?

*Jaffe:* I tend to agree with you that biotechnology is not number one in a list of food risks, in fact it would be fairly far down on the list. My organization contends that biotech foods are safe to eat. However, there are public concerns. NABC has been addressing these for many years at their conferences. Public perception, public acceptance issues are commonly written about in newspapers. Also there are *some* food-safety risks with the technology, and you solve

both of those problems through a mandatory approval system. Whether it is number one on your priority list, public-acceptance issues are under debate worldwide. There are ways to design a system so that it would not be much more expensive than it currently is, and that is what we are attempting to achieve. With user fees, for example, the cost can be borne by the developer rather than by the government. The system that is in place is already costly.

*Sraddha Helfrich (University of Minnesota, Minneapolis, MN):* Although there are so many ways in which we can manipulate DNA, it is important to bear in mind that humans are spiritual beings. Food is often at the heart of the spiritual and cultural experience across the globe. As scientists in positions of power, how do we respectfully engage in dialogue with people whose very cultural identity may be threatened by our science. I wonder if this is even an appropriate question.

*Thompson:* I think it's very appropriate.

*Kumanyika:* Can the ethical justification be extended to the process, not the outcome? In research on humans, we have to go through institutional reviews to determine whether such is justified—is it worth the human burden? When I think about this issue and about tying up the regulatory system, then I wonder how do you justify creating products just because you can, and then there is a burden to regulate them. You can imagine tying up the entire system with product development that might not have been vetted for a positive outcome. I wonder if there's a pre-approval process for product development that can include some of the concerns that you are raising.

*Burkhardt:* Isn't that what interaction with peers is supposed to be, in the basic sense, beyond sharing the results of the latest experiment to sharing the values and norms of science? There would be a pre-vetting process, if you will, if people would talk to each other about what they are doing and what they are planning to do. So, if someone says, "I want to make a tomato with legs," and someone says, "No, don't go there"—that would be the ideal communication system, within a university department, within a research laboratory, within a corporation, or among those entities. More directly pertaining to your question, one of the things that I am sick of hearing is the totally inappropriate response to the issue you raise: "They just need more information. Consumers want information." Well, if you gave them the information they wouldn't know what to do with it. With people from a very different culture, a very different set of ethical or religious convictions, you don't give them more information and say, "If you understand this you'd understand us." That's disrespectful at best. The alternative is to acknowledge that, in fact, they don't buy into our reductionistic, corporate, *etc.*, approach—you can run down the list of every complaint

that has been made about modern science. They don't buy into it, and you cannot make them, as much as many of those present may want to make them buy into it, you cannot force them to believe that this is the best way to go in all cases. That's where respect ends.

*Barrie Froseth (General Mills, Golden Valley, MN):* Can you give us some specific examples of outstanding communication or education of health and nutrition. On one hand we have the paradigm of "five a day for better health" driven by an industry group, and on the other hand we have CSPI going after specific cuisines, most recently pizza.

*Thompson:* I am going to interrupt and ask this room: how many of you have used the nutritional facts information that is shown on products? Almost everybody in the room. That is a very successful label. Food manufacturers and processors in this country came kicking and screaming about that label, yet everybody appreciates and uses it, and everybody is better informed as a result of it.

*Borra:* We don't have good communications on nutrition. If we did, we might not have such a problem with obesity. We need to find new and better ways to talk with consumers about nutrition—that's the key. We are trying all kinds of new communications approaches—sitting down and talking with consumers: "What are you dealing with in your life and how can I make my nutrition message fit?" With my professional nutrition colleagues, we have tended to tell people what they should do: "You should be doing this because I know the science and I know it's right." We have to change that approach. How many people eat according to the Food-Guide Pyramid in this country? Very few. We haven't gotten through with those messages. There is much work ahead to figure out the best way to communicate with consumers.



PART IV  
DINNER ADDRESSES

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## ***Back to the Future***

CHARLES C. MUSCOPLAT

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The past predicts the future. Improving health through changing foods and behavior is a continuum that started over four centuries ago.

### **DIET, LIFESTYLE, AND DISEASE**

A recent article in the *New England Journal of Medicine* (Diabetes Prevention Program Research Group, 2002) reported that diet and lifestyle were twice as effective as pharmaceutical therapy in preventing adult-onset diabetes in a high-risk population. Controlled dietary intervention to reduce caloric intake plus exercise reduced the incidence by 58%.

Type-2 or adult-onset diabetes, formerly called non-insulin dependant diabetes, is a serious and costly disease affecting 8% of adults in the United States. Sixteen to 17 million Americans now have type-2 diabetes, which consumes 10% of the national healthcare budget. Considering that the healthcare budget is a trillion and a half dollars, diabetes is more costly than many other problems combined.

The April 2002 issue of *Science* magazine contained a series of fascinating articles on the puzzle of complex diseases. The article by Walter C. Willett at the Harvard Medical School, Department of Epidemiology and Nutrition, showed that genetic and environmental factors, including diet and lifestyle, contribute to cardiovascular disease, cancer, and other major causes of mortality (Willett, 2002). Not all of these diseases are genetic in origin, many of them—probably the majority—are diet and/or lifestyle or environmental in nature. Lifestyle modifications can significantly reduce the incidence of four major diseases without medication: colon cancer, stroke, coronary heart disease, and type-2 diabetes, which cost us treasure and life productivity. The article also discussed the relationship between HDL cholesterol, the relative risk

of heart attack and alcohol-dehydrogenase genotype. The risk is higher for a person with the slow isozyme form of alcohol dehydrogenase who has more than one drink per day compared to someone who doesn't drink who has the fast form of the isozyme. Therefore, if you know what your genotype is, you can modify your diet to affect your expected clinical outcome—you can reduce your disease risk with a diet/lifestyle intervention. The basis of pharmacogenomics is that everyone responds differently to a drug and, in the same way, people respond differently to alcohol. It is said that one glass of red wine a day will reduce your chance of a heart attack—but, the effect may depend on your genotype.

### **HISTORICAL PERSPECTIVE**

The future of agriculture, food, and medicine lies along this pathway. By knowing our genotype, the content of the food we eat, including micronutrients, and metabolic pathways, we will have a better understanding of how to modify lifestyle to improve our health.

A book on the vitamins was published in the 1920s, when people were beginning to understand that some dietary components are essential. Vitamins are organic molecules that function in a wide variety of capacities within the body and are essential for health. There are two categories: water-soluble and fat-soluble. Polish scientists coined the term vitamin in 1911. In 1933, vitamin D was added to milk, introduced by the Borden Company to prevent rickets. By 1948, all thirteen essential vitamins had been isolated, and most were synthesized. In 1949, the essential amino acids were defined after a long and tortuous discovery process. One publication dates back to 1788, by William Stark who discovered that scurvy was diet-related. Stark, a physician, studied the effects of various dietary regimens upon himself. Keeping accurate records, he induced diseases in himself, and then observed the effects of eating certain foods. He died at the age of 29 with a serious case of scurvy, after depriving himself of vitamin C for a long period of time.

How we understand diet, health, and micronutrients thus has a long history. One manuscript, a treatise on the derivation of rickets, has a publication date of 1651 (in London by the College of Physicians). In 1922, vitamin D was isolated and used to treat rickets. In 1923 it was found that sunlight would substitute for vitamin D, and also could be used as treatment. Through the next 10 or 20 years, vitamin D became a supplement in our food, in butter and cheese and other dairy products, and bread. In 1911 the Morton Salt Company started adding magnesium carbonate to salt to make it flow even when it's raining, and the slogan was adopted in 1914, "When it rains, it pours." In the upper midwest in 1905, physician David Marine, while studying iodine levels in the great lakes, made the correlation between people who drank iodine-deficient water and goiter. He experimented with iodine supplements to treat goiter. Around 1920, iodine was first added as a salt supplement, and the Food and



LUGDUNI BATAVORUM  
apud GEORGIIUM WLSHOFF .  
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Figure 1. Nicolai Tulp's treatise *Observaciones Medicae*.

Drug Administration, in its early days, approved the language, “This salt provides iodide, a necessary nutrient.”

In his book *The Jungle*, Upton Sinclair drew national attention to shocking conditions in the meat-packing industry, which led to the 1906 Meat Inspection Act and greatly improved the quality of meat supply in this country. In 1911, Proctor and Gamble introduced Crisco® for cooking, which, over the years, largely replaced animal fats and butter for cooking foods. It probably was the start of the long, slow trend toward getting saturated fats out of the diet. In 1914, Joseph Goldberger published a book on therapy for pellagra, a B-vitamin deficiency (Goldberger, 1914). He described experiments that would be unethical today: diets of various compositions were given to people in orphanages and prisons to determine who got what disease and then various types of food were supplied to try to correct deficiencies.

The first clinical descriptions of beri-beri were by Dutch physicians, Bontius and Nicolai Tulp, in the seventeenth century. The frontispiece of Tulp’s treatise, *Observationes Medicae*, showed an individual with the disease (Figure 1), which is also caused by a deficiency of B vitamins. In the 1800s Christiaan Eijkman made the observation that individuals in Indonesia eating white rice developed lameness. At the same time he was observing chickens, inadvertently fed white rice, which also were lame. When switched to brown rice, which contains B vitamins in the bran, the chickens recovered. His experiments with Indonesians confirmed recovery from beri-beri with brown rice in the diet.

Clearly, clinical experiments on diet and lifestyle intervention go back a long way. In the 1920s, vitamin A was found and named by George Wald, who also discovered its importance for vision, for which he was awarded the Nobel Prize in 1967. During that time, concepts of food safety were changing, and sanitation laws were passed largely as a result of Upton Sinclair’s book. Food became safer, water purer, and life spans increased.

In the 1920s, George Whipple did some beautiful experiments on anemia. He took blood from dogs until they were severely anemic, then provided various diets: some were fed corn, some soybeans, some meat and muscle, and others liver. Those fed liver regenerated hemoglobin most rapidly. He determined that hemoglobin will return to normal in 8 weeks, but no more quickly than 8 weeks, whatever the initial level of hemoglobin. There is a certain set regeneration time as long as iron is not limiting in the diet. From this research, we developed iron therapy: eat liver to be healthy. This was a major milestone in understanding how food can affect human health, for which Whipple won the Nobel Prize for physiology and medicine in 1934. In the 1940s, as people went off to war, calcium and iron and vitamins were added as supplements to bread.

In the mid-1920s, Otto Rohwedder launched the bread-slicing machine after many setbacks. In 1928 the Peter Pan peanut butter company observed that the introduction of sliced bread greatly increased the consumption of peanut butter.

In 1929, when Popeye cartoons were introduced, spinach consumption dramatically increased, particularly among children.

Clarence Birdseye, born in the 1880s, attended Amherst and majored in biology but never finished. Instead he took a job as a naturalist in the Arctic. While fishing there, he observed that fish froze instantly on the ice and, when thawed, tasted just as good as fresh. He started Birdseye Frozen Foods, and, little by little, learned that many of the micronutrients and proteins are stable when kept frozen. The effects of Birdseye's discovery are probably among the most profound of the twentieth century.

### DIET AND HEALTH

In the 1920s, a publication described heart disease as the leading cause of death in the United States. In 1953, Ancel Keyes showed the correlation between coronary heart disease and diets high in animal fats.

An article in the May 2002 issue of *Science* magazine discussed how green tea can reduce fatty accumulation in the liver, and therefore reverse some of the chronic effects of alcoholism (Anon, 2002). For the past few years claims have been made that green tea prevents cancer and cardiovascular disease, and an article in the May 2002 edition of *General Dentistry* suggested that green tea can prevent oral cancers (Hsu, 2002).

There was a meeting in May, 2002, at the NIH—"Conjugated Linoleic Acids, Research, Current Status, and Future Directions"—sponsored by many of the major divisions of the NIH: nutrition research, diabetes and digestive kidney diseases, national heart/lung, national cancer, and the office of dietary supplements. The CLAs are a group of several linoleic acids called octadecanoic acids, which are essential fatty acids. They are present in animal products; dairy cows that graze on grass have 500% more CLAs in their milk than do cows given other types of feed. Conjugated linoleic acids may be among of the most potent cancer-fighting substances in our diet. They may delay the onset of adult diabetes, and have also been shown to reduce body fat in people who are overweight. So, this isn't only just a crop issue, it's an animal issue as well.

It appears that CLAs may be involved in gene regulation. In the future, foods may be designed to "dial up" a level of gene expression, depending on our genotype and disease.

### GENOMICS AND HEALTH

The understanding of one plant genome leads to a similar understanding of many others. Likewise, a simple understanding of a genome of one vertebrate can lead to a similar understanding in many others. Recently, the genome of rice was published, providing information about barley, oats, sorghum and corn, and even grass in your front yard. When you study the fruit-fly genome, it tells you about 40% or 50% of the human genome. The same applies with worms like *Caenorhabditis elegans*.

It doesn't take a genius to figure out that the various citrus fruits not only share a common genetic backbone, but are nearly identical. Understanding one teaches you nearly everything about the other. Understanding the fruit fly teaches us about the mouse.

We are rapidly approaching a time when we will understand the food genomes, and what's in our milk, and how animal metabolism produces beneficial compounds like CLAs. We will understand also how genes that encode antioxidants, vitamins, and other constituents are regulated. With an integrated approach, we will better understand how supplements and functional and medical foods affect disease.

### THE FUTURE

And we are rapidly approaching a time when farming with an "F" will also be done with a "Ph," but foods for health will go beyond that. Food can be manipulated in many ways using traditional technologies as well as by genetic engineering. Infectious disease is an important component of food safety, and Francisco Diaz, a professor of food science in the University of Minnesota College of Agricultural, Food and Environmental Sciences, has found that dietary changes directly before slaughter dramatically reduce the carriage rate of *Escherichia coli*.

There is also a political side to this. If you are in a policy position and suggest eating less red meat, you can be sure that animal commodity groups will be on your telephone tomorrow morning. If you say eat less sugar, sugar-beet growers will be on the telephone. And if you recommend applying more fertilizer to increase crop yields, someone from the Gulf of Mexico will say, "What about my dead zone?" It's a complicated issue, with profound implications for the future. It will probably be possible to eliminate much of the major economic and suffering diseases with changes in food and lifestyle. The questions that we must face are: "Can we do it?" "Should we do it?" "What will be the consequences of our actions?"

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## ***The National Safety First Initiative***

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Safety is a primary concern of consumers and scientists regarding the development and use of genetically engineered agricultural products. Debates are polarized and could well become more so over such questions as will genetically modified organisms (GMOs) irreparably harm genetic diversity in wild relatives and land races? Will they harm human health and ecosystems? At the same time, there is concern over whether another StarLink™-type case will hit and hurt not just one company but the entire industry by eroding public confidence. And the challenge of achieving broadly accepted environmental- and food-safety standards is that much greater for the next generation of biotech products, for example crops and even fish engineered to produce drugs and industrial compounds.

At the University of Minnesota's Institute for Social, Economic, and Ecological Sustainability (ISEES), our experience in other policy areas leads us to believe that it is possible to address biosafety issues and realize the promises of agricultural biotechnology. A coalition of diverse partners have come together in the National Safety First Initiative with the goal of developing and instituting industry-wide, publicly trusted, and scientifically reliable safety standards.

### **THE INITIATIVE**

The Initiative employs a representational, deliberative, and transparent process grounded in science. There are four fundamental aspects.

- Quick fixes to current biotech debates are not possible. We are convinced that the first step must be to break from the binary yes-or-no choice on biotech and food. No easy consensus has eluded others that we can somehow snatch. There are real differences of perspective on biotech-safety issues in American society, including within the scientific and business communities. Our starting point is to acknowledge the existence of these differences.

- The Safety First Initiative involves a forum and a process for identifying differences and then negotiating through them honestly in a collective effort to develop cross-industry safety standards.
- The Safety First Initiative draws from the history of safety work in various American industries that involve complex engineering processes. At the workshop that launched public deliberation of our proposed safety-first approach, economic historians and safety engineers and analysts reviewed safety successes and pitfalls from a broad range of industries. We looked at the steel, lead, aircraft, food manufacturing and nuclear-power industries. These experts deliberated with biotech and bio-safety experts and concerned parties from industry, academia, and public-interest groups on panels and in a variety of break-out groups to make recommendations to guide proactive safety governance in the recently emerged and diverse biotechnology industry. We learned that attention to safety has historically come from strong external pressures from consumers, politicians and various organizations as well as from enlightened leadership within industry. Some companies in the United States stuck too long to a “safety-second” approach that resulted in financial losses, liability problems and erosion of consumer confidence. And we also learned that in some companies—either a maverick firm, for example US Steel in the early 1900s, or a coalition of firms and external stakeholders, for example aircraft manufacturers in the late 1900s—took the lead in placing safety first as a smart business stratagem that eventually transformed industry as a whole. Therefore, the Safety First Initiative builds on a time-tested American approach. It seeks to recreate the systems that are in place in other industries that developed safety standards with consumer and public consultation and thus achieved improved safety records and built public trust of their products.
- The Safety First Initiative is a public/private-sector partnership that is neither pro-regulatory nor deregulatory.

After remarkably positive feedback and interest expressed by the wide spectrum of participants in our 2001 workshop, a coalition emerged from business, the public-interest, community, and academe to plan and conduct an innovative process for negotiating industry-wide safety standards.

## OBJECTIVES

The Safety First Initiative intends to draw up the nation’s first cross-industry and publicly trusted standards for *designing, producing, and monitoring biotech products*, with safety a primary criterion throughout: from the early stages of designing a genetic construct at the lab bench through R&D and the elaborate processes involved in developing a stable GM variety or line through pre-market regulatory approval and post-market monitoring. Long-established principles of safety engineering offer a series of logical and well tested steps

for addressing contentious and complex issues involved in the manufacture of safe products.

The Safety First Initiative plans to organize cross-sectoral working groups that will negotiate similar elements of environmental and food-safety standards for GMOs in agriculture and aquaculture. These elements are as follows.

- Safety-criteria setting. These standards set the safety objectives from which follow the safety standards. It involves systemic risk analysis and planning to reduce risk, emphasizing what can be done to build safety from the outset to the design of genetic constructs and the choice of traits to modify.
- Verification standards. Prior to marketing, these standards address whether the product meets safety objectives to reasonable, measurable levels. Verification standards drive the design of scientific, reliable tests to fully challenge the product, drawing on the best available science from all relevant fields. Obviously, verification standards also must address questions about quality and type of data obtained from these verification tests.
- Follow-up standards. These address uncertainty, recognizing that even the best criteria and verification standards cannot anticipate all problems. Therefore scrupulous monitoring of a product in all its uses is needed, with the monitoring system designed to be practical and cost effective, targeting the most likely problematical areas. Such an approach fosters timely discovery of problems and early application of corrective measures.
- Safety leadership standards. These aim to ensure that the prior three types of standards are implemented consistently and properly. This involves, for example, establishment of rigorously trained and independently certified safety engineers who would be valued employees of companies as well as in government regulatory agencies. Such professionals—with independent certification—exist in other industries, for example in companies that manufacture and install complex aircraft components. And safety-conscious leadership at all management levels is an essential element.

Although pioneering firms have not received appropriate recognition for their efforts, we recognize that some agricultural biotech companies have already established one or more of these elements, providing the foundation for an industry-wide program of safety leadership.

## CAVEATS

Two important caveats affect the negotiation of these standards. First is the issue of what is safe enough. One hundred percent safety can never be guaranteed. Defining what is safe enough will be a major objective of the representative deliberative process, involving negotiating an acceptable balance point between potential benefits—or, preferably, documented benefits—and the assurance level of safety for a given GM product. The second caveat

involves the distinction between non-living and living materials, because we are drawing on safety-engineering principles for manufactured non-living products. Qualitative differences exist between products derived from living organisms—such as foods derived from GMOs—and those from inanimate source materials. Our challenge is to draw on the history and rigorous methods of safety engineering of inanimate materials and apply lessons, where appropriate, to biological products.

How does this relate to HACCP<sup>1</sup>? There are several overlaps, and we plan to carefully study the HACCP process—which was designed to address safety issues in foods—focusing on food production from biological materials.

### INCLUSIVE DELIBERATIONS

The partners in our coalition recognize that achieving public trust in GM products that will be vetted through safety standards that will emerge from the initiative will entail important roles for the government and the public. For instance, government oversight should reinforce motivation for industry safety programs to be scientifically reliable, responsible, and responsive. Regarding public participation, the initiative involves transparent and inclusive deliberation, taking a cue from the airline industry where cross-sectoral working groups have been organized, including participants from business, consumer and public-interest groups and government agencies. Over a two-year period standards and procedures for industry-wide safety programs were negotiated, which, because there had been such an inclusive deliberative process, were endorsed by all parties. Companies adopted the standards and, in fact, went to their regulatory agency, the FAA, who rapidly incorporated them into the details of their regulations.

Similar inclusive deliberations have also been used for periodic review to update industry-wide standards in light of new information. Thus, the biotech industry can benefit from other engineering industries that have discovered that an open process grounded in science wins every time—in the long term reducing costs of product development and approval.

The Initiative's Executive Advisory Board is a partnership of prominent leaders of diverse private and public sectors. The co-chairs are Chuck Johnson, retired vice-president of DuPont, formerly with Pioneer HiBred, and Tim Penny, former US Congressman and presently director of the Humphrey Policy Center here at the University of Minnesota. Other members of the board are John Block, former US Secretary of Agriculture, Margaret Mellon, the program director of the food and environment program at the Union of Concerned Scientists, Vin Webber, former Congressman and co-director of Empower America, and John Woodhouse who recently retired as CEO of Sysco Corporation. The charge of the Executive Advisory Board is to provide

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<sup>1</sup>Hazards Analysis and Critical Control Points.

advice on planning and oversight for the Steering Committee and the Initiative's outcomes. They are providing important advice on the substantive and procedural aspects of a plan for moving forward.

On the Steering Committee are leaders from large companies such as Syngenta and DuPont, from small new biotech companies including ProdiGene, and from the very small Cape AquaCulture Technologies. It is important that the standards that emerge from this initiative do not have an exclusionary effect on small biotech firms. When approached, the president of Cape AquaCulture Technologies, Bob Curtis, was immediately interested as it was an opportunity to get over a difficulty that his company was in. Because of recent media focus on consumer jitters over genetically engineered salmon that are expected to receive government approval, venture capitalists and other investors have been uncertain about investing in the biotechnology that he would like to apply in fish. He was looking for a way to show that his is a responsible company, and, by contributing to the development of standards that would be applied across industry, he would have a means of allaying fears. And, interestingly, some investors have quietly been checking in with us and asking to stay apprised, because they seek publicly vetted procedures for guiding their decisions.

The Steering Committee includes representatives from the world of commodity farming, from organic farming, consumer organizations, other NGOs, and academia. Jean Kinsey, director of the Food Retail Industry Center and professor of applied economics at the University of Minnesota—a speaker at this conference—is one of the members of the steering committee, as is John Howard—also a speaker—chief scientific officer at ProdiGene. The members of the Steering Committee are committed to furthering the Safety First Initiative and to maintaining communication links with the communities they represent. Each has important experience and perspectives that will shape and the Initiative's work and outputs. The committee is charged to provide oversight on the cross-representational working groups—including the negotiation process—and their outputs. The Steering Committee will carefully review the standards drawn up by the working groups, and problems will be returned to the working groups. Ultimately the Executive Advisory Board will review the standards before release.

### **MODUS OPERANDI**

The Executive Advisory Board and Steering Committee convened for the first time on April 22, 2002, to initiate a draft plan for developing industry-wide safety standards and discuss *modus operandi*.

The cross-sectoral working-group negotiations will focus on (i) the broadest general safety principles applicable to the range of GM products that the Initiative will address, and on (ii) product-specific standards that will be tailored to issues raised by particular GM products that the initiative will address.

Each company that adopts standards for these two levels will accordingly create their own standards for use at the company-project level. We will not be involved in how they decide to meet these standards.

The ISEES staff will provide the Safety First Initiative with administrative and managerial support and will provide professional facilitation at all meetings. Some staff members, including the author, have expertise in biosafety science and technical aspects, and we work closely with a leading system safety engineer from the aircraft industry. The ISEES staff will work with the Steering Committee to identify, invite and bring together working group members. We envision four working groups meeting in parallel, with communication between groups and with the Initiative leadership. The reason for four main working groups relates to the four central elements described above. Each working group will have sub-working groups on specific products.

The working groups will be cross-sectoral teams with various technical expertise but will also represent consumer interests. Furthermore, they will put themselves in the shoes of a company safety engineer: how should the product be designed to ensure maximum safety from the outset—what will be the R&D needs—what will be the government-approval needs—and what aspects will ensure broad public acceptance?

There were two major outcomes from the April 22, 2002, meeting. The Board and Steering Committee provided a frank critique of our draft plan, offering various personal perspectives. After working through some questions and mid-course corrections, they gave strong and clear endorsement of the Initiative's goals and substance, and the proposed approach: *substance* in terms of the goal of developing industry-wide safety standards, and *process* in terms of cross-sectoral transparent deliberation. The second major outcome was the consensus to focus the Initiative on two types of GM products:

- crops providing non-food products, from pharmaceuticals to industrial materials (with the possibility that this might include farm animals), and
- food products from genetically modified fish and shellfish.

Over the next 6 months the Initiative will concentrate on forming and convening the working groups and thus move into the functional phase of negotiating safety standards.

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## *Dinner Addresses*

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### **Q&A**

*Mary Clutter (National Science Foundation, Washington, DC):* I applaud your efforts on your plans for the Safety First organization. On one of your committees you have people who represent companies from other countries—have you had much discussion about coordinating your efforts with other countries? You know there is a huge debate about what is going on.

*Kapuscinski:* You are right about that and we are very aware of it. Actually, from the outset, we wanted to work at an international scale, but didn't have the resources to start that. However, at our workshop last year, which was financed by the University of Minnesota, people came from Europe and as far away as Kenya. Many others wanted to attend and asked for sponsorship for their travel but we didn't have the resources. In the past year we have obtained a grant from Agency for International Development (AID) under their new Biotechnology and Biodiversity Interface (BBI) program, which, although primarily a research project includes funds for biosafety training workshops in years 2 and 4; in this case the focus is on Thailand. That got the attention of AID and we were invited to go make a presentation on the Initiative. We are now fundraising with the objective of working with people from other countries. We are in contact with the international centers—last week I had telephone discussions with the director of the International Maize and Wheat Improvement Center (CIMMYT) in Mexico, for example, and we are talking to people at the Global Environment Facility. I was recently appointed to the Global Environment Facility's Scientific Advisory Panel.

The short answer to your question is we would like to work at the international level. We think that is really important. We recognize that the deliberative process may be more difficult in other cultural settings, but we think it is important to attempt it. We had to start somewhere and it made sense to start in our own backyard.

*Anthony Shelton (Cornell University, Ithaca, NY):* It sounds like a very interesting program. I'm trying to understand the scope of it. You talked about international, what about at the national level—is there coordination with other land grant universities, and who is funding it for the long-term? Will this be a model for other consortia or are you hoping to be the national center?

*Kapuscinski:* We are proceeding day by day so I haven't gone as far as thinking in terms of a national center. We like to work in a collaborative coalition building mode, so if other land grant universities find this intriguing enough to get involved that would be great. We are developing from one phase to the next and currently the bulk of our funding is coming from the Pew Initiative on Food and Biotechnology with infrastructure support from the university. We will be working with our board to put together the resources to take the next step, and the door is open for any person or coalition who would like to get involved. We are not interested in keeping it to ourselves—we are interested in solving a problem and we think we have a viable means of achieving success.

*Shelton:* Primarily, are University of Minnesota resources going into this, or at least faculty time?

*Kapuscinski:* And funding from the Pew Initiative on Food and Biotechnology. We are doing this one phase at a time. Our experience has been that it is more important to take the time to build relationships and put at least some of the initial pieces together than to think immediately on the larger scale. That will come if people are interested and if they see that the process will be helpful.

In forming the working groups, we must bring in additional resources. Obviously we will draw on scientists, communication specialists, and people of varied expertise from the land grant universities across the country. We will look for people in industry of greater diversity, hopefully, than those on the board and Steering Committee and also from consumer and public-interest groups. We want to work with people who are serious about negotiating constructively. We are not interested in people whose objective is to obstruct the discussion. We intend to establish ground rules to achieve an open process with negotiation in good faith.

*Marshall Martin (Purdue University, West Lafayette, IN):* Could you clarify how you plan to coordinate dialogue and interact with regulatory and other government agencies.

*Kapuscinski:* Although I and other members of our group have been having informal conversations with people in regulatory agencies, we thought it was more important to initiate conversations between the producers of technology and potential users, taking a cue from the aircraft industry. We have known all

along of the need, at the right moment, to interact with regulatory agencies. We invited them to our workshop last year, but only a few were able to come because of administration transition, *etc.* If we get far enough along within the next 6 months in terms of forming working groups and we have the resources in place then members of the Executive Advisory Board will go to Washington DC for discussions with the top people in the regulatory agencies. Some of the people on our board have a lot of experience in the regulatory world.

We have had discussions on whether some FDA staff, for example, should be directly involved in the working groups. It's not clear whether they would be comfortable, as there could be a conflict of interest—but there may be a possibility of involvement in a technical advisory role. We actually invited some federal people to serve as collaborators on a research proposal that was submitted to a federal funding agency. There should be ways to work this out. We do not want to duplicate what the federal agencies are doing. The idea is to do something that will be win-win.

*Aijit Srivastava (Michigan State University, East Lansing, MI):* You made reference to food-safety engineers. Could you elaborate? Are you thinking of someone with engineering credentials?

*Kapuscinski:* Well, I actually used the term safety engineer. I didn't specify if it was food safety or environmental safety, and we are still considering whether we should use the word engineer or safety professional. We wish to have a recognized career path, for example in the biotech world as a safety expert working at company X or as part of the biotechnology staff at APHIS at USDA or at FDA. We realize that institutional biosafety committees and biosafety offices already exist—pieces of this are already in place—but we want to bring more cohesion to that—organize it more systematically—and have a nationally accepted curriculum for the training received. For example, in the world that I come from, environmental sciences, there is no clear agreement on what a safety expert needs to know to make a good environmental safety assessment, but we hope that this will emerge from the discussions of the elements of the safety standards to serve as a framework for a curriculum. There are several ways in which this could unfold; for example, professionals could take a short course (two to four weeks) followed by an exam. Or graduate students in plant molecular biology might take a minor in biosafety engineering, or whatever it would be called. At our institute we have developed one new course called Biosafety Science and Policy that we hope will be taught for the first time in the 2002–2003 academic year.



**PART V**

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**APPLYING AGRICULTURE TO MEDICINE:  
THERAPEUTICS AND TREATMENT**

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## Why Medicine Needs Agriculture

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According to some cultures, the practice of healing and the phenomenon of divine retribution have their roots in horticulture. Eve's transgression in the mythical, biblical Garden of Eden has manifold consequences; among them, pain in childbirth and the burden of knowing evil along with good. Tempted by the fruit from the tree of knowledge in a garden planned for divine sustenance of a people, Eve's act serves as an appropriate metaphor for the double-edged sword that nature represents. On the one hand, plants represent a bounty we depend on for the maintenance of health, while, on the other, they can cause great harm if used improperly. Taken one step further, appropriate use of the garden of nature leads to eternal health and happiness, whereas misuse leads to misfortune. Regardless of the path we take, the recognition that plants have the ability to cause harm and to prevent it stands at the center of the connection between agriculture and medicine.

### MEDICINE AND RELIGION

In fact, prehistoric recognition of the curative and harmful powers of plants and plant extracts served as the beginning of the practice of medicine and of the sciences of horticulture and botany (Janick, in press). Priests and physicians, who were charged with healing, depended entirely on their knowledge of the plant kingdom for curatives. For thousands of years, medicine and religion were practiced interchangeably by healers and religious figures who sought healing from spiritual cures and magic, as well as from living organisms in the natural world. Magic and healing were, and continue to be in some circles, inseparably linked. Janick (in press) has pointed out that the Egyptian word *pharagia*, which means making magic, is the origin of the Greek *pharmakon* and Egyptian *pharmaki*, both of which serve as the origin of the word pharmacy.

Although superstition ruled the practice of medicine for many thousands of years, widespread adoption of the scientific method, and the accumulation of

experimentally based knowledge, transformed medicine into a scientific discipline. This took place in approximately the seventeenth century, when botany and horticulture, as well as medicine, took on the look of modern, scientific disciplines (McCollum, 1957). Medical texts from this period began to de-emphasize plant-based remedies, even though they continued to be in widespread use (Janick, in press). For most of the world's cultures, the primary source of medicinals has been, and continues to be, plants. Current estimates are that more than 70% of medicines are, or were, plant-derived (Janick, in press). The domestication of crops is inextricably connected with healing properties, as medicinal uses may have preceded their more widespread use as food (Smartt and Simmonds, 1995; Rubatzky and Yamaguchi, 1997).

The primary source of information on this close connection between agriculture and human health are documents known as "herbals." The herbal is the primary physical link between horticulture, medicine, and human health (reviewed in Janick, in press). For example, herbals testify to the myriad health-related properties that have been associated with alliums, such as onion (*Allium cepa*) and garlic (*Allium sativum*) (Block, 1992). The frequent descriptions and uses of garlic in herbals by Babylonians, Egyptians, Phoenicians, Vikings, Chinese, Greeks, Romans, and Hindus suggest that it is one of the most widely used plants in folkloric medicine (Block, 1992; Amagase *et al.*, 2001). The herbal combined information about medical remedies, botanical features, and horticulture; thus, it stands as the crucial link between these fields and demonstrates a lineage of close cooperation with respect to human health.

#### **AFTER THE FALL: DIVERGENCE OF AGRICULTURE AND MEDICINE**

Many of the medicinal properties described in folklore and, to some extent, verified by modern medical research, have their origins as plant protectants (Block, 1992). Secondary compounds are often associated with defensive functions in plants, and many of these compounds are of great interest today as phytonutrients (Goldman, in press). Flavonoids, carotenoids, terpenes, glucosinolates, isoflavones, thiosulfonates, *etc.*, may, through their inherent toxicity, confer resistance to pests (Drewnoski and Gomez-Carneros, 2000; Briggs and Goldman, 2002). However, the astringency and toxicity that may be important for survival are viewed widely by consumers as negative from a culinary point of view. Thus, agricultural practices, including plant breeding and post-harvest handling, have attempted to reduce or minimize the astringency of secondary compounds that affect flavor (Drewnoski and Gomez-Carneros, 2000). Crops of today may, therefore, be modified significantly from their earlier domesticated counterparts with respect to such phytonutrients (Goldman, in press). For this reason, it is possible that consumers today do not see the close linkage between crops and human health that may have been apparent to societies living more closely to the period of transition between hunting-gathering and agriculture.

It is often said that the United States is a nation of immigrants. Natural remedies for disease, based on plants and plant extracts and described in herbals, likely served as the basic medicine for many immigrants. Until the beginning of the twentieth century, herb-based remedies were the norm. The Old-World traditions of cultivation of herbs and other medicinal crops remained strong in many parts of the United States, and immigrants relied heavily on them for their healing properties. However, there was a marked shift away from traditional practices toward synthetic medicines during the latter half of the twentieth century (Lawson, 1998), as synthetic pharmaceuticals were developed through advanced chemical means. These synthetic monomolecular drugs became a focal point for the practice of medicine in the United States and many other parts of the developed world, leading to tremendous gains in public health. However, with the shift away from plant-based remedies came a loss of knowledge of their uses and efficacy (Goldman, in press). Although this knowledge was retained and even strengthened in Europe, it tended to disappear in the United States to the point that those born following World War II were far less inclined to turn toward food-based remedies for health concerns; instead they focused on the more widely available and highly efficacious monomolecular drugs (Lawson, 1998).

Development of the food-guide pyramid, the emergence of a national school-lunch program (Gunderson, 2001), strategies such as “five-a-day,” and promotional efforts of the United States Department of Agriculture have had some success in increasing public awareness of the close connection between human health and nutrition. However, nutritional content still takes a back seat to taste, convenience, and cost when it comes to the food preferences of Americans (Tillotson, 2002). Furthermore, food-based approaches to health, particularly those aimed at long-term disease prevention, carry little appeal. This is perhaps due to a long history of reliance on synthetic medicine, and to our collective impatience manifested by a desire to see immediate results and to spend less time purchasing, preparing, and eating food, coupled with the almost-irresistible appeal of highly processed foods.

#### **WHAT WENT WRONG BETWEEN NUTRITION AND MEDICINE?**

Heber and Bowerman (2001) stated that “the evolution of human dietary patterns has been driven by necessity, economics and more recently, by the selection of foods carefully designed and promoted on the basis of taste, cost, and convenience, often without regard to their nutritional and health value.” Despite this de-emphasis on health value, clear evidence exists for the lowering of risk for many chronic diseases, such as cancer, as a result of increased consumption of fruits and vegetables (Anonymous, 1997; Doll and Peto, 1981). Phytochemicals may be at the core of what is believed to be “health functional” about a diet rich in fruits and vegetables. Increased consumption of fruits and vegetables in the diet along with cessation of smoking and increase in exercise have the potential to reduce the incidence of a wide variety of ailments,

including cancer and cardiovascular disease. Thus, they should be of great interest to us, both in agriculture and in medicine.

Nutritionists have examined the effects of dietary patterns based on single properties, such as high fiber, low fat, or reduced carbohydrates. In certain cases, the consumption of a single compound such as  $\beta$ -carotene or lycopene was investigated, thereby reducing the diet to a single measurable property (Heber and Bowerman, 2001). It has been argued that simplified definitions of these dietary patterns led to the idea that supplementation may substitute for the value of a complex diet. For example, if a laboratory study indicated that  $\beta$ -carotene supplementation may be associated with health functionality, then it followed that a reasonable experiment was to supplement diets with this phytochemical in a large, clinical study. Unfortunately, those studies did not demonstrate that such supplementation was efficacious; and in some cases supplementation with phytochemicals proved to be hazardous (Anonymous, 1994). The negative, and at times hazardous, effects of single-chemical supplementation suggests that whole foods, rather than their purified constituents, may be responsible for some of the health functionality of plants. Further research during the latter part of the past decade has done little to convince scientists that simple supplementation is a clear path toward improving public health through nutrition.

Other strategies have focused on manipulating the ratio of the major nutritional constituents of food in order to achieve improved health. For example, low-carbohydrate diets such as Zone™ are predicated on the claim that food is a powerful drug (Sears, 1995). While there is a great deal of public debate about the efficacy of such diets, one of the take-home messages for the general public pertains to the interconnectedness of food and health; a message that is many millennia old. An interesting spin on such diets is their alleged fit with the busy professional's life style. Zone™ products, for example, are marketed with the slogan "nourishment for a time starved world."

As agriculture has developed around the world, dietary patterns have shifted from whole-food, plant-based diets to those that include large amounts of processed sugar, grains, and oils. Heber and Bowerman (2001) argue that the American diet is focused mainly on three grain-based ingredients: refined flour, corn sweeteners, and vegetable oil. In many developed countries, obesity and diabetes are reaching epidemic proportions, despite the widespread availability of inexpensive fruits, vegetables, and other basic unprocessed foods. As agriculture has become more productive, efficiencies have increased, thereby lowering prices, which has benefited consumers and users of basic agricultural products, but has hurt farmers by offering continuously decreasing financial rewards for their efforts. With the lowest commodity prices in several decades in the marketplace today, the supply of inexpensive fruits and vegetables in the United States is abundant and accessible. Nevertheless, demand does not appear to rise accordingly.

Clearly, human dietary patterns are governed to a large extent by taste and convenience, and to a much lesser degree by nutritional content. If epidemiological data indicate that many chronic diseases can be reduced significantly with increased consumption of fruits and vegetables, and the public does not willingly choose to increase its vegetable intake, is it any wonder that agriculture and medicine have become polarized?

### VITAMIN DISCOVERY AND THE REEMERGING CONNECTION BETWEEN AGRICULTURE AND MEDICINE

The “biological era” in nutritional science began in the early part of the twentieth century and led to the recognition of specific elements of food and their functional properties, such as the discovery of vitamins (McCollum, 1957). This era marked a turning point in the relationship between agriculture and medicine. During the first decade of the twentieth century, agricultural scientists identified crucial constituents of foods, later known as vitamins, which were directly responsible for promoting and sustaining health. These discoveries were made on the campuses of land-grant universities, where agricultural and medical scientists worked in close proximity. In addition, there was a pressing need to improve animal nutrition through science, following in the footsteps of the successes of improving soil fertility through the pioneering work of agricultural chemists such as Justus Liebig.

The pioneering work of E.V. McCollum, a US Department of Agriculture employee at the University of Wisconsin, laid the groundwork for the discovery of vitamins (reviewed in Goldman, in press). McCollum made several important decisions in his research program that allowed these discoveries to take place. He was among the first to use rats instead of cows for research on nutrition, thereby greatly reducing the time and cost associated such experiments while increasing the potential for discovery. It is well known that the development of model organisms fueled the growth of many fields of science, and nutritional science was no exception. The purified diets McCollum used in his rat studies differed in only a single constituent, thereby allowing more-precise interpretations of experimental data. This came to be known as the method of biological analysis, which allowed more comprehensive and realistic analyses of food and its components in the animal diet than previous methods that focused solely on chemical composition. By feeding rats with purified diets, McCollum was able to unambiguously identify the important constituents for growth and sustained health (McCollum, 1957).

McCollum was the first to identify an important fat-soluble constituent of butterfat and egg yolk—which later became known as vitamin A—a water-soluble compound known as vitamin B, and his studies led to the discovery of vitamin D (McCollum, 1957). Although it had been known since perhaps the seventeenth century that a disease like scurvy could be caused by poor diet and cured by the addition of citrus fruit, the specific constituents were not

isolated until after McCollum's early work on vitamins A and B. By the 1920s, the specific causes of pellagra, rickets, and scurvy were attributable to vitamin deficiencies, and new support was found for the health-functionality of food.

These pioneering studies led to the discovery of many vitamins, opening up a new area of research in human nutrition. Agriculture and medicine had overlapping goals, thanks to the insightful work of these nutritional scientists. The role of vitamins also cleared the way for more concrete recommendations on the nutritional impact of vegetables. Marketing efforts were constructed with vitamin content in mind, thereby promoting a science-based value-added commodity to the public.

### AGRICULTURE AND SPIRITUAL HEALTH

Even though it provides the basic minerals, nutrients, water, and physical properties for plant growth and, thereby, for the sustenance of humanity, the soil is not only a source of physical health. It has been argued that a connection to the soil, whether through agricultural labor or other natural practices, is at the very core of the sustenance of the human spirit and is the foundation for human civilization. The name Adam, our biblical first human, is derived from *adama*, which means earth in Hebrew, suggesting that human culture is inextricably linked to the soil. Today it is obvious to us that the basic mineral elements of nutrition are literally from the earth. Thus, if the old adage “you are what you eat” is correct, we are made up of the soil and possess a very unique literal connection to the earth.

However, beginning with the rise of modern agriculture about 10,000 years ago, societal development has pushed the human population gradually away from direct contact with the soil. The largely rural population of the United States at the turn of the twentieth century has been whittled down to a very small fraction. Only 1.5% of the general population lives on the farm and are involved directly in food production.

Many environmental movements have urged a rekindling of a close connection with soil, with mixed success. In the nineteenth century, the transcendentalist movement in New England was based on the fundamental truth of this connection. Articulated by Henry David Thoreau in *Walking* in 1862:

*I wish to speak a word for nature, for absolute freedom and wilderness, as contrasted with a freedom and Culture merely civil, to regard man as an inhabitant, or a part and parcel of Nature, rather than a member of society. I wish to make an extreme statement, if so I may make an emphatic one, for there are enough champions of civilization; the minister, and the school-committee, and every one of you will take care of that.*

Although from a political point of view it would seem that acknowledgement of environmental issues has made great strides since the 1970s, it does not appear that the general public has a greater appreciation for the close connection between soil and human health. Thus, one could argue that the tremendous success of modern agriculture has come with significant costs to our spiritual health.

To the extent that modern medicine recognizes the crucial connection between mind and body, it is possible that significant inroads to improved human health could be made through an emphasis of our primal relationship with the soil. A number of modern-day efforts aim to build this bridge, including programs for community gardens in urban centers and food-assistance vouchers for the poor and elderly that can be redeemed only at farmer's markets. However, our culture has a long way to go before such bridges are readily crossed by the great majority of Americans.

#### FUTURE RELATIONS AND COALESCENCE

Medicine, horticulture, and botany have been closely linked since the pre-historic discoveries that certain plants are capable of healing and others are harmful. Priests and physicians were the first practitioners of the healing arts, based both on empirical work with plants and on a belief in magical substances with curative powers. With those discoveries, the fields of agriculture and medicine were closely wedded, supported by documents known as herbals that testified to the myriad uses of plants and their extracts to prevent, treat, and cure disease. In addition, the widespread practice of agriculture formed the foundation for a supply of food for the growing world population. Thus, agriculture and medicine were inseparable for many millennia. This close connection persisted until the seventeenth century, when scientifically based medicine became prominent, and medical treatises began to de-emphasize horticultural practices. From that point on, agriculture and medicine began to separate. As crucial discoveries of vitamins and minerals were made during the early part of the twentieth century through collaborations of agricultural and medical scientists, the two fields became reunited and it appeared that there was much common ground on which to build. However, the rising dependence on synthetic monomolecular drugs in the developed world resulted in a reduced dependence on the cumulative wisdom on plants and human health. In many cultures, such information was lost over a period of several generations.

Today, we are again interested in the relationship between food and health, from the point of view of food functionality. The functional food delivers some physiological benefit beyond nutrition, and thereby confers the possibility of both sustenance and health to the consumer. Given this definition, it is certainly possible that all food is functional, and it is only our limited understanding of its properties that prevents us from labeling it as such. On the other hand, our search for individual functional properties may prevent

us from seeing a larger, more holistic relationship between food and health that can be viewed only through the lens of a complex diet. Certainly, the simple fact that our relationship with the soil is a fundamental truth of human nature should encourage us to pursue the integration, rather than the separation, of agriculture and medicine. The minerals in the soil that form some of the most important aspects of our physical nature are indicative of the importance of this relationship. We can no longer afford to separate the two disciplines that started in unity and are waiting to coalesce for the sake of our healthy future.

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## ***Botanicals As Therapeutics***

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Many botanical compounds (“botanicals”) have the potential to prevent, ameliorate, or even cure some common health perturbations. When the beneficial plant materials or extracts derived from those materials are directed toward specific therapies, they are frequently referred to as nutraceuticals. In most cases, the acceptance of their therapeutic value has taken an inordinately long time, even though the ratio of benefits to risks is often very high. Much of the delayed recognition of therapeutic potential can be attributed to poor physician training in the basic rudiments of nutrition. In addition, the emphasis among practitioners has consistently been on prescription pharmaceuticals, not on over-the-counter nutraceuticals. Accordingly, physicians offer statin-type drugs to lower cholesterol rather than non-prescription garlic and soluble fibers; sibutramine to aid weight loss rather than *Garcinia cambogia*. Moreover, vitamins and antioxidants to maintain good health do not achieve the desired professional appeal necessary for many practitioners. On the other hand, the exaggerated, often preposterous, beneficial claims of many in the natural products industry make it easier to comprehend why potentially useful plant products have been overlooked or even dismissed for far too many years.

However, the pendulum is gradually swinging in the other direction, as more and more patients are, through necessity, taking responsibility for their own health. The policy of “getting them in and out as fast as possible,” emphasized by many large health organizations in order to increase profit margins, has made people aware that long-term health must, at least to some extent, become their own concern rather than that of the health professional. This coincides with a general recognition that, whereas modern medicine is good at treating acute and catastrophic illnesses, this does not hold for preventive measures. In certain vital areas of importance to health, such as obesity, where drug therapy has been less than satisfactory in its effects or has caused unacceptable side effects, natural products are fervently being sought as alternatives.

There are many other important health areas where botanicals have proven useful. In this discussion I will cite only some of the most promising of which I have first-hand knowledge.

### **MAITAKE MUSHROOM: IMMUNITY ENHANCER, TUMOR SUPPRESSOR, ANTI-DIABETIC**

Many natural compounds enhance nonspecific immunity, including biological agents of varied chemical structure. Herbs such as astragalus and echinacea have been documented to possess nonspecific immunity-modulating effects (Physicians' Desk Reference, 2000; Therapeutic Research Faculty, 2000). Medicinal mushrooms, such as reishi, shiitake, cordyceps, and maitake, show a common ability to enhance immune function by stimulating cell-mediated immunity (Lahnborg *et al.*, 1982). Quite simply, mushrooms seem to turn on cells in the immune system, including macrophages and T-cells, that appear to have significant cancer- and infection-fighting properties. This is primarily because some mushrooms are an excellent source of beta-glucans, which are non-digestible polysaccharides found in the cell walls (Borchers *et al.*, 1999). When beta-glucans are consumed prudently, significant benefits to immune health are common. The immune system is reactivated, regaining the ability to fight disease and to ward off infection. These complex sugars are the basis of multi-cellular immune intelligence—the ability of immune cells to communicate, cohere, and work together to keep us healthy and balanced.

Concentrating on the maitake mushroom, a logical question to ask is how does it work? Beta-glucans with certain molecular-branching configurations have been shown to dock onto receptors on the outer walls of macrophages and activate them, stimulating the immune response to pathogens (Brown and Gordon, 2001). Macrophages contain specific protein-based receptor complexes on their walls to which the  $\beta$ -1,3/1,6-D-glucan molecule readily attaches. The binding of  $\beta$ -1,3/1,6-D-glucan enhances the ability of macrophages to detect and scavenge a variety of health threats. Bacterial infections respond remarkably to these polysaccharides, as do many viral infections—from the common cold and influenza to herpes and HIV. Beta-glucans even mitigate the toxic effects of radiation and chemotherapy while augmenting their cancer-killing effects, resulting in prolonged survival and improved quality of life for cancer patients (Preuss and Konno, 2002).

It is now conclusive that the anti-tumor effects are the result of the activity of various beta-glucans located in the fruit body and mycelium (the mass of interwoven filaments that forms the vegetative portion of the mushroom in the soil) (Ohno *et al.*, 1985). Researchers have obtained various therapeutically useful fractions by continually refining the elements from the fruiting body of maitake. The results of much of this research were published in 1980s (Adachi *et al.*, 1987; Adachi *et al.*, 1989; Nono *et al.*, 1989; Ohno *et al.*, 1984; Ohno *et al.*, 1985; Suzuki *et al.*, 1984; Suzuki *et al.*, 1989). The D-fraction of the

maitake extract, obtained last, was found to possess the most potent anti-tumor activity, leading to the highest reduction rate in cancer proliferation (Preuss and Konno, 2002). Research on the specific beta-glucans found in the D-fraction has demonstrated effects not only on macrophages but also on natural killer cells and various T cells. Accordingly, the D-fraction demonstrates perhaps the highest cancer inhibition of any source of beta-glucans via oral administration (Adachi *et al.*, 1987; Nono *et al.*, 1989; Suzuki *et al.*, 1989).

A literature review on maitake confirms that its natural polymer is an important adjuvant in cancer therapeutics, for mitigating the damaging side effects of chemotherapy and radiation, as well as for improving the body's innate defenses and improving the chances of living cancer-free. Another way that beta-glucans may add therapeutic benefit is by stimulation of tumor inhibitors. In certain experimental models, systemic macrophage activation and certain cytokine releases seem to be critical for clearing tissues of tumor cells and inhibiting metastasis. In 1995, Dr. Mitsuhiro Okazaki and co-researchers (1995) demonstrated that the maitake mushroom stimulates release, or, rather, "primes" the body to release tumor-necrosis factor-alpha. Additional studies have corroborated that maitake is a potent, broad-spectrum cytokine inducer. In other words, maitake D-fraction exhibited an anti-tumor effect on tumor-bearing mice through both enhanced cytotoxic activity and stimulation of macrophages—helping the macrophages to function to their fullest potential. This enhanced activity of macrophages invariably results in elevated production of interleukin-1, thereby activating cytotoxic T lymphocytes and many additional cytokines. Finally, maitake has also been described as possessing anti-angiogenic (Matsui *et al.*, 2001) and apoptotic potential (Konno, 2001).

In a non-randomized clinical study, 165 patients, aged 25 to 65, diagnosed with various stages of cancers (III-IV) were given maitake D-fraction plus crude maitake powder tablets alone without chemotherapy or this same combination along with chemotherapy (Nanba, 1995). Tumor regression or significant improvements were observed among eleven out of fifteen breast-cancer patients, twelve out of eighteen lung-cancer patients, and seven out of fifteen liver-cancer patients. If taken with chemotherapy, these response rates improved further by 12 to 28%. In several cases with both liver and lung cancer, the patients went from dangerous stage III status to more manageable stages.

Recent studies in our laboratory using diabetic mice and rats further suggest that maitake mushroom favorably affects diabetes mellitus and hypertension (Manohar *et al.*, 2002; Talpur *et al.*, 2002). A group of eight diabetic Zucker fatty rats given a fraction of maitake designated SX showed significantly decreased systolic blood pressure and fasting blood-glucose levels when compared to eight rats in a control group. At the end of six weeks, the differences in systolic blood pressure between the two groups exceeded

20 mm Hg; and the differences in fasting blood-glucose levels exceeded 60 mg/dL (218 mg/dL $\pm$ 18.3 (SEM) vs. 151 mg/dL $\pm$ 11.2). It is believed that the specific beta glucans in the water-soluble fraction SX were responsible for these effects. Interestingly, the previously discussed fraction D, unlike fraction SX, did not affect either of these parameters.

### DEFINED POLLEN EXTRACT (CERNITIN)

Compared to another natural plant product, *Serenoa repens* (saw palmetto), a defined flower pollen extract commonly called cernitin has received, up to now, little recognition in the United States concerning its potential to benefit various perturbations of the prostate. Ironically, it may be the best natural product for this condition currently available. In 1950, a Swedish beekeeper found a way to collect pollen artificially (Preuss and Adderly, 1998). Since it seemed good for bees, his hypothesis was that the defined pollen extract would be good for humans. Initially, the flower pollen was used as a prophylactic agent against infections. The extraction process was eventually modified so that the active pollen was released and was non-allergenic. A water-soluble and an oil-soluble fraction were deemed therapeutically useful. Oily cernitin GBX and water-soluble cernitin T60 are a mixture of three different pollens—rye, timothy, and maize. Whatever the original hypothesis concerning overall health, the defined pollen extract (cernitin) has proven useful specifically in treating benign prostatic hyperplasia (BPH) (Loschen and Ebeling, 1991).

Leander (1962) published results of a carefully controlled clinical trial of cernitin. He compared placebo with cernitin pollen extract in 179 cases. Using defined pollen extract, he found a 60 to 80% improvement over placebo in symptoms of obstruction, probably occurring through elimination of inflammatory edema. In various subsequent clinical studies, a standardized, allergen-free whole extract of selected *Graminaceae* pollen was found to be suitable in the long-term treatment of prostatic congestion in BPH, chronic prostatitis, and prostatic dysuria (Leander, 1962; Ebeling, 1986; Becker and Ebeling, 1988). The usual dose in clinical studies is four to six tablets per day in divided doses. Each tablet contains an average of 63 mg of *Graminaceae* pollen.

In 1986, a field study of 2,289 patients being treated by 170 urologists was undertaken (Ebeling, 1986). The investigators examined the effectiveness of cernitin pollen extracts on chronic prostatitis and/or BPH. Improvement of symptoms was reported in 64 to 82%, in contrast to a low rate of adverse reaction found only in 2.9 per cent of cases. In the same year, Brauer (1986) compared the effects of cernitin and beta-sitosterol in thirty-nine patients. A significant reduction in circulating levels of prostate specific antigen (PSA) with cernitin therapy indicated a reduction of cell lesions in BPH. In contrast, no such change occurred with beta-sitosterol treatment. Although flower-pollen extract proved superior to beta-sitosterol in many respects, the mean values for residual volume fell under 15 mL for both at the end of treatment.

In a double-blind, placebo-controlled study performed in 1988 in collaboration with six practicing urologists, Becker and Ebeling (1988) compared forty-eight patients taking cernitin with an equal number of patients receiving placebo over a 12-week period. Patients were classified as having stage II/III BPH. Nocturia was claimed by 97% of the patients as a symptom. The results showed that there was a significant improvement using cernitin compared to placebo on nocturia, i.e. 69% vs. 37% ( $P < 0.005$ ). Not only the sensation of residual urine but the actual volume of residual urine was significantly reduced by flower-pollen extract. Mild nausea was reported in one patient. All in all, the “superiority of the active therapy is documented in the symptomatology, the results of the urodynamic investigations and by the global evaluation of the therapy by both doctor and patient.”

In conjunction with two other clinical centers, we conducted a study using a combination of cernitin and saw palmetto to treat the symptoms of BPH. In a randomized, double-blind, placebo-controlled study of 127 subjects (fifty-seven placebo and seventy verum), we found statistically significant improvement in nocturia, frequency, and overall prostate score by the American Urological Association Symptom Index (Preuss *et al.*, 2002).

A major mechanism behind the beneficial action of pollen extract is believed to be inhibition of edema formation and prevention of inflammation in the prostate. Inflammation of the prostate can cause edema of the interstitial tissue surrounding the acini and ducts of the glands leading to poor drainage. This, in turn, creates difficult voiding, dysuria, frequency, and nocturia—symptoms that have been shown to improve with defined flower-pollen extract usage. In addition, pollen extract has been reported to reduce prostatic volume and residual volume, to improve voiding difficulties and increase urinary flow rates of patients with BPH. Obviously, pain may result from such processes and will remit to some extent if these perturbations are overcome. It is believed that the anticongestive action is based upon the inhibition of prostaglandin and leukotriene biosynthesis. The activities of 5-lipoxygenase and cyclo-oxygenase enzymes are markedly reduced and the arachidonic cascade is interrupted (Loschen and Ebeling, 1991). Additional pharmacological effects reported for the pollen are: inhibition of prostate-cell growth in animals, influences on contractility of bladder and urethral smooth muscle as well as diaphragms of animals, and effects on metabolism of dihydrotestosterone (Loschen and Ebeling, 1991). In conclusion, the combined mechanisms behind the beneficial effects of cernitin pollen extract will go a long way toward ensuring overall prostate health.

#### ESSENTIAL OILS (CIDAL TO CANDIDA AND STAPHYLOCOCCUS)

It has been recognized for centuries that meat and fish can be preserved in oils obtained from various spice plants. In our laboratory, we examined the ability of essential oils to kill the fungus *Candida albicans*, and the bacterium

*Staphylococcus aureus* (Manohar *et al.*, 2001). The experiments were carried out both *in vitro* and *in vivo*. The spices examined included oregano, cinnamon/cassia, myrtle, bay leaf, lavender, and cumin. Oregano and cinnamon were found to be the most potent based on their ability to kill both *Candida* and *Staphylococcus in vitro* at the lowest dilutions. When prevention of death of mice infected with *Candida* was subsequently examined, a reasonable dose of oregano was found to save all the mice—similar to the effect of nystatin. Carvacrol, believed to be the major active constituent in oregano, was also shown in the same study to have therapeutic effects on the fungus. When the mice were sacrificed after 30 days of daily treatment, they were found to be clear of fungus with both nystatin and oregano.

In a second group of investigations, a dose of *Staphylococcus* was given that killed all control mice within a 5-day period. All the mice receiving carvacrol died eventually, but survived much longer, averaging 17 days. In contrast, half (3/6) of the test mice survived for 30 days while taking daily doses of oregano. Two of those receiving daily oral doses of vancomycin (2/6) survived the full 30 days and were free of *Staphylococcus* judged by postmortem examination and by kidney cultures.

#### MISCELLANEOUS USEFUL BOTANICALS

Other useful botanicals examined in our laboratory include:

- Wild garlic—a potential antihypertensive that works, at least in part, through its inhibitory effects on angiotensin converting enzyme (ACE) in rats (Mohamadi *et al.*, 2000; Preuss *et al.*, 2001).
- Grape-seed extract—a powerful antioxidant that can reduce circulating levels of the really bad cholesterol, oxidized LDL (Preuss *et al.*, 2000).
- Cinnamon—a potential anti-diabetic and anti-hypertensive agent and potentially fungicidal and bactericidal based on rodent studies (Berrio *et al.*, 1992).

#### CONCLUSION

Many nutraceuticals offer a reasonable approach to prevent, ameliorate, or cure chronic debilitating disorders safely and effectively.

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## ***Supplementing the Immune System with Plant-Produced Antibodies***

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Antibodies are inherently stable proteins found in all mammals and in fish. They have high specificity and low toxicity as potential therapeutics. In the drug industry today, they have much higher approval rates through the clinical process than do new chemical entities, small molecules. They have been formulated into injectable, topical and oral applications. They are appropriate for chronic conditions because they are relatively long-lived in the body and they have some potential long-lasting benefits as supplements to the immune system.

Secretory immunoglobulin A (IgA) and immunoglobulin G (IgG) are present in the human body in great abundance. The IgGs circulate in blood serum, whereas the IgAs are secreted by sebaceous glands and across almost all of the epithelial tissues, the oronasopharyngeal cavities, the pulmonary tract, and the gastrointestinal and urogenital tracts. Each of us makes in the vicinity of 2.5 g of IgA every day, most of which pass into the environment in one way or another. IGAs and IgGs constitute much of the protein component that is found in milk in mammals.

They are our natural defenses. Circulating antibodies protect against invading organisms, including viruses and bacteria, and also against toxins that are produced by ourselves and also by a variety of organisms with which we come in contact, including parasites, fungi, bacteria, and viruses. Secretory antibodies are our first line of molecular defense against invading organisms. These organisms populate the mucosal surfaces, which, because they are warm and wet, are conducive to the growth of bacteria and viruses. The presence of secretory IgAs prevents the colonization or even attachment of those organisms, and thereby prevents subsequent infection or invasion parenterally into our bodies.

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<sup>1</sup>Now with Chromatin, Inc., Chicago, IL.

Passive antibodies are received by infants when breast-fed. Colostrum is a rich source of antibodies, secretory IgAs as well as IgGs, and it is the first bolus of antibodies that infants receive. They absorb the antibodies through the epithelium of the mouth and via the gastrointestinal tract into the circulatory system. Each of us makes in the vicinity of 10 million different antibodies at any given time. No two people make exactly the same antibodies, partly due to the fact that the immunome, the genome of our immune system evolves with time as we are exposed to various antigens and depends on our state of health.

### **ANTIBODIES ON THE MARKET**

Antibodies are commercially available. They first appeared on the market in the mid-1980s. Called OKT3, it was used for organ-transplant rejection, but these molecules have a much broader array of disease indication. ReoPro<sup>®</sup> is for coronary stenosis. Retuxin is a non-Hodgkin's lymphoma anti-cancer molecule. Remicade<sup>®</sup> is an anti-inflammatory molecule. Synergis is an anti-infection molecule that is used in premature infants to prevent infection of the pulmonary tract with respiratory syncytial virus. And Herceptin<sup>®</sup> is a breast-cancer therapy.

Ten antibodies are on the market today, for organ-transplant rejection, cancer therapy, cardiovascular disease, epithelial infections, and inflammatory disease. A number of molecules are in clinical use for systemic infections and there are molecules in preclinical development to deal with oral and topical prophylaxis, primarily for infectious diseases. And several antibodies have been added to over-the-counter applications that are not related to infectious disease but are for prevention of a number of disorders.

### **PRODUCTION SHORTFALL**

The therapeutic markets that have the pharmaceutical companies enthusiastic—because there are large clinical unmet needs for which payer-providers are willing to reimburse—are, primarily, inflammatory CNS disease, cardiovascular disease, and infectious diseases.

The problem is that there is a production shortage; some antibody drugs are production-limited. Irwin Goldman mentioned the anti-inflammatory drug Enbrel<sup>®</sup>, which is used for rheumatoid arthritis. The manufacturers are unable to produce enough Enbrel<sup>®</sup> to meet market demands because manufacturing facilities are relatively expensive to construct, they take a long time to build and then they need to be validated by the Food and Drug Administration (FDA). Demand for these products is projected to exceed capacity by a factor of as much as four by 2005; in 3 years we may be able to produce only half, or less, of the antibody molecules that the market will demand. Manufacturing facilities can take 5 years to build and be validated, therefore the choice to build or not build has to be made before knowing whether the drug will get through the process of proving safety and efficacy to the FDA, and be a commercial success.

Factory construction for a successful molecule costs about half a billion dollars. The cost of the pharmaceutical in the marketplace is \$500 to \$1000/g, which is what most of them actually cost to manufacture. That means that the therapy cost to the individual or payer-provider for a chronic disease is probably in the order of \$10,000 to \$15,000. Enbrel® costs around \$10,000 to 12,000/year. Some of the anti-cancer molecules are of a similar cost for a course of acute therapy. Such high costs face resistance from payer-providers, but certainly if, as a consumer, you chose to use it yourself it would also be prohibitive. There is a significant cost challenge to using these molecules.

### SYNTHESIS IN CROP PLANTS

One of the solutions that seemed obvious to us as plant biologists was to use plants, which are highly efficient producers of proteins. Plants assemble and secrete very complex proteins of their own, and after transfer of the appropriate genes with the right regulatory sequences into plant systems they can synthesize and assemble functional antibodies. The endomembrane system in plant cells is very much like our own. The plant cell recognizes the signals on an antibody molecule and effects assembly in the same way as an animal cell—the same way as human B cells or plasma cells. And then of course we know that there are significant excess crop capacity in the United States that could provide high-value pharmaceuticals like antibodies. The required acreage would probably be less than 5% of the entire acreage for any of major crops such as soybean or corn. There is plenty of capacity.

Many plants and plant tissues have been shown to assemble antibodies with transgenic proteins. We use corn and direct the synthesis of these molecules into the endosperm. The endosperm is made up of cells that are fundamentally similar, therefore, we use a promoter that expresses genes in those cells so that the molecule is made by a single cell type or a small number of cell types that are similar.

When a murine protein is synthesized in a plant is it the same as the original? If you put an antibody gene in a plant, make the antibody and extract it, what does it look like? Does it look like a human-synthesized antibody? The answer is: pretty much. The peptide sequence is identical, and the molecule is folded and assembled and put together the same way. It binds to its target antigen exactly as it should—we now have about forty examples of that.

We can also make those complicated secretory IgA molecules in plants, the synthesis of which in the human body requires two different cell types. In contrast, we can convince the plant cell to make the molecule and assemble it in a single cell, which is more efficient.

One area in which differences exist between plant- and human-synthesized proteins is in post-translational processing. Antibodies are glycoproteins; sugars are attached at various amino acids in the backbone chain of the protein, and those sugars, or glycans, are characteristic for different systems. Mammals

use slightly different glycosylation pathways from plants. Although the backbone and the core glycans are identical the terminal glycans are different.

At this stage, we do not know enough in terms of impact of these differences on efficacy and safety. That information is part of what the FDA demands when a drug is approved. We do know that if you make a mouse antibody in a plant and put it back into a mouse then there is no antigenicity, there is no allergic reaction in the mouse. Also, the circulating half-life of the molecule and the pharmacokinetics or biodistribution are identical in the mouse for mouse- and plant-synthesized molecules. These data indicate that the plant-synthesized molecules are safe and will be treated much like the molecules that we have in our own bodies.

### **ADVANTAGES WITH CROP-PLANT PRODUCTION**

Why should we use plants? They have several advantages over the cell-culture and transgenic animal systems that are available today. Capital costs and operating costs are lower, which are considerations that make the pharmaceutical manufacturers happy, and should also make consumers happy, because these molecules might actually be affordable for a variety of diseases. The material costs are somewhat lower, given that agricultural inputs are relatively inexpensive. Also we can scale up very rapidly. It doesn't take 5 years to build a synthesizing facility. It only takes one season to grow out more acreage of the crop as long as the processing facility can handle the extra material. And, we can scale up very quickly to meet demand, which differs from the situation in the pharmaceutical industry where it takes 4 to 5 years. For instance if Enbrel® were plant-synthesized today, there probably would be a plentiful supply.

In addition, unlike transgenic mammals or cell-culture systems, plants have the advantage of not harboring viruses or replicating viruses that are infectious to humans. There are a number of other zoonotic and prion contaminants that, to this point, have not been found to exist in plant systems, so there are potential safety benefits as well.

### **REGULATORY CHALLENGES**

Regulatory challenges are of greatest concern: are antibodies made in plants—"plantibodies"—fundamentally safe? It depends on two things. First of all, it depends on the antibody itself; is it inherently safe? Secondly, has the antibody been altered by the plant, to make it inherently unsafe? And the only difference we have been able to identify is in the glycans; so the question that is being asked today, and fairly so, is: is the glycan suitable for injection? We know that plant glycans are suitable for topical applications because we are exposed to them throughout our lives and there are no known examples of the glycans on plant proteins being deleterious to humans. Actually, we are well adapted to dealing with those complex glycans.

The regulatory challenge is the clinical trial. To test one of these molecules costs in the order of \$100,000,000 to move all the way through a phase-3 clinical trial. If you are going to invest that resource you must be sure that you have a product that is going to be safe and effective. Furthermore, finding that resource is a challenge.

The FDA and United States Department of Agriculture (USDA) regulatory processes for this new technology are not completely vetted at this point. We await a document from the FDA that has been several years in the making to provide guidance to the industry for the manufacture and clinical evaluation of plant-based biopharmaceutical proteins. It is important that we understand and have good working relationships with the FDA and the USDA in order to move these molecules through the approval process.

### **FIRST CLINICAL TRIAL: HERPES**

Our first clinical trial, which we hope to start in spring or early summer 2003, will be of an antibody that neutralizes all of the known street strains of herpes simplex 1 and herpes simplex 2 viruses. Herpes is one of the most prevalent diseases in North America; over 50 million Americans are infected with herpes simplex 2. About a million and a half new cases are reported annually in the United States. The antibody that we have, is efficacious in an animal model both in the treatment and in the prevention of the disease, so we have two potential uses for the product. To treat a reasonable proportion of the 50 million sufferers, or to prevent the 1.5 million cases, a lot more antibodies will be needed than are available today for treatments such as for breast cancer or for non-Hodgkin's lymphoma or even for rheumatoid arthritis. Using corn, we have the ability to make large quantities at a scale and cost that will be appropriate for the marketplace.

### **THE FUTURE**

There are a number of targets for which antibodies are being developed by Epicyte and by other companies. Largely we are looking at infectious diseases. There are antibodies that recognize beta-amyloid and have a positive impact in Alzheimer's cases; and for oral health there are at least two organisms for which neutralizing antibodies are known to have positive effects on dental caries and gum disease and could probably be used as preventatives.

Our overall goals and challenges have nothing specifically to do with the fact that we are manufacturing molecules in a plant system. They have to do with the overall process involved in bringing a safe and effective drug to the market. Fundamentally, we believe the advantage that plants can bring is that these therapies can be cost-effective and scaleable to the extent that they could be used by the general public. Of course in order to achieve that, we need to make certain that we are protecting the safety and integrity of the food and feed

chains and also of the environment. These issues are part of the discussion that is ongoing with the USDA on guidelines for growing transgenic crops that synthesize pharmaceuticals.

In our view, the most important role at this early stage in the discussion is to inform the stakeholders of the benefits and the risks. People are not well informed of the benefits and some of the risks have not been well assessed, and that is part of the process of forming effective stakeholder partnerships. It includes the regulatory agencies as well as people who will eventually be involved in manufacturing and distributing these drugs.

Some 400 antibody molecules are in preclinical evaluation across biopharmaceutical and biotechnology companies and in academic organizations, and over a hundred are in or beyond phase-1 clinical trials. In ten years I think there will be more than fifty antibody products on the market, and—if we can use plant-based systems—we might see closer to a hundred. We will see a new generation of immunoglobulins, of which Enbrel® is an example (an immunoglobulin backbone with a soluble receptor glued to the end). We will see much lower-cost antibodies both as prescription and as OTC products.

We can succeed, but we have to find effective antibodies, we have to engage the regulatory agencies in order to make certain that these drugs are safe and effective. The agencies make their decisions based on sound science and the onus is on us to provide that. We need to focus on public benefits and risks, practice good stewardship of the environment in terms of the crop systems that we are using and, of course, we need to communicate with all stakeholders.

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## ***Applying Agriculture to Medicine: Therapeutics and Treatment***

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### **Q&A**

MODERATED BY

**RICK E. BORCHELT**

*Whitehead Institute for Biomedical Research  
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*Rick Borchelt:* In our session this morning, we discussed the intersection of biomedicine and agricultural biotechnology and what will be required to fulfill the promises of biotechnology that we are currently making. We may be foreshadowing next year's NABC conference—that biotechnology is at a crossroads between science and society. People of more-primitive or traditional cultures understand the power of liminal places. Initiations, for example, are done on high mountain tops or on seashores or in caves—at physical boundaries. In these societies, animals that regularly cross these boundaries are venerated.

I would like to engage the panel in some discussion of these boundary issues and how they are affecting their work, particularly in the areas of infrastructure, funding, and culture. Then we will take questions from the audience.

Irwin, please discuss the concept of physical proximity as an infrastructural constraint.

*Irwin Goldman:* It's a challenge that we have met before—there is a track record at the Land Grant Institutions and possibly some of the federal institutions. The granting agencies need to recognize the need for collaborative effort, which is most easily achieved when scientists are physically in the same place. I agree that it is a formidable challenge, but our institutions are set up in the United States in a way that makes that a little more possible than otherwise.

*Borchelt:* Harry, Mich—do your institutions support that kind of collaborative activity?

*Mich Hein:* I have not been in an academic institution since I left this institution, so I can't speak to what has transpired in academia over the last 20 years. But I worked at Monsanto and at PPG Industries for about 10 years and then at the Scripps Research Institute for about 10 years. Industry brings together people from disparate fields into relatively small groups to solve specific problems. The Scripps Research Institute, which was a biomedical research institute for many years and then in about 1985 expanded to include chemistry, in-silico chemistry for protein modeling, and also brought plant biology into the fold. That institution had probably 300 investigators in close physical proximity working on the cutting edge in five or six core disciplines, from which grew work on oral vaccines from plant systems. I think that the lessons from those successes could be applied to academic institutions where there is expertise in agriculture and basic science.

*Borchelt:* Harry, you are in one of the nation's premiere medical research institutions. Is there a medical culture issue that you find difficult to address with your colleagues—do they see this as a reversal to the shamanic days of dosing people with herbs?

*Harry Preuss:* Yes, we see a great deal of resistance. At one point I was getting together with the people who work with AIDS, and we had a proposal to look at the potential for monolaurin to affect HIV, which is an encapsulated virus. There had been some preliminary evidence that it could be useful. So, the idea of using coconut oil was just too much. But, we assured them that, with their cooperation, they would be watching the patients. Patients on standard therapies whose viral counts had remained very high were fed macaroons—I think that turned them off too. We said that we would feed them the macaroons—obviously we didn't think there would be any risk unless they liked them and ate too many—then do the viral counts a month later. I was amazed to find that they didn't want to bother.

Then, one of my colleagues at Georgetown had some patients with ovarian cancers and I talked about the potential of using maitake mushroom on those patients. He had just finished an unsuccessful regimen with gemcitabine and the other oral poisons they were using on the patients, and I remember his comment was, "Well I don't want anyone to know that I'm working with a mushroom." I said tell them that you are working with a beta-glucan—look it up in the literature and you will find a great deal of literature on beta-glucans as a stimulatory agent in cancer—but I never could get him interested. I look at this as lost time. I'm the type of individual if I am not putting the patient at risk I will try it and see what happens. They are very closed-minded, but they're starting to come around. We have had some lectures on mushrooms and people are starting to say, "Maybe there is some benefit." It's a slow process.

*Borchelt:* Is there an education issue at the postgraduate or postdoctoral level that would be helpful in this?

*Preuss:* Well Georgetown just received an NIH-funded grant to include alternative medicine in its teaching program. I am part of that, and sometimes I shudder because I don't like to be linked with *alternative* medicine. I usually tell people I practice medicine, it works or it doesn't work—the thought that you are in alternative medicine is very pejorative. So, I don't like that terminology, but certainly it includes working with supplements and nutraceuticals.

It took us 5 years to convince colleagues at the American College of Nutrition that we should be looking more at botanicals. Sure, you hear people on the radio and the television making exorbitant claims—but I put the idea before our group that this is what we were supposed to be doing, if there are some sham concepts out there then part of our job is to expose them. We should look at everything, and take the good and go on and do more work with it, and expose what is bad. But it's hard to win them over.

*Goldman:* On the question of education, I think that students are increasingly trying to choose the border or the boundary areas between fields. It is a humbling experience to make the jump to another discipline because there is so much new terminology and so much to learn. But, judging from the graduate applications that we see, students want to bridge gaps. Whether we need formal programs, I'm not sure, but students are choosing to work in collaborative groups that have already established a record of obtaining grants and running projects across a variety of disciplines. So, the student then needs to double her or his training. They need training in medicine and in the agriculture, which makes it more burdensome. But we are starting to see that, and I think it's a very positive indicator of educational opportunities.

*Borchelt:* Mich, where are you finding your workforce for Epicyte?

*Hein:* That is a very difficult question to answer. We literally have to look everywhere. We have found people principally who have experience in the biopharmaceutical industry already. Our best source of workforce are people who have worked in the gaps between existing disciplines and people who have used multiple disciplines in problem-solving. At Scripps they have a very interesting graduate program that is multi-disciplinary—macromolecular and cellular biology, and biochemistry—where the students have to use multiple disciplines. They do everything from in-silico protein prediction to molecular genetics and organismal studies. We have to find people who already have such experience or we have to spend 2 years training them.

*Borchelt:* I don't want to put you all on the spot, but Mary Clutter is in the audience today and I'm sure she would appreciate your thoughts on how to take better advantage of synergies between agricultural biotechnology and medical biotechnology. How would you go about designing or redesigning part of the granting process so that it captures those synergies in ways that may not be possible today?

*Hein:* One way to do that would be to engage more industry-trained scientists. Not business-development people who may be involved with small business innovation research (SBIR) programs, but rather the scientists who are deep in the core biotechnology and medical industries and, for that matter, even the agricultural industry, and get them on grants panels, because a lot of the cutting-edge and interdisciplinary research is being seen by those people. Recently we have been fairly successful in getting SBIR grants, but when we were trying to do this work 10 years ago at Scripps, we were being reviewed largely by academics and our proposals to make antibodies in plants came back with one-sentence reviews that it wouldn't work. Yet there were people in industry who had been working on similar systems and who understood that it would work. So, I suggest enriching the pool of people who are reviewing the science.

*Preuss:* I have been seeking support through industry mainly. Originally my research covered the area of nephrology and hypertension, which is what I am trained in. Then I started working on supplements and natural products, and my attempts to get grants when I was working with chromium were almost futile. I was working on chromium and on fractions of maitake, when rezalin came out. One of the manufacturers who gave us support said, "Why are they allowing rezalin out? It's a drug that has been killing people in Japan." I couldn't tell him why, and now it's off the market having caused a lot of liver problems. I have had a lot of difficulty working with natural products. Therefore, I go to manufacturers and usually they are interested and will put up some money to study their products.

*Goldman:* In relation to the communication issue that we spoke of earlier—when you have groups from disparate fields coming together and proposing projects they essentially speak different languages. One aspect that needs to come across very clearly is how these groups are going to collaborate. On the other hand, there are examples of where the flow of information—even from the production agronomist to the food chemist who is going to extract the compounds to the medical professional who is going to test the compounds—is well presented. That kind of dialogue has to happen first, with communication well established, in order to be successful. So, somehow, in addition to making modifications in the granting process, we need to initiate the dialogue—not

just because the money is available—by providing forums like this for people to get together and start to make inroads.

*Borchelt:* I'd like to open discussion up to the audience now.

*Kitty Smith (USDA Economic Research Service, Washington, DC):* We heard yesterday that most people get their information on food and health from television, which, while Lea Thompson thought that was a good thing, I wonder about it. And today in his introduction I thought I heard Randy Woodson make a negative reference to *Prevention* magazine where most of the contributors have a whole bunch of educational initials behind their names. I'm wondering, for those of you who are working on the borders between plants and human health, what are good references for those of us who can't read biochemistry journals?

*Hein:* I don't think there are any. You have pointed to a key issue and, as I suggested earlier, communication channels really need to be improved. I don't know what role the USDA might have in that process. The extension service might be a reasonable place to look to, as a system that is already working. I find that television is not particularly informative on these issues. In my experience, discussions on television always have a controversial fulcrum to get people's attention, which doesn't necessarily provide the best light. In terms of what people read, I would say the most accurate information with a broad scope is in journals like *Nature Biotechnology*, but that isn't something that the general public is going to read. So we need a way to bridge that gap. In some metropolitan areas where biotechnology industry is burgeoning, some newspapers are taking things into their own hands and doing a good job. In San Diego we have the *North County Times*, which has an entire section every Sunday on science and technology, written by Bradley Fikes who does an excellent job. But that is a single regional area—there is a need for something similar to be broadly accessible.

*Borchelt:* The situation actually is even worse than indicated by Susan Borra and Lea Thompson yesterday. I just finished chairing a 3-year blue-ribbon panel on the future of science communication funded by the Department of Energy and NASA, and we found that most people get their science, health and technology information from regional and local television, which probably has the highest error rate of any of the media that we looked at. We also found from the work of Jon Miller at Northwestern University that there is a particular audience out there—we call them science attentives, probably 20 or 25 million strong—who will dig past that, who will look behind *USA Today*. They get most of their references from the Web, which is a growing area that I suspect probably wasn't surveyed quite as directly in Susan's work. We are finding that the Web provides

a safety net for science and technology information. When people hear something on television, many then consult the Internet. This is particularly true of ages up to about 45. Not an ideal situation clearly.

*Bob Peterson (Montana State University, Bozeman, MT):* I lead the Agricultural Risk Assessment Program at my home institution and I want to follow up on Mich Hein's comments. Before joining Montana State I was in the private sector and worked for several years with the evolving regulations regarding plant-based biopharmaceuticals, vaccines, antigens in particular, and antibodies. I think there is some confusion in comments of yesterday and today in terms of thinking that some of these products will be regulated as foods. When you are talking about producing non-food proteins in food crops the regulations are very different and the field production is in no way capricious—it will be regulated as one step in the plan of production of a vaccine, antibody or other pharmaceutical. Even the title *Foods for Health* is confusing. In terms of the products that Dr. Hein was talking about, they are not considered foods any more, and they will not be regulated as foods. They will come under special regulations, which are still evolving, to prevent them from entering food channels. Vaccines will not be administered through food, at least in the United States, the way these regulations are evolving.

*Hein:* Those points are very well taken. I didn't go into detail about the regulatory process and I really appreciate you making the point. But, we as a company, and I think most other organizations public or private in the United States that are developing plant-based systems for producing pharmaceuticals, are very much aware of the need to maintain the integrity both of the food chain and of the pharmaceutical-manufacturing process. This is a new arena in which regulations and infrastructure are evolving, and part of the challenge for us as a small organization lies in not having the infrastructure of large pharmaceutical companies to interact with the agencies. So we need to take baby steps and we've done that. But the process is frustrating because of the cost in time and dollars. We are all interacting closely with the Biotechnology Industry Organization (BIO) as well as with the federal regulatory agencies to ensure that we are practicing good stewardship. I know of no one actively engaged in the industry today who would diverge from that. We are specifically looking at making drug molecules. On the issue of vaccines—a field I worked in for about 10 years then made a conscious choice to leave until we know significantly more about the impact of edible molecules on the immune system—progress has been made in the last 6 years on which John Howard will probably enlighten us.

*Samuel Lehrer (Tulane University, New Orleans, LA):* I want to comment on the problems of interactions of various scientific disciplines. In major cities,

medical centers were placed in areas of high population to provide patients for teaching students. Take Chicago or New York, and it is the case with Tulane in New Orleans and with Temple in Philadelphia—all of these medical centers are removed from universities, and that is a problem. Developing interdisciplinary programs is the way to go, but it takes real effort. People just don't feel like traveling 10 or 15 minutes to a seminar or to a discussion. Mich's point about the study sections is a good one. I think study-section diversity—groups that review grants—has been a real issue over the last 10 to 20 years. Maybe it is just bitter grapes on my part in terms of getting grants, but certainly the granting agencies need to make more of an effort to expand the pool of people in study sections so that they can take on new projects and encourage new ideas.

Two quick questions for you Mich: what are the sources of your antibodies, and are you planning to use the plant as a delivery system or just for production?

*Hein:* I'll answer the last part first. For the products that we are developing today, we are looking at two delivery methods. One is actually parenteral—highly purified injectable drugs, approved by the FDA, tested in clinical trials. And we are also looking at topical applications for prevention and therapy of mucosal infective and inflammatory disorders. While those formulations will contain highly purified antibodies they will have other excipients in them, much as other topical products. So they might be in gels or in lubricants. From the standpoint of production, we looked at many species of plant, most of which are capable of being used for manufacture. But, we made a conscious decision to focus on one, to make the system work. We chose maize, corn, because much of the technical know-how was already in place. And we chose the endosperm, specifically because it has a small number of soluble proteins, all of which are well characterized and none of which is known to be harmful to humans. Also, handling procedures were already available. People know how to grow it and we know a lot about the germplasm. But others are using different species and many of them work. We originally worked with tobacco because it was a great experimental organism. We will stick with corn for the near term, although we are still evaluating others.



PART VI

APPLYING AGRICULTURE TO HEALTH: FOOD TO PREVENT DISEASE

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## ***Where Do Functional Foods Fit in the Diet?***

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I will address what has been called the “functional foods revolution” and discuss some of the driving factors in this field. Let me begin by defining the term “functional food.” Certainly all foods are functional because they provide taste, aroma, and/or nutritive value, but there is a definition that is becoming generally accepted, for example by the International Life Sciences Institute and the International Food Information Council: a food that by virtue of physiologically active components provides health benefits that go beyond basic nutrition. Those with a grounding in nutrition will realize that we are talking about the essential nutrients—vitamins, minerals, macronutrients and micronutrients—that are essential for metabolism and for maintenance and repair of body tissue. Calcium, for example, is a mineral that is very important for skeletal health, but scientific discovery indicates that calcium may be linked to reduced risk of colon cancer, it may reduce PMS, and it may be linked to blood-pressure regulation. There has been a lot of information in the news recently on folate with regard to cardiovascular disease. Homocysteine metabolism is very closely linked to this, and in early 2002 a paper was published on the fact that those with a compromised folate status may be at risk for Alzheimer’s disease. Clearly, nutrients long known to be essential may have broader importance.

### **MEDICINE’S SHIFT OF FOCUS**

Over the past 100 years there has been a shift of focus from prevention of nutrient-deficiency diseases to interest in prevention of chronic disease. We now suffer not from diseases of deficiency but of excess, and the Surgeon General’s report first highlighted this in 1988:

*Over-consumption of certain dietary components is now a major concern [as is] disproportionate consumption of foods high in fats, often at the expense of foods high in complex carbohydrates and fiber such as vegetables, fruits and whole grain products that may be more conducive to health.*

We recommend a plant-based diet for the prevention of chronic disease because there is accumulating evidence that many plants contain physiologically active “phytochemicals” that may be linked to chronic disease risk reduction. Examples are soybean phytosterols, resveratrol in grapes, lycopene in processed tomato products for possible prevention of prostate cancer. Also lutein in spinach, which received GRAS (generally regarded as safe) status in May 2001, and which will probably go into food products for age-related macular degeneration, the limonoids in citrus products, the indoles and glucosinolates in the brassica family vegetables such as broccoli, the organo-sulfur compounds such as allicin in garlic and shallots, and the proanthocyanidins in cranberries and even in chocolate. Yes, chocolate—my favorite—especially with a glass of red wine, which also has a lot of polyphenolics. And there are animal products that contain physiologically active “zoo-chemicals”: conjugated linoleic acid in milk and the omega 3 fatty acids, for example.

If physiologically-active components are extracted from whole foods and put in capsule form, we can refer to them as “nutraceuticals.” In my opinion, broccoli is not a nutraceutical whereas the extracted component is a nutraceutical. Steven Zeisel, Head of the University of North Carolina’s Department of Nutrition, has defined nutraceuticals as diet supplements that deliver a concentrated form of a presumed bioactive agent from a food presented in a non-food matrix and used to enhance health in dosages that exceed those that can be obtained from normal food. An example is soy isoflavones.

The American Dietetic Association published a revised position paper in 1999 and I was privileged to be one of the three authors of this document. We felt that there are a number of foods that may be considered to be “functional,” although it’s an area of controversy. They certainly include whole foods, and also fortified, enriched or enhanced foods that have potentially beneficial effects on health when consumed as part of a varied diet on a regular basis at effective levels. The latter point is where regulations become critical, because the Food and Drug Administration (FDA) appraises health claims under the Nutrition Labeling and Education Act (NLEA) in terms of daily intake levels for foods such as soy, oats, etc.

### **FUNCTIONAL FOODS: EXAMPLES**

One of the best documented groups of functional foods are fruits and vegetables. Without question, one of the best things that we can all do to

reduce cancer risk is to consume at least five servings of fruits and vegetables per day. In 1997, the World Cancer Research Fund and the American Institute for Cancer Research published an excellent summary of data linking dietary modifications to cancer risk—including the consumption of fruits and vegetables—and demonstrated once again that dietary modification can reduce cancer risk by 30 to 40%.

Another well known functional food that meets a health need is calcium-fortified orange juice. Obviously, native orange juice does not contain calcium. However, since women still do not get nearly enough calcium, and for those who do not consume animal products (for whatever reason) orange juice is an excellent vehicle to provide calcium in the diet. Orange juice is high in potassium and the Food and Drug Administration (FDA) Modernization Act (FADAMA) of 1997 now allows two health claims on food. Potassium in relation to reduced blood pressure and stroke is the newest FADAMA claim allowed, and this information is important for public health as high blood pressure is largely undiagnosed.

Viactiv™ chews are another example of a functional food for women's health—currently a hot topic for marketers because women make most of the purchasing decisions in the grocery store. They are living longer past menopause—30 years in an estrogen-compromised state—which has implications for bone loss, for increased cancer risk and for increased heart-disease risk. So this is an excellent functional food for those who want to get calcium and other bioactive components for bone health, such as vitamin K, vitamin D, and magnesium.

Other functional foods available in the marketplace are Benecol® and its competitor product Take Control®. They are margarines containing stanol and sterol esters, respectively, that have been shown in numerous clinical trials to be effective in lowering cholesterol. The FDA approved an interim final health claim on these products in the year 2000.

And of course we have processed foods such as ketchup that marketers are using to increase awareness of the role of certain foods in chronic disease reduction. However, there is still some controversy over communicating the benefits of lycopene as a cancer chemoprevention agent, as the data are largely epidemiological.

## **DRIVERS**

A number of books have been written on this subject over the past few years, starting in 1994 with *Functional Foods* edited by Israel Goldberg. Also Ted Labuza, who is at this meeting, and his wife, Mary Schmidl, edited an excellent text, *Essentials of Functional Foods*, a couple of years ago. Why is it such a hot topic? It is driven by a number of factors: consumer demand, technology advances, liberalized regulations, certainly scientific research linking diet and health, and the business-opportunity component.

Consumer demand is being further driven by aging demographics, rising healthcare costs, and what we refer to as the “self-care” trend. In their annual reports over the past several years, the Food Marketing Institute (FMI) has shown that a significant portion of consumers feel that eating healthfully is a better way to manage their illness than even taking medication. Thus, consumers are turning to the kitchen cabinet rather than the medicine cabinet to meet their health needs.

The percentage of shoppers more likely to treat themselves before seeing a physician rose from 31% in 1998 to 64% in 2001. In a survey by Sloan Trends & Solutions, Inc., eyesight was the number-one concern—maintaining healthy eyesight as we age. Heart disease, the leading cause of death is also a major health concern, and it is not surprising to see a number of cholesterol-fighting functional foods on the market with attendant health claims. Oat beta-glucan, soluble fiber, psyllium fiber—these functional foods have NLEA-approved health claims. I mentioned the sterol and stanol esters. Soy protein had an NLEA health claim approved in 1999 and there is currently a qualified health claim for dietary supplement sources of omega-3 fatty acids.

The sequencing of the human genome has driven an area of study referred to as “nutritional genomics,” which is certainly one of the forefront biomedical developments: the interaction of the human genome, nutrition, and biochemistry. However, it must be remembered that about 70% of colon cancer, stroke, more than 80% of coronary heart disease and over 90% of type-2 diabetes are preventable by the right life-style choices. Walter Willett addressed this issue in the April 26, 2002, issue of *Science*, and stated:

*Overly enthusiastic expectations regarding the benefits of genetic research for disease prevention have the potential to distort research priorities and spending for health. However, integration of new genetic information into epidemiologic studies can help clarify causal relations between both lifestyle and genetic factors and risks of disease.*

Clearly we must keep the role of nutritional genomics in perspective. However, indications are that nutritional genomics has huge potential for designing diets and identifying specific genetic links to disease.

## **BUSINESS OPPORTUNITIES**

Certainly there are huge business opportunities for manufacturers of functional foods. Benecol® is significantly more expensive than typical margarine, about \$5/lb. There is interest on the part of food manufacturers to get into the functional-foods arena because products that deliver health benefits are growing at a much higher annual rate than are conventional foods. According to the *Nutrition Business Journal*, conventional foods have been growing between 2 and 4% annually over the last 4 years, whereas functional or health-enhanced foods have been growing at 7 to 9%—a trend that is expected to continue.

With respect to food manufacturing, there has been a shift away from removing negative ingredients to adding positive ingredients, which resonates well with the consumer. Consumers want to hear positive messages, so there is a focus on positive eating. Therefore, rather than focusing as much as we did 10 years ago on removing negative ingredients, we are adding the more positive ingredients to foods. For example, from the early 1990s to 2000, the number of low- or no-cholesterol products on the market has diminished, whereas the number of calcium-fortified products has increased.

#### **NO MAGIC BULLET**

There is a very narrow gap between foods, drugs, and dietary supplements and the Center for Science and Public Interest has called for scrutiny in this area particularly because of concerns over the positioning of conventional foods as dietary supplements and over herbal-fortified products because they may interact with certain drugs.

Functional foods need to be safe and their efficacy proven. Their health benefits need to be effectively communicated to consumers with the caveat that they are no magic bullets.



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## ***Can We Have Allergen-Free Foods?***

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Technology has been used to improve our food supply since primitive man first cultivated crops such as wheat and barley in Mesopotamia in 6,000 BC and domesticated animals such as sheep and goats in southwestern Asia over 10,000 years ago. Recently, improvement of our food supply has been achieved by the development of hybrids, notably of corn, and by breeding and selection which more than doubled wheat and rice crops in developing countries in the 1960s and 1970s (the “green revolution”). Breeding and selection has also increased the supply of domesticated animal species that are sources of foods; for example, chicken, one of the more expensive meats in the 1940s, is now one of the least expensive. Selection of certain traits in plants and animals did not occur without change, not only in the plant and animal species involved, but also in society.

What differentiates the so-called old technology described above from the new technology is genetic engineering, also referred to as molecular breeding. This technology facilitates the selection, identification, and transfer of genes encoding for specific proteins into the genome of another species. Molecular breeding precisely determines which proteins are introduced, where they are expressed and, in some cases, requires synthesis of only minute amounts of a protein in order to obtain the desired trait. Supporters of this technology believe that it will provide substantial benefits for mankind such as less expensive and healthier foods, foods that will help to eliminate diseases and aid in feeding the growing world population. Already, crops genetically modified for insect resistance are significantly reducing the use of synthetic organic insecticides in the United States. However, critics have raised concerns regarding environmental effects, such as gene spread from genetically-modified (GM) crops to indigenous relatives, and adverse effects on the health of mankind. A major health concern is the development of foods of greater allergenicity or containing novel allergens in new foods (Jacobson, 2002; Millis, 2002; NRC, 2002).

## DEVELOPMENT OF FOOD-INDUCED ALLERGIC REACTIONS

Food may be a major cause of severe acute hypersensitivity reactions, including fatal anaphylaxis, in some individuals. Food allergy has been estimated to be the most frequent cause of anaphylaxis treated in emergency rooms (Yocum and Khan, 1994). Severe reactions to foods can occur at all ages, from infants (Ellis *et al.*, 1991; Saylor and Bahna 1991) to children, adolescents, and adults (Sampson *et al.*, 1992). Currently, the only means of managing severe acute food reactions is strict avoidance and the immediate availability of emergency medications. However, accidental or inadvertent exposure to food allergens can occur even for the most careful food-allergic patient. The unpredictability of accidental exposures and long periods of time during which patients at risk may not come in contact with the offending foods make it difficult to have medications available at all times, as is necessary to prevent a fatal reaction (Yunginger *et al.*, 1988; Sampson *et al.*, 1992).

The vast majority of acute, severe reactions to foods appear to be IgE-mediated, although non-IgE-mediated reactions also occur (Hill *et al.*, 1995). The presence of IgE antibodies as the likely cause for severe acute food reactions suggests the possibility of changing this allergic reactivity to a less noxious or even protective form of immune response through immunotherapy or of altering the reactivity of major food allergens with IgE antibodies.

The induction and provocation of an IgE-mediated hypersensitivity food allergy is summarized in Figure 1. When an individual is first exposed to a food

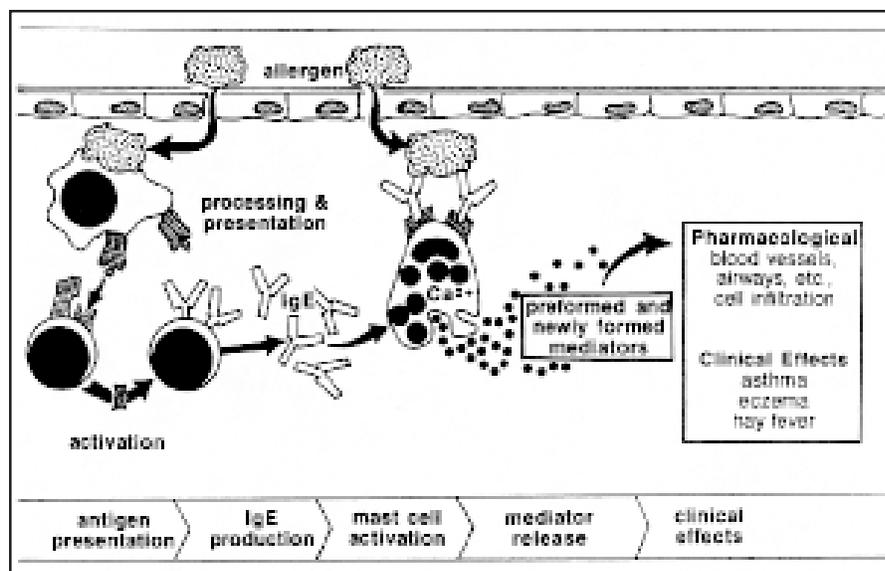


Figure 1. The induction and provocation of an IgE-mediated food-allergic response.

allergen, this molecule or a fragment thereof, crosses the mucosal barrier; following processing and presentation by macrophages and T lymphocytes, peptides (derived from allergens) can activate T and B lymphocytes. Interaction between these cells results in activated B lymphocytes that produce IgE antibodies that react specifically with the allergen that stimulated their production. These IgE antibodies (in addition to reacting to allergens) have the unique ability to fix to the surfaces of mast cells or basophils, cells that contain a number of potent pharmacologically active molecules called mediators. When an allergen cross-links two or more specific IgE antibodies bound to mast cell or basophil membranes, mediators are released that affect both local and systemic organ systems, resulting in the clinical effects seen in allergic reactions such as asthma, eczema, hay fever, and anaphylaxis.

### GENERAL PROPERTIES OF FOOD ALLERGENS

Although allergenic foods may contain over 10,000 different proteins, only a few (generally ten to twenty) elicit allergic reactions. The structural properties that are responsible for the allergenicity of a food protein are generally still poorly defined, although some broad characteristics of food allergens have been identified. These include abundance of a given protein in a particular food; physicochemical properties, such as acidic isoelectric point and glycosylation; and resistance to heat and digestion (Lehrer *et al.*, 2002). Although these characteristics have been associated with the allergenicity of proteins, some, if not all, of these properties characterize a vast number of non-allergenic proteins as well and, thus, are not unique to food allergens.

The portion of the allergen molecule that is recognized by, and interacts with, allergen-specific IgE is the allergenic epitope. Most allergens, as stated above, are resistant to heat; although heat denaturation may cause loss of the native protein's conformation, patients' IgE antibodies can still react with such denatured food proteins, suggesting that the allergens' epitopes are not dependent on the native conformation (Lehrer *et al.*, 2002). Thus, alteration of these epitopes is the focus of current technology—to reduce or abolish their reactivity with IgE, resulting in reduction of allergenicity.

Food allergens frequently account for a major fraction of the total protein content within a given food. For example, the major shrimp allergen, Pen a 1, accounts for about 20% of the total shrimptail-muscle protein (Daul *et al.*, 1994). An exception to this rule is the major allergen of codfish *Gadus callarias*, Gad c 1; this molecule, identified as parvalbumin, is not a dominant protein in cod muscle (Elsayed and Bennich, 1975). There are several aspects of molecular size that may contribute to a protein's allergenicity. First, the molecule must be large enough to elicit an immune response but small enough to cross the gut mucosal membrane barrier; second, it must be of sufficient size to contain at least two IgE binding sites to bridge mast-cell-bound IgE.

The ability of a food allergen to cross the mucosal membrane of the intestinal tract is most likely an important feature. As mentioned earlier, size is one parameter in this context; another may be a resistance to digestion. The results of one study, which used a gastric model of mammalian digestion to study the digestibility of food allergens, point in this direction (Fuchs and Astwood, 1996): allergens from egg, milk, peanut, soybean, and mustard resisted digestion for up to 1 hour, whereas nonallergens were digested within 1 minute. However, there is insufficient information to conclude that the resistance to enzymatic digestion is a property that distinguishes all food allergens from non-allergens, since some labile proteins can be allergenic and not all stable proteins are allergens.

### **PREDICTING FOOD PROTEIN ALLERGENICITY—DECISION TREE**

Over the last 10 to 12 years, governmental agencies (FDA, EPA, USDA), industry organizations (ILSI, AII, IFBC) as well as international health organizations (FAO, WHO) have addressed the issue of the allergenicity of GM foods. Their discussions have resulted in developing a decision-making process to aid companies and regulatory agencies in assessing the potential allergenicity of products being developed. Theoretically, there are three potential alterations that could affect the allergenicity of a GM food. First, endogenous protein levels could be affected and if these proteins are allergens, this could result in enhanced allergenicity. Second, the protein whose gene is expressed in a GM food could be a known allergen if derived from an allergenic source. Third, novel proteins expressed from sources for which there is no prior human exposure may be allergens.

A decision process developed to address these issues (Figure 2) is based on the source of the gene: is it from an allergenic or non-allergenic source? If it is from an allergenic source, there are solid-phase, immune assays that, with sera from allergic individuals, can be used to determine the allergenicity of the molecule being expressed or the enhanced levels of endogenous allergens. If the expressed protein is from a source for which there has been no prior human exposure, the assessment of its allergenicity is more difficult. This assessment is based on a comparison of the properties of the molecule to properties of known food allergens, such as amino acid sequence similarity, stability to enzymatic digestion, and stability to processing. Such an approach, while not yielding absolute definitive answers, can help in assessing the potential allergenicity of the molecule in question (Metcalf *et al.*, 2000). Clearly, as technology improves and our knowledge of food allergens increases, better assessment methods for allergenicity of novel proteins can be expected. Generally, the current risk assessment for allergens is reasonable, provides assurance of food safety and has worked well in avoiding the development of allergenic GM foods. Although risk assessment for known allergens is well delineated, risk assessment for novel proteins is more problematic and needs to be improved as our knowledge of food allergens increases.

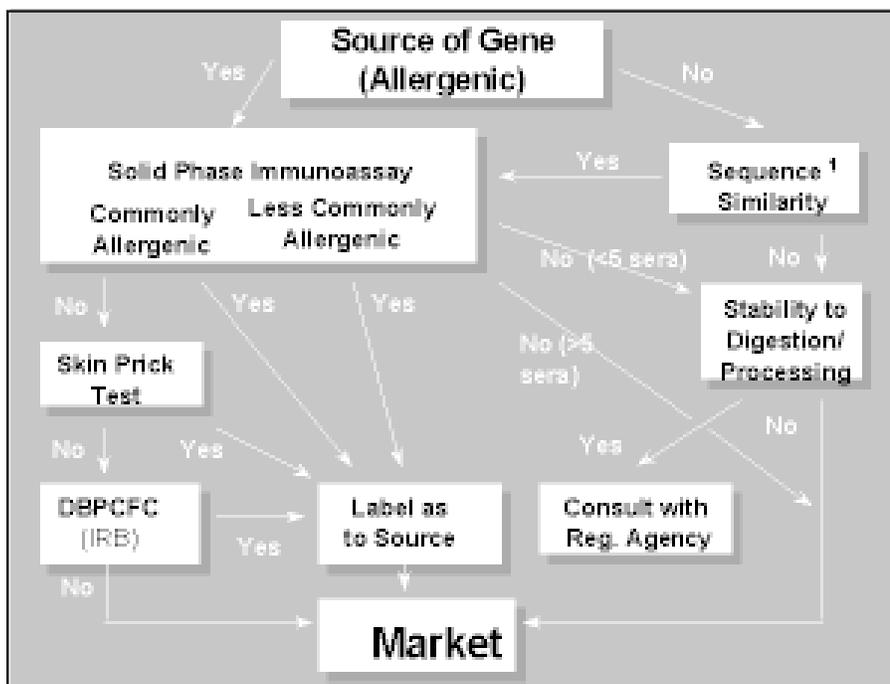


Figure 2. Assessment of the allergenic potential of foods derived from genetically engineered crops—International Life Sciences Institute (ILSI) decision tree.

#### USE OF BIOTECHNOLOGY TO DEVELOP HYPOALLERGENIC FOODS AND SAFER ALLERGENIC VACCINES

Genetic modification of plants and animals, may, in the future, improve the safety and quality of foods, by reducing allergenicity of known allergens. A number of major allergens have been identified in agronomically important crops such as soy and wheat as well as in less economically important crops such as peanut and tree nuts. Furthermore, important allergens have been demonstrated in a variety of animal products used for food, such as milk, eggs, fish and particularly shellfish (Bush and Hefle, 1996).

There are several approaches to reduce allergens in food. Traditional plant breeding has been used to identify strains with reduced allergenic activity. Food-processing methods have also been used in attempts to reduce or eliminate the allergenicity of various food products. Most recently, genetic engineering has been employed:

- post-transcriptional silencing to decrease the level of protein synthesized in a particular food;
- reduction of disulfide bonds to alter the structure of allergens to reduce their allergenicity;
- modification of genes encoding allergens.

For gene modification, extensive knowledge of allergen structure is needed, including amino acid sequences, as is gene-nucleotide sequence. Furthermore, the IgE binding sites—the portion of the allergen that actually binds IgE and is responsible for allergic reactions—must be determined (Bannon, in press).

Shrimp and peanuts are two foods that have been extensively investigated since they can induce severe anaphylactic reactions in sensitized children and adults that can result in death. The only major allergen in shrimp is the heat-stable muscle protein, tropomyosin, called Pen a 1 in *Penaeus azectus*, which is studied in our laboratory. Tropomyosin has a rather intriguing, highly stable structure: a coiled coil composed of two identical tropomyosin polypeptide chains in alpha-helix formation coiled around each other. Using overlapping peptides, five major IgE-binding regions were identified in the tropomyosin molecule. Further analysis of these regions by overlapping peptides of shorter length identified the minimal sequence that binds IgE from sera of shrimp-allergic subjects. Individually recognized epitopes of region 5 are shown in Figure 3.

	239	250	260	270	280	284
<b>region 5</b>						
	<b>A E F A E R S V Q K L Q K E V D R L E D E L V N E K E K Y K S I T D E L D Q T F S E L S G Y</b>					
<hr/>						
<b>249-260</b>	<b>L Q K E V D R L E D E L</b>					
<b>249-261</b>	<b>L Q K E V D R L E D E L V</b>					
<b>251-259</b>	<b>K E V D R L E D E</b>					
<b>266-273</b>	<b>K Y K S I T D E</b>					
<b>266-273</b>	<b>K Y K S I T D E</b>					
<b>266-273</b>	<b>K Y K S I T D E</b>					
<b>266-273</b>	<b>K Y K S I T D E</b>					
<b>273-281</b>	<b>E L D Q T F S E L</b>					

Figure 3. Shrimp tropomyosin epitopes 5a, 5b and 5c in IgE-binding region 5.

Region 5 is composed of three individual IgE binding epitopes (Lehrer *et al.*, 2002). A total of eight epitopes were identified in the five IgE binding regions. The epitope amino acid sequence, as defined by maximal IgE antibody reactivity, varies for some epitopes (*i.e.* epitope 3a) whereas is essentially identical for others (*i.e.* 5b). Alteration of these peptide epitopes by amino-acid

substitution was performed based on homologous amino acid sequences in other tropomyosin molecules (Figure 4). A number of amino-acid substitutions were demonstrated that completely abolished IgE antibody binding. These results are very encouraging since these amino-acid substitutions should not alter the structure of the protein molecule yet substantially abolish its allergenicity.

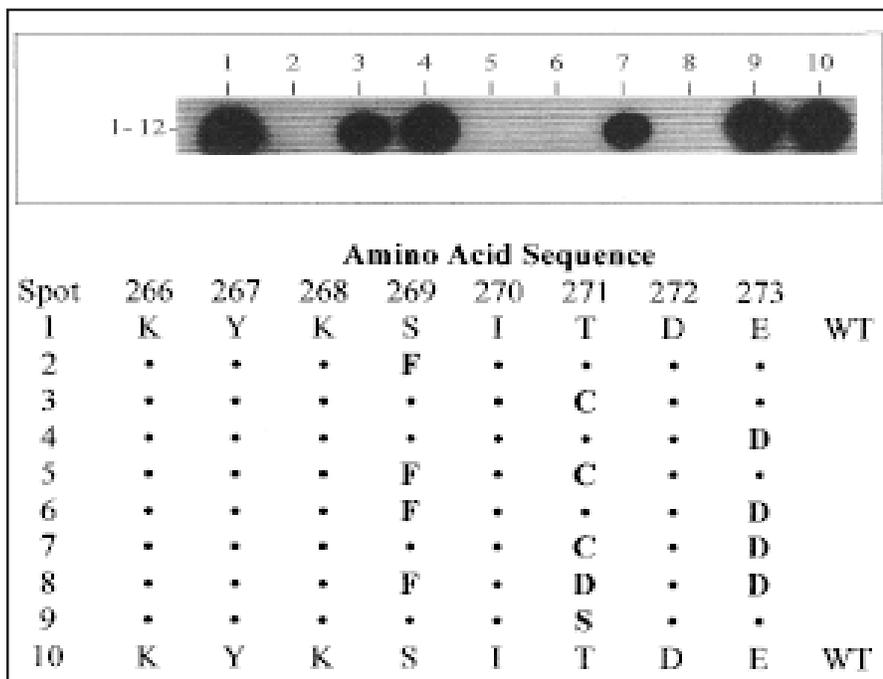


Figure 4. Amino-acid substitutions in epitope 5c that alter IgE binding.

Advances have also been achieved using a similar approach to modify peanut allergens. Three major peanut allergens have been identified: Ara h 1, Ara h 2, and Ara h 3 (Burks *et al.*, 1991, 1992; Eigenman *et al.*, 1996). Four other proteins have been identified as peanut allergens and designated Ara h 4-7. With the exception of Ara h 5, they all show significant homology with either Ara h 1, 2, or 3 (Kleber-Janke *et al.*, 1999). Ara h 5 is a member of the profilin family, but is only recognized by IgE from a small fraction (13%) of the peanut allergic population (Kleber-Janke *et al.*, 1999). As discussed for shrimp tropomyosin, the linear IgE-binding epitopes for the major peanut allergens were mapped using overlapping peptides and serum IgE from patients with documented peanut hypersensitivity. Twenty-one different linear IgE binding epitopes were identified throughout the length of the Ara h 1 molecule (Burks *et al.*, 1997). Ten IgE-binding epitopes were identified in Ara h 2 and 4 in Ara h 3 using the same methods (Stanley *et al.*, 1997; Rabjohn *et al.*, 1999). The

epitopes ranged in length from six to fifteen amino acids, but no obvious sequence motif was shared by all peptides. Four of the Ara h 1 epitopes appeared to be immunodominant IgE-binding peptides in that they were recognized by serum from more than 80% of the patients tested and bound more IgE than any of the other Ara h 1 IgE-binding epitopes. Similarly, three of the Ara h 2 IgE-binding epitopes and one of the Ara h 3 epitopes were determined to be immunodominant.

Each of the IgE-binding epitopes for the three major peanut allergens was subjected to site-directed mutational analysis. Single amino acid changes within these peptides had dramatic effects on IgE-binding characteristics. One or more amino acids within each epitope were found to be critical for IgE binding. Substitution of one of these critical amino acids led to loss of most of the IgE binding (Burks *et al.*, 1997; Shin *et al.*, 1998; Stanley *et al.*, 1997). Analysis of the type and position of amino acids within the IgE-binding epitopes that had this effect indicated that substitution of hydrophobic residues in the center of the epitopes was likely to lead to loss of IgE binding (Shin *et al.*, 1998). These results have been used to develop recombinant forms of these allergens for use in immunotherapy. The engineered hypoallergenic peanut protein variants display two characteristics essential for recombinant allergen immunotherapy: they have a reduced binding capacity for serum IgE from peanut-hypersensitive patients and they stimulate T-cell proliferation and activation (Bannon *et al.*, 2001; Rabjohn *et al.*, 2002; Bannon, in press).

## CONCLUSION

The studies reviewed are representative of investigations using genetic modification to alter allergenicity of food proteins. In spite of the initial success of such studies, significant challenges remain. The simultaneous expression of modified allergen genes with repression of wild-type allergen genes needs to be further developed, particularly in animal species. It is important that any altered allergens developed be demonstrated not to contain potentially new allergenic epitopes. Only further studies over time can delineate this. However, in spite of these issues, the impact of biotechnology on the future production of hypoallergenic foods appears to be bright.

The discovery and characterization of existing food allergens and their genes has occurred at a very rapid rate due primarily to progress in technology. In addition, numerous methods are being developed for enhancing allergy-diagnostic technologies and allergen therapy. One of these approaches is the development of hypoallergenic foods. It is to be hoped that, in the not too distant future, foods will be developed that will substantially reduce the number and severity of allergic reactions for already sensitized subjects while reducing sensitization of others. In addition, extracts of these foods will be important in developing safer vaccines for future treatment of food-allergic subjects.

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## ***The Role for Edible Vaccines***

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For centuries, plants have been used as sources of pharmaceuticals. Since the advent of recombinant-DNA technology, however, there has been a dramatic shift to microbial and animal cell-culture production systems. *Escherichia coli* was the first *in-vitro* system employed because of technical feasibility. Yeast, fungal, mammalian, and other bacterial cells are now used. Each has its advantages; bacteria provide systems of low cost and animal cell cultures are able to process eukaryotic proteins. For the first few decades of rDNA protein production, plants were not considered a viable option, primarily because the technology was not fully developed. In addition, plant biotechnology was focused on crop improvement.

Several groups are now exploring plants as “bio-factories.” The production of the first commercial recombinant products from plants has already been achieved for the diagnostic proteins, avidin and  $\beta$ -glucuronidase (Hood *et al.*, 1997; Witcher *et al.*, 1998). While these were proof-of-principle products and are used only in small quantities, they illustrate the advantages of plant-production systems for pharmaceuticals. These include up to a 100-fold reduction in raw-material costs and a ten-fold decrease in biomass needed for extraction and purification, which translates into savings for downstream processing. In addition, the risk of salmonella infection, which occurs when using chicken eggs for the production of avidin, is eliminated since plants do not harbor human pathogens.

Recently, the enzyme, trypsin, was produced from plants (Hood, 2002). The commercial quantities needed are more typical of pharmaceutical proteins. Therefore, commercialization of this third product addresses the practical issues of scaling up that most pharmaceutical manufacturing will face, including not only economic concerns but also the achievement of segregation from other crops.

The commercialization of these three sets the stage for the production of many new pharmaceuticals from plants, including therapeutic antibodies

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(Daniell *et al.*, 2001). One that we have worked on is aprotinin, which is effective in reducing blood loss in surgical procedures, but is costly based on its current supply from bovine lungs. Plants offer a low-cost production system, but it is critical that the protein is identical to bovine-produced material. We have been able to demonstrate chemical and functional equivalence *in vitro* (Zhong *et al.*, 1999) and are now preparing to show *in-vivo* equivalence.

These current and upcoming products demonstrate the role of plants as sources of materials free of animal pathogens and at lower cost. Plants, however, may provide additional benefits for the production of vaccines. This is being studied by a number of groups (Daniell *et al.*, 2001), and I will discuss our work in some detail. The basic question is: what are the benefits of using plants in contrast to other systems to produce vaccines? This can be summarized as safety, cost, and convenience, which extrapolate to greater accessibility worldwide.

#### ADVANTAGES OF EDIBLE PLANT-BASED VACCINES

*Safety* Although they have been used for decades, and benefits have far outweighed risks, there have been some problems with vaccines based on killed or attenuated viruses. With the advent of rDNA, however, safer vaccines called “subunit vaccines” have been the preferred choice. The protein from the viral capsid is used to produce the vaccine, and this protein alone cannot cause infection. In theory, these viral proteins could be produced in any of the current production systems, but plants offer particular advantages. First, some eukaryotic proteins do not express well in prokaryotic systems, possibly due to cellular processing requirements that are present only in eukaryotic cells. Therefore, many of these proteins are expressed in animal systems. However, animal systems can harbor human pathogens and must be screened to ensure that such are not part of the subunit-vaccine product. Plants, in contrast, are inherently safe since they do not harbor human pathogens (or prions, the agent responsible for mad cow disease). In addition, if we choose a food-based crop, there is added safety. Maize, for example, has been a source of food for humans for centuries and its safety is thus proven. There is no added risk from the production system or the delivery system. Furthermore, agronomic and food-processing aspects have been extensively studied; one can argue that we know more about the production of maize than of any other crop in North America.

*Cost of Goods* The cost of a vaccine includes the expenditures involved in producing the raw material, and purification and formulation. Raw-material costs are shown in Table 1. Best-case scenarios are shown for each of the systems, illustrating the advantage of using plants. Production of pharmaceutical proteins from maize is at least an order of magnitude less costly than from other systems. Compared to mammalian cell-culture systems, plants are several orders of magnitude more economical.

**TABLE 1. APPROXIMATE RAW-MATERIAL COSTS FOR PHARMACEUTICAL MATERIAL.**

System	\$/g
Chinese hamster ovary (CHO) cells	100
Transgenic chickens/eggs	1
Transgenic goats/milk	1
Microbial fermentation	1
Plants	0.1

*Rapid Scale-Up* Rapid scale-up of production is of particular importance to make vaccines available during epidemics. Table 2 compares time requirements for scaling-up for several different production systems. In this comparison, we assume that we have identified the vaccine product, and are limited only by our ability to increase production. Because of the rapid turn-around time for maize and the large multiplication factor for each generation (~200-fold increase every four months), we can go from 1 g to 8,000 kg in less than a year, a scale-up not achievable with non-plant systems.

**TABLE 2. RAW-MATERIAL SCALE-UP STARTING WITH 1 G OF RECOMBINANT PROTEIN.**

System	200 g	40 kg	8,000 kg
ProdiGene's	4 months	8 months	12 months
Transgenic animals	6 months	5 years	Not practical
Fermentation	4 months	3 years	3 years
CHO cells	18 months	3 years	Not practical

*Direct Delivery* The greatest benefit of plants such as maize is that they can be used as an edible product for the oral delivery of vaccines. Clearly, oral delivery has a tremendous advantage in convenience. The elimination of shots and need for medical assistance, with the formulated dose of medication as, say, a wafer, would be a leap forward in vaccine delivery. This also translates into reduced dependence on refrigeration. Since corn-grain proteins are stable, recombinant proteins could be stored (for years) and transported at ambient temperatures. This would promote vaccine use in developing countries that are in greatest need but are inadequately equipped with large-scale refrigerated storage and transportation facilities.

Another aspect of direct delivery relates to greater reduction of cost of goods. As stated above, the raw-material cost for pharmaceuticals can be reduced with plants, but, in addition, the cost of goods for the administration of the vaccine is reduced, as a result of elimination of needles, syringes, and medical assistance. Figure 1 represents an approximation of the overall costs of a vaccine. The raw-material expenditure represents a small percentage of the total cost of the delivery system. Edible vaccines in corn could reduce the overall cost to the patient by over 90% compared to injectables, by reducing the need for purification, needles and syringes, and medical assistance.

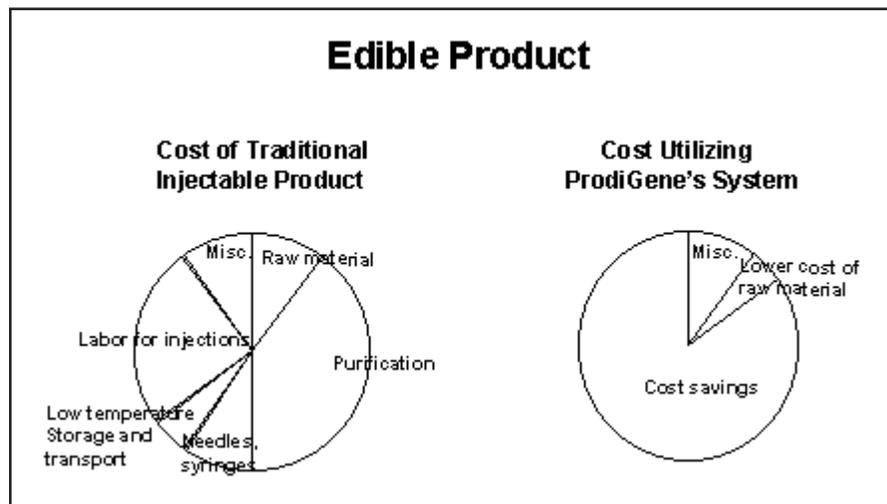


Figure 1. Cost comparison: injectable vaccine vs. ProdiGene's.

To appreciate the potential, let's consider a hypothetical example: the production cost of a purified vaccine is \$1 per dose, and a dose contains 10 µg of protein. We assume that it will take a thousand times more protein for an edible vaccine than for an injectable product. With current systems, this translates the cost of an oral dose to \$1,000. Of course, this would be unacceptable for most people in the developed world and impossible for those in developing countries. Using the same assumptions, however, the cost of a corn vaccine to give a 1,000-fold increase per dose could be as low as \$0.01. This translates not only into cost reduction, but, in many cases, the difference between obtaining a vaccine or not.

The next advantage of using corn as the delivery system relates to compliance with vaccination regimes. Having patients take booster applications would be much more realistic if they could take an oral vaccine instead of having to go to medical facilities for secondary injections months or even years later. This translates into a much more effective vaccine.

The advantages of convenience and cost will translate into vaccines being available in parts of the world where none were available before. This brings the potential for global vaccination, with the possibility of eliminating certain diseases. In addition, these vaccines may be added to feed to prevent infectious diseases for animals and to address food-safety issues where animal pathogens would put humans at risk (*e.g. Salmonella* spp., *E. coli* O157:H7).

## TECHNICAL CHALLENGES

While edible plant vaccines have tremendous theoretical advantages, none are on the market today. A series of hurdles must be overcome. The technical challenges can be divided into categories: the vaccine must survive the gut, must elicit an immune response, and, finally, must provide protection. Here are some examples to illustrate progress in these areas.

The first technical challenge for a potential edible vaccine is to keep the protein from being degraded upon ingestion long enough to have immunogenic activity. Current dogma predicts that proteins taken orally will be completely degraded in the digestive tract, with insufficient time to elicit an immune response. We tested this theory using avidin, as an example of a typical antigenic protein, by administering it to mice and looking for intact avidin in fecal material. When produced in transgenic maize and fed to mice in cornmeal, intact avidin, as well as major degradation products, was detected in fecal extracts (Bailey, 2001). However, when fed orally to mice in liquid form, fecal extracts contained no avidin or partial breakdown products. This “bio-encapsulation” could be the consequence of several factors, including higher degree of stability of the protein in corn or slow release of avidin from the corn granules. Current micro-encapsulation techniques for slow release of orally-fed protein products frequently include a carbohydrate matrix and protease inhibitors, components that exist naturally in maize kernels.

The next technical question beyond survivability in the digestive system is: can the protein produce an immune response? To test this, we cloned the gene for the S-protein from transmissible gastroenteritis virus (TGEV) and produced TGEV-S corn. Swine were then fed either control or transgenic corn prior to exposing them to live virus. The TGEV-S-fed swine demonstrated large increases in antibodies to the virus (Lamphear *et al.*, 2002). No significant response was seen with control corn. This illustrates that immune responses are obtainable via the oral route.

The next question was whether this immune response would provide protection. Animals were fed TGEV-S corn or given the commercial TGEV vaccine by injection. The results showed that treatment with TGEV-S corn was successful in protecting animals from disease symptoms with results similar to those obtained with the commercial vaccine (Streatfield *et al.*, 2001; Lamphear *et al.*, 2002).

This practical example clearly shows that technical challenges can be overcome to provide an effective vaccine. Since the vaccine is in feed-grade material, not only are costs lowered but there is added flexibility and convenience in delivery.

The fact that edible corn vaccines can be practical for animals leads to the next question: will they work in humans? To address this, we examined traveler's disease which is caused by a strain of *E. coli* that produces heat-labile enterotoxin. This molecule consists of one A subunit and five B. The B subunit (Lt-B) does not possess toxin activity, but can induce an immune response. We, and others (Haq *et al.*, 1995; Streatfield *et al.*, 2001), examined Lt-B first in mice to see if it would induce an immune response when produced in plants and given orally. When challenged with the heat-labile toxin, the mice were protected from its effects after being fed Lt-B transgenic corn (Streatfield *et al.*, 2001).

With efficacy demonstrated, our attention turned to how to make a practical version of a corn vaccine for humans. In its preparation, we examined homogeneity of the starting material, stability, processing requirements, and any adverse effects on the health of the animals.

The first practical question was: is the gene stable in maize? The examination of several corn lines revealed no indication of instability. In addition, the expression product was also found to be consistent in these seed lines and homogeneous in bulk grain samples (Streatfield *et al.*, 2002).

By fractionating the grain, enrichment in Lt-B is possible. The mechanical process routinely performed on corn seed increases the concentration of Lt-B in the germ more than 5-fold when compared to the whole seed. This results in much lower amounts needed to feed patients, which is critical to achieving a manageable dose (Lamphear *et al.*, 2002).

Palatability is also critical. Although eating whole kernels is conceivable, processed corn—as puffs, flakes, wafers, *etc.*—is more appetizing. Processing is typically done at high temperatures, which could result in loss of activity. As an example, Lt-B exists as pentamers that have high immunogenicity, but heat denaturation produces monomers with reduced activity. However, processing conditions have been modified to produce the Lt-B pentamers in corn puffs (Streatfield *et al.*, 2002).

The last parameter we examined was whether this material would have any adverse effects on the health of the mice. There is no reason to suspect health problems, and, indeed, we observed no differences in any way in a comparison with mice fed control corn, including no changes in weight gain and no signs of diarrhea associated with the disease (Lamphear *et al.*, 2002).

In conclusion, the edible Lt-B-corn vaccine has been shown to be efficacious in mice. We can process the corn into a palatable form for human consumption. The product is stable and safe. We are now preparing for human clinical studies, which are expected to begin shortly.

Traveler's disease is an excellent example of how edible vaccines can work, and we are now focusing on two other vaccines. The first is hepatitis B. We have already expressed the surface antigen in corn and have preliminary evidence of immune responses in animals. (B.J. Lamphear, personal communication). Hepatitis B is a major infectious disease with 300 million carriers worldwide. Symptoms include cancer, sclerosis of the liver, and, in some cases, death. It is the most common sexually transmitted disease. While an injectable vaccine exists, the availability of an edible vaccination would be a vast improvement, allowing its use in inaccessible areas and with better compliance.

The second major target is an AIDS vaccine. Many groups are developing injectable subunit vaccines for this disease. Although injections work well in some countries, this method of delivery will be difficult, if not impossible, in Africa and Asia because of cost and transportation and refrigeration requirements. Early results indicate that this type of subunit vaccine can be expressed in maize (M.E. Horn, personal communication).

#### SAFETY ASSESSMENT OF THE FOOD CHAIN

Although subunit vaccines in maize promise to provide a safe product with great advantages, there are concerns. In particular: can these products inadvertently enter the food chain and what preventative measures are in place?

In an attempt to address these questions, we have developed a general model for assessment. This is similar to other models used for a variety of non-food products that have the potential to enter the food chain. It is based on the fact that the risk is proportional to the inherent toxicity or activity of the molecule and the exposure.

$$\text{Risk} \propto (\text{inherent activity}) \times (\text{exposure})$$

The risk is zero if either the activity or exposure goes to zero. While this is the over-simplified version that the general public likes to hear, it is, in fact, a myth. Absolute zero cannot be achieved with any current food-safety concern, and this applies to rDNA technology. This is not to say, however, that our food is unsafe, rather that all compounds have the potential for detrimental activity when taken at high enough doses. The corollary is also true; all compounds will show no activity when given at low enough doses. This is true for commonly eaten items such as table salt, nutrients such as fats, and drugs. None of these have effects at low doses, all are beneficial at moderate doses, and, in extremely high doses, can be detrimental.

What is critical is the exposure to these compounds in relation to their inherent activity.

$$\text{Exposure} \propto (\text{concentration}) \times (\text{time})$$

The concern over food safety then is: what is the level of our exposure? It is impossible to prove that exposure is zero. It can be proven only to be below a certain limit. As an example, if we test for 1 part in 100, we can say our exposure is below 1 in a 100. If we set this for 1 part per 1,000, likewise, this will be our exposure limit. Therefore, the question arises of how do we set the limit: should it be based on safety or detectability?

We advocate that the unintentional exposure limits for edible vaccines be based on safety considerations. The first question then is, what kind of toxicity do subunit vaccines have? Generally these molecules are considered to be non-toxic. Primarily they are structural proteins for the virus. Although they may have some detrimental effects at high concentrations, it has not yet been observed. Furthermore, subunit vaccines have been injected into humans for decades without any known adverse effects. This is in contrast to pesticides, for example, which are known to be detrimental at low concentrations. Therefore, we would not expect any detrimental activity due to subunit vaccines unless one is exposed to much higher concentrations than known poisons. However, a true risk assessment cannot be done since we do not know the hazard. While we do not propose to keep giving higher doses until we see a hazard, we can use what is known about levels that have been shown to be safe and compare tolerances to other compounds. Regulatory agencies have examined exposure limits for pesticides, as an example, to determine the safe limit of exposure. Table 3 lists exposure limits for some compounds commonly present in corn. These limits have been set with the assumption of presence in our commodity-corn supply. Regulatory agencies have determined that these compounds show no effects when below the set tolerances.

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**TABLE 3. FOOD TOLERANCES FOR KNOWN HAZARDS.**

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Compound	ppm
2,4-D	0.5
Nicotine	2.0
Malathion	8.0
Paraquat	0.05
Glyphosate	1.0
Hexane	25

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In comparison to vaccines, which have not shown any toxic activity, these compounds have known detrimental effects at low concentrations. They also have other characteristics that create concerns, warranting lower exposure limits. As an example, pesticides are typically heat-stable, whereas proteins are readily degraded by heat. Pesticides are normally stable in the digestive system, whereas proteins are normally degraded in the digestive tract. In the environ-

ment, pesticides are relatively stable whereas proteins are usually degraded. Even though, in our system, the proteins are more stable than in solution, their instability is still high compared to other synthetic compounds. Many pesticides are halogenated hydrocarbons and, therefore, some of their breakdown products are toxic; proteins break down to amino acids, which are common nutrients. Therefore, logic dictates that the limits of exposure for vaccines are much higher than those for known toxins.

While subunit-vaccine toxicity seems unlikely, another concern is that a vaccine may evoke an unintentional immune response. What problems could this cause? At ProdiGene, we have spent the past five years and millions of dollars trying to evoke an immune response in animals utilizing oral delivery. We have found that high concentrations with repeated exposures are needed. It is illogical to argue from an efficacy position that oral vaccines will not work unless repeated high doses are given, and at the same time, argue that a one-time low dose entering the food chain would cause great danger. The answer to this dilemma is that we must address it in a quantitative manner to determine where the limits of exposure are set to see no effect or to see an immunogenic effect. A quantitative model can take into account the specifics of this system, including antigenicity of the vaccine, to set a limit of exposure that would be far below any concentration that would give the slightest effect. Containment systems can then be designed around the safety criteria. The containment system must include a series of steps to cover the growing, harvesting, transporting, storage, and processing of the grain. Because of recent fears of contamination, resulting largely from the StarLink™ story, the public has focused on corn pollen and there is confusion over the systems under which maize is grown.

Basically, there are three types of growing system. The first is for commodity grain. You can grow what you want, where you want, and however you wish to grow it. This system is used for producing most corn in the United States. The second system, identity preservation, allows you to grow when and how you like, however, there are specifications concerning the type of corn produced, and economic incentives exist to prevent commodity corn from mixing with the segregated product. The third system is the Identity Containment System, which specifies what crop is grown where, and how. These parameters are directed by companies such as ProdiGene, and include regulatory oversight.

ProdiGene's Identity Containment System includes many procedures that differ from those used to grow commodity food crops, and are summarized in Table 4. Included are a set of written standard-operating procedures for all steps in the process, and legal contracts between the grower and the company.

There are economic incentives for identity containment such that the grower will want to comply. The typical area requirement is around 1,000 acres for identity-contained crops—with which the extra steps must be taken—whereas 75 million acres of commodity corn are grown annually in the United States.

**TABLE 4. COMPARISON OF SYSTEMS FOR GROWING MAIZE.**

Component	Commodity	Identity preserved	Prodigene's ICS <sub>SM</sub>
	Objective		
	Maximize grain yield	Prevent exposure FROM commodity corn	Prevent exposure TO or FROM commodity corn
<b>GENERAL</b>			
SOPs	None	None	Required
Legal contracts	None	Optional	Required
Economic incentives above commodity	N/A	\$.15–.35/bushel	\$.50–1.00/bushel
Typical acreage	75,000,000	1,000,000	1,000
<b>GROWING</b>			
Grower's seed	Purchased	Purchased	Licensed
Location of plots	No restrictions	No restrictions	Pre-approved locations
Containment required	None	None	Regulated
Regulatory approval	None	None	Required
Regular field inspections	None	None	Required
<b>HARVESTING</b>			
Equipment	No special requirements	No special requirements	Dedicated equipment or standardized clean-out required
Transport	No special requirements	Segregated from commodity corn	ProdiGene or its designee must handle
Storage	No special requirements	Segregated from commodity corn	Dedicated storage containers/facilities
<b>PROCESSING</b>			
Requirements beyond minimum specifications	None	None	Regulated by FDA
Waste or by-products	Not regulated	Not regulated	Regulated by USDA

In addition to these general considerations, other conditions vary with the different systems. Identity containment requires approval for where the seed is grown. Agronomic support is also provided by the company and regulatory approval with field inspections is required. Harvesting of the grain also requires special consideration. Commodity corn cannot be mixed with the contained crop. Therefore, dedicated harvesting equipment or thorough cleanout procedures are necessary. The company dictates the transportation requirements of the harvested crop. It is segregated and stored separately, requiring special storage arrangements and facilities.

When the grain has met the specifications of the regulatory agencies and of the company, it can be processed. The FDA sets processing requirements, which are similar to manufacturing requirements for vaccines from other production systems. Any by-products are regulated by the USDA if they are to go into the food or feed stream. The system for keeping these products out of the food chain thus is highly redundant.

The qualitative description for keeping edible vaccines out of the food chain is useful, but a quantitative assessment is needed. In order to propose a model, we must take into account other parameters. Several characteristics of plants need to be considered, including the following.

- The potential for out-crossing. In the case of maize, there are no weedy relatives in the United States, therefore, out-crossing is not possible.
- If farmers save their seed for future crops, “contamination” could accumulate, carrying the foreign gene. Since corn growers buy new seed each year to capitalize on hybrid vigor, such enrichment of vaccine corn is unlikely.
- What systems are already in place to keep harvested seed segregated? Commercial systems exist for special food and feed corn. These systems have been used for years to grow millions of acres of corn and keep it segregated. Therefore, additional requirements for containment would be a direct offshoot of systems that are already in place.
- The potential for pollen drift differs with different crops. Maize pollen is heavy compared with that of other species. The majority falls within several feet of the parent plant. Also, the pollen has a short half-life, and can lose viability within minutes after it is shed. In addition, many factors are known to reduce pollen flow such as isolation distances, vegetative barriers, and genetic male sterility.
- There is a broad and long-term experience-base. Professional growers and processors have been working with maize for many years.

Using this information, we can construct a model to show the limits of exposure that are possible in the food chain. Some key assumptions are needed for quantitation. The first is that the transgenic crop is grown immediately adjacent to a corn crop with no isolation, and no temporal or genetic barriers utilized. We also assume a high rate of expression for the vaccines, 1% of the total soluble protein in seed. In addition, we assume that the vaccine-synthesizing corn is grown on 1,000 acres or less, typical acreage for most pharmaceutical products. Each year approximately 75 million acres of commodity corn is grown in North America. Therefore, our product represents approximately 0.001% of the total acreage. Any contaminated material entering the food chain would be spread over the total corn acreage if it were to be available to everyone. Alternatively, we could assume that the farmer adjacent to the transgenic crop also segregates that field and collects 1,000 acres, which

goes specifically into food applications. This latter case poses a situation to give the highest concentration of vaccine but least availability to the population at large. These two scenarios represent the extremes. Most situations will fall between these two cases. The last assumption is in terms of how much cross-pollination will occur. We have estimated this on the bases on our own experience and data available in the literature, for contained and non-contained growing conditions.

With these assumptions we can model the amount of antigen or subunit vaccine present in food corn (Table 5). The highest concentration is shown when the adjacent grower segregates her/his field, with no containment. In this worst case, the vaccine could be as high as 0.1 part per million. If this were mixed with all corn grown in a year in the United States, it would represent 0.000001 parts per million, again assuming no containment parameters. In either case, these amounts are well below levels that are accepted for most known toxins. Clearly, this model predicts that vaccines will not present any toxicity danger, even without containment. Toxicity then becomes a non-issue for vaccines, as well as for most other proteins that we produce.

**TABLE 5. THEORETICAL CONTAMINATION RATES IN FOOD CORN.**

Condition	ppm in grain of commodity corn	
	Segregated field	All corn in the United States
No pollen control measures	0.1	0.000001
660-ft isolation	0.004	0.00000004
1,320-ft isolation	0.00004	0.0000000004
Planting delay with border rows	0.0000005	0.000000000005

The next question is: would these levels produce an immune response? We explored the possibility that low exposures could induce an unintentional antigenic response. Based on our experience with antigens such as HepBS and avidin, as well as utilizing data in the literature, an antigenic response requires several doses of 1 mg each in humans. To obtain a 1-mg dose with corn grown without pollination control would require 20 lbs of unprocessed corn. This translates into eating the equivalent of 320 bowls of cereal or 320 tacos in one sitting just to receive the minimal dose for a one-time exposure. If we now factor in that corn for human consumption is processed between 100 and 200°C, it is likely that the protein will be denatured and generate a much-reduced exposure. If we grow the vaccine crop under containment procedures using physical isolation, temporal isolation, and planting border rows, this reduces adventitious presence by an additional factor of a million.

Models such as this can differentiate between real and perceived risks. They provide an excellent starting point and can be challenged and revised when new information becomes available. They can be used with large safety margins when we have not fully tested products for toxicity. They can address the concerns of how to keep safe vaccine products on the market and, at the same time, keep the food chain safe.

## SUMMARY

Edible vaccines represent a quantum leap forward in the ability to produce safe, efficacious vaccines for worldwide use. This quantum leap could make available vaccinations in developing countries where none exist today, and with greater ease and compliance in North America and Europe. These products have already shown efficacy in limited trials with oral delivery, for humans and animals. We believe that they will be instrumental in eliminating major diseases, such as hepatitis B and AIDS.

A perceived safety concern has been raised about unintended entry to the food chain. Containment procedures are in place to provide an extra buffer of safety while we obtain more information about these procedures. However, our model predicts no effect on food safety even without containment procedures. We need to treat corn as a valuable production factory for vaccines and other pharmaceutical products as we have done for other food-producing organisms. Yeast, for example, is used to produce pharmaceuticals and vaccines, as well as bread and beer. In this way, we will bring beneficial products to the marketplace, to save lives without unnecessary risk.

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## ***Applying Agriculture to Health: Food to Prevent Disease***

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### **Q&A**

MODERATED BY

**MICHAEL D. FERNANDEZ**

*Pew Initiative on Food and Biotechnology  
Washington, DC*

*Michael Fernandez:* We will discuss disease prevention as opposed to therapies or treatments which was the previous discussion topic. We know that many diseases could be prevented through relatively simple behavior and/or dietary changes without considering functional or other new categories of foods. Clare, you mentioned that in your talk.

*Clare Hasler:* You are right, but the issue of behavior change is not simple. A plethora of low-fat, no-fat products are on the market, yet we have more obesity than ever. And nutritionists have been telling people for years that one of the major things you can do to improve your overall health, and cut cancer significantly, is just to incorporate five to nine servings of fruits and vegetables a day in your diet. But, consumers want to hear a message that is more specific to them and one of the things that I alluded to was individualized nutrition. Rather than just the message of ‘eat a wide variety of foods,’ which makes us all fall asleep although it is important, people need to be aware of their own health profiles. That is where nutritional genomics may play a role, although I have doubts about how much it will impact prevention. With us knowing more about physiologically active components—like lutein and how it selectively accumulates in the macula of the eye—there may come a time when we can make more-specific recommendations for food groups or bioactive compounds for individuals at risk for certain diseases. If eye disease is not an issue, you may be concerned about prostate cancer or breast cancer. We are going to start focusing more, although we don’t want to lose sight of the forest for the trees.

*Fernandez:* Do you think that you run a risk of people hearing the message “if you eat this particular food then you will be okay” and ignoring the bigger picture.

*Hasler:* That does happen. People don’t always incorporate the messages that they hear or comprehend the reasons that health claims are worded as they are, such as “may reduce the risk of” in the context of a low-saturated fat, low-cholesterol diet is because we don’t want to tell somebody they can eat 25 g. of soy protein and consume a quart of ice cream and reduce their cholesterol levels. That is an important issue.

*Fernandez:* Another of these big themes that has emerged is the idea of blending categories or blurring the lines between food and drug and supplement. We are recognizing that although these areas are the most exciting, they present unique challenges—in the regulatory arena for example. With respect to products that are not foods, but are being made in food crops, edible vaccines for example. How is food safety to be assessed? John?

*John Howard:* Some of these organophosphate pesticides, though toxic, are present in food and we have accepted these risk models. Yet biologic molecules that we see every day are not accepted. In fact we make many of these ourselves. It seems to me that there is a disconnect at the regulatory agencies in terms of how they assess risk for pesticides and what they are looking for in biologics. Not that biologics should be exempt, but similar standards should apply.

*Fernandez:* Are there unique risks with respect to particular products or the technology *per se* that we need to consider?

*Howard:* We need to look at each on a case-by-case basis. Unquestionably, there will be cases that pose unique risks, yet generally we are dealing with proteins and other molecules that we consider to be of much less risk than what is already being regulated. So that is where I see a disconnect. We would like to look at the risk assessment in the same way, and look at the value of these things and at the benefits in the same way.

*Fernandez:* Sam, do you want to touch on that? I think it has a lot to do with what you were talking about.

*Samuel Lehrer:* Well, with assessment of products modified by biotechnology for allergy risk, some feel that it really isn’t a level playing field, in terms of the criteria that we are using for GM foods, many other foods would not pass. Allergy risks with GM foods might be much lower as compared to peanuts, soy,

wheat, shrimp, and other foods. Although we should err on the side of caution, we need to keep that in mind.

*Fernandez:* What is needed in the areas that each of you talked about to deliver on the promises of agricultural biotechnology?

*Hasler:* Certainly we have the technology to deliver genetically modified foods with health benefits, which raises the issue of the statement on the label. Such foods would need to be tested in appropriate scientific studies or clinical trials, according to certain criteria set out by the FDA. The health benefit then has to be communicated to consumers effectively, which is an issue that the International Food Information Council is addressing, how information should be disseminated to consumers. One of the hot-button issues regarding communication is at what point in time do we talk to consumers about what is good for them. Where should the line between emerging and consensus be drawn? And there are also free-speech issues. The FDA is being sued because they do not allow information on labels that some consumers feel they should have access to. Having demonstrated that a certain food can provide a health benefit in a controlled setting and getting that information to the consumer is one challenge. Whether consumers are open to the concept is another issue.

*Lehrer:* In terms of delivering on the promise of biotechnology—I believe that it can be done. It is a matter of resources and will. But will consumers be receptive to the products?

*Fernandez:* Following up on that—one branch of the decision tree you showed had properties like digestibility that are common to known allergens, and if you got a “yes” there the box led you to the regulatory agency. In the case of StarLink™, the developer was in a similar situation and went to the agency with information. One interpretation is that the EPA did not have the regulatory tools or enough knowledge to determine whether that information was sufficient. Do we need more work in that area to be able to deliver on that promise.

*Lehrer:* You’ve raised a number of issues. Let’s talk about the decision tree first. It had some problems, such as how to define the digestibility of proteins. Do you look at mixed proteins? Do you look at purified proteins? There has been a lot of discussion and it will be improved and defined. With regard to StarLink™—I should mention as a disclaimer that I have consulted for Aventis—there were several issues. The whole thing was a fiasco in my opinion. But with regard to the decision tree, StarLink™ was never approved for human consumption, so the failure wasn’t in terms of assessing it for the potential allergenicity. Actually, the protein was never shown to be allergenic. The

problem was in the split decision: approving it for animal consumption only. A lot of people said years ago that adequate segregation was impossible because of the way agricultural products are grown and stored in the United States. In that context, the folks who were supposed to be minding the shop weren't doing so, and it contaminated the human food supply. It had nothing to do with the decision process. It was the split-decision approval for animal feed; from what I understand, that will never happen again.

*Fernandez:* John, that brings me to you. Although there is an obvious difference with a commodity crop like StarLink™ you were talking about split approval in a sense for food and non-food uses. Is that going to be an issue? It becomes a matter of perception: “if it's in my corn is it in my cornflakes?”

*Howard:* I agree with what was just said. We have all been sensitized by StarLink™: the consumers, the regulatory agencies and the lawyers. In hindsight it can be viewed as useful. Something that turned out to be a non-problem sensitized us, made us all a lot more aware of what we need to do. These crops could, in fact, have been segregated, but it simply wasn't done. When we are making pharmaceuticals or vaccines, we are always under regulations, we're always growing under permits. We have training manuals and standard operating procedures. But what is very standard for making pharmaceuticals is not standard for agriculture. It is standard for food products such as yeast that are used to make pharmaceuticals. We should view it as analogous to making a pharmaceutical product, as has been done for decades, rather than as an agricultural product. I don't think we are risk-free, but I think our sensitivities are heightened.

*Fernandez:* I'm going to invite the audience to ask questions.

*Barbara Schneeman (University of California, Davis, CA):* My comment has to do with our traditional way of looking at risk analysis, which was developed for the food-additive system and actually works quite well. FDA has recognized that as we move into an era looking at whole foods or looking at macro-replacers in foods such that new factors need to be considered: GI tolerance, drug/nutrient interactions, allergenicity. Some have argued that perhaps the only way to deal with this adequately is to think about post-market surveillance or post-launch surveillance rather than putting our hopes completely on the pre-market approval process. I would like the panelists to comment on what role post-market surveillance might play; does it have any value, is it something we should be talking about?

*Lehrer:* There are varying opinions on this. I believe that it depends on the product. For example, if it is one that we have hard and fast information about

a product and there was little doubt about the decision, I don't know that it is necessary to have post-market surveillance. On the other hand there may be some, novel proteins for example, with which we won't have that kind of information. We will get better information on them, but we still won't have the final test that we can take the serum from an allergic individual and test it. They are working on a lot of interesting animal models now, which may help, but in that kind of situation there, I can see a need for some type of system to assess whether or not there is a problem. I gave a lecture recently at the American Academy of Allergy, to allergists and the other healthcare professionals in allergy, and I really was amazed because I think they really hadn't thought about it that much and they are the ones who should be the first line of defense, so to speak, at least in regard to allergy. Other health issues are another matter. But I think that these individuals should be educated more about what the issues are and should be aware of it. It is certainly more problematic to identify someone who may have an allergic reaction to a novel food because of the way our system is, nevertheless I think one can get information and they should be alert to that. I think some kind of assessment system would be useful.

*Myron Just (Minnesota Agri-Growth Council, St. Paul, MN):* The discussion this morning reminds me that Hippocrates, the father of medicine, made the famous comment that “food is medicine and medicine is food.” Is medicine coming full circle and are we now recognizing that he was on to something 2,400 years ago that we should have been thinking about? Also, some years ago I traveled extensively in China and was struck by how traditional medicine and modern medicine overlap there and respective practitioners work side by side. I'll be grateful for comments from the panel.

*Hasler:* You are right and I usually include that statement from Hippocrates in my presentations. I think we have come full circle. Many indigenous populations still use foods and plants for medical intervention. Forty percent or more of our synthetic drugs still come from plants. The 1800s saw the development of synthetic drugs and the ability to patent those technologies, which really stimulated the drug industry. But, the current focus is switching more to prevention—in which foods can really play a role. I'm not sure how much foods will be used as therapy. Drugs traditionally are used as therapy and I think that will continue. But a preventative approach needs to be taken in many diseases that result from lifestyle choices and environmental factors and foods can be very successful in that regard, recognizing that alternative or complementary therapeutic approaches are not snake oil. A couple of years ago a whole issue of the *Journal of the American Medical Association* was devoted to the issue of alternative medicine, which would have been unheard of 10 years ago. I agree. We are coming full circle in this regard.

*Phyllis Johnson (USDA, Beltsville, MD):* My question has to do with the relationships between those who are producing these unique pharmaceuticals and the processor and those who will sell the vaccine. In our conventional marketing system, if you get your high-grade malting barley mixed up with feed barley there may be a loss of profit, but it is not going to hurt anybody. I guess that is the kind of system that failed with StarLink™. It seems to me, if I were a farmer, I wouldn't want to start growing corn that was going to produce some pharmaceutical unless I already had a contract to sell it, and maybe knew that the processing plant was down the road. Are you vertically integrated? Do you have these kinds of relationships with producers, or how is this working?

*Howard:* I'd say some of it is out there, but there are some major differences. First of all the grower never buys the seed. He is only licensed. The grain must be grown under specific conditions. The grower is guaranteed the price. It is completely vertically integrated in that sense. In fact, it is what we call a closed-loop system. The transport is arranged, the storage, the harvesting, the dedicated equipment, all that is covered in this case by us or by another company. So the grower has an important role, but it is a very different role from that with normal commodity crops. So, in that sense, they are very separate. You have to ask yourself why would they want to do this in the first place, since it becomes a great pain to them. But the other part of it is that we pay them extra to do it. So they are being paid for these extra steps—there are economic incentives. There are also contracts such that if they don't do it they are legally liable. So it is a very, very different system from what you were talking about with barley segregation.

*David Poland [International Maize and Wheat Improvement Center (CIMMYT), Mexico]:* I work in communications so I have been in the middle of this transgene Mexican land-race issue. I'm a proponent of the technology, but it scares me—if I had to be a communications person responding to questions about pharmaceuticals in maize, I wonder how would I do it, given the questions we are already getting from Europe and other places. There is a tendency to say “well it's just a perception problem,” but it's a big perception problem. So my question is: given the costs that are going to be involved with convincing the public that this is acceptable, has any cost analysis been done on using a non-food crop for these same purposes?

*Howard:* Actually, some people are developing non-food crops, but we seek the benefits of using a food crop. Many companies are using corn for product safety. We could use a non-food crop, but the product would be less safe. Would you want to produce an edible vaccine in tobacco leaves? Although, potentially, non-food crops could be used, we would lose the knowledge base that Mich Hein mentioned, and we would lose product safety. Those are the choices.

PART VII  
LUNCHEON ADDRESSES

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## ***Supporting Comprehensive Foods for Health Research: A New Model***

MARY CLUTTER  
National Science Foundation  
Washington, DC

I will focus my discussion on three areas:

- twenty-first century biology,
- the enormous challenges that are facing us, and
- new models for partnerships.

### **TWENTY-FIRST CENTURY BIOLOGY**

Isn't twenty-first century biology the same as twentieth century biology? More than 10 years ago, Alan Bromley, Science Advisor to the elder Bush, made this statement: "If this century is the age of physics"—and he's a physicist—"the twenty-first century will be the age of biology." You have probably heard that from many people since. President Clinton talked about the twenty-first century being the age of biology. Al Gore thought he invented it. But when Bromley made the statement more than 10 years ago, we hadn't seen the sequencing of the human genome. Sequencing the *Arabidopsis* genome was just something that people imagined might be possible. Fantastic things happened during the last decade of the twentieth century, and the *Arabidopsis* genome is a particular achievement because it is the first eukaryote to be fully sequenced. I mean *completely*, because the human genome is still in rough draft and is not scheduled to be finished until 2003.

Twenty-first century biology is very different from the biology of even a few years ago. It is multi-disciplinary. Teams of scientists are working together and will continue to work together. Physicists, mathematicians, computer scientists, and social scientists: all are focusing on the major questions in biology that will be solved, I think, in this century.

Twenty-first century biology is also multi-dimensional. For the first 50 years of the biological revolution, *i.e.* since the elucidation of the structure of DNA by Watson and Crick, biology was mainly reductionist, whereas with the new technologies and new disciplines we will be able to put all of the pieces together and address questions from the atomic level through the ecosystem level even to the planetary level.

It is also information-driven. Enormous quantities of data are being produced and it is commonplace for scientists to “mine” databases like Genbank. New hypotheses are being derived from sequence data—a capability that was unimaginable a few years ago.

And, it is education-oriented because we need a new kind of scientist to work on these problems—one who is comfortable in a multi-disciplinary team setting, and that is different from the biology of several years ago.

And twenty-first century biology engages people internationally. Geographic boundaries no longer inhibit scientists. Because of the Internet we have what Jack Marburger, President Bush’s Science Advisor, called the power of a “global intelligence” to draw upon. Sometimes people find it easier to exchange ideas and data across the globe than to walk down the hall and talk with a colleague.

## SIX MAJOR CHALLENGES

*Boxology* Major challenges are associated with advancing twenty-first century biology, which really isn’t biology, it’s twenty-first century *science*. I see six major challenges, the biggest of which is to overcome twentieth-century barriers. A colleague of mine calls this “boxology” because we all work in boxes; we have to get outside of these boxes and think about the larger picture. These boxes exist everywhere. They certainly exist in my agency, the National Science Foundation (NSF), in which we have directorates, the Mathematics and Physical Sciences Directorate, the Biology Directorate, *etc.* Do we talk across those boundaries? Yes we do, but it’s a huge challenge because of differing cultures. You see this in universities. Certainly departmental barriers exist that work against interdisciplinary research. Think about tenure decisions. Tom Czeck talked to the National Science Board a week or so ago and said that he was appalled recently at a committee meeting in which a faculty member was being considered for tenure, and the question was asked, “How many times has this person’s name appeared first on a paper?” Even though the person had published lots of papers, the name had not appeared first on many of them. Yet when you look at journals today, especially with these multidisciplinary projects, like the *Arabidopsis* genome project or the human genome project, you will see long lists of names. What happens to the person whose name is in the middle? In some journals a statement is made that all the authors contributed equally. What do tenure committees do with that kind of information? It is an academic barrier that has to be overcome in some way.

Federal agency barriers exist not just at NSF. The Office of Management and

Budget, where the budgets of the agencies are determined, exists in compartments because the budget examiners focus on each agency separately. They hardly ever coordinate across agencies. Only with cross-cutting efforts like the global climate change project do they bring agency representatives together to talk about coordinating budgets.

*Broadening Participation* A second major challenge is in broadening participation. It is essential that we tap the diversity in human resources in the United States. It is a national scandal that we have not been able to increase the participation of underrepresented minorities in science. But it is more than underrepresented minorities. More and more students are opting out of science—a recent report showed that 50% of undergraduates who major in science drop out within the first couple of years. The major cause is not poor grades but that courses aren't interesting—the curriculum fails to engage the student largely because of lack of faculty interest.

To broaden participation we must include diverse institutions, including community colleges where many minority students get their start. Some 46% of underrepresented minorities attend community colleges, so we at the NSF are putting a lot of emphasis on including *all* colleges and the tribal colleges. It is a major challenge.

*Reshaping Education* A third challenge relates to reshaping the education of scientists and engineers to broaden the horizons of students who are interested in majoring in science and engineering. Some of the programs that we support at NSF, like the IGERT Traineeship Program, are exciting because students and faculty work in multidisciplinary teams. We also think that postdocs need to have a number of options. They should have the opportunity to teach, therefore we are changing our postdoctoral programs at NSF to allow a semester or a year to gain teaching experience. There should be possibilities for graduate students and postdocs to have internships in industry, which we have not allowed until now. And finally, all of them need international experience, which is essential for the future.

*Public Perceptions* My fourth major challenge is public understanding of science. A recent survey indicated broad popular acceptance internationally that solar energy and computers will improve our lives. As for genetic engineering, however, a sizeable number of people expressed the conviction that it will make things worse, similar to attitudes on nuclear power. This is something that requires much thought, and foods for health should go a long way to improving public perceptions of agricultural biotechnology.

*Infrastructure* The next major challenge is infrastructure and research facilities. Costs of maintaining cyber-infrastructure—instrumentation, security, *etc.*—are

going to skyrocket for universities. In 1998, research-one universities issued a report in which the cost of maintaining facilities, not including upgrading with the new technology, was estimated at over \$11 billion. Clearly, the NSF cannot address this issue alone. In fact, the whole federal government will have trouble meeting this challenge.

*Funding* My final major challenge is funding—something that I know a lot about. In an NSF publication, *Science and Engineering Indicators*, published in May 2002, it was shown that the federal government supplied 66% of the funds for R&D in 1960, whereas in 2000 industry supplied 72% and the federal government only 28%. But, the 72% supplied by industry in 2000 was mainly the “D” part of R&D—development of products. Only 5% of that 72% was invested in fundamental research and the 28% provided by the federal government was almost entirely for fundamental research and some applied research. In short, industry will not replace the federal government’s support for fundamental research.

From 1967 to 2000, the United States Department of Agriculture (USDA) and NSF grant funds were pretty flat in constant dollars. In contrast, federal funding for Health and Human Services, which goes mostly to the National Institutes of Health (NIH), has grown and is still growing, and will have doubled by 2003 at over \$27 billion. When I say that NSF needs a big increase, people sometimes say, “Take it out of the Farm Bill.” However, we don’t want to take money away from any other agency. The NIH can use their increased funding very profitably—there is no suggestion that we want to transfer money from NIH to any other agency. We need increased overall investment in research by the federal government. Less than \$350 million—not billion—were invested by the government in competitive grants in plant biology in 2001. Clearly we have a long way to go to reach adequate funding for twenty-first century biology.

## NEW PARTNERSHIPS

How are we going to meet these challenges? We need new kinds of partners. We need effective partnerships involving private and public sectors. State governments should also be involved and we need international partners.

In 1997, it was decided that we needed a long-term plan for plant genomics, which was clearly a promising area. Under the leadership of Ron Phillips, an interagency working group was established with a 5-year plan. The first thing that we recommended was to complete the sequencing of *Arabidopsis*, which has happened. We will hold a stakeholders’ workshop at the National Academy on June 6 and 7, 2002, to plan the next 5 years.

The interagency national plant-genome initiative involves the NSF, the Department of Energy (DOE), the NIH, and the USDA. As already stated, the first priority was to sequence model-plant species, then we addressed the research resources that would be needed, the databases, the kinds of technology

development that needed to occur and, very importantly, data management and informatics. In fact we now insist on an informatics component in all of the projects in plant genomics now funded by NSF. So *Arabidopsis*-genome sequencing was completed. The first completely sequenced plant genome—found to have about 25,000 genes—was published in 2000 as a result of a successful international partnership. Japan and the European Union were involved, as was France in its own right through Genoscope. And, in the United States, NSF, USDA and DOE all supported the effort. One of my guiding principles for international projects is that each country pays its own way so that it feels that it is a full partner, and this happened beautifully with *Arabidopsis*—there were no problems. But, as I have said before, the reason for such great cooperation was probably that there was no money to be made.

Next we said that rice needed to be sequenced, because the genes of rice are very similar to those in all of the grasses. Corn has a rather larger genome, about the size of the human genome. We are receiving suggestions from the corn community that it should be sequenced next, and then wheat.

The international rice genome project was another interesting partnership as a new model of international collaboration. The members of that team are from Korea, China, Taiwan, Thailand, India, the United Kingdom, France, and Brazil. Japan is the lead nation, but China is catching up fast. China has sequenced *Oryza indica*, whereas Japan and the other partners are sequencing *O. japonica*. It is noteworthy that Monsanto provided data that was useful in completing the rice genome project. The data are being deposited in Genbank and will be publicly available. Discussions are going on now with Syngenta. I would like to think that companies will cooperate with the federal government and private and public sources to produce the kind of model that will work for us in the future.

We are coordinating well on a couple of other projects. In the microbe project we are doing everything we can to build the infrastructure, to connect the dots, to learn as much as we can. This interagency working group involves the CIA, FBI, Department of Defense, the Food and Drug Administration (FDA), and NASA, *etc.* Our goal is to build the necessary infrastructure to learn as much as we can about microbes, 99% of which have received little, if any, study. Only a few that are pathogenic to humans have been thoroughly studied—even then we have learned over the past few months how much we don't know about anthrax.

Recently the National Academy held a workshop on domestic-animal genomics, the result of which is an inter-agency working group that is chaired by Joe Jen the Undersecretary for Research, Education and Economics at the USDA. They are just getting started, discussing what kinds of sequencing need to be done, *etc.*, related to animal genomics.

The 2010 Project is another that involves international collaboration to determine the function of all of the genes in *Arabidopsis*. It began last year and

we hope it will be completed by 2010. All of the 2010 Project reports are available on the Internet. Another international collaborative activity is the USEC task force on biotechnology research, which was established in 1990 as a forum for discussion of new ideas. A Blue Sky Workshop—predicting what biotechnology would look like 20 to 25 years from now—was in session on September 11, 2001, in Washington, DC, and was rescheduled for June 2003 in Brussels.

In closing, I will reiterate that we need new kinds of partnerships for twenty-first century biology. Now only scratching the surface, we need involvement of the public sector, the states and local government as well as the federal government, because we cannot do it alone.<sup>1</sup>

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<sup>1</sup>The Q&A session with Dr. Clutter is on p. 185.

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## ***Our Healthy Future: The Global Context***

GEORGE MCGOVERN

*US Ambassador to the Food and Agriculture Organization  
of the United Nations  
Rome, Italy*

I received a call from President Bill Clinton early in his second term: “George how would you like to go to Rome as an American Ambassador for the three United Nations agencies that are located there?” I wasn’t sure—possibly it was the kind of job they give to defeated presidential candidates, to get them out of the country! After some thought, I decided it would be a good venture to undertake, as I have been interested in food and agriculture all of my public life.

### **HALVING THE NUMBER OF HUNGRY**

After about three months in Rome, I realized that it was exactly the job I should be doing at this stage in my life. I have been there for about four years, and the year before I arrived there had been a World Food Summit, attended by representatives of 180 countries, including forty-three heads of state. They had committed themselves to halving the number of chronically hungry people in the world—800 million out of a global population of a little more than 6 billion. In other words, about one out of seven of all of the people on this planet suffered every day of their lives from hunger, and the commitment was to reduce that figure to 400 million by the year 2015. That’s only thirteen years down the road.

If you’re going to take 400 million people off the hunger roles in fifteen years, you have got to take them off at the rate of 27 million per year. The most reliable figure I could get was that over a period of four years we had reduced the number to 790 million, about two and a half million per year, which was not going to get the train to the station.

## UNIVERSAL SCHOOL-LUNCH PROGRAM

I considered my experience in this country, including what I had learned from people like Bob Bergland and Orville Freeman, and came up with the idea of a school-lunch program for every hungry child. Here in the United States and in some other developed countries, most children receive a school lunch, but not in Africa, Asia, Latin America, or the Middle East. So, I proposed that the United Nations, with the United States in the lead, commit to providing a good, nutritious lunch every day to every school child in the world.

The first person I called on was my friend Bob Dole. When I was running for president in 1972, he was the Republican national chairman. He used to take a bite out of me every day before breakfast and usually another before dinner. Subsequently, I became chairman of the Select Committee on Nutrition and Human Needs in the United States Senate on which Senator Dole was the ranking member. We let political bygones be gone and started a bipartisan effort to deal with the problems of food and nutrition in this country.

As things developed on the universal school-lunch program, I went to the White House to seek support from President Clinton. The secretary told me he wanted to see me in the Cabinet Room, where half of the cabinet was already assembled—the Deputy Secretary of State, the Secretary of Agriculture, the Director of the Budget, the Health and Human Services people—and half of the White House staff. The president came in, sat down and asked, “George, what new subversive idea have you got now?” So, I made the pitch outlined above, explaining that when you start a school-lunch program like this, we know what happens from pilot studies that have been in operation for the last ten or twelve years in thirty countries. First, school attendance jumps dramatically. I mentioned that about 300 million youngsters from grade one to grade six, or years six through twelve, are now not receiving any lunch. They trudge off in the morning, walking maybe a mile or two to the village school, where they are expected to study for five or six hours with nothing to eat. I’ve seen such children in villages all around the world. They yawn. They are sleepy. They are lethargic. About 130 million of them have dropped out, or never started school at all. Most of them are girls because of cultural forces in so many societies. However, once the word gets out in a village that a good nutritious meal is to be had just by showing up, parents get the girls and the boys to school in increasing numbers. Academic performance, athletic performance and health all improve.

In the United States, the school-lunch program started in 1946. Its chief sponsor was Senator Richard Russell of Georgia, the long-time chairman of the Senate Arms Services Committee. During World War II, 30% of all of the young men in this country were physically ineligible for military service, many because of malnutrition. The Armed Services Committee came up with the idea that a federal school-lunch program was a way to improve national security. In this country, any time you put a defense label on a bill it goes through

Congress with a hoot and a holler. We had wonderful results from it in this country, and we are having wonderful results with the pilot school-lunch program in other parts of the world.

Another change that results from school lunches affects girls. In many parts of the world, illiterate girls get married as early as 10, 11, and 12 years of age. In Ethiopia recently, a little girl on a donkey approached our party wearing a white lacy dress and a little tiara. I asked her through the interpreter where she had been. She said that she was coming from the church where she had just been married. She smiled very proudly and told me that she was 10 years old. That little girl had no schooling and that white dress would soon be replaced by rags. In the developing world, illiterate women have an average of six children. Those who attend school—even for only six years—get married later, have a better understanding of the values of life and have an average of three children. With better nutrition and education you can cut the birth rate approximately in half without surgical procedures of any kind. There is no society where the birth rate does not drop with improved education.

I am not against big families. My wife and I have five children, but we could afford it. We gave them health care and provided education, clothing, recreation, and direction. Illiterate women who produce six children can provide none of those benefits.

Lawrence Summers, former Secretary of the Treasury, once a senior World Bank executive and now president at Harvard, said, “Dollar for dollar, the best return we get on any of our foreign assistance is the education of girls.” And no one has found a more successful magnet for pulling them into school and keeping them there in developing countries than school lunches or breakfasts, depending on the local preference.

## FUNDING

President Clinton gave us \$300 million to get started, without any action by Congress. I don't know where he found the money, but I don't really care. Senator Dole and I worked hard to advance the idea on a bipartisan basis, then we went to Congress and got a coalition to introduce what has a wonderful title: *the George McGovern, Robert Dole, Food for Education and Child Nutrition Act*. Congress recently authorized \$100 million the first year, and we may be able to increase that to \$300 million via the Appropriations Committee. Failing that, there are two ways to find another \$200 million. One is through foundations, of which there are 12,000 in this country. We will also go to corporations with an interest in food and agriculture: Cargill, ADM, General Mills, Quaker Oats, etc. I think we can raise \$100 million and then get another \$100 million from other governments: the British, French, Germans, Scandinavians, Japanese, and Russians. These other countries could provide commodities, which is what the American contribution will largely be, or cash. If we get the United Nations on board, we will have a program that will literally transform life on this planet.

## HELPING FARMERS AND BIOTECHNOLOGY

School lunches are not the whole thing. We need to provide help to farmers around the world in the form of scientific knowledge, advice, and procedures. In the 1960s and 70s, the green revolution—another term for scientific farming—circumvented the necessity of plowing 12 million square miles of soil to feed the growing population. This was achieved by drawing on the knowledge generated at our agriculture experiment stations and by corporate and public-sector scientific research. It was done by men like Dr. Norman Borlaug, the Nobel laureate, who showed countries like Mexico, India, and Pakistan how to increase crop production, not by cultivating additional acreage, but by increasing the productivity of acreage already being farmed, which is the best way to preserve natural ecosystems, including wetlands.

I want to see us move ahead carefully on biotechnology. It can make a big difference. Every environmentalist ought to be for it because it will increase our productivity without plowing up new land. Those who believe in preserving the natural ecosystem should be the firmest advocates for biotechnology. I am particularly interested in using biotechnology to help farmers in developing countries

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## *Luncheon Addresses*

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### **Q&A**

WITH MARY CLUTTER

*Audience member:* How are we going to take account of the concerns of activist groups about science when the federal government isn't providing the necessary resources?

*Clutter:* I am sorry that I didn't make it clear that social science was key to twenty-first century biology. I did say that social scientists have to be part of every team and we are insisting on that at NSF I addressed only six concerns—but social and ethical aspects are very important, especially in terms of the public attitudes that I talked about toward science and genetic engineering. So I didn't mean to slight the social sciences. I can't tell you exactly what the federal investment is, but certainly it is part of what we support from the National Science Foundation.

*Audience member:* You did a very good job on the federal level on behalf of the NSF in making the case for funding interagency research. I think it will be very important in the future to address aspects of foods for health. When we submit a proposal to USDA they say it would good for NIH. And when we submit it to NIH they say it would be appropriate for USDA. It would be good to have an interagency group for foods for health.

*Clutter:* That is part of what I was talking about—the fact that we are all compartmentalized. It is certainly something that I have been disturbed about for a long time. If you look at our FY'03 budget request, you will see for biology something called *Emerging Frontiers*, which will be a program open to people who have ideas that don't fit any particular box. These interagency working groups are really to bring agencies together to talk about issues such as the one that you just brought up. One thing that I have seen happen at NIH recently that I think represents real progress is that they have a working group that is looking at white papers produced by various groups proposing that their organism be the next one to be sequenced. NIH is now looking at honeybee, they are looking at chicken, *etc.* There is a lot more talk going on among agencies today than there was just a year ago.

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## Q&A

WITH GEORGE MCGOVERN

*Audience Member:* Senator, you are right that in some societies boys have preference in education over the girls. I'm from Bangladesh, where, in the rural areas, there are not enough schools even for the boys. Now girls are getting preference, but, when they are ready for marriage, there are insufficient numbers of educated men.

*McGovern:* That is why we need education for all children. It never should be a contest between boys and girls in a family. Education has to be universal. I can appreciate that problem—I saw it in Vietnam some years ago. Sometimes we overemphasize the imbalance and neglect some of the other people. But it can be corrected.

*Audience Member:* Mr. Ambassador, I'm wondering about the nutritional value of the lunches. In certain areas of the world there are deficiencies, such as in iron. Is specialized fortification part of the program in specific regions?

*McGovern:* The World Food Program of the United Nations, the principal administering agency, is working diligently to find ways to make the food as nutritious as possible. Some private companies are helping. Land O'Lakes is now providing school lunches for about 500,000 children in Indonesia, Vietnam, and Bangladesh that include real milk and a fortified biscuit containing iron, zinc, and vitamins. It has worked out very well. You can literally see the difference in the children who have been on the Land O'Lakes regimen for a while as compared to those who have not. I saw it very dramatically in Indonesia recently.

I am hopeful, as we move along, that we can give even more attention to the nutritional factor. We also should be prepared, if other countries join with us, to use some of the cash to buy fruits and vegetables from local producers. That will ease anxiety about western food coming in and disrupting local markets.

*Kevin Kephart (South Dakota State University, Brookings, SD):* As director of the Agricultural Experiment Station at South Dakota State University I want to thank you for your recognition of agricultural experiment stations around the country, and I am happy to hear your other comments. If we look at the energy situation of America, people are turning their eyes to agriculture as part of the solution. We have been discussing the relationship between agriculture and health. Do you have any guidance, or a forecast, on the search for balance between the various options?

*McGovern:* When the Russian leader Nikita Krushchev first came to this country, President Eisenhower said, “You can see almost anything. If you want to visit some of our defense installations, or our strategic air bases, to see how we do things, that is fine. Krushchev said, “We have missiles and we have airplanes. I’m not really interested in seeing those, but I would like to visit Disneyland and I would like to see a corn-hog farm in the state of Iowa. A man by the name of Garst has been writing me. I’d like to go to that farm for a couple of days.” He was fascinated with what he saw out there.

In Siberia recently, I asked to visit a typical farm and noticed twelve tractors sitting there. For a farm that size in South Dakota, we’d have one. The farmer told me, “They don’t all run at the same time, we have to keep taking parts off.” He took me out for a little drive around the yard and there were six more tractors. He explained, “Those don’t run at all.” Then he said, “Let me tell you something, I would rather have one good American John Deere than all eighteen of these.” We have great advantages in the United States with mechanization, and with modern insecticides and fertilizers. We know how to handle water. We don’t always do it right, but we know how it should be handled.

I’ve always thought we have to have some kind of a farm price-stabilization program. It may be old fashioned, but that’s my view. I think a totally free market for agriculture is a disaster. It just means that when we farm or produce a little too much the price of everything collapses. So, we need some kind of a stabilizing system. If farmers comply with that system they should be assured of a reasonable price for what they produce. You’re talking about balance. I don’t know whether you’re thinking about the international scene, but there we have to be progressive and forward-looking in our ideas. We have to be willing to trade. We have to be willing to function without artificially high trade barriers if we expect other people to lower theirs. I do believe that any kind of balance of American agriculture requires price- and crop-stabilization programs. I’ve believed this all my life and I’ve never seen anything about the Freedom to Farm Act that convinces me that it was a good idea.

The energy policy for the United States is fairly simple and direct. Exhaust America first, and that’s what we are about to do. We all know about our fossil fuels: energy originated from the sun. That’s agriculture of sorts. Scientists are testing ways of short-circuiting the system. Instead of taking 18 million years to produce coal, or gas, or oil, why can’t we do it directly? It’s called renewable energy. There’s a great deal of interest in bio-diesel—adding vegetable oil to diesel oil. There’s renewed interest in gasohol. Although those things are very interesting, they are not important, which is not politically smart to say in this state. They’re not important because they’re too expensive. The future of renewable fuels has an agricultural base: growing and processing fiber, enormous numbers of tons of fiber using a non-depleting source. We can do it on land that is not suitable for corn and soybeans. We have enormous energy-producing capacity.



PART VIII

TOWARDS HEALTHY PEOPLE: LIFESTYLES AND CHOICE

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## **Wellness Trends in 2002**

**LAURIE DEMERITT**  
*The Hartman Group*  
Bellevue, WA

It is safe to say that American consumers will change at an accelerated rate in 2002. The result of this acceleration will not necessarily equate to “more and faster,” but, perhaps, to “less and slower.” Though this may seem contradictory, it represents a shift in the mindset of today’s consumers in terms of quality vs. quantity. Trends in the health and wellness market—a progressive and essential industry—will echo larger cultural changes in American-consumer perceptions and behavior.

While it is impossible to predict specific cultural impacts of September 11 and effects on the economy, one thing is certain: it made people think. Consumers have been forced to question, reflect upon, reexamine, explore and analyze, both on organizational and on individual levels. This process is ultimately about cultural change. So, what is changing?

### **WHAT IS REALLY IMPORTANT?**

Consumers’ behavior and purchase decisions are shifting to reflect what they feel is most important, what products and services they value and what they are most willing to pay for and invest in.

*What We Need?* Alongside the reprioritization of values, consumers are being pushed to redefine essential and non-essential needs: “Do I really need that new J. Crew sweater, when I already have seventeen sweaters filling up my closet?” Emotional and/or spiritual needs that are amplified now may include the need to:

- slow down,
- simplify,
- feel in control,
- take responsibility,
- feel healthy,
- feel informed,
- be oneself, emphasizing authenticity and individuality,
- spend on what is important, rather than on what is extravagant.

The shifting of consumers' needs—material and non-material—will not only reflect an either/or dynamic; shoppers will not simply stop buying one product and replace it with a more-valued alternative. Instead, this shift will appear as an expansion as consumer perceptions broaden to encompass a wider range of needs. For example, wellness consumers who desire to slow down, feel connected, and simplify, may dramatically increase their total-wellness consumption (measured in dollars as well as in time invested) with the prioritization of their real needs, physically, mentally, emotionally and spiritually. For example, they may want to take more time to shop instead of rushing in and out, because they enjoy learning about new products and connecting with others in the retail environment.

Expanding consumer needs mirror the intensification of wellness behaviors. In light of this, consumers will behave less logically and predictably, and instead do what “makes sense.” Determining what “makes sense” to their consumers (consciously and unconsciously) is the challenge facing the wellness industry in the year 2002.

### CULTURAL SHIFT AND SOUL VALUES

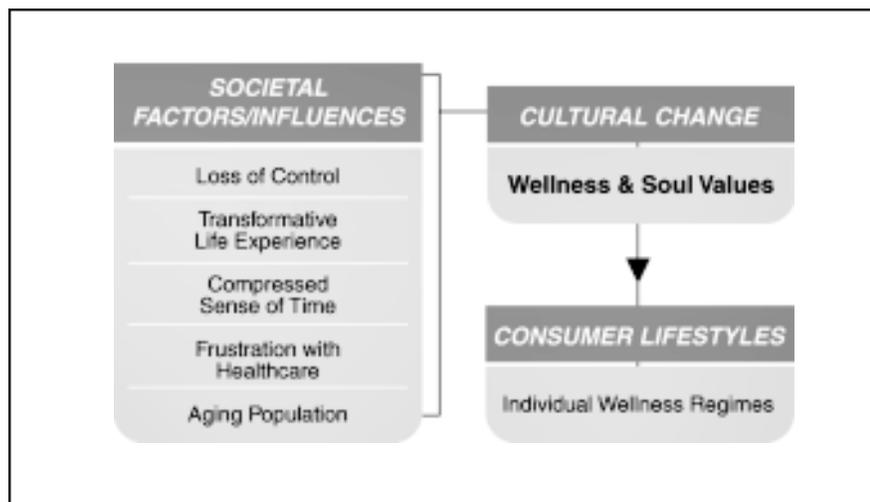
Since The Hartman Group's groundbreaking report, *Natural Sensibility: A Study of America's Changing Culture and Lifestyle*, in 1998, we have been analyzing trends and forecasting shifts in consumer lifestyles. A major shift has been catapulted into consumer consciousness in recent months due to external forces, particularly September 11. From our numerous discussions with consumers, there has emerged a single, unifying theme that links narratives. Respondents are virtually unanimous in their quest for wellness, yet no two individuals are on the same journey.

Regardless of the paths, we think that the shift is driven by a deep cultural longing to find a more “soulful” way of living. People wander into and out of this new aspirational lifestyle in response to the longing for soul; some, of course, are more conscious of their reasons for doing so than others (Table 1).

We have identified five larger, societal factors driving the trend toward wellness and their soul values (Figure 1). Some are directly related to the general evolution of the modern world.

**TABLE 1. SOUL VALUES IN 2002.**

Old ways	Soul ways
Hierarchical	Interactive
Chain of command	Web
Authority	Authenticity
Functional	Beautiful
Mass market	Individual consumer
Rationality	Intensity of experience
Information	Knowledge/wisdom
Analytic	Integrative
Reactive	Proactive
Technology	Art
Synthetic	Organic
Big	Small
Health	Wellness



**Figure 1. Model of cultural change; factors influencing individual wellness regimes.**

*Generalized Loss of Control* A distinguishing feature of the modern condition is the large, impersonal, bureaucratic nature of social, economic, and political institutions. Not surprisingly, people often have a sense of alienation and frustration with the perceived unresponsiveness of these institutions. Therefore, many of the consumers we have spoken with suggest that their interest in dietary supplements, for example, is part of a desire to manage their own health and well-being, lending a sense of empowerment:

*I took personal responsibility for my well-being. That was the big major point. [I] just said, you know what? If you want to have an athletic body, you want to have energy, you want to always look great, you want to look fresh—it starts from within.—Female, 30s, New York City*

*Transformative Life Experience* Many of the consumers we have interviewed identified a specific medical crisis or other event that served as a catalyst for wellness participation. We are examining whether the events of September 11 are affecting the long-term mindset of wellness consumers:

*...it didn't affect what I do on a day-to-day basis, but it did make me stop and think about what's important to me. I think about happiness in my job, spending more time with my family, not stressing out so much, trying to enjoy things more fully. I'd like to think that this will be permanent, but, long term, I just don't know.—Female, 50s, Seattle*

Several of our respondents explained that a cancer diagnosis served as the transformative life experience that helped them enter the world of wellness:

*I started taking that [omega-3 fish oil]. Actually, a friend and I started taking that because we read some of the research about that and breast cancer. And since I've had breast cancer and my friend has, I thought, well, it's certainly not going to hurt me.—Female, 50s, San Francisco*

*Compressed Sense of Time* In the twenty-first century, time seems ever more compressed. Advancements in technology, such as electronic paging, cellular phones, e-mail, video conferencing and hand-helds, have left many people the victims of a “time famine.” Thus, consumers pursue wellness as a strategy to cope with the stress and hectic pace of the modern experience:

*... [with] more stress in my job or my life—life with a 5-year-old— [I'm] just trying to maintain my health, well-being and sanity. —Female, 50s, San Francisco*

*Growing Frustration with Healthcare* Consumers often express general frustration with the nature and efficacy of the current healthcare system in the United States. Specifically they are dissatisfied with the impersonal, bureaucratic nature of managed-care systems. Likewise, they are frustrated with the perceived arrogance of conventional healthcare professionals—especially when faced with a host of chronic conditions for which western

medicine appears incapable of offering any long-term solutions (colds, asthma, allergies, arthritis, stress, etc.).

*...after the [chiropractic] treatment, I feel more invigorated...I respect [the chiropractor]. She doesn't tell me what to do. She lays out alternatives, you know, diets, all this, "you may want to walk, not run."—Male, 40s, San Francisco*

We should add that—dismay and frustrations notwithstanding—consumers have not abandoned their conventional, managed-care facilities and physicians. Instead, they appear to integrate alternative practitioners where they perceive the most efficacy (holistic care for long-term well-being and for chronic conditions) and retain conventional medical professionals for care for serious, acute conditions.

*Aging Population* Consumers commonly responded to our questions regarding motivation to enter the wellness world by stating a desire to take better care of themselves as they age. A number of our older respondents started using multivitamins in recent years to help them stay strong and feel “young.” Often, older consumers react to the onset of aging by building wellness social networks to compare products, services, and lifestyle activities:

*The older I get, the more I get interested in health. It's interesting, a lot of the people I work with are...health conscious too, and we get to talking about things that we take and what works for us and what doesn't work for us. Most of my friends are interested too, because I guess we're all getting [older]. And I recommend things and then people recommend things to me, and it's like a little network.*  
—Female, 50s, San Francisco

From a wellness perspective, the year 2002, still overshadowed by September 11, marks a deepening of this shift. Consumers are pursuing wellness as a coping strategy—an antidote—to the stress and accelerated pace of society. Some consumers make incremental lifestyle adaptations toward wellness, whereas others utilize wellness as a concrete, pragmatic solution. After September 11 and with the continued strain on the economy, consumers' quest for wellness takes on new significance.

Today, consumers are discovering and identifying themselves in the products and services they choose for their wellness lifestyle—in essence, branding themselves. We have termed these social rituals of consumer behavior “individual wellness regimes.” An individual's wellness regime consists of the collection of specific products, services, and behaviors they choose in an effort to achieve their definition of wellness. Individual consumers can choose from the array of options and move into and out of product worlds as their definition of wellness evolves over time.

Most consumer participation in the wellness arena reflects a pragmatic, piecemeal approach, integrating products and services in some sectors of their lives and not others. We have found that many consumers “enter and exit” these worlds, participating more heavily in some areas than in others. Movement within specific wellness-product worlds is frequently non-uniform, at times is unpredictable, and is often subject to other, more immediate factors associated with the demands of everyday living: how consumers live, where they shop and what they buy.

### FINDING CLARITY IN CONSUMER CONTRADICTION

Lifestyle means “way of living.” Consumers lead messy lives, full of contradictions. No longer are we analyzing specific data points, rather we are reconciling how consumers say they live to what they really do day to day. Wellness lifestyles transcend demographic and cultural boundaries; today, consumers of all generations and backgrounds subscribe to the concept of wellness and its soul values.

It should come as no surprise that individualistic, psychological approaches dominate the field of consumer research. If one wants to understand consumer behavior, what better way than to measure attitudes, preferences and opinions of individuals and relate them to consumer purchasing habits (behavior)? This approach is historically so widespread that virtually any market-research strategy includes some attitudinal/opinion-based components. Unfortunately, as anyone who has carefully scrutinized attitudinal and opinion-based information is painfully aware of, this approach does not always work.

Simply put, attitudes and opinions tend to be transitory and rarely serve as robust predictors of behavior.

The larger debate regarding links between attitudes and behavior has rankled academics in the social sciences—primarily psychology and sociology—for decades. Since this debate may never be settled, many in the market-research industry have sought new perspectives on consumer behavior. Popular examples seen in the natural-products arena today are the LOHAS (Lifestyles of Health and Sustainability) and Cultural Creatives consumer surveys, which attempt to shift the research focus from attitudes and opinions to values, which are thought to be more deeply held, entrenched and, hence, less transient. This approach views individual behavior as largely self-driven, with motivations coming from within the individual as mediated by a specific value set.

While this and previous individualist-centered approaches may tell part of the story, we contend that something is to be gained by shifting the lens of the research camera. That is, rather than interpreting consumer behavior as the outcome of individual, psychological dynamics—attitudes, values and beliefs—we suggest examining consumer behavior as a response to larger societal and institutional forces. Specifically, we consider how individuals translate changes

in the broad, cultural sphere into everyday actions, and, reciprocally, how these changes in individual behavior eventually culminate in changes in cultural trends.

So, what is the best way to talk about wellness consumers? Based on the integrated research methods of the social sciences and analysis of over 13 years of quantitative data, The Hartman Group has developed a model of consumer behavior in wellness from a world perspective: at the center of this world are core wellness consumers, behaviors, and product and service offerings. All of these dimensions are linked by a common world theme (e.g., wellness shopping), with different dimensions applying more strongly as a customer progresses from shopping at the periphery (the mass market) to the core (independent health-food store) (Figure 2).

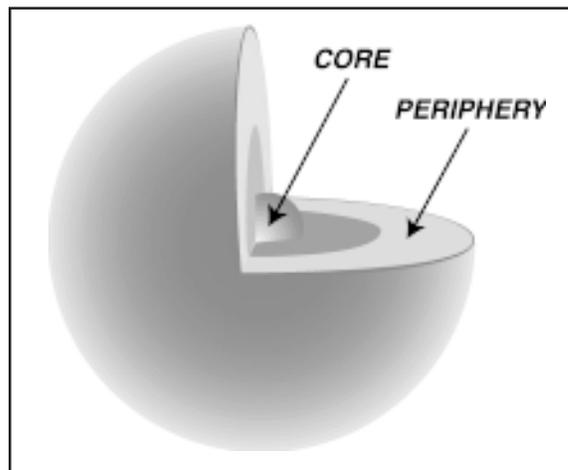


Figure 2. The world of wellness.

Central to this world perspective are dimensions that organize the world. At the periphery are familiar key buying factors, such as price, brand, and convenience, while closer to the core are areas of perception critical to the wellness consumer. Within this world are dimensions that organize and affect some areas more strongly than others. Through careful research we have identified the following key dimensions in the world of wellness:

- convenience,
- price,
- brand,
- expert opinion,
- knowledge,
- authenticity.

Cross-cutting these dimensions is the retail experience while shopping for wellness products. By designing retail experiences that reflect different dimensions of consumption, marketers can appeal to consumers occupying various locations in a particular world.

While wellness consumers and their lifestyles are evolving, The Hartman Model, and its world perspective, allows us to segment along key dimensions of consumption identified as critical to understanding core, mid-level and periphery shoppers (Figure 3).

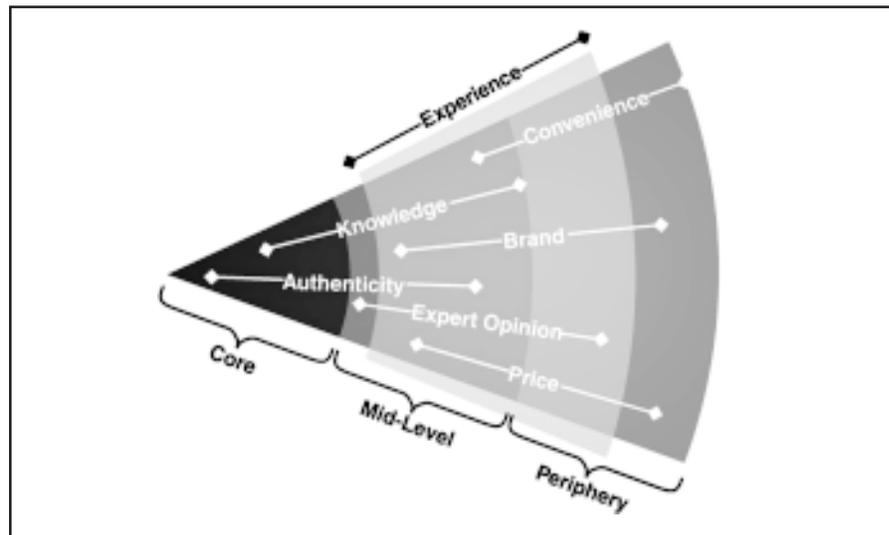


Figure 3. Dimensions of the world of wellness.

To understand attitudes and behavior in the rapidly evolving wellness market requires a multi-phase research approach that begins with lifestyle and cultural analysis. This sociocultural landscape is then deconstructed through an exploration of how the overall category of wellness products are first adopted and then used.

It is worth noting again, for purposes of consumer research, that people lead “messy” lives. In other words, consumers will not always remain in the core or the periphery for everything; they may reevaluate the importance of authenticity and knowledge, or price and convenience. The extent to which consumers hold attitudes and engage in behaviors that comprise activities at the core of the world of wellness determines their position relative to the core. Those in the core exhibit the widest range and highest levels of participation in core activities, whereas those on the periphery participate only infrequently in a narrow range of core activities.

*Rethinking Old Methods* As consumers acclimate to the twenty-first century and make their subsequent lifestyle adaptations, we too must move with the consumer:

- New methodologies are needed to follow and identify common threads and patterns that direct consumers in their journeys within the marketplace.
- Increasingly, those common threads and patterns will be seen to be associated as much with lifestyle and consumption practices as with easily identifiable consumer needs.
- Those who best identify the themes, threads, connections that affect consumers will stand the best chance of success in this emerging marketplace.

## HOW CONSUMERS LIVE

Realizing that it is no longer effective to simply rely on demographics to tell the story of what is happening in the marketplace, we need to understand lifestyle changes by examining how today's wellness consumers are changing how they live, where they shop, and what they buy.

Our recent quantitative findings show that the market for wellness products and services is vast: 13% of households in the United States are core participants in wellness. This means that consumers in this segment rate highly on all of the following:

- proactive health and wellness lifestyle (includes regular exercise, healthy eating habits and an overall self-assessment of being proactive),
- purchase and use of dietary supplements,
- purchase and use of organic and/or natural foods and beverages.

Importantly, a full 62% of households make up the mid-level segment. As such, these consumers have a mixture of high and low ratings on use of dietary supplements, organics, and for proactive lifestyle. Periphery consumers, making up 24% of households, have low ratings on all three dimensions (Figure 4).

A wellness lifestyle emerges from specific attitudes and behaviors. Because location on the wellness continuum is fluid, however, consumers share overlapping characteristics regardless of where they are placed in the world of wellness. Consumers' attitudes and behaviors, such as purchase and use of dietary supplements, natural and organic foods, and proactive health and wellness lifestyle shape how they live. Some of the key attitudes and behaviors are:

- definition of the term "wellness,"
- personal assessment of health,
- proactive, healthy lifestyle,
- interest in and level of knowledge about wellness lifestyles,
- focus on environmental issues and community activities.

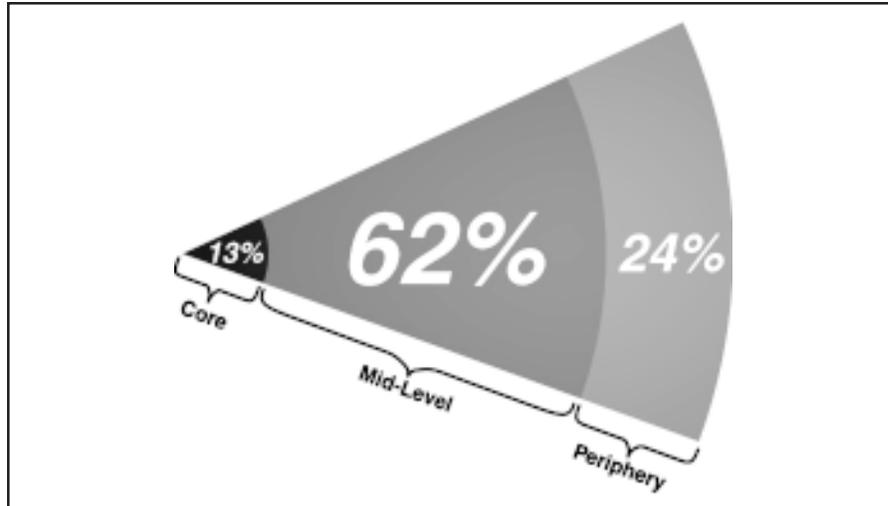


Figure 4. Wellness segments.

#### WELLNESS LIFESTYLE TRENDS TO WATCH

- As consumers reorder their work/life priorities, we will see greater significance placed on family and community, which will manifest itself in mealtime activities with family and friends, as well as community involvement and participation. Decrease in hours worked each week will lead to more focus on finding and making time for “what really matters.”
- There will be more emphasis on the economy than on the environment. As the economy continues to struggle, people relegate environmental concerns and move their efforts to more practical concerns, such as financial matters. Successful environmental initiatives will focus on individual health and community concerns.
- Increased focus on prevention will continue, as we see people turn more to food as medicine and therapy. There will be increased demand for healthy comfort foods replacing more extravagant gourmet items.

#### WHERE CONSUMERS SHOP

The wellness retail landscape comprises a wide variety of distribution channels. Traditional venues, such as grocery stores and drugstores are ubiquitous, with the related mass discount stores and club stores (*e.g.*, Wal-Mart, Sam’s Club, Costco) penetrating virtually every major (and some would say minor) population center coast to coast. Because these channels in general offer similar retail propositions to consumers, despite claims of price discounts, they can

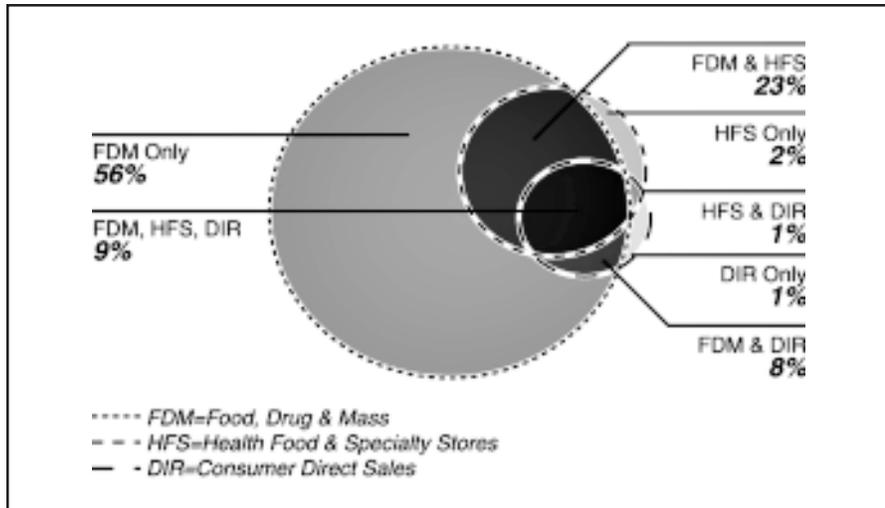


Figure 5. Where consumers shop for wellness products.

be grouped together for general analysis as the food, drug, and mass (FDM) channel (Figure 5). The second major group is called the health food and specialty store (HFS) channel. It includes health food stores, vitamin stores and farmers' markets; common among these three is the more limited and specialized product offering, such as dietary supplements and natural and organic products, typically targeted at the more discerning consumer. The remaining distribution channel is often called the direct channel, (DIR), which includes the Internet, direct from manufacturer, direct sales, and direct from healthcare professionals.

The traditional FDM channel captures the bulk of the market for wellness products, with grocery stores enjoying patronage from an astounding 75% of consumers. World-of-wellness products include a large number of traditional grocery items, such as fruits, vegetables, dairy, poultry, and seafood, which, in turn, affect channel selection, particularly for consumers seeking shopping convenience. With this in mind, it is important to understand the other factors influencing where consumers shop and why they buy products where they do. Some of the differentiating factors influencing consumers' selection of where they shop are:

- presence of knowledgeable salespeople,
- positive shopping experience,
- reasonable price.

## WELLNESS RETAIL TRENDS TO WATCH

- Retail outlets with a smaller footprint and neighborhood presence will increase, catering to consumers on-the-go who still crave a retail experience. More specialty and prepared foods, all with store-to-consumer interaction, become critical, as well as store events and classes incorporating community experience.
- Consumers will shift towards wellness retailers who make their lives easier: places that are not so overwhelming that decision-making becomes a chore, people who help consumers navigate through massive amounts of wellness information, and products that are easy to understand and easy to prepare.
- Consumers will gravitate towards retailers who provide them with community and share experience, acting as trusted lifestyle advocates (e.g., providing networking opportunities to other effective health resources/events, as well as connecting people making similar lifestyle choices).
- Consumers will expect wellness companies to focus less on producing the latest, greatest, newest item and more on making sure that their current products maintain high quality. Likewise, we will see continued acquisition of smaller niche manufacturers as larger corporations opt for backing and promoting established, trusted brands rather than creating and introducing new products.

## WHAT CONSUMERS BUY

It is no wonder that, from a market researcher's perspective, consumers' wellness lifestyles seem messy. How are we to understand the logic behind the complex aggregation of products that consumers include in their particular wellness regimes, e.g. the consumer who eats soy products and red meat or who takes herbal supplements but hates fresh vegetables?

Understanding how consumers use different products and ascribe importance to their wellness lifestyle is one of the mainstays of Hartman Group research. Using this comprehensive model of consumers' wellness lifestyles, we establish a framework for analyzing just what people do and do not do to maintain their health.

For consumers who have a low level of involvement in wellness activities, periphery wellness consumers, products such as organic foods and soy products play a very limited role. Figure 6 compares a wide variety of products in terms of the role they play in periphery consumers' wellness lifestyles.

Traditional food products such as dairy items, red meat, and fresh vegetables are significant parts of the periphery consumer's wellness lifestyle, both in terms of how frequently the products are used and their importance to the wellness regimes. The significance of these products is graphically represented

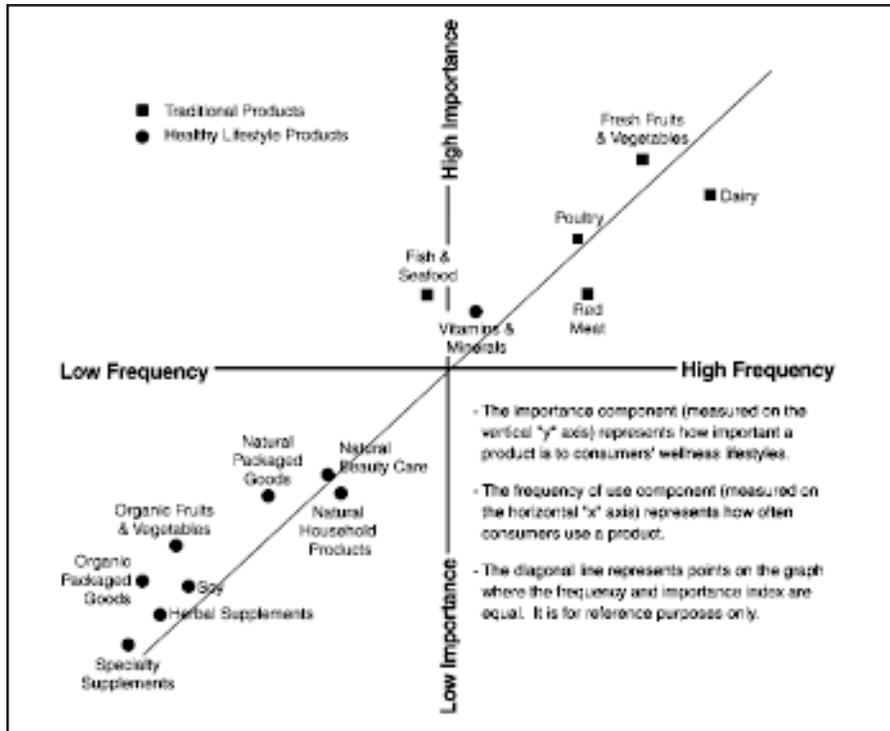


Figure 6. Periphery wellness consumers: product frequency of use and importance.

by their location in the upper right quadrants (Figure 6). At the other end of the scale, in the lower left quadrant, are what are commonly considered the healthy-living food categories: organic fruits and vegetables, soy products and herbal supplements. For the periphery consumer, these products have a very limited role in their wellness regimes.

Comparing the same analysis for mid-level (Figure 7) and core (Figure 8) wellness consumers reveals marked increases in the importance and use of the healthy-living products.

Along the continuum from the periphery to the mid-level and from the mid-level to the core, consumer use of the healthy-living products registers marked increases, both in the importance and in the frequency-of-use indices. Focusing on the transition from the periphery to mid-level, we find the importance of healthy-living products as a group increases 37%, and the frequency of use increases 12%. The same analysis of the transition from the mid-level to the core reveals the importance index for the same products increasing 38%, and

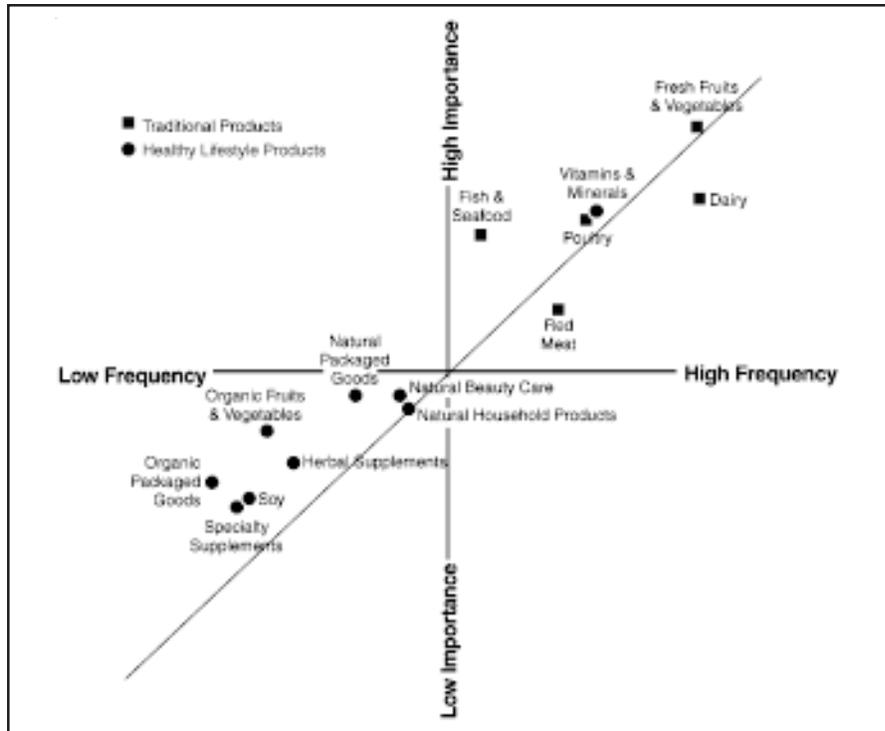


Figure 7. Midlevel consumers: product frequency of use and importance.

the increase in the frequency-of-use index is 22%, nearly twice what we found for the transition from periphery to mid-level. In terms of what this implies about the different wellness lifestyles of consumers, we surmise:

- Periphery consumers are relatively uninvolved and unconcerned about incorporating products in their wellness lifestyles outside of the traditional “meat and potatoes” food groups.
- Consumers at the mid-level are rapidly increasing their awareness of the importance of various types of healthy-living products as they consider alternatives to the traditional way of eating. At this point though, consumers are on a very steep learning curve and have not significantly changed many aspects of their diets to reflect their increased awareness.
- At the core, consumers have significant involvement in their wellness lifestyles both in terms of the information they are gathering and the variety of products they are incorporating into their wellness regimes. It should be noted that, even for core consumers, learning about the opportunities to change their lifestyles for the better is still a primary

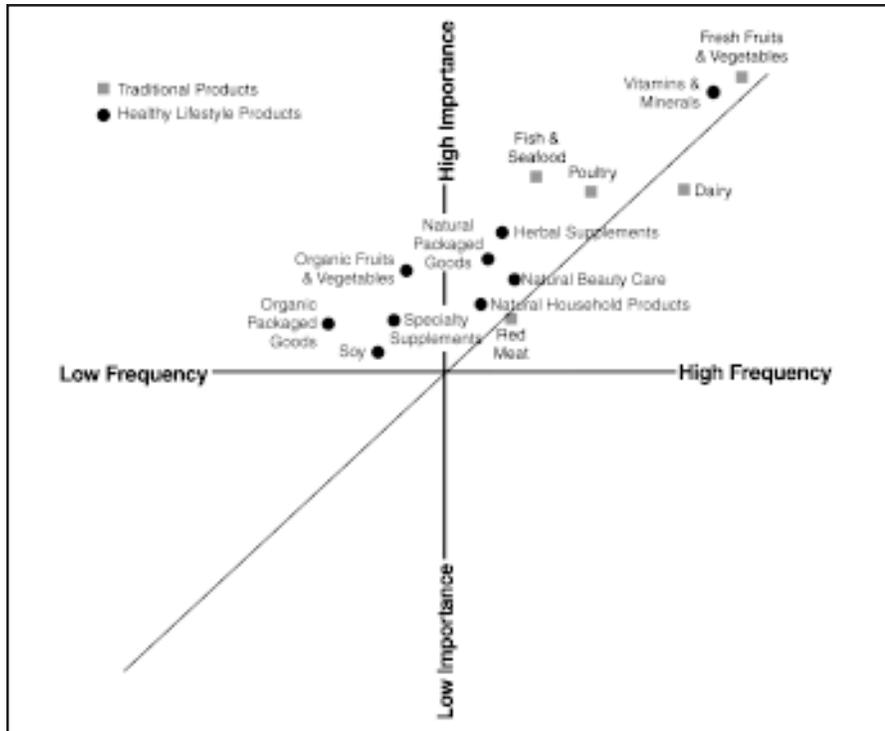


Figure 8. Core consumers: product frequency of use and importance.

activity, but, as opposed to the mid-level wellness consumers, the information assimilation occurs in tandem with lifestyle changes to improve health.

#### WELLNESS PRODUCT TRENDS TO WATCH

- Spa services market will continue to grow as consumers seek small indulgences to reduce stress and contribute to their overall health and well being. We will see increased day spa visits made possible by more in-and-out spas in convenient locations such as shopping malls, fitness clubs, airports, and hotels. This growth will spur increased use of home-spa products that consumers will enjoy between visits. In addition, more Americans will choose destination spas for their vacations where fitness, pampering, and fine dining are all-inclusive.
- Though the dietary-supplement category as a whole is lackluster, specialty supplements will grow on a product-by-product basis, such as glucosamine/chondroitin and probiotics.

- The functional-food industry will continue to grow as companies receive patents specific to particular organisms or varieties of plants, and large manufacturers market the benefits of existing products such as orange juice with calcium and other standard beverages fortified with dietary supplements. Despite their insistence that they want their supplementation in food, it remains to be seen if consumers will be accepting of functional foods.
- As consumer demand for organics is met at mainstream retail grocery outlets with the expansion of natural and organic departments, consumers will also be looking to restaurants to provide more organic options. Similarly, more organic ingredients will be available in prepared foods made in grocery delis.
- With continued focus on prevention, alternative medicine will increasingly be integrated with conventional medicine. Consumers will not turn away from the conventional approach, but will supplement it with new techniques and approaches. Economical home remedies will be increasingly favored, e.g. natural medicine kits, herbal teas, compresses, videotapes, books; and use of alternative medicine will increase, especially massage, aromatherapy and homeopathics (especially among new mothers).
- Children and teens will show greater interest in wellness products, demonstrating independence in purchase decisions, with particular emphasis on on-the-go wellness products and niche brands that create and carry a certain status.

## CONCLUSION

Our experience at The Hartman Group has led us to understand that there is one fundamental constant regardless of how chaotic and fast moving the marketplace may seem: *change in the marketplace is consumer driven*. Although this is obvious to most, the implications may not be. For, in order for business people to be proactive, they need to understand that consumers lead, and the only way to understand consumers trends is to understand the forces that drive them.

These complex forces become clearer when consumers are viewed not as isolated individuals but rather as participating in larger lifestyle or cultural worlds. A basic assumption that lies as a foundation for the information presented here is that consumers do not operate in a vacuum. They operate within the larger social context we call culture, and culture shapes lifestyle. The forces shaping lifestyle and the product worlds that serve them are the forces shaping our culture as a whole.

During this time of flux and recovery from the cataclysmic events of September 11, it is dangerous to assume that consumer reactions will be extreme. Reactions to these events will not manifest in total lifestyle shifts; rather, consumers will continue to strive for the “aspirational lifestyle.”

As consumers choose new products and services, and new lifestyle behaviors, we have to give them the freedom to be human, contradictory, and, most importantly, messy.

The pursuit of wellness, with construction of individual wellness regimes, is a common goal among consumers seeking respite and differentiation from an increasingly complex society. Based on increasing sophistication in manufacturing and retailing, and a wide range of natural products and services, manufacturers and merchandisers can now interact on a more personal level with consumers to create more customized lifestyle worlds. These lifestyle worlds represent interpretive arenas centered on a specific product and its associated method(s) of consumption.

In such worlds, consumers come not only to identify themselves, but also to promote the identities they adopt within each associated lifestyle world. It is important to recognize that although merchandisers create the lifestyle associated with a particular product, consumers are still the ones who organize themselves into specific product worlds.

Defining target markets and anticipating future wellness lifestyle trends based solely on demographics provides little or no guidance to wellness marketers, because consumers adopt wellness lifestyles at different paces and pick and choose from a wide selection of products and services that no longer depend on age, income, or education. And, interestingly, wellness adoption is so widespread that the demographics of the wellness consumer are nearly identical to those of the general population. The Hartman Model's "world perspective" segments consumers based on their attitudes, behaviors and level of participation in a wellness lifestyle. Looking at how these consumers live, shop and buy in the current marketplace reveals meaningful consumption patterns that cut across demographic boundaries—it's about lifestyle, not just lifestage.



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## ***Delivering on the Promise of Safe and Healthy Foods***

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Perhaps the quest for the fountain of youth is an impossible dream. Nevertheless, a longer life, a healthier life, is achievable for many. We know more about what foods are good for us, what medicines are beneficial, and what lifestyle changes may ensure that we at least have a chance to live to be octogenarians or even into our nineties. But how do consumers learn how to have that longer life, healthier life—do they know the magic formula to avoid diabetes, stroke, cardiovascular disease?

We are told to eat the right foods, see a physician regularly, exercise, and not to smoke, drink, or take drugs. We know that we should eat fruits and vegetables and consume plenty of fiber, read every label, and know exactly what foods are good and what are bad. We are even told what states and cities to live in for cleaner air and better water quality and to decrease the likelihood of having an auto accident or being the victim of a crime.

### **INCREASING CONCERNS OVER FOOD SAFETY**

But even following all the right rules, there is no promise of good health. Let's consider, for example, food safety. Although safe food is an important public-health priority for the nation, an estimated 76 million illnesses, 324,000 hospitalizations, and over 5,000 deaths are attributable to contaminated food in the United States each year. For some consumers, foodborne illness results only in mild, temporary discomfort. For others, especially preschool-age children and the elderly, these illnesses may have serious and/or long-term consequences, and can be life-threatening. The risks are of increasing concern due to changes in the global market, aging of our population, increasing numbers of immunocompromised and immunosuppressed individuals, and changes in food-production practices. These illnesses can strike anyone, as those who have lost a family members to *Escherichia coli* O157:H7 or *Listeria monocytogenes* poisoning will attest.

From the consumer's perspective, choices have to be made every day, with or without adequate, reliable information. In fact, sometimes choices are made using misinformation or incomplete information, with the potential for misguided thinking. Consumers often have to weigh risks, both voluntary and involuntary—the former are always more acceptable—and often have to rely on someone else's opinion. Ultimately, the consumer may ask, "Am I in control of the decisions I am making? Am I willing to live with the consequences, no matter what?"

How do consumers make choices, if food might be unsafe? Whom can you trust? The government? Isn't the government supposed to make sure our food is safe? Industry? Don't they want to make sure that we return to that restaurant or grocery store? How can they sell unsafe food? How much of what you see on TV or read in the newspaper should you believe? And what about the latest newsletter from your favorite consumer group?

Earning and keeping public trust is a major challenge facing the government, industry, and consumer groups. In the last decade Americans have changed both as citizens and as consumers. We have become a "harder sell," and trust must now be earned, not taken for granted. In the complex reality of science-based approaches using technology to make our food safer, consumers hear one thing from industry, another from some consumer groups, and often confusing, contradictory messages from government.

Whether you are a businesswoman from San José, a construction worker from Arkansas, whether you work for a major restaurant chain or a small grocery store, whether you are a senior citizen from Buffalo or a consumer advocate from Washington, how you make decisions for yourself and family is dictated to a great extent by prior knowledge and experience of the world. In short, attitudes and perspectives are shaped by interests, knowledge of what foods are safe, and by professional expertise. For most consumers, friends, family, colleagues at work, and acquaintances at church or synagogue most influence their attitudes and knowledge—be it fact or fiction—about everyday products and services, and about safety and harm from food.

#### **NATIONAL CONSUMERS LEAGUE AND IRRADIATION**

One of the goals of the National Consumers League (NCL) and other consumer groups is to reduce foodborne illness. We have encouraged government and industry to adopt policies and practices that will reduce bacterial contamination of food products. The FDA has approved irradiation as safe and effective in reducing pathogen contamination in meat, poultry, and other food products. And the majority of consumer groups—there are exceptions—accept that irradiation is a useful tool and can contribute to reducing foodborne illness. We emphasize, however, that a tool like irradiation must never replace sanitary practices in the processing of food.

The NCL and other consumer organizations support clear labeling of

irradiated foods. However, we believe that irradiated foods should not be labeled with terms such as “cold pasteurization” or “electronic pasteurization”—terms that mean nothing to consumers. And it would be a mistake and serve to confuse and mislead the public if “treated with radiation” or “treated by irradiation” were not used on the label. Conspicuous, easy-to-read labeling is the only way for the consumer to make an informed choice about irradiated products. Numerous studies have demonstrated strong support for such labeling. In 1999, the Center for Science in the Public Interest and AARP conducted a nationally representative survey of over 1,000 consumers to examine attitudes toward irradiation labeling, and found overwhelming support (89%). They wanted information placed on the front of the package (59%) and were opposed to language such as “cold pasteurized” (91%).

A recent survey of consumers in the aftermath of irradiation use to decontaminate mail in November, 2001, indicated a 50% support for irradiation of all food. And Food Marketing Institute studies demonstrated that consumers accept irradiation if they are properly informed about it. Upon provision of science-based information, willingness to buy increased from 50% to 90%.

Disclosing whether a food product has been irradiated also satisfies another generally accepted principle: the consumers’ right to know. That right was recognized by the General Assembly of the United Nations in its Guidelines for Consumer Protection, which are intended to provide consumer access to adequate information to enable informed choices according to individual wishes and needs. The UN guidelines were inspired by President John F. Kennedy’s pronouncement in his landmark message to Congress in March 1962, that consumers have a right to be given the facts they need to make informed choices as well as a right to be protected against fraudulent, deceitful or grossly misleading information in advertising, labeling, and other practices.

Labeling serves the needs of at least two important groups of consumers. It imparts valuable information to those who would seek out irradiated products for people at increased risk of developing foodborne illnesses—children or nursing-home residents, for example—or because they generally desire for themselves or their families foods that have an extra measure of safety added during processing. At the same time, clear labeling reaches those who wish to avoid irradiated products, because they prefer fresh, or minimally processed foods or because they are concerned about potential environmental and worker-safety problems, or find irradiated foods unappealing for any other reason.

### **WHAT IS NATURAL?**

In all avenues whereby consumers obtain information—labeling, advertising, patient inserts, information on Web sites, on the radio or TV, the daily newspaper or favorite magazine—whether choosing a food, an over-the-counter drug, or a dietary supplement, one word is commonly used to make the product more attractive: “natural.”

The NCL commissioned a national random-sample survey to find out how Americans understand the claim of “natural” or “plant-derived” on various products, including drugs, dietary supplements, personal-care products, cosmetics, and food items. The League also commissioned four focus groups, composed of women over age 45, to explore their views of products labeled “natural” or “plant-derived,” as an extension of past NCL research on women and dietary supplements.

That “natural” products come from nature is a commonly held belief that may be imparting a false sense of security. While aging baby boomers have a desire to stay young and healthy through the use of “natural” or “plant-derived” products, they must understand that just because a product is labeled or advertised as “natural” does *not* guarantee that it is safe or harmless for consumers or safer than similar products not bearing the “natural” label. The Food and Drug Administration, the Federal Trade Commission, and the US Department of Agriculture, which regulate drugs, food, and personal-care products and advertising, have been warning consumers that “natural” is not synonymous with safe. But studies by the NCL show that the message is not resonating. While over 75% of those surveyed believe that when they buy “natural” they are buying products that are unprocessed, pure, and gentle, those products can be powerful and have serious side effects. When consumers compared a product labeled “natural” with a similar product not labeled thus, 74% believed the former was safer, 76% believed it had fewer and less-serious side effects, and 70% believed it was less likely to cause interactions with other medications.

The NCL survey revealed that the majority of the participants (64%) were very or somewhat confident that the claim of “natural” accurately describes the ingredients and processes for that product. Many consumers are turning to “natural” products to improve their health. Eighty percent of those surveyed believed that “natural” products were “good for me,” and nearly 70% believed that the “natural” product was something their body needs; and if they use it, their overall health will improve. As one participant of the focus group stated, “I tend to idealize ‘natural’ products.”

There is a strong assumption that products labeled or advertised as “natural” are, indeed, natural. Three quarters of consumers polled expected at least 90% of the ingredients in “natural”-labeled products to be natural. Yet, studies show that this is often not the case. In a random sample of herbal stores, the California Department of Human Services found that nearly a third of “natural” remedies contained either heavy metals (such as lead, arsenic, and mercury) or undeclared pharmaceuticals. Products containing unsafe levels of heavy metals or prescription drugs could be disastrous to unsuspecting consumers purchasing a “natural” product.

Just because something is on the shelf at the grocery store or drug store does not render it harmless. When taking drugs and dietary supplements, consumers

must always be cautious of interactions with foods and medications and possible side effects, even if the product is labeled “natural.” And while consumers may think that when they buy “natural” they are buying unprocessed, pure and gentle products, “natural” products can be quite potent and pharmacologically active, resulting in serious side effects.

### **FEDERAL REGULATION OF “NATURAL”**

For consumers to understand what the “natural” label says about a drug, dietary supplement, personal-care product, or food item, they need to understand how the government regulates the claim of “natural.” The government agencies regulating the labeling and advertising of drugs, dietary supplements, personal care products, and food have not issued much guidance on the use of “natural” on labels and in advertising. Because there is a lack of consensus on what the term actually means for a product, there has been little regulation on its use.

Focus groups unanimously agree that there is a need for greater regulation of the word “natural” in marketing and advertising. Specifically there is interest in the classification and standardization of the definition of “natural,” and enforcement of standards regarding the contents and degree of processing of “natural” products.

For meat and poultry, the USDA allows the use of the term “natural” only if the product contains no artificial ingredients, coloring ingredients, or chemical preservatives, and the product and its ingredients are only minimally processed. Even though a meat or poultry product bears the “natural” label, the animal itself may have been raised using antibiotics or growth stimulants since the label does not cover animal-production practices.

For other food products, the FDA regulates the use of “natural flavoring” on food labels. For a food in which the only flavor is a natural flavor, it may be labeled accordingly, *e.g.* “natural strawberry flavor.”

Many food items are now labeled “organic” which is not the same as “natural” While “natural” is not defined by the FDA for food products, the USDA has published a final rule for the production, handling, and processing of organically grown agricultural products: “organic” entails the integration of cultural, biological, and mechanical practices that foster cycling of resources, promote ecological balance, and conserve biodiversity.

The FDA does not specifically define or regulate the use of the claim “natural” or “plant-derived” for prescription or over-the-counter drugs. Generally, drug-product labels or advertising cannot make false or misleading statements. The FDA, which regulates the claims made on dietary supplement labels, does not define or standardize the use of the word “natural” although it prohibits labeling that is false or misleading. The Federal Trade Commission, which has jurisdiction over the advertising of dietary supplement products, will take action against false, deceptive, unsubstantiated, or misleading advertising.

The FDA does not define or regulate the use of the word “natural” on personal-care or cosmetic products.

### **CAVEAT EMPTOR**

As consumers navigate the marketplace of “natural” and other products for their health and try to decide what is best, they should not assume that their first instinct is always best. They should remember that not all things natural are safe:

- Understand the label. Talk with your healthcare provider. Check with your physician or pharmacist about all medications and dietary supplements you are taking.
- Be aware of possible interactions between dietary supplements and foods and drugs, prescription or over-the-counter.
- Be a savvy consumer. Ask yourself if the claim is just advertising or hype. Is there an explanation of the ingredients/origins of the product?
- Compare similar products. Are the ingredients/processes the same or different?
- Check ingredient lists carefully. Are there any ingredients that may be harmful? If you are unsure, check with a health professional.
- Read and follow product instructions carefully.
- Research products before you use them.

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## ***Farmers As Consumers: Making Choices***

WILLIAM HORAN

*Horan Brothers Agricultural Enterprises  
Rockwell City, IA*

I am the dirt farmer here at the meeting—operating on the lowest rung of the biotech ladder! As operators of a farm in northwest Iowa, my brother and I use the products of biotechnology and try to make them commercially viable. We have one employee, so three of us make a living from about 4,000 acres of corn and soybeans. We grow seed beans for three seed companies, all genetically altered. And we grow tofu beans that are exported directly to Japan. We have commodity corn and waxy corn for salad dressing and mayonnaise, corn for juvenile poultry, and we also grow pharmaceutical corn.

We have been planting *Bt* corn and Roundup Ready® soybeans for the last 3 or 4 years. About 80% of the soybeans this year, and some people say more, in this country will be genetically altered. Approximately 25% of the corn will also be genetically altered in this country. This is the most rapidly adopted technology that has ever come to agriculture, including steam power, electricity, commercial fertilizer, and hybrid corn. None of those innovations were adapted as fast as biotechnology.

### **MORE TIME FOR WHAT MATTERS**

With Roundup Ready® beans we have a \$12/acre savings right from the start, which, in today's agricultural economy, is very important to the family farmer. When I was growing up, I spent my summers walking soybean fields with a garden hoe, cutting out the weeds that were competing for nutrients and moisture. Because of biotechnology and Roundup Ready® soy, my children are involved in Little League baseball and the swim team, and attend dance lessons, *etc.* And, as a parent, because of Roundup Ready® beans, I get to watch them. As a user at the ground level, biotechnology gives me time, the most precious commodity that any of us can find today. It helps me be a better husband and a better father, and that is important to me.

## **BIOTECH AND ZERO TILLAGE**

Of course, it is environmentally friendly. Roundup is a contact herbicide. It does not function in the soil, so it doesn't get into the ground water, unlike other crop-protection products that have been available for the past 15 to 20 years. The Roundup Ready® technology also allows us to no-till drill our soybeans directly into the stubble of the previous crop. No-till crop production has been around for 20 years; but it worked well for only 2 or 3 years before the weed pattern would shift and give problems. With Roundup Ready® soybeans, continuous no-till is possible. It is the technology that will be written about 500 years from now. From the first time that a human being took a stick, put a hole in the ground and planted a seed and became the first farmer thousands of years ago, farming has always been connected with soil erosion. In Europe where they have been farming for three or four millennia, soil erosion is a very serious problem. In this country, we have lost half of our topsoil in the past 150 years. When historians write about this period 500 years from now, it will not be about Bill Clinton or George Bush or Saddam Hussein, it will be about how biotechnology allowed us to go to no-till and *stop* soil erosion—stop the deterioration of the food factory of the earth.

## **GPS AND TRACEABILITY**

Today's tractors and combines use global positioning system (GPS) technology. The steering of the tractor is controlled via microprocessors such that when it gets to the end of the field I have to turn it around and relocate the line and it then takes off on its own, planting perfectly straight rows in any direction and any heading that you wish to log in the computer. This will be part of the traceability system. With GPS equipment on board we record what the seed is—the genetics come with that information—we document the longitude and latitude of where that seed is planted and when it is planted. The information is time-stamped and eventually will be available to everybody in the value chain for traceability efforts. The average farm tractor and the average combine that is harvesting crops have more computing power in the cab than the rockets we sent to the moon and back.

## **BT CORN AND TIME AVAILABLE FOR HARVEST**

The leaves of *Bt* corn plants are toxic to the larvae of European corn borer, which is great, because this insect is the most serious pest for corn. On the other hand, in the real world where I live that is not the chief benefit. To me the longer harvest window—because of improved late-season plant health—is very critical. If my harvesting goes from a 2-week period to a 4-week period, it means that I can use the same \$200,000 combine on twice as many acres or I can use a smaller combine on the acres I have today. That has a greater financial benefit effect for me than anything else the *Bt* technology brings. It is critical for farmers everywhere. And of course, again, the technology is

environmentally friendly. When we used to spray fields that had corn borer in them, we killed all the insects. Now the plant itself is the herbicide, and it is specific to only that insect pest, and beneficial insects are not harmed in any way.

### **REVITALIZED RURAL COMMUNITIES**

In 2001, we were among the first to grow, under contract, corn that synthesizes a pharmaceutical for the treatment of cystic fibrosis patients; we grew it again in 2002 for phase-3 clinical trials in Europe. This is going to be a very important part of rural development and rural revitalization. Biotechnology eventually is going to take a lot of the plywood down off the small towns in the corn belt. It will take us from a low-margin mature-commodity business to a higher-margin management-responsive new business to allow farmers to generate some real dollars. Accordingly, we are trying to set up a technology-support program in Iowa. In our little group, we have written our SOPs for experimental transgenic crop production. We are also growing some tobacco that is genetically altered to not have nicotine, and in 2002 we will grow some safflower crops from Canada that in 2003 will produce another human pharmaceutical.

Thus, biotechnology is opening the door of opportunity for development of family farms in rural communities. And this technology, as it expands and grows in the corn belt, will not bring traditional unskilled, low paying jobs. Instead it will draw degreed people back into the rural states. It will change the flavor of Minnesota, Iowa and other states that grow traditional commodity crops.

About 450 drugs are in the pipeline. We are involved with the first one, but many more will follow in the next 24 to 48 months. We are excited about this, as are lots of other farmers. In Iowa we are taking a three-part platform to try to draw industry back into the corn belt. Almost all of the tech companies tell us that it makes sense to produce these biotech pharmaceutical and industrial enzyme crops in the corn belt, especially in areas with low hail rates (hail is the #1 weather problem for these crops). Corn is the domesticated crop of choice for drug production, and we think that we can enhance the potential of traditional corn-growing areas. Novecta is a certification program for producers, put in place by the Iowa and Illinois Corn Growers Associations. Through self-funding and our check-off money, we have devoted \$600,000 to develop web-based coursework for farmers to become qualified in technologies to reduce risks for biotech providers in producing these crops. Written exams will be involved, and farmers who obtain certification will receive a card saying that they are certified producers of a particular industrial enzyme or pharmaceutical who understand the technology, the SOPs, and critical aspects of containment. One of the reasons that we got the contract to grow pharmaceutical corn is that we convinced the company that we had a 100% identity-preservation system. Because of Starlink™, that is the number-one issue. We found that our

traditional commodity system was totally inappropriate for these high-value crops, therefore, we have dedicated planting machinery, dedicated husbandry, dedicated harvesting equipment, dedicated transportation and storage equipment so that our pharmaceutical production gets nowhere near our commodity corn. Our SOPs are written around that.

The idea of a technician program came from a community college in Iowa that is working with an animal pharmaceutical company to set up a curriculum to train technicians for animal-vaccine production in that company. We have been working with Iowa State University, the community college system and the University of Iowa to put together a program that will train 2-year technicians on one hand through to advanced biochemists on the other end of the spectrum such that they all understand their place in the chain, why they do what they do and why it is important. Iowa is the only state that has a parallel-constructed curriculum.

And lastly, the third leg is a multi-tenant biologics facility. A \$20-million facility is under construction at the Research Park in Ames, Iowa. Companies will take their table-top test-tube work, which they can replicate in the lab, to this facility and lease a suite for the time required to commercialize the product. This facility will be large enough to run one tenth of a commercial batch to see if it is scalable:

- Do they have the right equipment, the right process, to scale, and if they do, what does it cost? How much time does it take?
- What percentage of product do they get?

All such issues can be figured out at this facility, which is the only one of its kind in the world. This is Iowa's approach to this situation.

### THE REASON FOR THIS CONFERENCE

A letter was sent to my brother and me by a mother who has two sick children, after she saw an article written about us:

*My step-dad subscribes to Top Producer and forwarded the January 2002 issue to me. My son Justin, age 13, and daughter Candice, age 8, have cystic fibrosis. We were thrilled to see your involvement in the fight against cystic fibrosis and other diseases. Thank you for your dedication thus far. I'm sure it hasn't been easy. Justin wrote a book, enclosed, when he was 8 years old to explain to his friends why he couldn't do some of the things that they could do. The title is 99 Bottles of Pills on the Wall and it's illustrated by Justin. He wants you to have a copy because of your help with this disease. Justin prays about this disease. Thank you for being available for His purposes. God bless you.*

Jennifer Colson

This is the reason for this conference. Agricultural biotechnology is where the rubber meets the road.

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## ***Towards Healthy People: Lifestyles and Choice***

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### **Q&A**

MODERATED BY

**JEAN D. KINSEY**

*University of Minnesota  
Minneapolis-St. Paul, MN*

*Jean Kinsey:* Biotechnology is science-driven in its research but is consumer-driven in its marketing, and we have been talking about the consumer-driven part of the biotech industry and its development. Bill Horan agrees that it is a consumer-driven technology. He also pointed out that there is a difference between biotech in medicine and pharmaceuticals and biotech in the food we eat. We think of our food as being natural. But, who authenticates food for us—who guarantees that it is safe? Who provides that information, that knowledge, that security versus who authenticates the medicines that we take? We are now combining these, raising new questions. For example: compared to the pharmaceutical industry, profit margins in the food and agriculture industries are small and will be smaller if traceability and identity preservation are needed.

Linda discussed consumer education, and Laurie told us that consumers don't know or care a lot about biotech, but they do care about getting food on the table. What is the best way to provide information to the consumer? What do we have to do differently?

*Linda Golodner:* Susan Borra mentioned that scientists are from Saturn. In other words, scientists, unless they can present it in consumer-friendly language, should not be sources of information. Consumers already have trusted sources of information. The media could do a better job in explaining to consumers exactly what biotech is and what it is not, and what is being done. For example, there is a tremendous opportunity to explain to consumers that those who pick our foods will be less exposed to pesticides. There are important messages—but they must come from trusted sources.

*Laurie Demeritt:* Clearly, the government is not an information source that consumers use. If another consumer tells them not to do something they will usually follow that advice. But it is important to know where they are getting information, in addition to friends and family. Let's identify those individuals—we call them “gurus” or “campaigners”—the people who are out there spreading information. Let's bring them in and have conversations with them. Let's study their behavior and find out how information travels from source to source. We can talk about educating consumers, but, at the end of the day, the consumer does not want to be educated. They do not want to be lectured to. They want access to information on their own time and from their own sources. We have got to understand that, otherwise we will spend a lot of time, energy, and resources trying to educate them when in fact many don't want to know until they are at a certain stage in the wellness evolution, then they look for choice in accessing information that they want. So, within a particular category or particular ingredient, it is important to understand how they behave and how they get their information.

*Kinsey:* Bill, you said that this technology gives you time. And Laurie talked about the quest for convenience in food selection and about consumers wanting more time for themselves rather than spending time cooking. I like your idea about how this will lead to rural development. On the other hand, some of the people at the University of Minnesota, including Norman Borlaug, have spent a lifetime worrying about how we are going to grow enough food to feed the world. To what extent will the production of pharmaceuticals limit resources—land, labor, and capital—that would otherwise be used to grow food?

*William Horan:* That needs a two-part answer. First of all, the area that will be used for pharmaceuticals will be relatively small. Eighty million acres are producing corn in this country today. Because of the 400-meter setbacks that are required around corn, there will be many small plots all over the corn belt, which is a good thing because it reverses the development of the integrated hog industry for instance—where we have very few, but very large, hog buildings. There will be opportunities for producers to provide those buffer strips of corn even if they don't actually grow the pharmaceuticals, because the field across the fence will need to be soybean or some other crop that won't cross with corn. Secondly, as Norman Borlaug has often said, biotechnology is the solution to world hunger. It allows us to produce very intensely on smaller acreages. If we went completely to organic production in this country, or around the world, estimates have been made of the numbers of extra acres that would have to come into production to provide the same amount of food. Biotechnology will allow us to intensely farm the acreage we have today, and still provide enough food for a growing world.

*Kinsey:* Let's take some questions from the audience.

*Audience Member:* Laurie, the core group that you described, how influential are they on the other consumers? How green are they, and what is their attitude to GM foods?

*Demeritt:* Unlike most people who are concerned about their health mostly selfishly, a small group has environmental concerns. Positioning biotechnology as being environmentally friendly is likely to resonate only with a small number of consumers. Most of them want to see benefits to themselves in terms of price, convenience, or health.

Most core consumers—the campaigners—can be very vocal and serve as sources of information for many consumers. If their friends, relatives, colleagues, and neighbors see them as well informed, they will tend to go to them for information. Since we now know that social networks are important, certainly there is need for investigation rather than simply saying, “Well it's just a small vocal minority that we don't have to worry about.”

*Golodner:* One of those networks is the Internet. One e-mail to many people can certainly spread a lot of information, good and bad.

*Horan:* Just anecdotally, last year the French government published the location of experimental biotech plots. One company had five experiments, three of which were destroyed. They put up signs at the remaining two—“This biotech crop is not for food, it is for medicine”—which were not touched. Also, Europeans use GM bacteria and yeasts to produce their wine and cheese, but never talk about that.

*Janet Tietyen (University of Kentucky, Lexington, KY):* I'm a registered dietitian and a consumer educator. I develop programs to help consumers learn more about where food comes from and about the role that biotechnology could play. This involves some basic science education and I think Laurie is right: consumers don't want to be educated, generally speaking. My question has to do with the segments in the core, the middle, and at the periphery. Do you have a sense yet whether those percentages are fairly stable? Is there anything that we can do, even if it is disguised education, that might help people move from the periphery to looking for more authentic information?

*Demeritt:* We have dietitians who visit stores and talk to consumers and conduct interviews for research purposes. Invariably, at the end of the interview the consumer will ask the dietitian or nutritionist to walk through the store to seek advice on what to purchase. When they are very involved, when they have a need for certain information, then they welcome being educated.

In terms of how to move them, opportunities exist at the retail level. If your product lowers blood cholesterol, maybe you should do cholesterol screenings. If it has to do with osteoporosis, bone-density screening may be provided in conjunction with the retailer. Such interactions at the retail level probably are the least costly and the most effective means of getting information to the consumer.

*Gene Sander (University of Arizona, Tucson, AZ):* Mr. Horn, you told a fascinating story regarding developing a new agricultural industry in Iowa. I am curious: what approach have you taken with the ag lenders? Are they willing to lend money to allow you to buy all the additional equipment you need to segregate your crops for example, or is that a problem for you?

*Horan:* If you have worked with lenders you know that they look at the bottom line. You must have a business plan and many producers don't want to, or cannot, provide that. At this early stage, our whole focus is on making sure it is done right, done safely and correctly with no mistakes. Any mistake, like Starlink™, with a pharmaceutical product would set us back 10 years, maybe 20 years. We absolutely cannot have that. So we have gone the extra step with dedicated equipment and dedicated storage and handling, although I'm not sure if this will be necessary in the future. For instance, John Deere is working on harvesters that have stainless steel components in contact with the grain so that proteins cannot become lodged; particles of protein can actually lodge in the pores of ordinary steel. They are building machines with on-board compressed air so that you can open a valve and blow everything out. The regulators that we work with in Washington at the Animal and Plant Health Inspection Service (APHIS) are satisfied if we clean everything in the field, because it is all biodegradable. Many possibilities exist to upgrade and modernize conventional machinery to make it adaptable to these new products.

*Audience member:* The consumer perception of functional food may need to be altered. In my definition the prune is a functional food because it is used for a certain function much of the time. Do we need to change this perception? And another question connected to that: how do we explain to the customer that immediate results may not be obtained from a functional food? To reduce cancer risk, a functional food may have to be taken for 10, 20, 25, or 30 years—will there be a market for that?

*Demeritt:* We saw this in the herbal-supplement industry. Consumers thought that they would see benefits in a very short period of time, which probably contributed to decreases in that market. Consumers are moving into areas where they do see benefits right away, such as specialty supplements and glucosamine. So, I don't have a magic answer. Consumers are accustomed to

taking over-the-counter products that provide immediate benefits, and it is hard to change that perception. They don't necessarily want to hear about long-term benefits unless they have a very particular health concern. Perhaps it is best not to assume that a product is going to be attractive to everyone with heart disease, for example. The market may be restricted to those people who are extraordinarily concerned. Manufacturers with perceptions of immediate multimillion-dollar markets are probably deceiving themselves.

*Horan:* That is a very perceptive question. Many preventative medications, preventative therapeutics, are becoming available because baby boomers who are approaching retirement have little patience for physical maladies and have disposable income that other generations have not had. Huge markets are developing for edibles that will help to avoid high blood pressure, arthritis, and other maladies now preventable, as Laurie said, through diet.

*Golodner:* The message to consumers has to be reinforced by health professionals: you should take this particular product and you are probably going to have to take it for many, many years.



PART IX  
CONFERENCE SYNTHESIS

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## Conference Synthesis

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### Moderator's Overview

JEFFREY KAHN

University of Minnesota  
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This is an interesting challenge: to provide an overview and capture themes of the past few days, some of the “golden threads.”

#### BIOTECHNOLOGY'S PROMISE

The promise of biotechnology is obviously a very important thread that ran through the entire meeting, and that term has multiple meanings. It's not just about promise, it's about the promises we make. It's about public perception—about how we as members of the public perceive what's being done in biotechnology, in particular in terms of food. It's about the distinction between food on one hand and nutrition on the other, which is something that I had not fully appreciated until this meeting. And it's about shared responsibility and, most importantly, trust. We've heard that stated so many times, but I think it's almost impossible to overstate its importance. Obviously, trust is a key factor.

We heard much about promising aspects of agricultural biotechnology and about functional foods, and how we should think about differences between putting supplements into food versus taking them as medicines as pills, and how that is a leap that technology will offer. We have to think differently about functional foods and nutraceuticals. Merging healthful eating with medicines in our foods is part of the promise of biotechnology—we learned a lot about food-based products that may have medicinal capacity. Biotechnology and agriculture offer new ways to make vaccines, more cheaply, more effectively, and with greater capacity, actually *growing* medicines, or “pharming.” The take-home message is that although agriculture and health—in particular, public health—have always been linked, a new relationship is evolving that requires interdisciplinary approaches and new thinking. Who should be involved and what should they be thinking about?

We have heard about the promise of biotechnology and we have to consider what promises we are making to the public, to producers, and to all others involved in this endeavor; are we promising too much? Whose responsibility is it to ensure that the promises of biotechnology are actually realized?

### **RESPONSIBILITIES SHARED**

We have shared responsibility for a number of things. First and foremost for safety. How do we decide what counts as safe in the context of foods for health? That is a very important question that, from the perception of the public, we have not yet answered. How do we measure safety? We saw calculations for what contamination might be expected from crops that cross-pollinate, but how do we measure that in a way that will provide a sense of what counts as safe? First of all what are the criteria, and how are they measured such that people will understand?—whoever is at the table will strongly influence what is acceptable in terms of the answers to these two points. And we heard that, just as real estate is about location, location, location, functional foods are all about process.

We must have a process that people can support, which goes back to those other points. Therefore, the chief issues are:

- who's involved,
- what are the criteria,
- how do we measure safety, and
- is the process credible?

We have shared responsibilities in terms of being accountable for how this progresses. Our promises must be realistic. Some people argue that we are over-promising, that we are hyping—which certainly is true in stem-cell research, for instance. If we are promising more than can ever be realized, it is for reasons that are not entirely objective—it results from attempts to obtain funding and to garner popular support, which raises political and moral issues and may result eventually in finger-pointing.

Responsibility runs all the way through the chain, including producers, industry, and regulators, which raises the question of whether the present structure is up to the task of assuring this shared responsibility. Can we say to concerned individuals—which should be all of us—that we have a process, a structure, in place that will help answer these questions? Can we point to who is accountable and why? We need to have a process in place to assess what's working, and what's not, and to decide what is to be done when we have answers to those questions. It's an evolving process.

### **PUBLIC PERCEPTIONS**

All of this, of course, is influenced very heavily by public perceptions. “Who is minding the store?” is a colloquial way of asking if someone is appraising issues

of safety and accountability. Who is doing that for the public-perception issue? We have heard a great deal about risks, not only to our own health and that of our children, but also to the environment. How do we assure that the public understands what those risks are? To answer that question, we have to go back. We can't tell people what the risks are until we know how to answer these questions. We are stuck way back there, before we can ever make it to here. How can people be told what the risks are when we haven't set criteria for risks?

Risk to health, of course, is a huge issue, and risk to children's health obviously falls under that as a subheading. Also people are worried about risks to the environment at large. People want reliable information from trusted sources, meaning credible and objective, or at least perceived as being objective. And, from the public perspective, where is that oversight coming from?

Communication is an important factor in public perception. We know that words matter: "biotechnology" is an acceptable term whereas "genetic engineering" and "genetically modified food" are less acceptable. Genetic engineering and nuclear power are equal in popular acceptability. We have to use different words or educate people differently. It was important to be told that "we are not talking about a plate of risk factors, we are talking about a plate of food." In other words, we have to be careful how we use terms. Risk factors apply to food in general, not genetically modified food in particular. A fundamentally important question is: who is responsible for getting such messages into people's homes, and into people's heads? The media have assumed that responsibility, but it is also the responsibility of the community as a whole.

Food and nutrition are not necessarily synonymous in people's minds. We all eat. One of the reasons that this issue resonates is because food is something we all buy, sometimes grow, and we all consume. When things apply universally they tend to get particular attention. In the same way, on the health side, people get up in arms about the role of genetic information because we all have genes and genetic testing may affect all of us.

There is a cultural aspect to food, and rituals and traditions are not to be trifled with. When we talk about modifying food we have to consider possible cultural implications. The take-home message here is, "Don't mess with my food."

We eat for health, not to cure sickness. We don't eat bananas because we feel ill. We eat them because we know they'll help keep us healthy. We should not think that people will eat for health at the expense of other considerations, like taste. My wife expressed it like this: "I go to Whole Foods, but if what I buy there doesn't taste good, I won't buy it again even if it is wholesome and organic." Obviously, these are the most important factors. It's got to taste good, and it has to be safe.

## TRUST AND ITS PRESERVATION

Clearly, a package of concepts is involved, that may be labeled under the heading of trust. And this is where we should focus. It's about trust at every level, most significantly trust on the part of the public, the consumers of genetically modified foods. If they don't trust it, they won't buy it. They want to be assured of effective oversight. We heard about authentication of food—an interesting concept and one that we've worked very hard at in terms of medicine. Maybe it's not always deserved, but when a medicine is on the market we feel that it is safe, having gone through an authentication process. As foods become more like medicines, will a similar authenticating process apply? To preserve trust, the authentication process will have to be transparent and public. And although it's always better to be open, it's not always achievable, especially at large institutions. When the newspaper reporter calls, our first reaction often is, "I don't want to talk to you," or we get defensive. But, generally speaking, this is not the best approach. It is better to be transparent, to be public about what we do—to communicate effectively with reliable information. When bad things happen, it's not appropriate to pass the buck. We must show that there's accountability for when things go well and when they go poorly. We can all point to events in our own lives, in our own institutions, and in the world at large that demonstrate that when trust is undermined it is extraordinarily difficult, sometimes impossible, to recapture it. The Starlink™ corn debacle is a good example. Popular brands of tacos are still viewed with suspicion—that's trust lost.

Producers need to trust that what they produce they can actually sell, otherwise they won't plant it. And there has to be a process by which they feel like what they are sowing is authenticated through oversight and regulatory processes. And producers must be trusted by the public so that the latter feels that their food is wholesome.

As already stated, trust in the regulatory and oversight processes is essential. If the US Department of Agriculture (USDA), the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA) have a consensus on oversight and regulation of foods for health, then it needs to be regulated accordingly. And gaps found in the system need to be fixed; again, Starlink™ is a good example. The public good—or the public goods, as they are sometimes plural—must be protected, the main considerations being human safety and environmental safety. The regulatory process is supposed to protect what we think is important, not as individuals necessarily, but as a collective. We also have to trust the professionals who work in these areas. Those in agriculture and health and nutrition and science all must be deemed trustworthy, and equally so, for this to work. The costs of mistrust are extraordinarily high. What is going on in Europe is an example of what we ought to hope to avoid.

## BENEFITS LOST?

If we fail to adopt new technologies, then we will forgo real benefits. That side of the coin is often not articulated clearly enough—it's not only about economic costs, its about loss of benefits. If we don't adopt technologies that could be beneficial to health, then people will get sick and, in certain cases, die needlessly. Where does the balance lie? Risks need to be considered against potential loss of benefits. If there is public mistrust, then research funding will be affected in the long term. We heard that National Institutes of Health (NIH) will double its budget over 5 years, but is the public sufficiently sophisticated as to understand that the Starlink™ problem, for example, is not NIH's responsibility? And if there's a problem with human-subject research, could that affect funding for agricultural biotechnology? Interdisciplinary collaboration will be essential—involving scientists, producers, policy makers, social scientists, and industry—not only nationally, but also internationally. And it must be integrated such that producers, for example, are not solely responsible for a particular aspect.

The most important aspect is transparency in what we do: tell what we know and what we don't know. We must communicate what the risks are, even though many people are unwilling to accept some risk in their lives. On the other hand, we drive our cars blithely in ways that are much more risky than the tiny amounts of allergens that might be in our corn products. We have to give people a real sense of what the risks and the benefits are and tell them what we don't know. In addition to transparency, there needs to be accountability: who is responsible and for what? If the professions and industry won't exercise accountability, then Congress will step in, and we don't want that to happen. They are not the right people to make rules about how these things are done. It is better to be proactive to protect the public good. And if we do that, if we keep our promises, then consumers will adopt this technology, and funders like the National Science Foundation will continue to invest money in the research, and, hopefully, the promise of biotechnology will overtake the hype.



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## Conference Synthesis

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### Q&A

JEFFREY KAHN

WITH

MICHAEL D. FERNANDEZ, IRWIN L. GOLDMAN,  
GREGORY JAFFE, AND CHARLES C. MUSCOPLAT

*Phyllis Johnson (USDA, Beltsville, MD):* I have a comment more than a question. An unstated assumption has underpinned much of our discussion: we know everything there is to know about people's nutritional requirements. In fact, we don't even know that for all nutrients for the population as a whole, much less in terms of understanding the genetic variability in what our individual requirements are, although the human genome and nutritional proteomics are going to lead us to a better understanding of that. The other thing that I think we have to be conscious of is that we also don't understand very well the interactions of nutrients in the diet. We don't consume nutrients in isolation, as a general rule. That's not how they come packaged in food. And our current approach in this first generation of functional foods—whether we create them through a food processing technique like fortification or through genetic enhancement—is based on our traditional reductionist approach of looking at one nutrient at a time. In fact, because we don't understand those interactions, if we drastically change the level of one nutrient in food, we may be creating interactions or eliminating interactions that we are not aware of.

*Charles C. Muscoplat (University of Minnesota, Minneapolis-St. Paul, MN):* When I think about looking at one nutrient at a time or whether or not we understand the human condition as far as nutrients go, I would reflect back on my presentation about drinking and heart disease. The questions are complicated. We have a new set of tools. When we look at people who are low converters for isozyme 3-alcohol dehydrogenase, they can benefit strongly

by having one to two drinks per day. Now we never thought of nutrients—if we look at wine as a nutrient—only for people with certain genotypes. Now if you are on the crop or horticulture side, you could breed varieties to produce micronutrients that are beneficial to people with a certain genotype. So, if we put those technologies on the table, we change the way we think about these things. And then perhaps in time we will study multiple nutrients simultaneously. Will aspirin become a nutrient to prevent heart disease or will Advil prevent Alzheimer's disease? Traditionally they are called medicines but taken life long will they be part of the required diet to treat or prevent chronic disease? I have a colleague at the University of Texas who believes that the future of treatment of diseases is prevention. So we could be at an era where all the definitions are changing as are the technologies. I think we wind up with stacked challenges. Not only do we have the ethical trust challenges that Jeff pointed out, but a whole set of new tools in the tool box that we are just experimenting with at the moment.

*Kahn:* There is a move to say, “Let us test your cytochromes and we will predict what are the best foods for you to eat or to avoid, or lifestyle changes to help you,” which speaks to the problem of over-promising. It's a complicated interaction between what's happening at a genetic level, and nutrition, lifestyle, and environment. All of those things are obviously going to play a role, and there is much that we don't understand. So I think its coming and Chuck is absolutely right—but the question is, what do we tell people in terms of what it means now?

*Audience Member:* When you have a specially prepared wine, and you ask a person of a specific genotype to use that wine for health, it sounds like wine is becoming a medicine. Can that particular wine be prescribed for that particular person?

*Muscoplat:* I would probably not want to suggest anything like that. I was mainly pointing out, as a provocative answer, that we have to think about things very differently. Research indicates that conjugated linoleic acids can delay the onset of type-2 diabetes. The best source of conjugated linoleic acids is milk from cows that are grazed on grass, as opposed to fed via silage. That causes a cascade of events back to the farm to a higher value for milk that contains conjugated linoleic acid. It would probably mean that the person who drinks that would have to have a family history of at risk for type-2 diabetes. Perhaps there is some weight control in the process. You can see the complexity escalate dramatically when it comes to making some of those decisions. Where does food become medicine, where does food become nutrition, and when does it taste good? Two hundred years ago, there was a point in time when that was probably true for vitamin C—if you didn't eat your limes, in the British Navy on

Admiral Nelson's ship, you got sick. Your commanding officer probably ordered you to eat those limes. If you recall, they had square plates on Admiral Nelson's ship, which is where "three square meals a day" comes from. So things don't always look the same, given the context of time. So the three square meals a day in the early 1800s looked a lot different from milk from grass-fed cows and the glass of red wine before you go to bed to deal with your diabetes and heart disease. So we just could be entering a new level of understanding, a new level of required dialogue among the players.

*Jerry Cohen (University of Minnesota, Minneapolis-St. Paul, MN):* The basic premise of all of this is that we have a fixed diet of a known amount. I'm reminded of the story of a scientist years ago in my lab from Israel where they had figured out that persimmons would ripen without getting soft with ethylene. He was in charge of overseeing importation while he was in my lab so he would occasionally sneak away on the weekends. One weekend he got an urgent call that he had to fly to New York because a woman had intestinal blockage from having eaten Israeli persimmons treated with ethylene. She had eaten forty-seven at one sitting. It sounds humorous, but it wasn't. One of the things I would like you to consider, is that in deciding what's good for people we have to consider extremes of behavior as well as ideal behavior. This is certainly true when you seek to modify people's intake of food.

*Muscoplat:* That reminds me of the time when I was a young assistant professor in the College of Veterinary Medicine, someone brought a cat in, and the complaint was that the cat would not eat. It was gigantic. We asked the owner what he fed the cat: a whole chicken every day. There are extremes.

*Anthony Shelton (Cornell University, Ithaca, NY):* Steve Pueppke made a good point when he said that much of this is not a science-technology issue, but rather a social-science issue. I guess I would like to reframe that a little bit, although I agree with it. It's really a quality-of-life issue. When I hear the farmer say that agbiotech allows him to spend time with his family, I think that is an important thing that farmers have not been able to do. When I hear the health professionals ask, "Will it be healthful and prevent diseases?"—that's a quality-of-life issue. The consumer asks will it taste good, will it make me younger, will it make me thinner, make me look like I just came from Lake Wobegone? And the social scientist, Jeffrey Kahn said that quality of life involves a democratic process where people feel involved in the decision-making. I guess I think that that is a quality-of-life issue. As an ag scientist who works in biotechnology, I think of it in terms of quality-of-life for the environment too: will it enhance the environment? Can this science and technology improve the quality of life for each of us in our different forms, as a farmer, as a healthcare person, and as an agricultural scientist?

*Kahn*: If it all pulls in one direction, I don't think we have much to argue about. But the difficulty is when *you* think it is improving the quality of life from your particular perspective while others say it is degrading theirs. I'm an environmentalist, therefore what you think is an improvement in quality I see as degradation. Although we should not view this through only one lens, I think it's certainly a beneficial lens through which to view it. You might step back and say: from a public-health perspective, really all that matters is making sure that people have clean water to drink and that their sewage goes away from where they live—that's the big stuff, quality of life, and everything else is around the fringe and isn't saving lives. We attended to the really big stuff a hundred years ago, and all the rest is gravy. I don't share that view, but some might stand back from that perspective and say, we are really working on quality of life now. There's life saving, there is health improvement, there is quality of life improvement, but I don't think they are all the same thing.

*Gary Gardner (University of Minnesota, Minneapolis-St. Paul, MN)*: One issue that has not been discussed very much has been the issue of dietary supplements. It seems to me if there is any topic where trust could be destroyed it's the potential for unethical behavior of people in the dietary supplement industry. I would especially like Mr. Jaffe to comment on the regulatory issues here, and what strategies we should use to bring science to bear in that industry.

*Gregory Jaffe (Center for Science in the Public Interest, Washington, DC)*: I agree with you that dietary supplements are a problem, and that they aren't regulated in the way we think they should be. I'm not an expert on dietary-supplement issues, so I won't comment on specifics of how they should be regulated. There is a much greater potential for fraud, misrepresentation, and health concerns from some of the dietary supplements that are out there. We are pushing for stronger regulation of those, but I can't give you details.

*Muscoplat*: [audio lost]...legislation that created them. I saw specifically that it was intent on not regulate them. There are two or three requirements. One is that there is some nominal safety so long as the product is natural. We all know, as scientists, that there are many toxic things in the world that are natural. Mycotoxins are natural. There is nominal safety, usually 30 days of safety when we know that most people who take them, actually take them for longer than 30 days. So long as you are not making a claim, you can sell it as a dietary supplement. But many of the supplements are trying to make claims through media, other than what is on the bottle or in the store. The third issue is that, to my knowledge, there aren't any products sold as over-the-counter medications that can be taken more than 2 weeks without a doctor's advice. If you look at your antihistamine or Aleve® or Advil®, the label says that if symptoms persist more than 2 weeks please see your doctor. Well, many of the symptoms or

conditions that people take supplements for are present for longer than 2 weeks. So we have several cascading issues of what I think are conflicting philosophies. One is safety—it's okay to sell it so long as you don't say what it does, in the same medium as where the purchase is made. There is no restriction on time. So it's almost the antithesis of what we would imagine. Now many of us think that dietary supplements have some benefits, or could have, theoretically, if they were proven, if they were labeled and if they were taken according to some direction. There are also issues about assuring potency. To my knowledge, all pharmaceuticals in over-the-counter medications have a required shelf life: at the end of 4 years a minimum standard must apply. I don't believe that applies similarly for dietary supplements, largely because they are complex materials.

*Irwin Goldman (University of Wisconsin, Madison, WI):* I would say, too, in response to Gary, and to pick up what Chuck just said, there is confusion and that leads to misunderstanding and undermines trust. When people see a laxative on drugstore shelf, few have the sophistication to know whether or not it has gone through FDA, or whether it's a dietary supplement. And that is the problem. You pointed at all the regulatory differences, but I don't think people know which is which. That is problematic because they don't treat them as distinct entities.

*Theodore Labuza (University of Minnesota, Minneapolis-St. Paul, MN):* Jeff, in your slides, you talked about authenticating food. In fact, that system is in place. For a food to be put into the market place it either has to be generally regarded as safe (GRAS), which has a specific procedure for approval or, if it's a food additive, it has to go through toxicological testing, which in fact is more rigorous than for a drug. For drugs, we allow some risks. The Dietary Supplement Act, which Gary brought up and Chuck commented on, in fact is a system that has destroyed confidence in the Food and Drug Administration, which is bashed by the media. Yet, in fact, it was Congress who passed the law and tied the FDA's hands. One good example of what Chuck was talking about, is in 1997 the FDA proposed a regulation to require manufacturers to put a warning label to consume it for only 2 weeks at a certain ingredient level. In fact that regulation has never been finalized because Congress won't let them do it. FDA knows that if they try, Senator Hatch will come down on them very hard. The system is out of whack.

*Kahn:* We do have that authentication, but the system is not working right now with dietary supplements or the whole concept of functional foods. If it's a functional in terms of health then it has to have a health claim. Barbara Schneeman has said that a number of times at this conference. And when people are looking at functional foods, it's much narrower than the typical health claims that we have on most products today. That is where we have to

get some trust in the system. Somebody in the regulatory system must educate the public and researchers. If we don't understand how new functional foods fit into the regulatory system, we may fail from the outset.

*Muscoplat:* I would guess that the large food-company representatives in the audience would say that their most valuable asset is their brand name, and they will do nothing that will put at risk the public trust in the brand name. When a product is changed, it is made more beneficial, and a lot of work goes into that to ensure the preservation of trust. The “improved” product has to actually deliver on the promise. It has to be approved and be validated and authenticated, all the way back through the system. On the dietary-supplement side, the leading brands of the vitamins now—I heard this last night on CNN—are many of the private-label brands and not the big brands. If brands have no value then other brands take them away or “no-brand name” takes them away.

*Michael Fernandez (Pew Initiative on Food and Biotechnology, Washington, DC):* We have a system to deal with foods, to deal with drugs, and to deal with other types of products. But, when you blend those categories there are going to be challenges to that system. Issues about transparency and public confidence in that system are going to be very important. Where there are potential cracks or gaps in the system, then we need to do everything that we can to make sure that we fill those in. Because, as has been said, once public trust is lost it is very difficult to regain it.

*Jaffe:* I would agree that authentication is extremely important. I question whether we really have that with the current food-additive and GRAS process. For biotech foods there may be some authentication by the companies, but not necessarily by the FDA. With authentication comes transparency, with participation of the public and of an independent third party with no stake in the outcome. So, I question whether there really is authentication of foods in general, of biotech foods in particular, or of the other new foods that are coming on the market—mycoproteins, *etc.*—that may cause problems for people.

*Audience member:* To what extent should we allow the regulatory process that we endorse to be influenced by the extreme cases? Should we decide how these things should be regulated on the basis of the fact that every now and then people do stupid things and end up hurting themselves? This ties into how we should properly respond to, for instance, potentials of allergenicity, which affect only a minor portion of the public. To what extent should we as a whole share a burden in making sure that these people are protected as opposed to saying, well you have to protect yourself?

*Jaffe:* If you look at examples that exist already in regulatory systems, for example with pesticides, we don't examine the effects of the average level of pesticide eaten by the average person. We look at sensitive individuals—a child or an elderly person—and we then add a safety factor, 50-fold or 100-fold, partially because nothing is 100% safe and we are not expecting to prove safety to an absolute number. I would advocate that we do need to look at that. Maybe we don't look at the extreme of someone eating forty-seven persimmons, but we do need to take into account the range of population. It would be wrong to add risk for a small, but not miniscule, portion of the population.

*Muscoplat:* Recently an article in the *New England Journal of Medicine* focused on over-consumption of certain foods. They had pictures of individuals who ate 100 to 200 carrots per day and their skin color was exactly the same as that of a carrot. It is called carotenemia. Now how do you plan for something like that? Or the people who are elderly who have mild renal disease and like eating bananas and they elevate their serum potassium and become hyperkalemic. Or I think of the few tenths of a percent of the population who suffer from hemochromatosis and shouldn't eat iron. Dealing with the extremes is difficult. I would guess that most men over age 50 should not consume vitamins with iron because a high serum iron level in people my age and older means that they are at risk of a more-damaging heart attack. So, as we learn more, the issues get more complicated rather than less so, and I'm not sure how to deal with that.

*Goldman:* I don't know what the article said, but it has been my understanding that hypercarotenemia by itself has no inherent toxicity, even though the skin definitely changes color. What I found interesting about this was the debate about biotech and particularly golden rice. There is this idea that we can get vitamin A from a biotech product like rice, and there was a blurring on the part of the general public on vitamin-A nutrition and toxicity, which is very real, vs. carotenoid-based nutrition, which is not toxic. So just as a general comment: beta-carotene from a carrot, or from another natural product, is converted into vitamin A in the body by cleaving the carotenoid molecule, which is very safe even apparently at very, very high levels where your skin turns orange. Vitamin A as a supplement or as a vitamin can be very, very toxic and so there is an interesting interplay in the way people understand these things.

*Muscoplat:* I think the only known toxic source of vitamin A is polar bear liver.

*Goldman:* But vitamins, and particularly for pregnant women, is an issue that has been raised with respect to vitamin supplementation where you are taking it as vitamin A.

*Kara Slaughter (University of Minnesota, Minneapolis-St. Paul, MN):* I'm a student and have learned a lot from this conference. One of the messages that has had a big impact on me is the idea that consumers are not monolithic. When you talk about consumers you have to understand that they are as diverse—perhaps even more so—as opinions in the scientific community. Is it true that as consumers become more educated on the intricacies of what is genetic modification, what is biotech, do they become more receptive to those foods? My contention is that being well educated does not always mean being more receptive. Also, what is your opinion on the impact that these technologies will have on rural development?

*Jaffe:* Regarding consumers and education—consumers don't know a lot about genetic engineering and biotech foods. The education level is very low as we have heard in the last couple days, and that can only improve. When it does improve, you will find some people who will embrace it. As you said, consumers are not of one type, so you will also find that some will still question it. But I think everyone will feel that the process has become more transparent and more open and they will feel more comfortable with having those foods on the shelf even if they do not choose them for themselves for whatever reason—they think it is not helpful for the environment and so forth—but the education process will be beneficial overall.

*Kahn:* I'm not sure that it is education so much as it is getting used to having it around. We have a lot of experience on the medical side with this, what people technically term the “yuck” factor. Heart transplant is a good example: “What, do you mean we're going to take a beating heart out of one person's chest and put it into another person?” It was viewed very skeptically at the outset, but now we can't find enough hearts to transplant into the people who want them. There are people who study the way that technologies are viewed and adopted and it doesn't track necessarily with education. It's not the same as food, but there are useful parallels. It takes time for a new technology to find acceptance.

*Goldman:* To comment on your first question again: to some extent agriculture is a tremendous disruption of our environment, but it's one of the most important such disruptions that we have been able to create. Over time, as technology has crept into agriculture, there has been resistance and then there has been, as Jeff just mentioned, acceptance. But we see people drawing lines in the sand—even after education—about adopting certain technologies. I'm not convinced that with the information being available and even well understood, people won't still draw their lines in the sand and say, “Here's where I'm willing to accept it and here's where I'm not.” Food is a very sensitive issue for a whole variety of reasons that we have discussed. So I agree that the information has to be out there, but I think we will see people more willing to say no.

*Muscoplat:* Rural development is a complex topic and many forces have operated on the rural American scene for the last 150 years. Some of these technologies and potentials will have some effect on some individuals. To contend that it will have a major reversal on rural-development trends would be misleading. Other, vastly greater forces are at work: the recent Farm Bill, the aging population. Successful rural development will have many sources of activity, this being but one—it will benefit some, but, my fear is, not many.

*Audience member:* There is a lot of information on labels and on packages. There is a lot of food and nutrition information you can get from magazines, but what would be the best, most trustworthy, easily accessible information source on nutrition and diet that you would recommend? I'd like to go to a Website and type in what I've eaten over the past day or so and find out whether I've gotten too much of something or not enough of something and I might mend my ways.

*Kahn:* Does anybody on the panel have any thoughts? Otherwise maybe we will refer to our experts in the audience.

*Pam Vanzyl-York (Minnesota Department of Health, St. Paul, MN):* I would like to respond. Over the last year we have been improving our Website to provide credible information and to lead consumers to other similar sources. A variety of credible sources of information exist through universities, through many of the extension sites, through many of the other public-health outlets, and through other federal agencies. But consumers need guidance as to how to get there and how to evaluate that information. Another point that I want to make: I have heard numerous times over the last couple of days that changing behavior doesn't work and educating consumers doesn't work, particularly you, Dr. Khan, today. In fact, we have put virtually no resources into consumer education and behavior-change programs in this country. Coca-Cola spends more on one brand than the entire budget for the national five-a-day program. What do you think we are going to do about some of these resource issues in the future, and how are the actions that you outlined going to come about?

*Kahn:* You are right—we need to ask that question. Resources are always strapped, obviously. A problem of silence, I guess. You come from a department of health. How do people like you talk to people who come from industry and academia? How do we get people in the same room to have this conversation? That is part of the goal of the inter-disciplinary piece. But, how do you push that so that the right people are around the table to ask that question—not so that you look at each other and shrug, but where there are checkbooks to actually make things happen? I am hopeful that there are ways to do that.

*Fernandez:* I want to make a shameless plug for my organization's website, which actually does not provide the nutrition information that you are looking for, but which we hope is a reliable source of information on agricultural biotechnology: [www.pewagbiotech.org](http://www.pewagbiotech.org).

PART X

SPOTLIGHT ON MINNESOTA:  
HIGHLIGHTING INNOVATION IN AGRICULTURE,  
FOOD AND MEDICINE

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## ***A Two-Pronged Approach: Food Safety and Nutritional Quality***

**KATI FRITZ-JUNG**  
*The Schwan Food Company*  
Marshall, MN

Schwan's is a \$3.3 billion privately owned business that focuses on frozen food sold via home delivery, retail, and food service. We do not purposely market our products as nutraceutical or functional foods because we recognize that, even if consumers might know what is good for them, that knowledge is not necessarily reflected in their purchases or eating behavior. That is not to say that Schwan's is not interested in providing consumers with healthy foods, because in fact, we are. We take a two-pronged approach in delivering healthy foods to consumers. The first, food safety, is obvious. The second is incorporating enhanced nutrition into the products that consumers want to eat.

### **NUTRITIONALLY ENHANCED PRODUCTS**

Nutritionally enhanced products must meet two requirements. They must be foods that consumers want to eat and be products they feel safe in eating. Enhanced nutrition is an added benefit to our products. It is not a primary driver to sell the food, but secondary to what motivates the consumer to make the purchase. We know that we cannot change the consumer's eating behavior significantly. All of us find it difficult at best to modify our eating habits. It is even more difficult to convince others to change their eating behavior. Therefore, our approach is to explore opportunities to enhance the nutritional quality (or characteristics) of our products without affecting consumer demand.

Thus, when we design and develop a new product, we consider three primary criteria:

- Safety
- Consumer Acceptance
- Nutritional Enhancement

For Schwan's, as well as the food industry as a whole, safety is an imperative. There is no other option. Food related illness continues to be a serious problem in the United States. Despite the fact that we know more about food-borne pathogens today, and despite the fact that we have developed multiple technologies to address the issue, the problem has not abated. It has not leveled off, but continues to increase.

Consumer acceptance results from the right combination of taste, value, and convenience. If we fail to meet these criteria, consumers will not buy our products and we cannot help them become healthier. We understand that expressed purchase intent and consumption behavior are not always consistent with each other. Therefore, we listen less to what consumers tell us they want and pay closer attention to what they do. In that process, we have learned that taste is the most important criterion of repeat purchase. Rarely will consumers continue to purchase a product that they do not enjoy eating.

A product's value relates to the price that one is willing to pay for its perceived convenience and taste. For the most part, consumers are going to eat what they are going to eat, regardless of how good or bad the food is for them.

Nutritional enhancement is not an imperative; however, we use it not only to our advantage but also to that of the consumer. We view nutritional content as an added benefit, keeping in mind the three primary drivers for purchase and consumption (taste, value and convenience). This approach recognizes that eating behavior is not easily changed and that nutritional messages can be confusing. Consumers are bombarded with nutritional information from a variety of sources.

Our experience with food supplements indicates that consumers look for rapid effects. If they do not experience beneficial results in a short time, they lose interest. In addition, benefit from a nutraceutical or functional food requires consumption compliance; the product must be consumed on a regular basis (most often, daily) and at a sufficient level. Our approach is to provide consumers with their favorite foods, but to make them better for them than the alternatives in the marketplace. We focus on nutritional needs that are easily understood by consumers and are related to endemic problems within the United States. Consequently, we focus our efforts on obesity, which is related to type-2 diabetes and to heart disease.

#### **FOOD SAFETY—ELECTRON-BEAM PASTEURIZATION**

In 1999, sales of raw beef patties from our home delivery trucks were booming. Schwan's did not manufacture the patties, and, to meet demand, needed to extend the supply base to multiple suppliers. Because managing multiple suppliers of a high safety-risk food product was unacceptable, we were faced with the decision of either getting out of the business of selling raw ground beef

altogether, or finding an acceptable means to reduce the risk. To that end, we evaluated various technologies and settled on electron-beam pasteurization, an effective means of reducing harmful pathogens that is approved and endorsed by a wide variety of public-health organizations and has a history of beneficial use with other food products. In addition, it has benefits for manufacturing and is environmentally friendly.

At that time, there was little information on how consumers would accept electron-beam technology. We recognized that in home delivery we have a unique business model, *i.e.* regular one-to-one contact with our consumers through our route drivers. Part of what makes our home-delivery business successful is the trust a consumer develops in the route driver. Therefore, another risk was the erosion of that trust if we were to proceed without careful consideration of the effect on the element of trust.

We took the approach of complete and proactive disclosure, and were prepared to pull the product off the market if our consumers indicated dislike of the new technology. Specifically, we labeled our product, not only because it is a requirement, and made it clearly evident on the package. The route drivers explained what we had done and why, and were prepared to answer questions.

We moved quickly and were the first company to launch electron-beam irradiated frozen raw ground beef products nationally soon after the technology was approved for this type of food. Much to our pleasant surprise, consumer acceptance was huge, a response we attribute to our direct and honest approach, and the earned trust of our home-service route consumers.

#### **NUTRITIONALLY ENHANCED PRODUCTS:**

##### **A MORE HEALTHFUL PIZZA FOR SCHOOLS**

Our food-service business includes provision of school food, products for which specific nutritional requirements apply. There are clear and rigorous standards, which must be met by companies that make products for school breakfasts and lunches. Because we take our school food-service seriously, our goal is to exceed requirements. We were the first company to go into school food-service with pizza 27 years ago and have 70% of the pizza volume. Because pizza is always rated as children's favorite food, it is featured more frequently than any other menu item. Consequently, we have good reason to believe that we can improve school food nutrition in general because we have a huge presence in this market.

One of the unusual luxuries of working for a privately owned business is that many decisions are based not only on classic financial considerations but also on company values. This portion of our business is very competitive and the profit margins are very lean. But the primary reason that we compete, the reason that we spend significant amounts of time studying our products and enhancing their nutritional value, is because of the commitment that the owner Alfred Schwan has made to ensuring that children eat nutritious food at school.

One of our most recent challenges, because we have such dominance in that area, was to take our pizza line and increase its nutritional component. Many modifications could contribute to a “healthier” pizza. However, because of the increasing problem of childhood obesity and its health-related issues, we decided to focus on improving the nutritional profile as it pertains to obesity. Although our existing pizza was lean in the first place, we decided to make it more so, with less total fat, less saturated fat, and fewer calories, while maintaining acceptability by the children. We certainly did not want to alienate them and if we gave them a lesser-quality pizza, they would eat less of it and we would miss our goal. An additional requirement was to maintain the standard identity of pizza, while functioning within the constraints of the nutritional profiles required by schools. Consequently, we took a holistic approach and recreated the product from scratch.

Because of their high nutritional value, soy-based ingredients were included in the crust and other components of the pizza. We also reformulated the pepperoni and cheeses to make them more healthful, and enhanced the sauce to meet specific taste requirements to ensure that kids would like it. With this holistic approach we reached our goal, creating a pizza that is 20% lower in fat, has 10% less saturated fat, fewer calories and less sodium, and is higher in fiber. To boot, we found that the kids actually preferred the new pizza to the old one. It was a great success. The beauty of this is that the children don’t even know that their pizza is healthier, which is probably a good thing.

This has been marketed towards the school not to the pupils, who are happy that their pizza tastes better. This has been such a success for Schwan’s that we have taken the same approach with our Smart™ Pizza, and we are working on a broader platform of Smart™ products for schools. Again, we are focusing on foods that children like, thereby making them healthier in the long term.

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## ***Innovations for Safe Egg Products***

**HERSHELL BALL, JR.**

*Michael Foods, Inc.  
Gaylord, MN*

Michael Foods was established in Minneapolis in 1987 and has grown steadily through internal development and acquisitions. There are four operating companies: Kohler Mix (dairy products), Northern Star (refrigerated prepared potato products), Crystal Farms (refrigerated retail foods), and Michael Foods Egg Products Company. The latter, the largest of the four, is a world leader as a full-line value-added egg-products company. There are five egg-processing plants in the United States (New Jersey, Pennsylvania, Iowa, Nebraska, and Minnesota) and two in Canada (Manitoba and Ontario). Our company operates farms and contracts egg production from approximately 14 million hens providing about 30% of raw eggs used for processing, with the focus primarily on value-added products.

In the past, discussing eggs and egg products in a meeting on foods for health would have seemed unlikely in view of negative opinion of eggs as food, because of cholesterol content and associations with food poisoning by *Salmonella enteritidis* (S.e.). However, opinion on cholesterol is changing; it is declining as a major issue for consumers. And public discussion seems to be moderating in terms of “bad food” vs. “good food” viewpoints.

Egg-associated S.e.—an ongoing concern—resulted in an action plan prepared by the President’s Council on Food Safety (PCFS, 1999). I will discuss background information on the action plan and approaches used by Michael Foods to provide safe egg products.

### **BACKGROUND**

Over the period 1976 to 1994, the Centers for Disease Control noted an eight-fold increase in isolations of S.e. from humans. In the mid-1980s, a large portion of human illness from S.e. was linked to the consumption of contaminated shell eggs. Unexpectedly, the illnesses appeared to be related to sound-shell, clean, grade AA eggs. Studies in the United States and Europe then demonstrated ovarian transmission—eggs were contaminated by S.e.-infected hens during formation.

Current understanding indicates that trans-ovarian contamination occurs in one egg in every 20,000, with between twenty and a hundred S.e. cells per egg, at time of lay (USDA, 1998). Poor shell-egg handling practices and poor food-preparation practices are necessary for development of illness due to S.e.-infected eggs. As a point of perspective, the *per-capita* consumption is approximately 234 eggs per year in the United States, about 200 of which are consumed either at home or at food-service establishments provided with shell eggs. The other thirty-four eggs are consumed as processed products provided by companies such as Michael Foods Egg Products.

In 1996, the United States Department of Agriculture (USDA) and the Food and Drug Administration (FDA) began a comprehensive risk assessment (USDA, 1998). It is one of the first large-scale risk-assessments studies conducted on a basic food by government agencies. They developed a quantitative risk-assessment model that is being used to shape policy decisions and develop regulations. Following the risk assessment, the President's Council on Food Safety developed an aggressive egg-safety program (PCFS, 1999). The action plan covers all aspects of production and distribution, from farm to table, to reduce the risk of S.e. contamination of eggs. The overarching goal is to eliminate S.e. illnesses associated with the consumption of eggs by 2010, and the interim goal is a 50% reduction by 2005. It is likely that these goals will be met.

Two strategic choices were outlined (Table 1). One of them, being on-farm testing with diversion of eggs from infected flocks for use in pasteurized egg products. The second strategy, calls for the application of a lethal kill treatment achieved by pasteurization at the packer or processor level.

**TABLE I. STRATEGIES FROM ACTION PLAN TO ELIMINATE S.E. ILLNESSES DUE TO EGGS.**

Strategy	Description
I	S.e. testing and egg-diversion system at the farm level using a consistent, nationwide S.e. risk-reduction program
II	The application of a lethal treatment or S.e. "kill step" (pasteurization) at the packer/processor level

An important point about egg-associated S.e. illness is that all of the documented cases have been associated with the consumption of shell eggs. There has been no S.e. or salmonella-associated illness due to consumption of pasteurized or precooked egg products. Egg-pasteurization standards (USDA, 1969) have been the basis for safe egg products for the past 33 years.

## INNOVATIONS FOR SAFE EGG PRODUCTS

As noted above, egg-associated S.e. illness results from poor handling and preparation of internally contaminated shell eggs. Recent innovations in processing now provide the basis for safe egg products:

- the development of a pasteurization process for shell eggs,
- the development of in-line breaking of eggs to produce liquid egg for processing, and
- the development and production of high-quality precooked egg entrees.

Figure 1 presents an overview of the time-temperature relationship that provides a one-log reduction in the numbers of S.e. that may be present in the yolk of an intact shell egg. The time in minutes to achieve a 90% reduction is the D-value. As temperature increases, the D-value decreases.

It is often asked, “How is it possible to pasteurize shell eggs without cooking them?” The answer is that it is a controlled heating process that balances process efficiency and quality of the egg, while achieving a 5-log-reduction in salmonella as required by the FDA standard. There may be a small amount of opacity in the white of the pasteurized shell egg—influenced by the pasteurization temperature and chemical characteristics of the egg, such as the initial pH of the albumin. A range of cloudiness in the egg white is acceptable to most retail and food-service customers. Pasteurized shell eggs function as non-pasteurized eggs, except that it takes a little more time to whip the whites to make meringue

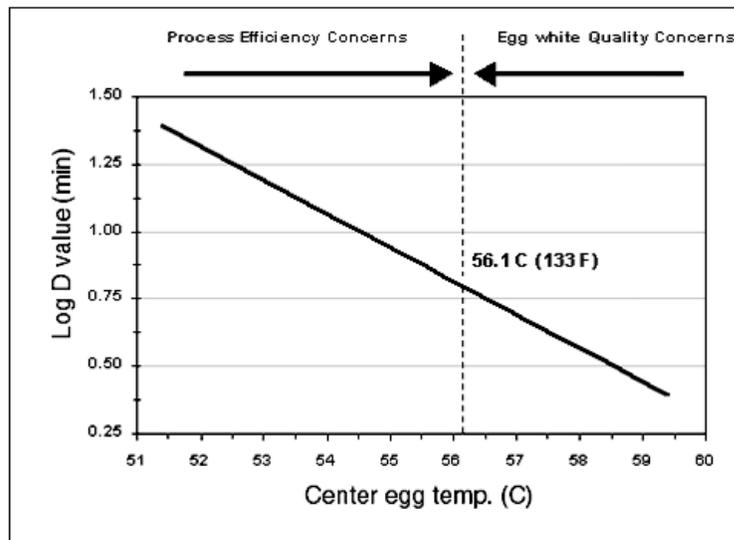


Figure 1. Decimal reduction time curve for *Salmonella* spp. within intact eggs.

The second innovation is the adoption of in-line breaking to produce liquid egg for further processing. In-line breaking is the close coupling of production of shell eggs with conversion to liquid egg. This operation is usually associated with large farms from which eggs are conveyed directly to breaking machines. The shells are washed before being presented to the breaking process for content removal, allowing conversion to a chilled liquid within hours of laying. Table 2 presents a summary of microbiological data collected from in-line breaking and off-line breaking over a year. All of the egg samples were from USDA-inspected plants and were considered wholesome. The results clearly show that in-line operations are capable of producing raw egg with significantly lower total microbiological content (<5,000 cfu/g compared to <100,000 cfu/g). It would be expected that pathogen and non-pathogen contents would both be reduced, enhancing the effectiveness of pasteurization. Cotterill (1995) anticipated the advantages of in-line breaking and attributed them to breaking stock with lower initial bacterial counts and more active natural bacterial inhibitors because of the “freshness” of the eggs.

**TABLE 2. AVERAGE AEROBIC PLATE COUNT BY MONTH FOR 2,328 TANKER LOADS OF LIQUID EGG FROM IN-LINE BREAKING AND 325 TANKER LOADS FROM OFF-LINE BREAKING.**

Month	In-line <sup>a</sup>	Off-line <sup>b</sup>
	Log cfu/g	
January	3.17	4.95
February	3.30	5.09
March	3.34	5.17
April	3.23	5.54
May	3.61	5.39
June	3.53	6.17
July	3.55	6.24
August	3.59	5.11
September	3.53	5.69
October	3.18	5.09
November	3.18	5.69
December	3.20	5.69

<sup>a</sup>From three in-line breakers in two mid-western states.

<sup>b</sup>From eleven different off-line breakers located in seven mid-western states.

Precooked egg entrees are a growing area of innovation for safe eggs. Prepared entrees—scrambled eggs, omelets, fried/poached eggs, and scrambled egg patties—are being successfully used as safe-egg products by quick-service restaurants, convenience stores, and catering. Their quality is excellent. Advances in ingredient and processing technology have allowed development and production of entrees that have widespread acceptance. The replacement of shell eggs with precooked entrees provides food-service operators with an enhanced margin of safety while reducing the amount of skilled labor required to prepare meals.

#### SUMMARY

Pasteurized egg products have an excellent safety history. Shell eggs can be pasteurized to provide a safe alternative for foods made with raw or minimally cooked eggs. Closely coupling egg production and breaking results in very high-quality raw material for processing. Pre-cooked egg entrees provide safe high-quality alternatives to using shell eggs. Strategy II of the President's Council for Food Safety—lethal treatment—is enhanced by innovations in safe-egg products.

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## ***The Food Industry: Promoting Public Health***

SUSAN CROCKETT

*Bell Institute of Health and Nutrition*

*General Mills, Inc.*

*Golden Valley, MN*

The Bell Institute, formed in 1998, symbolizes General Mills' vision for health and nutrition—of creating a world in which healthy eating is easy. The Bell Institute is an interdisciplinary group of scientists committed to providing healthy food solutions without taste or convenience compromised. Disciplines represented include mammalian molecular biology, food-process engineering, food-product development, physical chemistry, nutrition science, dietetics, law, food science, epidemiology, and chemistry.

The food industry is key in the integration of agriculture and medicine, through its role in producing and marketing healthy foods and its role in enhancing the public health. The role of the food industry in public health goes back at least 50 years to the Food and Nutrition Board's national policy for enrichment of flour. Today the industry plays a significant role in funding health and nutritional research, in educating health professionals and consumers, and in forming nutrition policy.

### **GENERAL MILLS AND PUBLIC HEALTH**

The Bell Institute and General Mills are very involved in promoting public health through education both directly and indirectly. Direct communication is via messages on consumer packages, through trade promotion in grocery stores and other retail outlets, in advertising and in public relations. Indirect communication focuses on policymakers and implementers, government agencies, health professionals and educators, and research scientists.

Since its integration with Pillsbury in November of 2001, General Mills has been the number-one purchaser of oats and wheat and the biggest supplier of whole-grain cereals in the United States. Because of this significant stake in whole grain, General Mills has funded between \$2 million and \$3 million dollars in epidemiology and clinical research on the association of whole grains

with prevention of heart disease, cancer, and diabetes. Results of collaborative research with the United States Department of Agriculture on dietary intake showed that only 8% of Americans consume three servings of whole grains per day, which is the recommended intake level.

In 1998, General Mills initiated the first authoritative health claim that was authorized in the new Food and Drug Administration Modernization Act. That claim allowed General Mills and other manufacturers to label food products saying, “In the context of a low fat diet, whole grain foods like (fill in the blank), reduced the risk of heart disease and some cancers.” We selected Cheerios as the initial product to display that wording.

The benefits of whole grains were directly communicated to consumers by placing the health claim in banners on our products, in advertising, and through public relations, which reached 20 million consumers via TV, radio, and print. Indirect communication focused on educating health professionals. When the Dietary Guidelines for Americans mentioned whole grains explicitly for the first time in 2000, we produced a kit to teach health professionals about the underlying science.

The Bell Institute has a speaker bureau available to health professional groups, usually at state meetings around the nation. Speakers are provided on requested topics to health-professional groups, with speaker fees and expenses paid, so that those health professionals can learn about public-health initiatives.

## CALCIUM

In 1997, General Mills started fortifying children’s cereals with 10% DV of calcium. This decision was based on assessment of scientific research on dietary intake. Cereal is a logical vehicle to deliver calcium because it is so widely consumed by American children, and because it can be supplied in a bio-available form. Market research found that consumers widely supported calcium fortification. Follow-up research indicates that they continue to appreciate this addition.

Prior to this fortification, we determined that significant numbers of children did not have adequate intake levels of calcium. Research showed that mothers understand that calcium is significant for themselves, but they have low awareness of calcium’s importance during childhood bone-forming years. They think that their children get enough calcium, when, in reality, significant numbers do not. Mothers don’t know much about their children’s calcium needs, nor how to achieve adequate intakes.

We offered education about calcium on our cereal boxes and placed a “button” there showing that extra calcium is supplied. Also, we published advertisements promoting the fortification. Because it takes at least six messages from various sources in order to penetrate consumers’ awareness, advertisements and cereal-box messages have become important in the overall scheme of nutrition education.

General Mills also partnered with the National Osteoporosis Association to create educational materials that were distributed to health professionals on cereals as a source of calcium in the diet. The brochure discussed the importance of peak bone mass, regular physical activity, calcium during pregnancy, recommended intake levels, and food sources of calcium.

### FOLIC ACID

Folic acid has been mentioned by several other speakers. Our enrichment policy has been a successful public-health initiative. Each year about 2,500 babies are born with *spina bifida* or other forms of neural tube defects. Since folic-acid enrichment was initiated, there has been a 19% reduction in neural tube defects. Recently, General Mills partnered with the March of Dimes to produce teaching material on folic acid for use by WIC professionals in patient education. The handout for participants and the brochure for professionals give a brief background of the importance of folic acid and provides a teaching outline via facilitated group discussion. This is a technique that has been shown to promote behavior change. It's not perfect, but it absolutely is advantageous in encouraging people to change behavior over the traditional method of telling people what they should do.

### CHOLESTEROL

The last example of public-health communication is a kit on the recently revised national cholesterol-education program and American Heart Association dietary guidelines. The Bell Institute worked with two health professional organizations, the Preventive Cardiology Nurses Association and the American Association of Cardiovascular Pulmonary Rehabilitation. We found that they knew little about nutrition and that they lacked teaching tools. We addressed these needs by developing the kit that has now been distributed to every member of these organizations. A Web site was developed for health professionals who can sign on and then order materials or other support for teaching public-health issues.

### SUMMARY

The food industry provides a key link between agriculture and health, and is an important contributor to public health. Direct and indirect communications are necessary in order to reach consumers with public-health messages. The potential is enormous for benefit through reaching a broad spectrum of Americans with well designed public/private partnerships. I applaud the organizers of this conference because it symbolizes that kind of partnership. We must work to develop and maintain trust among the government officials, healthcare professionals, and food-industry representatives in order to maximize positive public-health messages.



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## ***Consumer Impact on Nutritional Products***

STEVE SNYDER & ROBERTA ROSENBERG  
*Cargill Health & Food Technologies*  
Minneapolis, MN

At Cargill Health & Food Technologies we believe that consumer insights are critical to the development of our nutritional and specialty-ingredient portfolio, and to the continued growth of the functional-food industry.

### **THE NUTRITION INDUSTRY**

The nutrition industry in the United States consists of three sectors—supplements, natural / organic foods, functional foods—and is currently estimated to be a \$49 billion market (Nutrition Business Journal, 2002). It has grown 81% over the past seven years, with growth in all three sectors (Figure 1).

Functional foods represent almost 40% of the nutrition industry at \$18.5 billion. *Nutrition Business Journal* defines a functional food as:

*fortified with added or concentrated ingredients to a functional level,  
which improves health and/or performance,*

OR

*a product marketed for its inherent functional qualities.*

They include enriched cereals, breads, sports drinks, bars, fortified snack foods, baby foods, and prepared meals.” Interestingly, in the year 2000, functional foods surpassed supplements as the largest sector of the nutrition industry. Experts project sales of functional foods will continue to grow at a steady rate such that by 2010 they are expected to reach \$31.2 billion in the United States (Figure 2) (Nutrition Business Journal, 2002).



Figure 1. Consumer purchases of supplements, natural/organic foods, and functional foods, 1994–2001.

### CONSUMER DRIVERS OF GROWTH

To understand the reasons for this growth and, more importantly, the growth opportunities ahead, we look to consumer trends and consider three primary components to be critical. Demographic trends are the biggest driver, but much is to be learned also from lifestyle and attitudinal trends.

*Demographic Trends* Currently, about one-third of the population of the United States is over 55 years of age. This group will double in number over the next 30 years to represent about half of the population (Figure 3). This shift implies that incidence of many age-related health conditions will be affected, increasing the need for development of functional foods. Figure 3 shows the most common complaints among those over 50, with arthritis, overweight, high blood pressure, high cholesterol, and diabetes most prevalent (Multi-Sponsor Surveys, 2000), all of which affect mobility, functionality, and longevity.

In the meantime, younger age groups are more familiar with functional foods and will look to those products to address their health and wellness concerns. In contrast to older consumers, “complaints” from those under 50 relate to lifestyle hindrances such as stress, colds/flu, and overweight (troublesome for different reasons) (Figure 4).

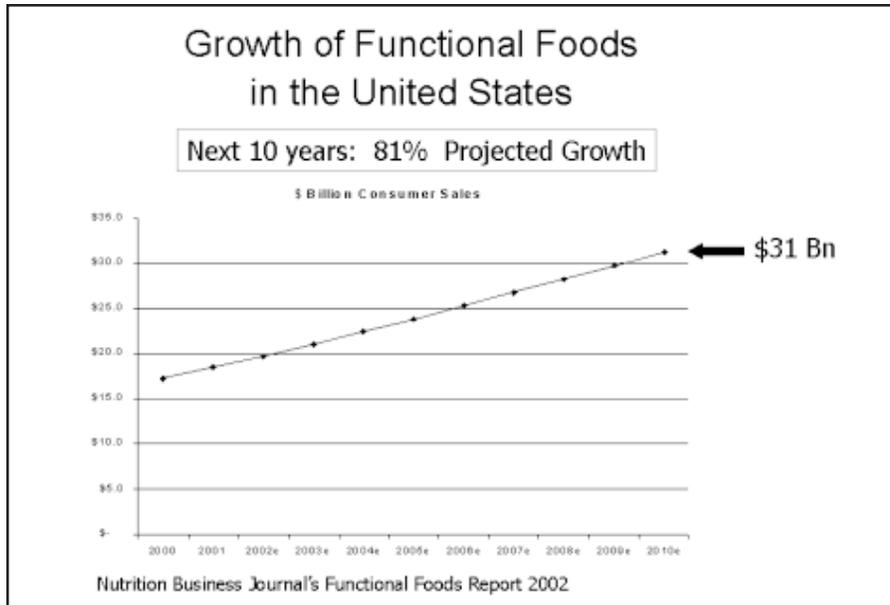


Figure 2. Consumer purchases of functional foods projected through 2010.

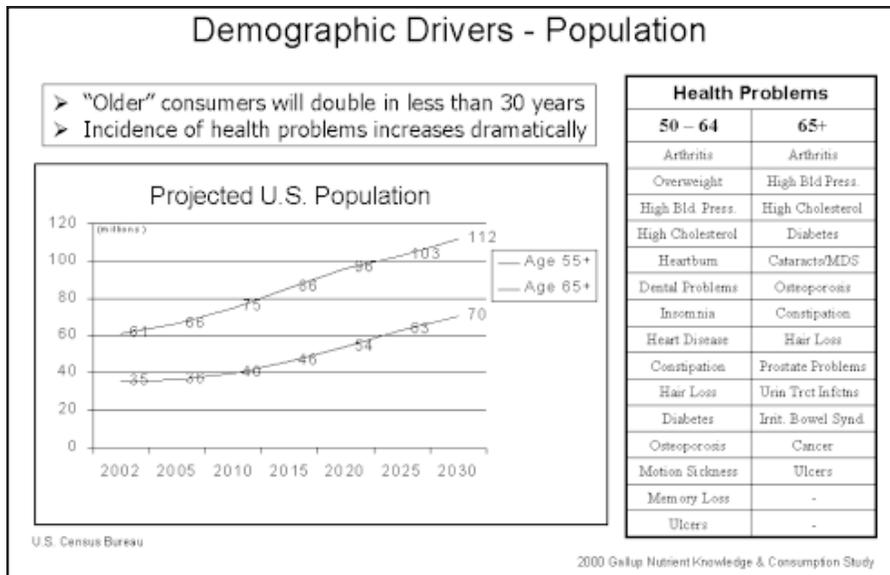


Figure 3. Projected demographic changes in the population >55 and >65 years old and expected accompanying increases in health problems.

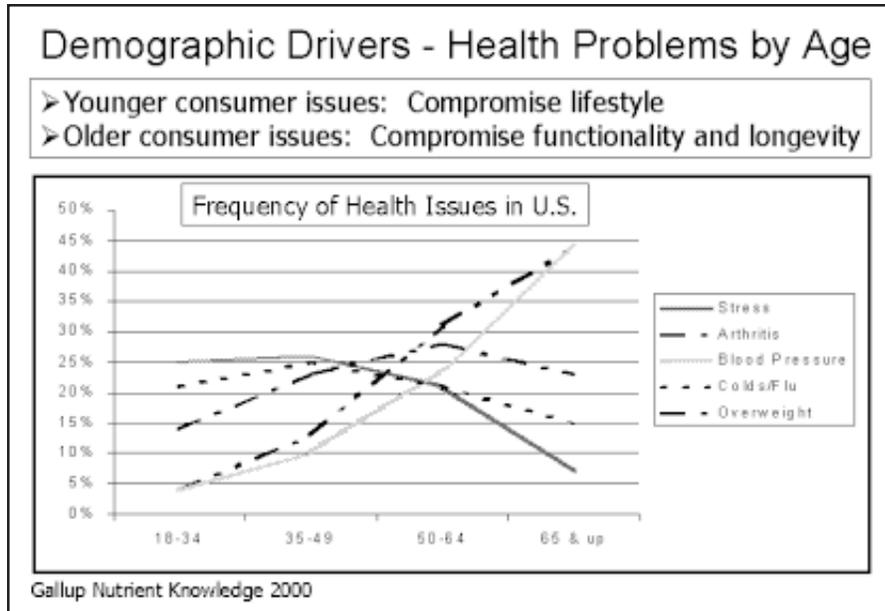


Figure 4. Frequency of selected health issues across four age groups, 18 to >65 years old.

*Lifestyle Trends* Demographics alone do not fully explain consumers' choices regarding functional foods. Changing lifestyles are also influential. The prevalence of dual-income households has had enormous impact on purchasing and consumption habits. Long working hours, technology enabling the blurring of the lines between home and work, and fragmented family activities have precipitated a reliance on convenience foods and foods prepared away from home. Consumers are simplifying their preparation tasks by making fewer dishes at meals (especially dinner). There is a tendency to eliminate side dishes, which often round out the meal's nutritional content, such as fresh vegetables (Figure 5) (NPD Group, 2001).

Declining nutritional intake is not going unnoticed by American consumers. One-third of adults believe their typical daily diet falls short of the recommended daily allowance (even with vitamins included). This proportion increased gradually throughout the 1990s (Multi-sponsor Surveys, 2000). Therefore, it is not surprising that many commonly consumed foods and beverages are now nutritionally fortified (e.g. milk, juice, cereal, yogurt). These trends also help to explain the growing popularity of nutrition/energy bars and beverages. Nutrition/snack bars are a \$1.4-billion business that has grown 45% in the past five years. Liquid meal-replacements, including weight-loss beverages, represent \$1.4 billion in sales, about 33% higher than five years ago.

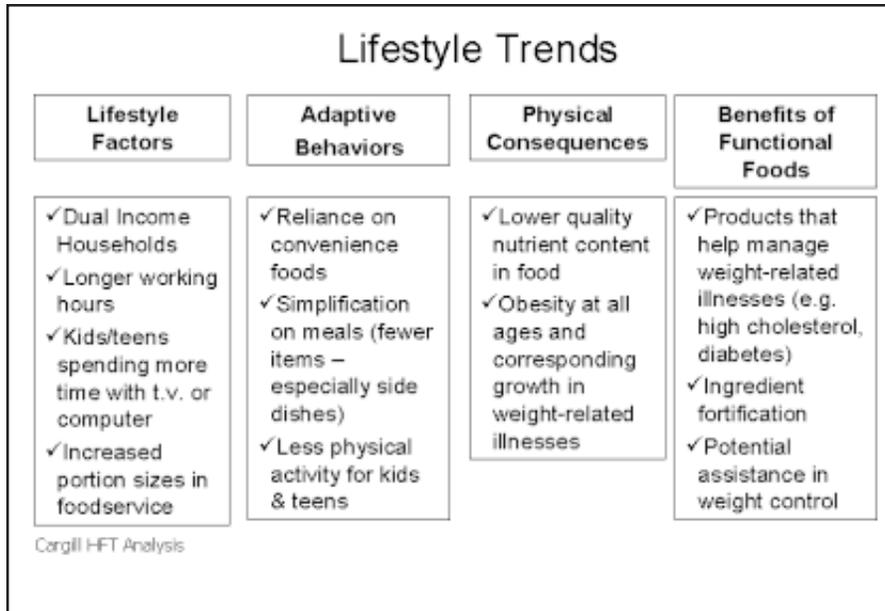


Figure 5. Benefits from functional foods relevant to modern-lifestyle trends.

Childhood obesity is a dangerous result of the changes in eating/food preparation discussed above, along with increased portion sizes in food service, and a more sedentary lifestyle. Thus, weight-related health problems formerly associated with older people are now prevalent in children and teens.

Products in this relatively new category will play a role in improving dietary nutritional quality and will contribute to the management and/or treatment of specific conditions. Specifically, efficacious, safe products for weight control will find a receptive public. Likewise, markets will exist for safe and effective products for the management of cholesterol level, hypertension, and diabetes.

#### ATTITUDINAL DRIVERS

Many excellent sources of information are available on attitudinal trends. We have found three that have been particularly useful: the Daniel Yankelovich Group, HealthFocus (2001), and various articles published by Dr. Elizabeth Sloan of Sloan Trends and Solutions. From these and others we have developed our strategy with respect to functional foods.

The first trend is **Positive Nutrition**. Healthy eating used to be defined by avoiding negatives (e.g. fat, sugar, salt). The emphasis is now on seeking foods that are beneficial (e.g. calcium, fiber, antioxidants). Likewise, there is a growing interest in health maintenance and disease prevention, rather than just treatment.

Another trend is **Nutritional Individualization**. There is a growing awareness that one size does not fit all when it comes to health and wellness. The HealthFocus® Trend Report (HealthFocus, 2001) shows that 74% of shoppers believe that nutritional needs are different for each person. The increasing numbers of products targeted by age, gender, activity level, and need-state are a response to this trend.

**Self-Education and Self-Medication** is a two-pronged trend. Today's consumers are the most highly educated in history. We have unparalleled access to information, which is both good and bad news. Consumers have the ability and the opportunity to gather information on health management. However, it is difficult to assess the quality of the information, which is often complex and conflicting. This makes the consumer-education task crucial, but very difficult. Consumers gather information from a variety of sources ranging from informal (friends and family) to published sources (including opinion leaders such as Oprah Winfrey and the Internet with targeted sites such as WebMD®), to health-care professionals (doctors, pharmacists, physicians' assistants, and alternative providers). In developing a functional food, it is important to learn which sources are most consulted by the target consumer and develop plans to reach those sources.

Once educated, consumers show a growing willingness to act without medical professional intervention, and feel an increasing confidence in treating themselves. Over half (58%) of consumers are "very confident" about the decisions they make in taking care of their health. About three-fourths (73%) prefer to try to treat conditions themselves rather than go to a doctor (Roper Starch Worldwide, 2001).

A trend driven by the baby-boom generation is **Extending the Middle Years**. With the increasing average life span and improved quality of life, consumers are unwilling to age gracefully. Baby boomers essentially deny the whole aging process and are unwilling to accept age-related physical changes. This drives opportunities for new products that will help preserve health, appearance, performance, and, ultimately, independence. This trend also has significant implications for how we communicate with the consumer. This generation will not want to be approached as "old": the nutrition industry must minister to the aging population in a positive, proactive manner.

The final trend is **Oxymoron-ism**. American culture has become adept at blending seeming opposites. One interesting example would be a consumer who is willing to risk laser surgery, yet seeks alternative medicine approaches for certain ailments. Other examples include business/casual, organic/junk food, and reality/television. Thus, natural additives and sophisticated natural solutions in functional foods will likely be tolerated and perhaps embraced.

## **INNOVATIVE PRODUCT RESPONSES**

A number of companies have introduced innovative products in this category in

response to these trends, some of which were discussed during the conference. Notable examples include:

- Viactiv™ (McNeil-PPC, Inc.) calcium “chews” for women—a unique and appealing form.
- Luna® bars—the makers of Clif® bars (Clif Bar Inc.) recognized an opportunity for an energy bar targeted to women with fewer calories than existing energy bars and nutrient fortification specifically for women’s health issues. They support the product through sponsorships of women’s events and causes.
- Take Control® (Lipton Investments, Inc.) and Benecol® (Raisio Group) margarines—these products represent a sophisticated natural solution to help lower cholesterol. They contain a plant-based extract that is clinically proven to reduce cholesterol. These products are promoted both to consumer and to medical professionals.
- White Wave Silk® (White Wave, Inc.) soymilk—consumers are becoming more familiar with the benefits of soy, due in part to the recent FDA health claim. However, there has been resistance to the taste of soy foods. White Wave offered an improved tasting product, packaged in familiar milk cartons, and placed in the refrigerated dairy section of the grocery store. This combination of elements resulted in a \$130 million business in just five years.
- Kashi Heart to Heart™ (Kellogg’s) cereal—is the first national brand cereal targeted for heart health. It is a high-fiber cereal fortified with antioxidants, grape seed extracts, green tea, and B-vitamins.
- Harmony™ (General Mills, Inc.) cereal—targeted for women. It is fortified with calcium, folic acid, antioxidants, soy, and iron.

## ROLE OF INDUSTRY

Industry will continue to play a valuable role in developing healthy, effective, and safe ingredients, and in making exciting, new functional foods available to the consumer. These contributions fall into four major categories: innovation, safety, credibility, and marketing and business development / management (Figure 6).

To drive the first category of innovation, we are taking a health-platform approach in order to build condition-specific expertise, as well as an ingredient-specific approach in order to gain cost-, quality-, regulatory- and formulation-specific expertise. The model in Figure 7 shows the elements required for a successful new functional food product. Of course, we believe this is founded in sound consumer insight and backed by the appropriate healthy ingredients, food applications, good taste, health benefit, and product positioning and delivery. Much of this is simply strong execution of fundamental marketing.

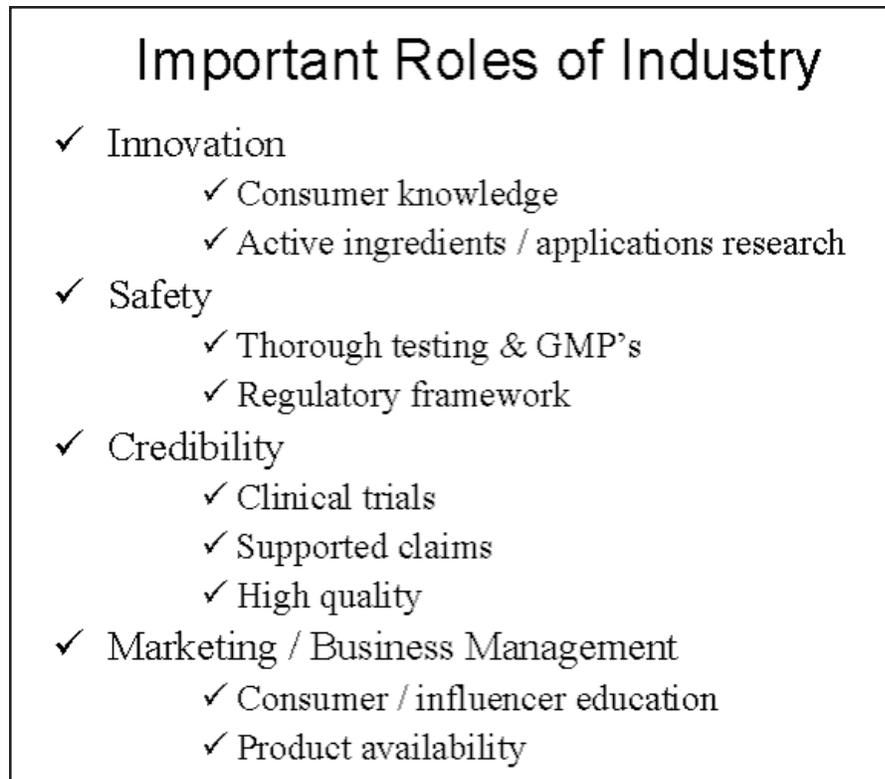


Figure 6. Contributions of industry to the provision of functional foods.

As new ingredients and products are developed, consumer and ingredient companies will provide increased credibility through their consumer brands, and increasingly through their ingredient brands which will stand for their commitment to healthy, good-tasting, safe, and effective products. Consumer-product brands, and increasingly ingredient brands, will provide consumers a reason to believe that the products are safe and deliver on their promises. Additionally, the industry will need to help educate the consumer, build awareness of new product options, and make those options convenient.

#### CHALLENGES AND OPPORTUNITIES

A major challenge for consumer and ingredient companies is to recoup the investment required to develop and support this new product-development process (Figure 8). Active ingredients for functional foods require much larger investments in science and in regulatory and clinical aspects than other food ingredients. Without sound business management leading to tangible company profits, the necessary funding and developmental efforts will be cut back, thus

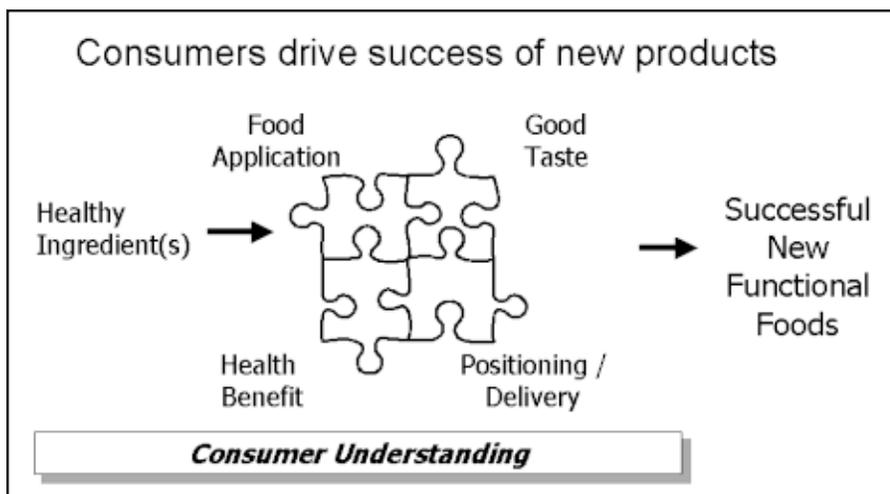


Figure 7. Schematic representation of new-product development.

**Business Challenges and Opportunities**

Challenges	Opportunities
➤ Recouping investments - Will consumers pay more?	➤ Consumer trends are positive
➤ How to share in value along channel?	➤ Conventional health care costs increasing
➤ Communication & education of non-scientific consumer	➤ Selected product successes
➤ Regulatory process & Claims	➤ Increasing research
	➤ Experience with functional foods

Figure 8. Challenges and opportunities related to the development of functional foods.

slowing growth of this segment. One essential element of this management effort will be effective partnerships between ingredient companies, consumer-food companies, and retailers. Partnerships will allow cost sharing on the development of ingredients and the education of consumers. Ultimately, value will be created for all points on the chain.

Other challenges include:

- how to share value along the channel to the consumer,
- how to effectively educate and communicate with the consumer, and
- how to manage and leverage the regulatory / claims processes and agencies.

A number of positive signs indicate that these challenges will be met. Strong favorable consumer trends are evident, as discussed above. Consumer need and receptivity is increasing. Health-care costs continue to increase and will drive the move to more functional foods. Although some products are already successful, disappointing product introductions have allowed the industry to learn from mistakes and make next-generation products more acceptable to consumers. Finally, increasing emphasis on solid scientific and clinical research will drive new discoveries and improved products.

#### FUTURE OF FUNCTIONAL FOODS

Based on a number of indicators, we believe the functional-foods segment will continue to show above average growth. This will be exhibited by a number of visible indicators (Figure 9) such as more sophisticated product “solutions,” increased mainstream consumer acceptance, healthy brands both from consumer and from ingredient companies, and more individually tailored products driven by breakthroughs in information and genomics technology (*i.e.* “nutrigenomics”).

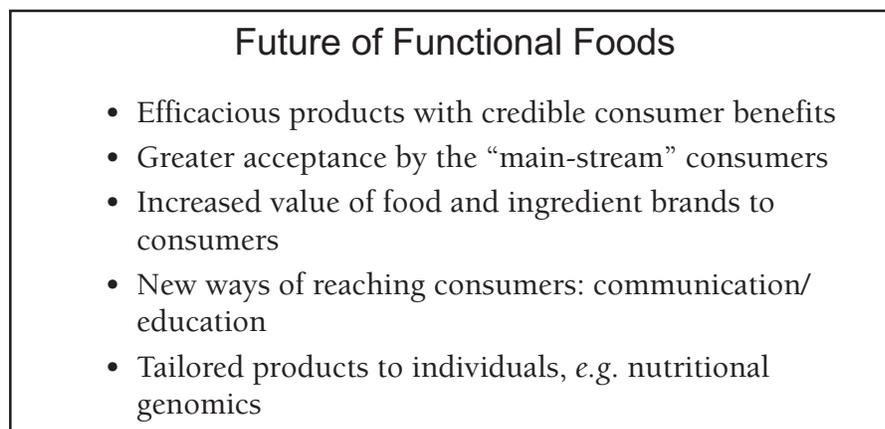


Figure 9. Visible indicators of the future of functional foods.

In summary, the future of functional foods is bright, but not without challenges. We believe that a detailed understanding of consumer behavior and patterns will play a major role in ensuring success.

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## ***Spotlight on Minnesota: Highlighting Innovation in Agriculture, Food and Medicine***

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### ***Session 1 Developments In Safe And Healthy Foods***

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#### **Q&A**

MODERATED BY

**CHARLES C. MUSCOPLAT**

*University of Minnesota  
Minneapolis-St. Paul, MN*

*Charles Muscoplat:* Susan, you mentioned General Mills' health messages. What is happening nationally and internationally in terms of delivery of such messages by retail or wholesale companies? What's the magnitude of that effort?

*Susan Crockett:* Obviously, we are delivering lots of messages to consumers. The challenge is to have them hear it and hear it often enough so that they actually can apply it. For instance, on the calcium issue, interestingly we found that gatekeepers understood their own needs for calcium, particularly women, but they just assumed that their children were getting sufficient amounts and they didn't understand the importance of building bone mass. We were then able to craft messages that helped fill in those blanks.

*Muscoplat:* Kati, are you thinking about irradiating any other products, and what consumer issues will be raised?

*Kati Fritz-Jung:* We continue to survey emerging technologies as they pertain both to food safety and to nutritional benefits. Quite possibly we will find opportunities to apply radiation to more products.

*Muscoplat:* Let's take some questions from the audience.

*Audience member:* You all talked about listening to consumers and also creating messages. With about 80% of the soybeans genetically engineered, what are you hearing from consumers about this and what messages are General Mills and Cargill creating in response?

*Steve Snyder:* I'm not sure I can comment for Cargill as a whole, but inside Health and Food Technologies we do hear comments about that and they are quite varied. They vary by region around the world and they vary by customer. Clearly, this is an evolving area where listening to the consumer is going to be absolutely critical. We have seen what can happen when consumers aren't considered and aren't well informed.

*Crockett:* I help to manage many issues for General Mills, but biotechnology isn't one of them. I am not an expert, but I can tell you that we don't get as much negative input from consumers as you would anticipate.

*Muscoplat:* Hershel, who should use pasteurized eggs and why?

*Hershell Ball:* Our consumer information, although limited, indicates that our customers buy them for the reasons you would expect. They want to do some special cooking, whether it be under-cooked eggs or making cookie dough for their kids. Also, the population is increasing in age and is potentially more at risk for salmonellosis. The pasteurized shell eggs would be appropriate for nursing homes and other healthcare institutions serving so-called at-risk populations.

*Chris Kwong (University of Minnesota Clinical Research Center, Minneapolis-St. Paul, MN):* I'm a registered dietician. Kati, please briefly summarize the education process that you use with your sales people. Your truck drivers provide a different point of sales contact—how are they trained to bring messages back?

*Fritz-Jung:* I have a two-fold answer to this question, as our school-food services are very different from our home-delivery business. We have 4,000 route drivers who are trained in our products, both when they come into the company and on a continuing basis. It is very unusual for a company to have direct contact with every single one of their consumers on a regular basis. Consequently, it's relatively easy for us to respond to their needs, both from a product standpoint as well as a nutritional standpoint. Many of our products aren't necessarily marketed or sold for their health benefits, but were designed because of feedback and requests from our consumers. There are ice cream

products, for example, that are not labeled for diabetics but have all of the attributes for diabetic people who want to consume ice cream. We have a line of breakfast products that are fortified and enriched, pancakes for example: many women who consume our pancakes asked that they be enhanced in calcium. So we have a unique means of targeting people, filling their needs, without a heck of a lot of education, quite frankly and quite fortunately for us. In terms of educating the sales force for our school-food service, that entire group is in Marshall, so it is relatively easy to disseminate that information to our sales force. We use all the normal venues: press releases, brochures, fliers, and packets of information that describe what we do and why, and we target those directly at the people who make purchasing decisions at the schools.

*Audience member:* In reference to utilization of pasteurized eggs: in Maryland, my home state, it is illegal in long-term care facilities to serve shell eggs that have not been pasteurized. With respect to industry application and Dr. Crockett's discussion of partnerships with public-health organizations and development of messages—I'm a registered dietician and, generally speaking, I am reluctant to use industry-produced materials unless there is some evidence that they have been developed in partnership with a public-health organization, for example the American Dietetic Association or the Cardiac Rehab Nurse Association. Is there any industry organization promoting that approach with respect to materials that are distributed to consumers, for those of us who are reluctant to use industry-logoeed teaching materials?

*Crockett:* At General Mills, we believe very strongly that partnerships are powerful, and we partner with health professionals to produce educational materials that suit their needs. This kit, for teaching American National Cholesterol Education Program (ANCEP) and American Heart Association (AHA) guidelines, for instance, is better precisely because we developed it after listening to health professionals who use it. I mention only these two nursing groups, but we make this kit available through our Web site to dieticians and 8,000 other health professionals. General Mills has also partnered with the American Dietetic Association and the President's Council on Physical Fitness and Sports: we are awarding fifty grants of up to \$10,000 each to grassroots nonprofit organizations that develop innovative programs to improve nutrition and fitness for youth. We are working together on an issue of common interest.



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## ***Targeted Nutrition in Health and Disease***

CLARENCE JOHNSON

*Bioenergy, Inc.  
Minneapolis, MN*

The use of food and nutrition in treating and preventing disease is certainly not new. But the Dietary Supplement Health and Education Act of 1994 created a new, and sometimes controversial, industry based on diet and health. Functional foods and nutraceuticals are foods or ingredients that are perceived by the consumer to be beneficial to health. The functional food industry has shown meteoric growth over the past several years, and is currently estimated at around \$18 billion in annual revenues. Growing acceptance of the role of nutrition in disease coupled with an expanding demographic provide strong fundamentals for continued growth of this industry.

However, major challenges remain. Early entrants to the nutraceuticals market relied heavily on advertising to gain market share, without strong evidence of product efficacy. Only in recent years, with the involvement of larger and more sophisticated companies, have science and proven efficacy brought broader support.

### **A GROWING MARKET**

It is estimated that over 50% of the adult population now use some form of nutraceutical product for health reasons. Consumers report that the most common use of nutritional products is for cardiovascular health, general health concerns, and to promote a healthy lifestyle. Cold treatment, joint health, and energy-enhancement follow with a variety of other applications also gaining widespread use. Products such as coenzyme Q-10, carnatine, B vitamins, and antioxidants are promoted for cardiovascular benefit. Zinc has recently been introduced for cold treatment. Glucosamine and chondroitin are available for joint health, as are a variety of energy-enhancing supplements, some that work

and some that don't. There is growing evidence, as indicated by the recent report by the Harvard Medical School, that conjugated linoleic acid may play a role in slowing the progression of certain cancers, notably of the colon and prostate. All of this adds up to the fact that consumers are aware of the health benefits of certain nutrients, that they pay attention to scientific reports, and that they are prepared to follow the recommendations of health professionals with respect to nutritional support for disease management.

In the early years, the nutrition industry was built almost solely on marketing hype and short product lifecycles, reflecting lack of proven efficacy or scientific foundation. Bad press related to product safety led to regulatory and consumer pressure and the industry was forced to look hard at realignment. Now there is considerable emphasis on proven scientific findings, product safety, and the interaction of nutritional products with drugs and other therapeutic compounds. And so, while in the early going there was reliance on marketing to create the premise of health, a growing emphasis now is being placed on science to prove that premise.

#### **A GROWING SCIENCE BASE**

Many well founded factors support the growth of the nutritional/health industry. With regard to health, many factors contribute to a growing emphasis on nutrition at some cost to pharmaceuticals. Many nutraceuticals do indeed provide therapeutic or preventative benefits. And although these compounds typically are naturally occurring, their use can be patent-protected. Pharmaceuticals and nutraceuticals are tested clinically, and clinical results are published in respected peer-reviewed journals. Clinicians are beginning to see the value of nutritional products with proven efficacy, and a number of healthcare providers are recommending their use. At the same time, nutraceuticals and pharmaceuticals provide solid business opportunities. In some cases, in fact, nutraceuticals have advantages over pharmaceuticals as a business model. Because the compounds are not new and are typically naturally occurring, the route to market is generally shorter, faster, and more clearly defined. Safety issues are addressed by the FDA through food rather than drug evaluations, leading to safety affirmations as generally apply to foods. And the real advantage to industry is that mandatory generics are not required after compounds or compositions come off-patent. At the same time, however, third-party payers typically do not reimburse for nutritional products and patients are forced to bear the cost of their use.

#### **BIOENERGY, INC., AND RIBOSE**

So as an example of how nutritional products can be successfully employed in health, I will now shamelessly promote our company, Bioenergy, Inc. It was founded on the basis of enhancing lives by improving cardiovascular health and tissue function. John Folker, a University of Minnesota pediatric cardiovascular

surgeon, formed the company after completing studies of the effects of D-ribose on cardiac metabolism and heart function. D-ribose is a five-carbon sugar, or pentose, that occurs naturally in every living cell. The ribose that we use in our product manufacture is derived from corn sugar through a fermentation process. Ribose regulates the metabolic pathways used by the body to produce a class of compounds known as adenine nucleotides. The metabolic processes controlled by ribose are essential to existence. Energy production, formation of genetic material and compounds essential for cellular communication are all formed by pathways limited by ribose in tissues and in cells.

In the body, these compounds become deficient when there is insufficient oxygen supply. When under stress, hearts, skeletal muscles, blood cells, and other tissues lack the enzymes that are required to produce ribose. Therefore, giving ribose to these tissues speeds up the recovery process and improves function. Although other tissues—such as liver, adrenal cortex and mammary tissue—are active ribose producers, they are unable to transport the ribose that they produce to deficient tissues.

The use of ribose as a nutritional therapeutic is well founded in science. Our research has shown that its administration is effective in treating sick hearts, improving skeletal muscle metabolism, enhancing immune function, and preserving blood cells harvested for transfusion, all using the same metabolic pathways as a mechanism.

### **CORVALEN®**

As a result of our research, last December we launched CORvalen® for treating patients with congestive heart failure and for those recovering from cardiac events such as surgery or heart attacks. This product is regulated by the FDA as a medical food and is distributed to patients by hospitals and other healthcare providers. The product works by increasing the energy in the heart and is effective in improving heart function in our targeted patient population. It enhances physical performance and quality of life.

We also provide ribose as a bulk ingredient for use in general health and nutrition. Sports-nutrition applications are expanding, and users report improved performance, reduced soreness and stiffness, and enhanced recovery from heavy exercise. Again, these effects are directly related to the biochemistry associated with ribose and stressed tissue. Many nutrients have been used in sports and energy products for years. However, recent concerns over the safety of several ingredients have caused the FDA to step up enforcement. As such, food and beverage manufacturers have been looking for effective ingredients with known and accepted safety profiles. Bioenergy ribose is included in many sports-energy and general-health products now on the market, because it has been affirmed safe. PepsiCo for example uses ribose as a drink supplement being sold as a sports-nutrition product. The distribution of ribose-containing products continues to expand.

The market opportunity for ribose is dramatic. As a heart supplement, we estimate the market potential to be in excess of \$3 billion. And as a sports- or general-use supplement, the market exceeds \$500 million. These numbers are given only as indications of the expansive potential of the nutrition market in health, and go a long way toward explaining why companies have invested so heavily in research and development in this industry.

Nutraceuticals are gaining wide market acceptance and many significant uses continue to be identified. There is a large and growing demographic now using nutraceuticals for health, and the market continues to expand. Physicians and other healthcare practitioners are gaining an understanding and approval of how nutrition products affect patient health. Historically, gaining acceptance by the medical community has been a significant challenge. But the redirected focus on research has forced open this door.

### **RESIDUAL RESISTANCE**

Major challenges still exist, however. The industry has come kicking and screaming to the realization that science matters. But considerable resistance persists. Until this approach is universally adopted, there will continue to be grave concern that nutritional therapies are more hype than science. However, there are strong business reasons to continue the effort. It is incontrovertible that nutritional products founded in strong science can provide a meaningful contribution to health, laying the groundwork for solid business platforms and creating value for shareholders.

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## ***Genomics Education at the Mayo Clinic: A New Model for Data and Information***

**MARK BOLANDER**

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I have been presented with a significant challenge, having been asked to discuss how genomics, specifically medical genomics, is being integrated into medical practice at the Mayo Clinic, a tertiary care, a highly scientific, and—if you are familiar with the people who are there—a very formal type of institution. I will explain the approach we are taking to provide some insight into:

- how an institution like the Mayo Clinic tries to assimilate new information that's important in diagnosis and treatment, but yet somewhat problematic for the physicians involved, and
- the possibility that there are overlapping areas of interest between nutraceuticals and the effects of diet on health, and genomics.

I believe that diet has very strong effects on health. I believe that it is also true that disease is almost exclusively determined by genes and abnormalities in genes. I don't think that these are contradictory positions, and I think that the challenge for conference attendees, and the challenge for those of us who are more classically interested researchers, is to find areas of overlap.

Sequencing of the human genome has had a profound impact in the medical community. The effects have been to focus attention on medical genomics, and it is clear that there are significant implications for clinical practice.

### **EVOLUTION OF MEDICAL GENOMICS**

Major advances in medical genomics began in the late 1940s and the 50s with progress in genetics, and with genetic engineering in the 1970s. The human-genome project represented a major conceptual step forward, and when it was

completed, it was clear that there was tremendous potential for impact on the diagnosis and treatment of disease. This new information will gain entrance to medical practice through cardiomics and bioinformatics, and will assist in the diagnosis of disease, the identification of diseases in relation to genes, the identification of predisposition to disease, the identification of new therapeutics, and understanding of individual responses of particular patients to particular therapeutics.

The key then is that using the new medical-genomics information is going to transform diagnosis, therapy, and treatment, and approaches to predisposition to disease in practices such as we have at the Mayo Clinic.

We have always known that some diseases are genetic, or have a genetic component. Since the early '90s, there has been an exponential increase in the identification of diseases that have a strong genetic contribution. There has been, as another example, quite a bit of interest in pharmacogenomics, where it has been determined that specific genes or specific polymorphisms in genes will determine the response of a particular individual to a drug. Why, for example, will one person take aspirin and have success in treating their arthritic pain, while another patient will not? The most likely answer is that differences in the genes that those patients have determine those variable responses.

Along with these opportunities, however, there are challenges and, indeed, problems. The potential exists for a loss of patient privacy and confidentiality of medical information, which is of concern to all physicians in all institutions. There is also the potential for a loss of control on the part of the patient over their medical care. Some would argue that this is already occurring. The potential is certainly there for this to get worse. Discrimination on the basis of genetics and on the basis of finances is, of course, real. Expectations are going to change from the physician perspective in a way that is unpredictable, and, unfortunately, as it always has been in the past, more-technical medical care will be associated with much higher costs.

## **MAYO'S MISSION**

These changes and opportunities are reflected in our mission statement, "The Mayo Clinic prides itself in its ability to elucidate the goals that it has," and one of the current major goals is to include genomics in the integrated practice of medicine. The difficulty is that for the majority of physicians there is very little understanding of genetics, little understanding of its principals, little understanding of the practice, and little understanding of the tests. And so the challenge for the individual physician, for the clinic, and for the medical community at large, is to develop paradigms and opportunities to educate physicians in practice about the new opportunities, and also the new responsibilities and problems.

The guiding principal at our institution is that all physicians, not just medical geneticists as a subspecialty, but all physicians can participate in this

process. But without a strong knowledge base, to achieve that goal is going to require a significant educational effort. To achieve this educational effort a Genomics Education Steering Committee was formed with three goals and charges:

- to transmit information to all physicians of the clinic,
- to transmit to the clinicians the significance and importance of this information, and
- to develop an educational plan to maintain the standards of education and the standards of care.

The group, of which I am a member, has initiated efforts in several areas. There has been provision of resources, primarily on a Web-site. There have been educational activities, including seminars. There is also coordination of research activities at the clinic, which is being done in consultation with the communications department.

One of the first things that we did as a committee was assay the level of knowledge and the level of comfort of our physicians with genomic tests and with ethical, legal, and social issues, termed “elsi.” Interestingly, a high number of the physicians were not at all comfortable. As a corollary, a high number of physicians expressed strong desire for educational materials, reinforcing our initial concept of both a strong need for education and also a very good opportunity for education.

There has been significant activity in continuing education. We have organized a large number of lectures and several symposiums, videos are available to physicians and we are coordinating activities with allied health staff. We will continue these activities to bring new genomics information to our clinicians. We have given a major introductory course on medical genomics, in which a large number of people from the committee participated. We are planning a major continuing educational course; Alan Bradley, the director of one of the major genome-sequencing centers in the world, the Wellcome Sanger Center in the UK, will be our keynote speaker.

We have also put together as a second area of activity, a group of interested faculty members who are supporting the effort as liaisons between our committee and the different departments and committees. Clearly there is a need for information that is specific for particular physicians’ practices or the practice of a particular group or division. And, by identifying interested individuals in each group, we hope to facilitate the educational process.

We have put together a web site, which, unfortunately, is not yet available outside the clinic. We are working diligently to construct something that will be transportable and will be usable by physicians other than those at the clinic. As the director of this process, I have to say that this is an incredibly time-consuming and resource-consuming activity, and it will be some time before we will be fully operational.

## THE CHALLENGE

In conclusion, the Mayo Clinic is engaged in what I think is reasonably termed an aggressive effort to prepare the staff and the allied healthcare for changes in medicine, with genomics and medical genomics becoming a central part of the therapies that we will offer. To reach this goal, to effect this education, we are expending effort as I've described, we are identifying key staff developing web sites and supporting material for those individuals.

This is a little different from the interests of most of those attending this conference, but I would stress the need for integration of the new genomics information, new nutraceuticals information and foods-for-health information towards a more comprehensive understanding of health and of disease. That's a challenge for all of us.

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## ***Integrative Medicine: Agriculture's New Opportunity***

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In 1998, at the national meeting of the American Heart Association, former United States Surgeon General David Satcher, MD, noted that in the previous year our nation spent 425 billion medical-care dollars to treat chronic disease. However, the *per-capita* expenditure for chronic disease prevention was only \$1.21 (SoRelle, 1998). A political realist, Satcher's proposed response for prevention then is our challenge now: Partnerships.

Who is included in those partnerships? Then-president of the American Heart Association Martha Hill, RN, PhD, noted that AHA partnerships working toward reduction of cardiovascular disease included the Centers for Disease Control, the Health Care Finance Administration, the Health Employers Data Information Set, the National Committee for Quality Assurance, the National Heart, Lung and Blood Institute as well as corporate partners in the pharmaceutical and medical device industry (SoRelle, 1998). Missing from this list was agriculture and the prepared-food industry, which is both surprising and tragic for many reasons.

I will address two surprisingly new understandings from the emerging field of integrative medicine that deserve to be highlighted. First, food is pharmacologically active. Second, food's pharmacologic activity is of significant public concern. I will use the documented pharmacologic activities of omega-3 polyunsaturated fatty acids to draw the conclusion that now is the time for medicine and agriculture to partner to positively affect public health.

### **FOOD AS MEDICINE**

There is no question that Hippocrates's injunction to consider food as medicine is supported by modern science. Cross-cultural epidemiologic studies of disease prevalence have revealed that risk factors for disease are, for the most part, culturally rather than genetically determined. For example, studies of Japanese

living outside of Japan demonstrated a two- to three-fold higher incidence of diabetes compared to age, sex and body-mass-index matched Japanese. (Hara *et al.*, 1994; Huang *et al.*, 1996; Robinson *et al.*, 1995). Likewise, the adoption of westernized diets appears to play a very significant role in the development of diabetes in Pima Indians (Williams *et al.*, 2001; Ravussin *et al.*, 1994).

There is no question that food fortification has played an important role in promoting public health. Agriculture and the prepared-food industry deserve much praise for their delivery of medically important therapies to the broad public. Successes include prevention of goiter with iodized salt; rickets with vitamin-D-fortified milk; beriberi, pellagra and anemia with B-vitamins and Fe-enriched cereals; and neural-tube defects with folic acid. (Darnton-Hill *et al.*, 2002)

Although the culture of medicine tends to dismiss the importance of dietary interventions in disease management and prevention, medical research has identified the potent role that dietary elements play, both in regulating gene expression and in modifying inflammatory responses. These major activities represent just some of the pharmacologic activities of foods. For this reason, dietary supplements and foods can be considered drug therapies. As noted by Rick Kingston of the University of Minnesota College of Pharmacy, drug therapies are “regulated and non-regulated substances or modalities that exert a pharmacologic or physiologic effect in the human body.”

Insights on the positive pharmacologic properties of food have not been lost on practitioners of integrative medicine who prescribe dietary supplements responsibly both for disease prevention and for treatment. Nor have insights on the negative pharmacologic activities of food been lost on lawyers who are now equating “Big Food” with “Big Tobacco.” This has garnered much media attention including a front-page article in the *New York Times* during this conference. *Newsweek* magazine’s August 2002 article “Fighting ‘Big Fat’” described the growing coalition of professionals targeting agriculture and the processed-food industry (Tyre, 2002). The impetus appears to be the skyrocketing rates of childhood obesity, hyperlipidemia, and type-2 diabetes mellitus.

These reports in the media reflect what might be called “the stick.” However, there is a carrot. The positive spin is that agriculture and the prepared-food industry have an important window of opportunity to positively affect public health. There has been no better time in which to partner with medicine, and in particular with the integrative medicine community. The evidence base is strong enough to take a more proactive stance in partnering for the public’s health. I will use the deficiency of omega-3 polyunsaturated fatty acids in the diets of North Americans and Europeans as an example.

## OMEGA FATTY ACIDS

Fatty acids of the omega-3 and the omega-6 series are crucial components of cell membranes and are considered essential: humans cannot synthesize them,

only plants can. Neither can we interconvert them—our intake and the ratio of our intake of omega-3 and omega-6 fatty acids determines their content in our bodies. Truly, we are what we eat.

Their presence and the ratio of their presence in our cell membranes directs three functions important to health: gene expression, inflammatory responses, and intercellular communication. An imbalance in intake results in imbalanced physiologic functioning and markedly increased risk of disease.

In the past 30 years, North American and European diets have seen increased intake of omega-6 fatty acids. Vegetable oils rich in these include corn, grape-seed, safflower and sunflower at 60 to 70%, and soy, cottonseed and sesame at 45 to 50%. Increased use of cereal-based livestock production means that meats and many fish are now rich in omega-6 fatty acids. Processed foods rich in omega-6 include: infant formula, margarine, mayonnaise, salad dressings, crackers, cookies, prepared-dough products, snack foods, as well as meats and seafoods.

As meats and fish were traditionally our sources of omega-3 fatty acids, we have experienced an unprecedented shift in the balance of these two essential fatty acids. Omega-6 intake has skyrocketed and omega-3 intake has plummeted. What used to be a 2–4:1 balance has shifted to 10–25:1, as documented in breast milk and in serum (Sanders, 2000; Simopoulos, 2001). The scientific literature documents or supports that omega-3 deficiency, and the imbalance of omega-6 and omega-3 fatty acids, have important negative effects in:

- coronary artery disease,
- breast and other cancers,
- post-partum depression,
- major depression and bipolar disease,
- attention-deficit disorder,
- osteoporosis,
- inflammatory arthritis, and
- inflammatory bowel disease.

The mean current intake of omega-3 fatty acids in a typical North American diet is approximately 130 mg/day or about 0.15% of total dietary fat intake (Kris-Etherton *et al.*, 2000). The American Heart Association's 2000 guidelines recommended an omega-3 fatty acid intake of 900 mg/day based on the results of large intervention trials that demonstrated significant benefit at that level (Krauss *et al.*, 2000). This means that current intake of 130 mg/day is just 14% of the recommendation. Of note, the dietary intake of omega-3 fatty acids is about 14 g/day in Eskimos (Feskens *et al.*, 1993).

In this paper, I will share evidential data regarding the power of omega-3 fatty acids in cardiovascular disease. Given the interest of the American Heart Association and others in partnering for improved cardiovascular health, there clearly exist new opportunities for agriculture.

## OMEGA-3 AND CARDIOVASCULAR DISEASE

Mechanisms for cardioprotection from the omega-3 fatty acids include:

- reduction in malignant ventricular arrhythmias,
- inhibition of atherosclerosis,
- improved endothelial relaxation,
- lipid lowering, including reduction of both fasting and postprandial triglycerides, and
- antithrombotic effects, including reduced platelet reactivity.

The positive consequences of these actions have been reflected in a large number of studies from basic science to randomized controlled trials. Two significant articles were published just before this conference. Albert *et al.* (2002) used a nested, case-control analysis of apparently healthy men followed for 17 years in the Physicians Health Study. The fatty-acid composition of blood for 94 men in whom sudden cardiac death occurred as the first manifestation of cardiovascular disease was compared with that of 184 matched controls for age and smoking status. The authors documented that the base-line blood levels of omega-3 fatty acids were inversely related to the risk for sudden cardiac death both before and after adjustment for potential confounders. Compared to those in the lowest quartile of omega-3 blood levels, those in the highest had an adjusted relative risk of just 0.19 (95% CI: 0.05–0.71); the *P* for trend was 0.007. This is considered a very strong association with great statistical strength. This finding is consistent with the large volume of basic scientific research, and is also supported by other epidemiologic studies of primary prevention both in men and in women (Hu *et al.*, 2002).

Critics will point out that even with a well established mechanism of action and supporting studies, correlation does not equal causality. Therefore, Bucher *et al.* (2002) reviewed all of the randomized controlled intervention trials that compared intake of omega-3 fatty acids with a control diet or placebo in patients with established coronary disease (secondary prevention): was there a positive causal effect? They identified eleven trials that included 7,951 patients in the intervention arm and 7,855 patients in the control groups. They documented that the risk ratio of a fatal myocardial infarction was significantly reduced at 0.7 (95% CI: 0.6–0.8, *P* <0.001). In five trials, sudden cardiac death was associated with a risk ratio of just 0.7 (95% CI: 0.6–0.9, *P* <0.01). Consistent with the multiple effects in other disease states noted above, including cancer, the risk ratio for overall mortality was also significantly reduced at 0.8 (95% CI: 0.7–0.9, *P* <0.01) (Bucher *et al.*, 2002).

In essence, omega-3 fatty acids appear to be both important and absent in our diet. And this represents just one natural product known and used by integrative medicine practitioners to positively effect health states. There are literally dozens more that should be of interest to agriculture and to the prepared-food industry.

## RESPONSIBILITY AND OPPORTUNITY

In regard to the public's health, agriculture and the prepared-food industry have both a significant responsibility and a significant opportunity regarding the public's health. Sticks and carrots exist to promote innovations in health-promoting foods; I believe in carrots. And I believe in new partnerships to identify the best business- and best health-promoting opportunities. And, clearly, partnerships are also needed to transform public-opinion and consumer-purchasing patterns.

In summary, I hope I have conveyed two points: food is pharmacologically active, and this pharmacologic activity is of great public concern. I also hope that I have conveyed the importance of looking to the integrative medicine community for partnerships in new-product as well as market development. The University of Minnesota's Center for Spirituality and Healing plus the Center for Plants and Human Health represent two such potential partners with expertise and interest in effecting positive change in our nation's food supply.

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## ***The Center for Plants and Human Health: An Interdisciplinary Approach***

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The Center for Plants and Human Health is a new interdisciplinary initiative that will serve to stimulate collaboration among scientists at the University of Minnesota who are interested in how plants and plant products may be used to improve human health and nutrition.

In recent years a great deal of attention has been drawn to the potential for plants and plant products to contribute to human health. This interest goes under a wide variety of labels—phytonutrients, nutraceuticals, functional foods, complementary and alternative medicine, *etc.*—and encompasses plant science, natural-products chemistry, pharmacology, nutrition, and laboratory and clinical medicine. It includes the development of raw produce and processed foods that are effective in prevention and treatment of disease, as well as identification of naturally occurring plant products that may have preventative and curative properties when used in a purified form. It also includes the testing of these foods and compounds for efficacy and toxicity in humans and animals. The University of Minnesota Twin Cities campus is one of the few major research universities in the country that has both an academic health center and a college of agriculture. We have a large number of faculty members who have active programs in this area, but we have had no formal mechanism to bring them together to develop interdisciplinary research programs directed toward the interface between agriculture and medicine.

The Center provides a forum for the development and interchange of information relevant to plants and human health and serves as a stimulus for interdisciplinary collaboration leading to new research opportunities and funding in this vital area. The Center for Plants and Human Health complements and collaborates with previously existing groups such as the Center for Spirituality and Healing and the Center for Addiction and Alternative Medicine Research to stimulate interaction among scientists and clinicians at the University of Minnesota.

## CENTER STRUCTURE

The Center for Plants and Human Health is funded as an Initiative in Interdisciplinary Research, Scholarly, and Creative Activities by the Office of the Vice-President for Research of the University of Minnesota, with additional support from the Deans of the Medical School and the College of Agricultural, Food, and Environmental Sciences (COAFES). The Center is governed primarily by a Steering Committee of six faculty members representing the health sciences and agriculture. Current members are:

- Jerry Cohen, Bailey Professor of Environmental Horticulture, Horticultural Science,
- Vincent Fritz, Professor, Horticultural Science and Southern Research and Outreach Center,
- Stephen Hecht, Wallin Professor of Cancer Prevention, Cancer Center,
- Greg Plotnikoff, Medical Director, Center for Spirituality and Healing,
- Joseph Warthesen, Professor and Head, Food Science and Nutrition,
- Gary Gardner, Professor, Horticultural Science.

I serve also as Director of the Center, the day-to-day activities of which are managed by Program Coordinator Karen Kaehler.

## CENTER PROGRAMS

The study of plants and human health can be approached from many directions. At the Center we are examining the interface of agriculture, defined as the art and science of purposeful breeding, cultivation, and harvesting of plants for human use, and of medicine, defined as the art and science of purposeful action to maintain human health. To assist us in developing opportunities for collaboration between COAFES and the schools of the Academic Health Center, we created a map of this interface (Figure 1). Grouped around the general themes of Production and Consumption are specific activities or topics, such as Cultivation, Disease, or Culture. From there, colleges and departments, such as Horticultural Science, or Public Health, were identified. This endeavor has brought together over a hundred researchers from sixteen colleges, departments, and institutes within the University of Minnesota.

The Center is not contained within a building, neither is it an academic department. It is a virtual organization that exists to be a matchmaker by bringing scientists together. Our focus is on research on plants and plant products, broadly defined. Our programs fall into three general categories:

- Interdisciplinary Forum on Plants and Human Health, with monthly meetings of scientists and practitioners from throughout the Twin Cities campus and community. Thus far, the Forum has focused on three activities:



realistic opportunities for funding of interdisciplinary research related to plants and human health (hence the focused discussion groups mentioned above), to assist the Principal Investigators in writing such proposals, and to coordinate the bureaucratic details that are required to submit them.

### **ONGOING RESEARCH RELATED TO THE MISSION OF THE CENTER**

Although the Center is new, many examples of current research at the University of Minnesota fall within its scope, a few of which are described below.

*Propolis and HIV Infection* Propolis is a resinous substance collected by honeybees from certain species of trees and shrubs. It is used to seal the hive and has thus been called “bee glue,” although “bee caulk” may be more appropriate. It is a complex mixture of over 180 compounds, including flavonoids, caffeic acid, prenylated *p*-coumaric acids, and acetophenone derivatives. Propolis has been used as a natural biocide, literally, for centuries; a large database supports *in-vitro* antimicrobial activity of propolis against a variety of pathogens; and it has been shown to have broad anti-inflammatory and analgesic properties as well.

Philip Peterson of the University of Minnesota Medical School and the Hennepin County Medical Center and his colleague Genya Gekker have been evaluating the effects of propolis on HIV expression in CD4+ lymphocytes and microglia. In preliminary experiments they find that propolis has antiviral activity against HIV-1 variants in both cell types and that it does not antagonize the anti-HIV activity of standard antiretroviral drugs such as zidovudine (AZT) or indinavir. Propolis may have an additive effect on AZT activity (P.K. Peterson, personal communication). Currently, experiments are being planned with collaborators in clinical medicine and pharmacy to determine the clinical efficacy of propolis against HIV and with scientists in entomology and horticultural science to determine the biological and chemical nature of the active components.

*Effects of Soy Consumption on Blood Lipids* Since Minnesota is a leading soybean-producing state, it is not surprising that there is a great deal of interest in the beneficial aspects of soy consumption, both for chemoprevention of cancer and for cardiovascular health. One such example of on-going research comes from the laboratory of Mindy Kurzer in the Department of Food Science and Nutrition. Dr. Kurzer and her colleagues (Wangen *et al.*, 2001) carried out a randomized crossover trial of eighteen post-menopausal women who consumed three different isolated soy proteins for 93 days. These treatments provided three levels of isoflavones: 7 (control), 65 (low), or 132 (high) mg/day. Plasma LDL cholesterol was significantly lower during the high-isoflavone diet (Figure 2A), and the ratio of LDL:HDL cholesterol was significantly lower during the high- and low-isoflavone diets than during the control diet (Figure 2B).

Isoflavone consumption did not significantly affect total cholesterol, HDL cholesterol, or the total cholesterol:HDL ratio. Although these effects were small, it is possible that isoflavones would contribute to lowering the risk of cardiovascular disease if consumed over many years in conjunction with other lipid-lowering strategies.

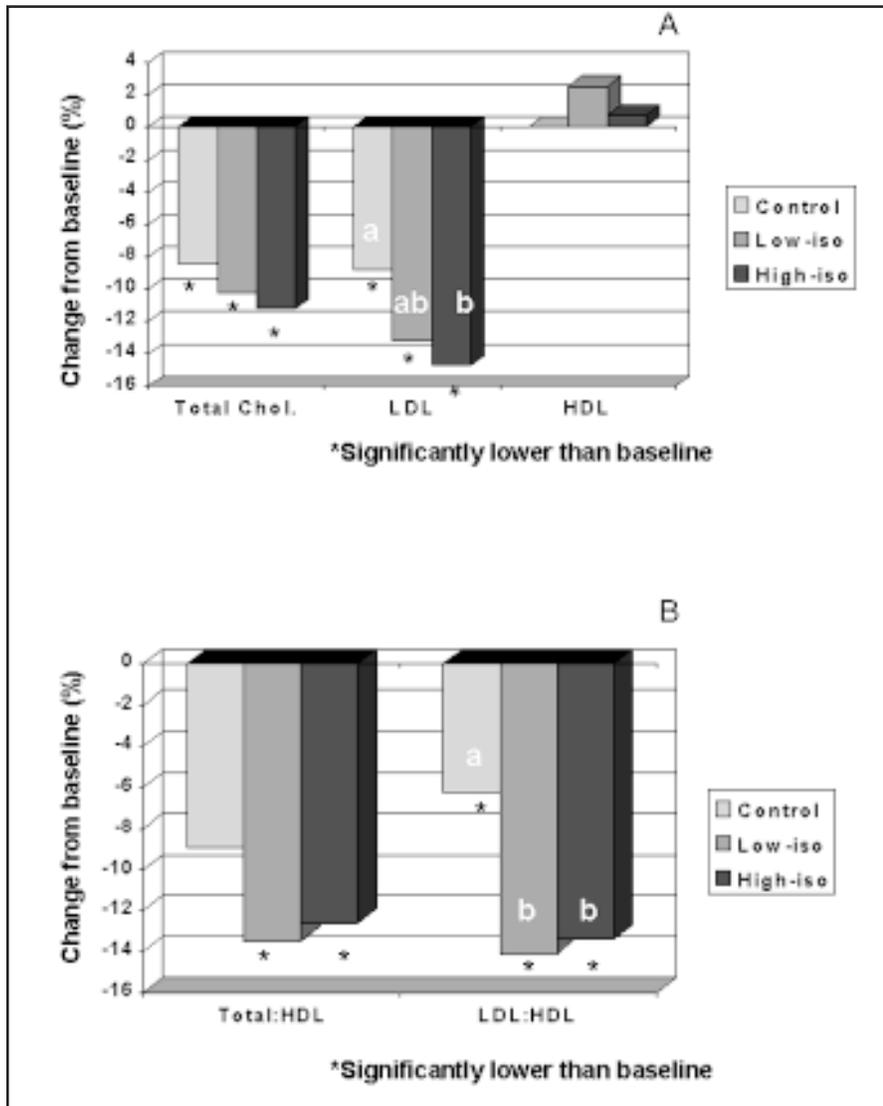


Figure 2. Effects of soy on cholesterol and lipids in post-menopausal women (adapted from Wangen *et al.*, 2001).

The breadth of research on soybean at the University of Minnesota offers significant interdisciplinary synergy. For example, the potential for collaboration between scientists in Nutrition and the Academic Health Center and those in Agronomy and Plant Genetics in the areas of soybean breeding and soybean molecular biology could lead to more-precise identification of the components of soybean that are responsible for beneficial effects on human health.

*Isothiocyanates for Chemoprevention of Lung Cancer* The University of Minnesota has a long history of research on the relationship between vegetable consumption and chemoprevention of cancer, largely due to the pioneering work of Lee Wattenberg of the Department of Laboratory Medicine and Pathology (e.g., Wattenberg, 1977). This tradition is being continued in the laboratory of Stephen Hecht in the University of Minnesota Cancer Center.

Consistently, studies demonstrate that vegetable consumption, including cruciferous vegetables, is protective against lung and other forms of cancer. These observations led to the hypothesis that there are chemopreventative agents in vegetables. A likely candidate for this activity is a class of isothiocyanates. These compounds exist in cruciferous vegetables as their glucosinolate conjugates, and when these vegetables are chewed or otherwise macerated, the plant enzyme myrosinase catalyzes the hydrolysis of the parent glucosinolate, releasing the isothiocyanate. There is considerable evidence in the literature that isothiocyanates have chemopreventative activity in animal models (Hecht, 2000).

One example of the chemopreventative effect of isothiocyanates comes from Dr. Hecht's laboratory. Phenethyl isothiocyanate (PEITC) occurs as its glucosinolate conjugate, gluconasturtiin, in a variety of cruciferous vegetables, including watercress, turnip, Chinese cabbage, and cabbage. Dietary PEITC was tested as an inhibitor of lung tumorigenesis induced in rats by the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (Hecht *et al.*, 1996). In the rats with NNK (2 ppm in the drinking water), 70% had adenoma or adenocarcinoma of the lung (Table 1). In the rats treated with PEITC (489 ppm in the diet) and NNK, complete inhibition of lung tumorigenesis was observed. PEITC alone had no significant tumorigenic or toxic activity.

*Regulation of the Chemopreventive Constituents of Vegetables in the Diet* The work of Drs. Hecht and Wattenberg, as well as many other reports of the chemopreventative properties of isothiocyanates, has led to a fourth example of work related to the mission of the Center for Plants and Human Health. This project is funded by the SOTA TEC Fund of the Blandin Foundation, and it developed in parallel to the Center although it exemplifies the kind of broad, interdisciplinary work that we seek to foster.

The overall goal of this project is to maximize the concentration of cancer

TABLE 1. LUNG TUMOR INDUCTION IN RATS TREATED WITH NNK OR NNK PLUS PEITC (ADAPTED FROM HECHT ET AL., 1996)

Treatment	Number of rats	Rats with lung tumors(%)
NNK	56	39 (70)
NNK + PEITC	59	3 (5)
PEITC	19	2 (11)
None	18	1 (6)

chemopreventative agents in vegetables, *i.e.* in the diet rather than as a supplement. The project has focused on glucosinolates, because of the results discussed above, and has three objectives:

- whole-plant studies to determine the environmental conditions that influence the biosynthesis of these compounds;
- applied (field) studies to optimize the content of these compounds in harvested plant material; and
- applied studies to determine the effects of various postharvest and processing treatments on the content of these compounds in vegetables in the diet.

The organization of this project is complex. There are ten co-principal investigators in four departments: myself, A. H. Markhart, and John Erwin of the Department of Horticultural Science directing growth chamber experiments; Vince Fritz of the Southern Research and Outreach Center and Horticultural Science, and Carl Rosen of the Departments of Horticultural Science and Soil, Water, and Climate directing field studies; Jerry Cohen of the Department of Horticultural Science and Steve Hecht of the Cancer Center directing the chemical analyses; Cindy Tong of the Department of Horticultural Science directing postharvest studies; Bill Schafer of the Department of Food Science and Nutrition directing the processing studies; and Dan Gallaher of the Department of Food Science and Nutrition carrying out animal feeding studies to evaluate the chemopreventative properties of the produce in diet.

This work is in progress, and I have three examples of preliminary data from our controlled environment studies. The first is from A.H. Markhart and Lynette Wong who are examining the effects of water stress on the gluconasturtiin content of watercress. Ms. Wong stressed watercress plants by withholding water until there was visible wilting in the youngest leaves. At that time, tissue was either harvested (one stress cycle) or plants were re-watered daily for three days. In separate experiments, plants were subjected to a second water-withholding treatment followed by re-watering. These results are shown in Figure 3. After two cycles of water stress, plants showed a highly

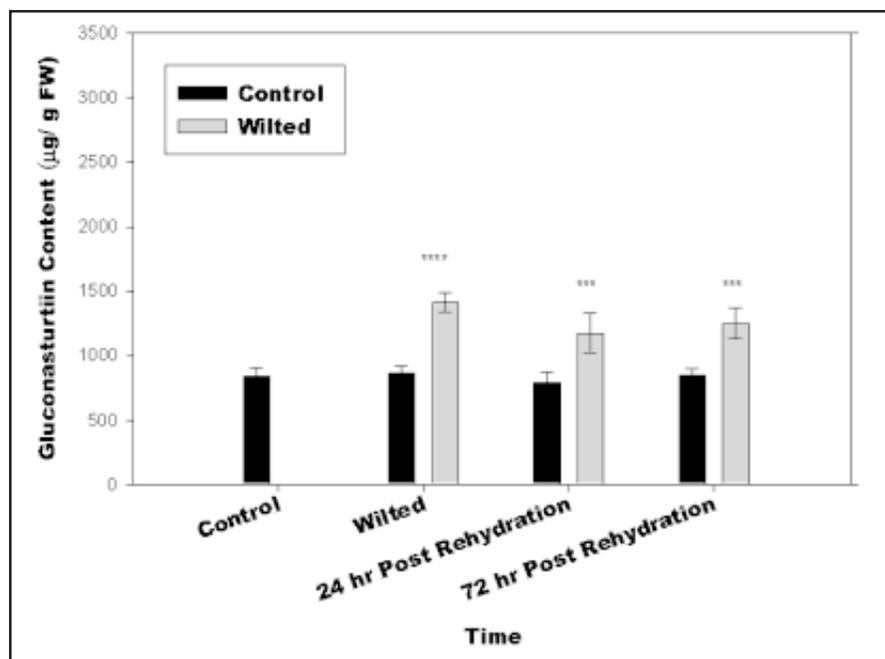


Figure 3. Two cycles of water stress on mean fresh weight gluconasturtiin content in watercress (\*\*\*) $P \leq 0.025$ , \*\*\*\* $P \leq 0.001$ ).

significant increase in gluconasturtiin content (on a fresh-weight basis). After 24 and 72 hours of re-watering, stressed plants had lower gluconasturtiin levels than the wilted plants (not re-watered); however, levels were still significantly greater than in plants that had never been stressed.

Two other examples of preliminary data from our controlled-environment experiments come from the work of Gerard Engelen-Eigles in my laboratory. Figure 4 demonstrates a temperature effect on gluconasturtiin content. Plants grown under a 20°C day/16°C night regime had a higher gluconasturtiin content on a fresh weight basis than those grown under a constant 20°C, and this difference increased over time. Therefore, cooler night temperatures seem to favor glucosinolate production. We are also examining various aspects of the effects of light on the gluconasturtiin content of watercress. One example is shown in Figure 5. Plants grown under metal-halide lamps (white light) showed an increase in gluconasturtiin with red-light supplementation from fluorescent lamps. This increase did not occur if the metal-halide light was enriched with far-red light. Our studies are continuing to further define environmental conditions in the laboratory and field that influence the biosynthesis of these compounds.

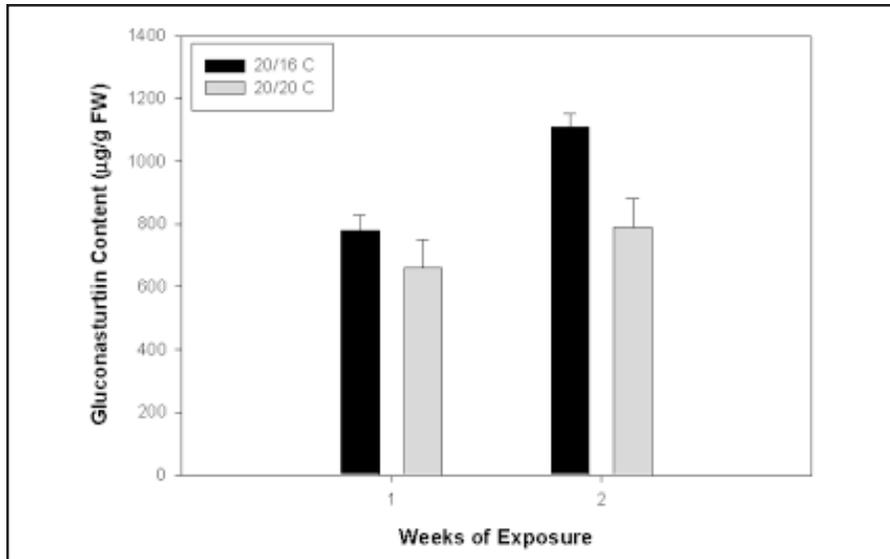


Figure 4. Effect of day and night temperatures on gluconasturtiin content in watercress. [photosynthetically active radiation (PAR): 450  $\mu\text{mol}/\text{m}^2/\text{s}$  from metal halide lamps]

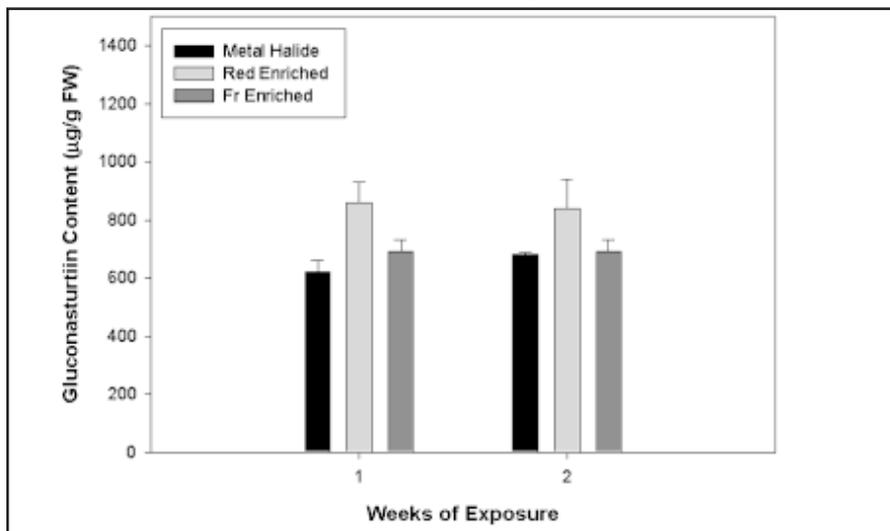


Figure 5. The effects of red- or far-red-enriched light on gluconasturtiin content in watercress. [Exposure to R, FR, or no enrichment (metal halide lamps alone) at the fifth mature leaf stage, grown under long days (16-h day) at a constant 20°C, and PAR from the metal halide lamps of 450  $\mu\text{mol}/\text{m}^2/\text{s}$ .]

## THE CHALLENGE OF INTERDISCIPLINARY RESEARCH— CHANGING THE PARADIGM

The current model for competitive research funding in the United States is primarily single-principal-investigator grants in a single discipline. As is apparent from the examples cited above, new approaches to the relationships between plants and human health will require collaboration among multiple investigators across several disciplines. At present, funding for this kind of work is rather limited. The United States Department of Agriculture (USDA) competitive grants are generally too small to fund multiple-investigator projects of this type. National Institutes of Health (NIH) grants can be of sufficient size, but generally the scope of such programs has not included agricultural components. The National Center for Complimentary and Alternative Medicine funds important work related to this topic, but its scope and funding base are limited.

It is important to note that plant-derived compounds constitute a major fraction of our mainstream drugs, not just those used in “alternative” therapies. If agriculture is to change its focus from the producer to the consumer in order to remain viable in the United States, and if medicine is to take full advantage of our knowledge-base in plants and nutrition and their role in the prevention of disease as well as cure, we need to define a new paradigm for funding this interdisciplinary work. It is our hope that the Center for Plants and Human Health will help to initiate a national dialogue on this issue. Additional information on Center activities is available at <http://cphh.coafes.umn.edu/>.

### ACKNOWLEDGMENTS

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## ***Spotlight on Minnesota: Highlighting Innovation in Agriculture, Food and Medicine***

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### ***Session 2 Developments in Medicine and Health***

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#### **Q&A**

MODERATED BY

**FRANK CERRA**

*University of Minnesota  
Minneapolis-St. Paul, MN*

*Frank Cerra:* How is a consumer to know what works and what doesn't? My frame of reference is this: we have only begun to teach evidence-based practice in the health-professional schools for the critical evaluation of data, and now we have nutraceuticals and medical foods. How is the consumer to deal with that?

*Gregory Plotnikoff:* Good decisions are always based on informed judgments. The question is: where are people getting their information? At least two surveys exist for which consumers were asked where they get information to make decisions regarding dietary-supplement purchase. At the very bottom of the list were physicians and pharmacists. At the very top of the list was what everyone fears: supermarket tabloids, neighbors and strangers. Surveys have shown that 70% of complementary therapies employed by people are not shared with their physicians. Part of the reason is that consumers fear being ridiculed or shamed by their doctors. The one message I take to physician groups that I address is: every patient encounter is a cross-cultural experience—listen for understanding before trying to be understood. Secondly, good resources are out there for evidence-based practice, and we can talk about those. My sense is: we

need a lot more randomized, controlled, phase-3 trials on these, and we need public sentiment or private industry to provide funds. These are not being funded right now to the degree that is necessary for the public's health.

*Cerra:* Clarence, I need to ask you to comment. You've had experience with the FDA's system for nutraceuticals and medical foods. Is labeling actually followed through—for instance, is your own product labeled as a medical food? And is the FDA's bar high enough to give comfort to consumers—is it not only something that works, but is the risk low?

*Clarence Johnson:* Historically, the bar has not been very high. There have been a number of instances in recent years where companies have gotten in trouble with the FDA for promoting medical food products directly to patients, which is not permitted under the guidelines. We are a small company and cannot afford to have too many run-ins with the FDA. So we are careful about that, and perhaps we even go too far the other way. We give our products to patients only through hospitals or other healthcare providers. We can't make health claims or promote our products directly to patients, but, historically, that has not always been the case. And there is no question that food companies and clinical-nutrition companies stretch the limits of the code.

*Gary Gardner:* We are trying to define problems where we can bring pressure to bear, and we are doing that with focused discussion groups. We are in the process of scheduling one on botanicals and herbals because it's an area that needs research, especially in standardization of pharmacological ingredients. I'm hoping we can define researchable topics and move ahead in that area.

*Mark Bolander:* From my perspective as an orthopedic surgeon who does mostly joint replacements, it is interesting to compare the experience 10 years ago with DMSO and the experience recently with chondroitin sulfate and glucosamine. I no longer have patients saying that they are using DMSO, yet I, not surprisingly, have a lot of patients who say they are using chondroitin sulfate. I don't know how many say they are not using chondroitin sulfate but actually are, but I suspect it's a lot. It seems to me that there are many reasons for the difference, and it seems like glucosamine and chondroitin sulfate are here to stay. One of the reasons might be that an NIH-funded study showed that they are efficacious. It seems to me that although that doesn't answer everyone's questions, that type of NIH-funded study has value especially from the perspective of small companies that not only cannot afford a run-in with the FDA but also can't afford a major clinical trial. Recently a new NIH institute for alternative medicine was established, and I would think that that is a potentially good source of support for these types of activities. But I don't know how successful or how active it has been.

*Plotnikoff:* Frank, what is the total budget of NIH for 2002? Is it 22.3 billion?

*Cerra:* Twenty-three billion dollars, I think.

*Plotnikoff:* Okay, and approximately \$96 million of that is devoted to the National Center for Complementary and Alternative Medicine Research. It has the lowest percent of R21- and R01-funded studies. The interest is overwhelming. It is far more competitive and more difficult to get something funded through there than through other NIH organizations.

*Cerra:* That is all true. On the other hand, it's amazing that we have such a center at NIH, and that alone means we are heading in the right direction to get the science done to tell us what works and what doesn't.

*Audience member:* Older people frequently overmedicate themselves with pharmaceuticals—over-the-counter as well as the prescription medications—and now we are talking about introducing pharmacologically active foods. How will we standardize these to prevent cross-reactions and more overmedication? Has that been thought about?

*Plotnikoff:* That's a very important question. Many things control drug metabolism. Red wine, cigarettes, charbroiled meats, grapefruit juice, *etc.*, can affect very commonly prescribed medications such as calcium channel blockers and anti-cholesterol agents. In fact, we do need to raise consciousness and this is a competency issue for health-science students. Your particular question about the geriatric population I would switch: there are pharmacologically active compounds in food, which, because of their concentrations, would be very hard to overdose on. Should those be the first-line approach rather than the pharmaceutical agents with an associated higher risk of toxicity? In a country such as Japan, I would say that 88% of their OB-GYN, 83% of the cardiologists, and 70% of all physicians incorporate traditional herbal medicines as part of the routine care for common conditions such as arthritis, rheumatism, fatigue, and menopause, and for cancer support. They do so because of reduced toxicity, and because you don't need a very aggressive pharmacologic agent for the elderly. As a society we probably won't be able to afford it either. This is an area of huge interest to this audience in terms of how can non-traditional pharmaceuticals enhance the health of our aging population.

*Paul Otten (St. Paul, MN):* I am director of a corporate health organization in St. Paul and work directly with about 500 consumers who are self-pay and, therefore, have choices that they would not have if they were third-party payers. First of all a comment. I think that we assume that if it is FDA regulated then

consumers will trust the end-product. I find that that is not necessarily the case. I applaud what Gary Gardner at the University of Minnesota is doing. I also am grateful for the double appointment of the dean in terms of being connected with the medical school. However, I have a problem in trusting our public messages—no matter what the nutritional question is, you should consult with your medical doctor. Yet, until this year, there wasn't a single required course at our own medical school on nutrition. Why am I sent to a medical doctor for nutritional consultation when they have no educational background? When I am sent to the plumber, I don't ask questions about electricity, or *vice versa*. Many of my people say that when they go to the medical doctor and ask about nutrition they are told that nutrition has nothing to do with their cancer or cardiovascular disease. And when they go to the hospital they may be given donuts for breakfast—as happened to my granddaughter. As for getting trustworthy information, I find I have to go to multiple sources and finally may depend on intuition—my fifth or sixth sense—to determine what is right and what is wrong. I also believe that what Dr. Gardner and his staff are doing in terms of finding basic answers makes people trust a lot more than high technology that is over the head, hard to explain and, above all, requires a lot more dollars than simply going back to the basics. Where can someone like myself—responsible for the health of 500 people, on the preventative end as well as on the repair end—where can I go for the best possible reliable information to share with my people?

*Plotnikoff:* Reliable sources of information are available to help people make informed decisions, such as [consumerlab.com](http://consumerlab.com), which is a subscription service where independent third-parties provide evaluations of quality of nutritional products. Second, would be the *Pharmacist's Letter*. Again pharmacists and others have come together and prepared very reliable sources. Third, the American Botanical Council has taken a leadership role in herbal issues. In fact, I have been in contact with the Minnesota Board of Medical Practice which is raising the very same question, and so the Center for Spirituality and Healing and the Center for Plants and Human Health at the University of Minnesota are going to take seriously the commitment to be a public resource and to engage in educational activities that are appropriately science-based at the undergraduate, graduate, and professional levels. I would take it as a positive thing if the public would support a move in this area to enhance competence in our graduates to be able to council, from an evidence-based perspective, in both prevention and treatment by low-cost, low-tech, low-toxicity interventions.

*Cerra:* That last question, in the form of a statement, is correct. There is not enough nutrition in the curriculum of health professionals either in the didactic portion or the applied portion. This is near and dear to my heart. I spent 20 years in research on human nutrition and the situation is slowly changing.

However, I do not think this university has captured the value of its investment in nutrition. We have more resources in nutrition than almost any of the top-five world universities. We have not captured it in an inter-disciplinary approach. But it is getting better. I think this new center is going to help, the Center for Spirituality has helped, the School of Pharmacy is replanting its herb garden, which it gave up in 1930, and so on. So it is just going to take some time. Your point was well made. Last question.

*Ilya Raskin (Rutgers University, New Brunswick, NJ):* This has been a wonderful meeting. I have attended most of the talks and feel that an important category has been almost completely omitted from the discussions: botanical drugs. The FDA has the guidelines for botanical drugs and is actively pushing them. They include phenylethyl isothiocyanate (PEITC), ribose, and free omega-3 acids that can be developed as drugs. And then there is no issue about where information will be available. They'll be labeled, and physicians will prescribe them. As you know, some pharmaceutical companies—progressive ones, Pfizer for example—are quietly developing botanical drugs as standardized extracts, which are very similar to the products you are discussing. So my question to the panel is: why won't you consider some of those products and put them into the mainstream?

*Johnson:* Speaking from my own perspective, we have been fairly aggressive in the last few years in looking at the effects of ribose given as a drug intravenously post cardiac surgery or as a diagnostic enhancer for cardiovascular disease. We have completed phase-2 clinical trials for the use of ribose as a diagnostic, and we are, in fact, taking this product through ethical drug channels to make it available by prescription for post-cardiac surgery, for trauma, and for cardiac diagnosis.

*Cerra:* Clarence, you might want to comment on what I think goes to the core of this: patentability. I was 10 years into the study of omega-3 fatty acids in signal transduction before we had a standardized source that the NIH finally took over. That's part of the problem. The second part of the problem is omega-3 itself is a GRAS substance, so how does a company protect itself in moving forward to make the investment to get something classified as a drug instead of as a medical food?

*Johnson:* It is very difficult. Obviously you can't patent the compound because it's naturally occurring. However, you can patent uses for the compound. If you find a compound—in our case it was ribose—that's effective in treating ischemic tissue for recovering function, you can patent that use. And there are certainly composition of matter patents. But when taking technology from a company like ours to Baxter or Abbott or whomever, and trying to partner up

with them—because it is horribly expensive and long-term to bring these products to market—it's difficult to get the classical pharmaceutical companies to understand the value of use patents when they are so traditionally locked into compound patents—after they make a new compound. So we are working very hard to build a patent picket fence around the compound so that when we do take it to someone they will see that, although it isn't as strong as a compound patent, there is so much protection that we have something valuable.

PART VI  
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