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Biotechnology: Enhancing human nutrition in developing and developed worlds

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ABSTRACT While the last 50 years of agriculture have focused on meeting the food, feed, and fiber needs of humans, the challenges for the next 50 years go far beyond simply addressing the needs of an ever-growing global population. In addition to producing more food, agriculture will have to deal with declining resources like water and arable land, need to enhance nutrient density of crops, and achieve these and other goals in a way that does not degrade the environment. Biotechnology and other emerging life sciences technologies offer valuable tools to help meet these multidimensional challenges. This paper explores the possibilities afforded through biotechnology in providing improved agronomic "input" traits, differentiated crops that impart more desirable "output" traits, and using plants as green factories to fortify foods with valuable nutrients naturally rather than externally during food processing. The concept of leveraging agriculture as green factories is expected to have tremendous positive implications for harnessing solar energy to meet fiber and fuel needs as well. Widespread adaptation of biotech-derived products of agriculture should lay the foundation for transformation of our society from a production-driven system to a quality and utility-enhanced system.

Over the last 50 years, our society has faced the challenge of feeding an ever-growing world population. Human population has literally doubled in the last 40 years and increased 6-fold in the last 200 years. Since the beginning of this century, agriculture has intensified—first, with the discovery of economic, chemical processes to reduce nitrogen to ammonia and the use of nitrogenous fertilizers in agriculture, superior genetics with hybrid as well as varietal crops, resulting in a global green revolution, and finally, with the discovery and use of chemical pesticides to manage a range of pests, including weeds, microbes, and insects. Intensive agriculture as practiced today fully leverages all of the above advances and in addition is benefited by superior irrigation techniques, better tillage systems, etc. Global cereal yields practically doubled between 1960 and 1990. Yields of both rice and wheat, crops largely consumed by the rapidly growing Asian population, have dramatically increased.

These agricultural technologies, however, have not kept pace with projected population increases. If population outstrips food availability, more marginal land will necessarily be placed into agricultural use, heavier inputs will be applied, and food self-sufficiency, especially in emerging economies, will be compromised. The challenge over the next 50 years will be to not only feed more people, but to do so in such a way that takes into account these facts:

- There will be less arable land. A combination of overplowing, overgrazing, and deforestation has caused soil erosion to exceed soil formation. Countries particularly hard hit are those in continents like Africa, where soil is shallow to begin with. The next generation of farmers in Africa will need to feed not the 719 million people of today, but 1.45 billion people in the year 2025 and with far less topsoil (1). Even so-called low-tech agriculture, sometimes viewed as more sustainable, still relies on chemical inputs and involves techniques, such as plowing, that degrade the soil.
- There will be fewer resources, particularly nonrenewable resources like phosphorus and potassium, which go into fertilizers. The U.S. Bureau of Mines showed a 7-fold increase in consumption of U.S. industrial minerals, including fertilizers and feed stocks from 1900 to 1980, and this trend is expected to continue (2). While it could be argued that we have sufficient natural deposits of these minerals to last another 200 years, technologies that minimize ore extraction and dispersion over vast areas of land will enhance the sustainability of our agricultural systems.
- There will be less water, and the quality of remaining water also will be reduced as demand increases. Also, competition for reduced water supplies between rural and urban societies will increase. Water use has tripled since midcentury (3), and water tables are falling all around the world. Seventy percent of all the water pumped from underground or drawn from rivers is used for irrigation, and if we face a future of water scarcity, we also face a future of food scarcity.
- Fewer people will be engaged in primary agriculture in both developed and developing countries. In the United States, less than 1% of the population is engaged in primary agriculture, compared with 60% of the population in the early 1900s (U.S. Bureau of the Census).
- People engaging in primary agriculture will be older. The breadbaskets of the world, particularly Western Europe and North America, have the most graying population. The generation born in the U.S. during the baby boom of the 1950s will be in their 60s by 2010, ushering in an age of unparalleled increase in absolute numbers of elderly. According to the U.S. Bureau of the Census, by 2010, half of the U.S. population will be 37 or older—a very high median age (4). This aging society will need technologies that will allow it to produce food in a more cost-effective, less labor-intensive, and more convenient way than they have done in the past.
- Health-care costs will continue to increase as the population ages, putting more demands on public aid. Governments' ability to pay for Social Security and health care will decline as the population increases and the number of people contributing to Social Security, once the baby-boom generation retires, will decrease. This will be particularly critical for the developed nations of this planet. For the developing economies, health care oriented toward prevention and

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health delivered inexpensively is critical as their middle class expands and human longevity dramatically increases.

- As a result, food that can provide more than just calories and essential nutrients but has the ability to delay the onset of degenerative diseases and aging will be a powerful contributor to a healthy, global society.

We need an array of new and improved technologies, which can form the foundation for infrastructure and cultural improvements, to help address these challenges.

Luckily, we are entering an epoch rich with opportunity for breakthrough technologies. Termed the information revolution, this era is certain to have at least as big an impact on society as the agricultural revolution and the industrial revolution. Information-driven agriculture will have two components. The first is information based on genomics, the study of genes, the strands of life, which is an enabling link across life sciences, including agriculture, food and nutrition, and pharmaceuticals. This constitutes the next tier in scientific understanding and opportunity and is discussed in greater detail later.

The second component is information that is based on the silicon revolution of the present time. Computer and modern electronic communication systems can be applied across the life sciences to maximize value. Today, in agriculture, farmers are taking advantage of the system for precision agriculture that optimizes inputs, characterization of outputs so that they can match the needs of their customers with specific products as well as managing their business based on real-time information.

Biotechnology is a discipline that has developed rapidly during the last two decades. This technology is based on our fundamental ability to precisely introduce genetic changes into an organism. Plant biotechnology in particular has evolved rapidly over the course of the last 15 years. Every major crop can be subject to precise genetic modifications based on our ability to introduce and express genes in crops. Plant biotechnology therefore should substantially augment plant breeding, which in many respects was based on our ability to harness genes into plants either by sexual crossing or laboratory techniques such as cell fusion. We anticipate that plant biotechnology will go through three phases of development, creating significant value at each stage. The first is agronomic trait development, the second is differentiated crop development, and the third is use of plants as factories. These are discussed in detail below.

Agronomic Traits

Since 1995, major products with improved agronomic traits have been introduced in the U.S. and other parts of the world. These are mostly single gene traits where a single gene has had a dramatic positive impact on grower productivity. This is reflected in the widespread acceptance and use of genetically improved crops in the United States, which is estimated to be 46 million acres. A few examples of these products are Monsanto's Roundup Ready soybeans and YieldGard corn and are discussed below.

Roundup Ready soybeans contain a gene encoding the enzyme 5-enolpyruvylshikimate 3-phosphate synthase (EPSPS) involved in the biosynthesis of aromatic amino acids in plants. The EPSPS gene naturally present in soybeans produces a form of the enzyme sensitive to glyphosate, the active ingredient of Roundup, whereas the gene in Roundup Ready soybeans encodes a catalytically active and glyphosate-tolerant form of the same enzyme (5). Expression of this gene in plants renders adequate commercial tolerance to this herbicide.

Roundup Ready soybeans are one of the most widely accepted products that have been introduced in the history of agriculture. Within 3 years of commercialization, the crop has grown to the point where it now accounts for almost 40% of total U.S. soybean acreage. Roundup Ready soybeans offer several benefits to farmers, including a superior weed management system. Roundup, a post-emergent, broad spectrum herbicide controls most weeds in the field and needs to be used only when weed control is needed. Indeed in 1997, U.S. growers used only Roundup on 83% of the Roundup Ready soybean acres. Another benefit is yield optimization (5% higher yield with lower operating costs). Roundup also has demonstrated favorable environmental characteristics. It breaks down over time in soil to innocuous products (ammonia, phosphate, carbon dioxide and water), is highly unlikely to move in groundwater, does not accumulate in the environment or food chain, and is practically nontoxic to multiple life forms such as aquatic, avian, animal, and human. The combination of the Roundup Ready soybeans and Roundup also enhances the ability of the farmer to use the seeds in conjunction with less resource-intensive farming practices like conservation tillage, which helps conserve topsoil.

Before the introduction of this product into the marketplace, we conducted a number of safety assessments for not only the herbicide but also the genetically improved soybeans. Those studies demonstrated the nutritional equivalency of the soybeans containing the Roundup Ready gene to those without the gene. The gene product also was investigated for its safety and digestibility and demonstrated to be a rapidly digested protein similar to many other proteins found in our food chain (6).

YieldGard corn uses a plant-modified version of the gene encoding an insecticidal protein from a naturally occurring bacterium, *Bacillus thuringiensis* (7, 8) to help the plant resist the European corn borer, which annually infests some 40 million acres of crops in the U.S. Average annual yield loss caused by the corn borer is 6% and can be as high as 20% and represents $1–2 billion in losses to farmers depending on the extent of infestation of the corn borer. With YieldGard, farmers achieve 11–15 additional bushels of corn per acre. Even subclinical infestations, which otherwise would go untreated resulting in smaller yields, can be avoided, thereby boosting yields. The YieldGard gene significantly reduces the damage caused by the European corn borer to the corn crop—damage that has the potential to cause onset and spread of fungi and other microbes in the corn plant and produce undesirable toxins. Safeguarding the corn plant against the corn borer therefore provides secondary benefits of yield protection from other pests as well as quality protection.

While our discussion above has been restricted to two examples of products of biotechnology, it should be pointed out that several other products within the category of agronomic traits have been introduced into the marketplace. These include Bollgard cotton, Roundup Ready canola, cotton, and corn, Liberty Link canola and corn, New Leaf potato, virus-resistant squashes, and melons.

Near term, a number of other agronomic traits are expected to be commercialized. In our own laboratories at Monsanto, we are working on a trait that will protect corn from corn root worm, a major insect pest of corn that causes losses approaching $1 billion in the U.S. Healthy root systems, crucial for water and fertilizer uptake, are destroyed by this pest. By controlling root worm, it is our expectation that not only is the yield likely to be better protected but the crop also will have greater drought tolerance and fertilizer use efficiency, leading to better grain quality.

Resistance against head scab disease in wheat, caused by the fungus *Fusarium graminareum*, is another agronomic trait under development. Longer-term agronomic traits such as crop architecture redesign, better fertilizer utilization, heat, frost, and drought resistance, as well as salinity and heavy metal tolerances are expected to be developed. Understanding the functions of many of the genes in plants will be critical for these advances to occur. Plant genomics will play a pivotal role in this endeavor.

Differentiated Crops

While agronomic traits discussed in the previous section have largely focused on input traits, differentiated crops are more focused on grain quality or output traits. Classical breeding has produced a diverse array of differentiated crops such as canola vs. high erucic and glucosinolate containing rape; waxy and high amylose maize vs. yellow dent corn; basmati vs. long grain rice; durrum wheat vs. regular wheat, etc. With biotechnology, our ability to create differentiated, value-added products that create value downstream of production is greatly enhanced. Such differentiated crop offerings are beginning to appear in the marketplace and are discussed below.

A vast majority of the grains in the Western Hemisphere are used for feeding animals, and it is not surprising that a significant activity in the differentiated crop arena is focused on improving the feed quality of crops. Two types of products now are being created—one focused on increasing caloric density of the grain by increasing its oil content and another on nutrient density, particularly the levels of protein, essential amino acids, and other micronutrients.

High-oil corn, introduced by DuPont, is the first example of this type of product. High-oil corn typically has an oil content of more than 6% as opposed to the 3–4% found in commodity corn. This near doubling of the oil content is expected to dramatically reduce the exogenous addition of fats in the diets of animals and birds. One of the major problems with high-oil corn germplasm has been the yield drag associated with the product. This has been substantially addressed by a technique known as TopCross. Although high-oil corn is not strictly a biotechnology product of the type described earlier for agronomic traits, molecular aspects of breeding have facilitated the rapid creation and commercialization of the product. Our understanding of the genome of corn and other cereals should facilitate molecular breeding and harness the genomic potential of these crops much more powerfully in the future.

High-oil corn now is being improved by the addition of high-protein genes as well as by increasing the essential amino acid content of the grains. The high-protein trait itself is also a product of molecular breeding, while high lysine is derived by introduction of critical genes altering the flux of carbon and nitrogen via the lysine pathway in the seed. In the future, we should expect cereals fortified with all the critical essential amino acids such as lysine, methionine, threonine, and tryptophan, and thus be able to reduce the exogenous applications of these amino acids in feed rations. In addition to corn, other crops such as wheat, soybeans, and canola are being subjected to similar improvements.

Direct utilization of the grain by improvements in nutrient density and taste/texture appeal for human consumption will go a long way toward meeting not only the food demands of our ever-growing population but also indirectly will benefit our society by increasing the levels of phytonutrients, which are being increasingly shown to have health-promoting attributes in humans (9, 10).

Our research efforts have focused on oil modification of canola and soybeans. Most of the oil derived from oil seeds is used in human consumption. Vegetable oils generally are preferred to oils and fats from other sources because of their higher content of mono- and polyunsaturated fats. Fats and oils are one of the most important flavor and texturizing components of food. To create the appropriate texture and mouth feel in foods, it is often necessary to hydrogenate vegetable oils, a process that results in the production of trans-fatty acids. There is a growing body of evidence that suggests that trans-fatty acids found in hydrogenated fatty acids may potentially increase total and low density lipoprotein (LDL) cholesterol in humans. Total and LDL cholesterol now are widely accepted as some of the important biomarkers of the risk of cardiovascular disease in humans, and a number of countries are making significant efforts to educate people on the benefits of keeping the levels of these two biomarkers in the healthy range (National Cholesterol Education Program).

By inhibiting the conversion of stearate to oleate in plants, it is possible to produce a trans-fatty acid-free solid or semisolid fat directly in oilseeds. One of the advantages of stearate over other saturated fatty acids is that it is not hypercholesteremic (11). High stearate soybean and canola now have been produced and are being evaluated for their commercial utility.

Grain legumes are some of the most valuable sources of vegetable protein in the human food and feed chain. Soybean, a legume grown on a majority of the legume acreage of the world, is a vital protein source for many people living in Asia. Its use as a protein source can be further enhanced if several attributes such as flatulence, beany flavor, texture, and emulsification properties can be addressed. A number of laboratories are attempting to address these issues.

Plants as Factories

Plants, nature's best manufacturing system, provided the sole source of food, feed, and fiber to society for many centuries until fossil fuel use began. The concept of using plants in place of chemical or nutrient factories to supply food, feed, and fiber is gaining significant attention and constitutes the first step toward biotech-based, nutritionally fortified foods.

An important example is high carotenoid canola, rich in beta carotene—a precursor to vitamin A. Many of the western countries address the problem of vitamin A needs of humans by fortifying milk with this vitamin. However, this system is impractical in most parts of the world. According to WHO (12), vitamin A deficiency is today a global epidemic—250 million children are at risk of vitamin A deficiency on an annual basis, and somewhere around 10 million people suffer from significant illness and death resulting from a vitamin A deficiency in their diets. This deficiency results in impairment of vision, protein malnutrition (vitamin A affects amino acid absorption and utilization), and impairment of immune functions.

Essentially all countries in Latin America, Asia, and Africa are either clinically or subclinically deficient in vitamin A (13, 14). The best sources of vitamin A are the carotenes, particularly beta carotene, found in many fruits and vegetables. These carotenes are effectively converted into vitamin A and generally are accepted to have much higher safety than vitamin A itself. Fruits and vegetables with high carotene content are not routinely available at affordable prices to poor people, and for those who can afford them appropriate food sources that are fortified with these precursors are not available. One of the most important contributions that biotechnology can make to world health is to produce crops naturally fortified with this important nutrient that people can grow in varied global regions and that would become part of their regular food intake. This also would reduce the need to exogenously fortify foods with nutrients produced outside of the plant.

Fortification within the seed enhances nutritional quality for all types of farmers. With fortification, local crops grown by subsistence farmers and best suited to their growing conditions naturally would include these nutrients. Large, commercial farmers would reap the same benefit. This represents a whole new way of thinking about food fortification. Biotechnology could be used as a delivery system that benefits all levels of farming from the subsistence farmer to the large-scale, global grain grower.

We have introduced the gene *phytoene synthase* into canola and demonstrated that the expression of this gene results in high levels of beta carotene accumulation within the rape seed (Table 1).

Rape seed, popularly known as mustard seed, is grown in many parts of the world, including Africa, Asia, and Latin America, and its use is increasing. These are the same regions with high levels of vitamin A deficiency. Interestingly, in addition to containing high levels of beta carotene, rape seed oil expressing the *phytoene synthase* gene has a higher level of alpha carotene, lutein. In comparison with other sources of provitamin A, such as red palm oil, this annual crop has the ability to provide a varying range of carotenes, vitamin E, and a healthier profile of fatty acids. Harnessing the full genetic potential of the rape seed crop can go a long way toward addressing the nutritional needs of our ever-growing population—the high beta-carotene canola is expected to be commercialized within the next 3–4 years.

While the example provided above illustrates the power of biotechnology for addressing the nutritional needs from the perspective of a well-established nutrient, the same technology can be harnessed to address the nutritional needs of even advanced countries of the world by producing new nutrients in grains. As our understanding of the human genome and the biochemical reactions associated with the onset of degenerative processes in the body increases, we are likely to understand the role of many nutrients in our food that can both accelerate as well as inhibit such processes. By using biotechnology, we can eliminate antinutrients (which will accelerate the degeneration of health and progression of disease) and increase the levels of nutrients that can help us live healthier lives. One example of such a nutrient is provided below.

At the present time, cardiovascular diseases account for most deaths in Europe and North America and are becoming more prominent in urban societies in the rest of the world. The cost to society in the United States is estimated to be $260 billion annually from cardiovascular-related disorders, including heart disease, coronary artery disease, stroke, hypertensive disease, and congestive heart failure. As described earlier, total and low density lipoprotein cholesterol are important biomarkers of cardiovascular health and are routinely monitored to assess the health status of individuals (15). High total cholesterol levels contribute to cardiovascular disease and levels below 200 mg/dl are desirable. Approximately 115 million people in the United States appear to have cholesterol levels between 200 and 239 mg/dl and have a higher risk of death caused by myocardial infarction (American Heart Association data). While people with cholesterol levels above 240 mg/dl are given prescribed drugs, drug therapy generally is not recommended for people with lower cholesterol levels in view of the considerations of cost, safety, etc. Very few people who have these intermediate levels of cholesterol strictly follow the recommended practice of reducing the saturated fat intake and exercising, thereby increasing the risk of contacting the disease and cost to society.

It has been known for quite some time that phytosterols have the potential to reduce cholesterol in humans by 10–15% by interfering with cholesterol absorption in the gastrointestinal tract (16, 17). Indeed products containing these phytosterols such as Benecol and Take Control are beginning to appear in the market to assist individuals in managing their cholesterol levels more aggressively. Phytosterols are not currently available in adequate quantities in the foods that we ordinarily consume. It has been known for some time that expression of genes in the phytosterol pathway in plants increases the sterol content of plant tissues. Based on these and other novel genes, we now are working on increasing the phytosterol content of several grains.

Table 1. Composition of high carotenoid canola

	High carotenoid canola oil, μg/gm	Red palm oil, μg/gm
Carotenoids (Total)	2025–2466	480–672
β-carotene	690–920	280–392
α-carotene	470–530	175–245
Lycopene	8–33	7–9
Lutein	85–196	0
Phytoene	760–820	10–15
Tocopherols	400–500	90–150
Tocols	400–500	600–1000

While the above example serves to illustrate the power of the technology in the context of cholesterol, several other nutrients and their relationship to human health now are being investigated. A range of fatty acids that modulate inflammatory reactions in the human body, and antioxidants that have sparing effects on antioxidant vitamins such as vitamin C and E and that also boost the levels of antioxidant defense enzymes in the human body are just a few examples of a multitude of discoveries that are likely to emerge in this area in the near future (18).

Most of the progress to date has been made by using either single genes or first-generation molecular breeding capabilities. Rapid accumulation of sequence data from both chromosomal DNA and expressed sequence tags of plants and other species is giving us significant insights into the genetic makeup and functions of several genes in plants (19). Complementation of the sequence information with high throughput gene expression analysis and mutation/gain of function biological analysis is beginning to open the doors to a vista of knowledge on the role and functions of many of these genes. Plant genomics, which is only a few years old, is expected to provide whole new insights into designing crops that are superior in every aspect of both input and output traits that are described here.

In summary, biotechnology adds value across the system from crop to farmer, customer and consumer. Biotechnology can, and is, enhancing the quality of food in addition to improving the quantity of food. Biotechnology can improve the sustainability of production systems by requiring fewer inputs to control pests and better protect the quality of water and land mass around us. Biotechnology can add health and vitality to humans. As we look at food production in a more holistic way, biotechnology will be an important component of that holistic system.

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