The past, present and future of crop genetic modification

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The introduction of science and technology into agriculture over the past two centuries has markedly increased agricultural productivity and decreased its labor-intensiveness. Chemical fertilization, mechanization, plant breeding and molecular genetic modification (GM) have contributed to unparalleled productivity increases. Future increases are far from assured because of underinvestment in agricultural research, growing population pressure, decreasing fresh water availability, increasing temperatures and societal rejection of GM crops in many countries.

Introduction

The world has experienced a succession of shocks over the past two years: a global food crisis, spiraling energy costs, accelerating climate change and most recently, a financial meltdown. The food crisis sparked riots in countries on every continent (http://www.time.com/time/world/article/0,8599,1717572,00.html).

But even as each crisis sweeps the previous one out of awareness, it is crucial to recognize that the food crisis is not a transient phenomenon. Indeed, crisis is a misnomer.

The current situation developed over a very long time as a result of relentlessly increasing demand pushing against a shrinking natural resource base, even as investment in agricultural research and development declined decade by decade. The oil price spike combined with widespread droughts in 2007 and 2008 to aggravate the underlying trends and send grain prices spiraling. Prices have come down since, but the overall upward trend persists. Indeed, the adequacy of the food supply will increasingly be a crucial issue, if not *the* crucial, of the 21st century [1].

Integration of science and technology into agriculture

Food security is not a new concern. In recent times, it was Thomas Malthus' famous 1798 Essay on Population that crystallized the problem of balancing food and human population [2]. Indeed, Malthusian has entered the language to denote the prophecy that humanity is doomed to poverty and famine because the growth of the human population must inevitably outstrip mankind's ability to increase food production. Malthus penned his essay at about the time that science began to enter agriculture in earnest. Late 18th century milestones were Joseph Priestley's discovery that plants emit oxygen [3] and Nicholas-Théodore de Saussure's definition of the chemical composition of plants [4]. Malthus could not have envisioned the extraordinary increases in productivity that the integration of science and technology into agricultural practice would stimulate over the ensuing two centuries.

Both organic and mineral fertilization of plants have ancient roots. Long before the reasons were understood, people knew that certain chemicals, such as saltpeter and lime, as well as a wide variety of biological materials ranging from fish and oyster shells to manure and bones stimulated plant growth [5]. Justus von Liebig laid the foundation for the modern chemical fertilization methods in the early 19th century by identifying the major chemical requirements for plant growth [6]. Although it was known by mid-century that biological sources of nitrogen could be replaced by chemical sources, supplying nitrogen in the reduced or oxidized forms that plants use remained a major limitation until the development early in the 20th century of the Haber–Bosch process for fixing atmospheric nitrogen on an industrial scale [7]. Today agriculture in the developed world relies primarily on chemical fertilizers.

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Crop domestication

Long before chemistry entered agriculture, people were doing what we now call genetic modification (GM), transforming inedible wild plants into the crop plants that feed people and their animals today. Corn, also known as maize (*Zea mays*), remains arguably the most spectacular feat of genetic engineering ever accomplished. Its huge ears, packed with starch and oil, provide one of humanity's three top food and feed crops. Corn bears little resemblance to its closest wild relative, teosinte. Indeed, the two are so dissimilar that when teosinte was first discovered in 1896, it was assigned to a different species and named *Euchleana mexicana*. Although it was already known in the 1920s that teosinte and corn have the same number of chromosomes and readily produce fertile hybrids, controversies about their relationship and about the origin of corn continued throughout most of the 20th century.

It was the work of Dr John Doebley and his colleagues starting with the genetic analysis of teosinte–corn hybrids that precisely defined the genetic changes that transformed teosinte into modern corn (http://www.teosinte.wisc.edu/publications.html). Perhaps the most remarkable outcome of his genetic sleuthing is that the difference between teosinte, a grass with hard, inedible seeds and modern corn resides in just a handful of genes. Fossilized cobs recovered from caves in Mexico and dated as more than 6000 old already have the multirowed character of the modern corn ear, as do almost 4000 year-old cobs from the Ocampo Caves in northeastern New Mexico [8]. Doebley's later work with the evolutionary geneticist Svante Paabo traced the key genetic changes that transformed teosinte into corn to the Balsas River Valley in Mexico and dated them to roughly 6–10,000 years before the present. What is even more remarkable is that once this handful of mutations had been brought together, the suite of genetic changes stayed together and spread very rapidly, so that the same group of alleles had already penetrated into the American Southwest more than 3000 years ago.

Perhaps the most important insight that has been gained through the molecular analysis of crop domestication is that people have vastly changed wild plants to transform them into crop plants and that this has been done over many thousands of years. All of the changes are genetic changes. This is as true of wheat and rice as it is of tomatoes, cabbage and oranges. Each crop has its own interesting history [9]. Among the most important traits that distinguish wild from domesticated plants is the retention of mature seeds on the plant. Plants have a variety of mechanisms for dispersing their seeds, central to which are the shattering of the seed structure upon maturation. It is much easier for people to harvest seeds if they remain attached to the plant, hence the selection of genetic changes, technically known as *mutations*, that prevent seed dispersal is thought to be among the earliest steps in crop domestication.

Among the many other traits altered during domestication are the size and shape of foliage, tubers, berries, fruits and grains, as well as their abundance, toxicity and nutritional value. The underlying genetic differences that distinguish a domesticated crop plant from its wild progenitors are many, but molecular analysis is revealing that key changes are often in genes that encode transcription factors, proteins that regulate the expression of many other genes [10]. Differences in nutrient composition among varieties of the same crop are attributable to mutations in genes coding for proteins of certain biosynthetic pathways. For example, mutations in genes for enzymes involved in the conversion of sugar to starch gave rise to sweet corn varieties.

Modern crop improvement

Crop improvement benefited from both the Mendelian and the molecular genetic revolutions of the 20th century. Austrian monk Gregor Mendel's pioneering observations on inheritance, published in 1865, were made independently by Dutch botanist Hugo de Vries, only then gaining the interest of other geneticists [11]. Indeed, a simple demonstration project to illustrate Mendelian inheritance led to the discovery of hybrid vigor, a phenomenon whose incorporation into crop breeding resulted in a dramatic expansion of the corn ear and, thereby, crop yield. The discovery is attributed to George Harrison Shull, working at the Carnegie Institution of Washington's Station for Experimental Evolution. He was asked by the Station's director to develop a demonstration of Mendel's rules of inheritance. In the course of these experiments, he grew curious about why some kinds of corn made more rows of kernels than others, so he inbred the respective varieties and then crossed them to see whether row number trait segregated in the simple way that Mendel had observed with round and wrinkled peas. What he discovered instead is that when he crossed the inbred lines to each other, he got tall healthy uniform plants with much bigger ears [12]. This phenomenon, called hybrid vigor or heterosis, is the basis of today's extraordinarily productive hybrid corn varieties [13].

Curiously, when they were first introduced in the US during the 1930s, corn hybrids faced a good deal of the kinds of resistance that biotech crops face today. They were complex to produce and agriculture experiment stations were not interested. Eventually a company was formed to produce hybrid seed. But farmers accustomed to planting seed from last year's crop saw no reason to buy it. It was only when farmers realized the yield benefits and the drought-resistance of hybrid corn during the 1934–1936 dust-bowl years that hybrid corn was rapidly adopted in the mid-west [14].

Techniques for accelerating mutation rates with radiation and chemicals and through tissue culture were developed and widely applied in the genetic improvement of crops during the 20th century [15]. Such techniques introduce mutations rather indiscriminately and require the growth of large numbers of seeds, cuttings or regenerants to detect desirable changes. Nonetheless, all of these approaches have proved valuable in crop improvement and by the end of the 20th century, more than 2300 different crop varieties, ranging from wheat to grapefruit, had been developed using radiation mutagenesis [16].

Mechanization of agriculture

Another major development whose impact Malthus could not have envisioned is the mechanization of agriculture. Human and animal labor provided the motive force for agriculture throughout most of its history. Early tractors powered by steam engines were large and unwieldy, but the invention of the internal combustion engine at the turn of the 20th century led to the development of smaller and more maneuverable machines. The mechanization of plowing, seed planting, cultivation, fertilizer and pesticide distribution and harvesting accelerated in the US, Europe and Asia following World War II [17]. Agricultural mechanization drove major demographic changes in all developing countries. In the US, 21% of the workforce was employed in agriculture in 1900 [18]. By 1945, the fraction had declined to 16% and by the end of the century the fraction of the population employed in agriculture had fallen to 1.9%. At the same time, the average size of farms has increased and farms have increasingly specialized in fewer crops.

The Green Revolution

Malthus penned his essay when the human population of the world stood at less than a billion. The population tripled over the next century and there was a resurgence of Malthusian predictions of mass famines in developing countries that had not yet incorporated science-based and technology-based advances into their agricultural systems. Perhaps the best known of the mid-century catastrophists was Paul Ehrlich, author of The Population Bomb [19].

It took the work of just a handful of scientists, principally plant breeders Borlaug, Swaminathan and Khush, to avert the predicted Asian famines [20]. The Green Revolution was based on the development of rice and wheat varieties with mutations in genes that controlled their growth rate, resulting in dwarf varieties able to respond better to fertilizer application without falling over. Subsequent breeding for increasing yield continued to increase the productivity of these crops by as much as 1% per year. Instrumental in these discoveries were the first two institutes established by the Consultative Group on International Agricultural Research (CGIAR), the International Rice Research Institute (IRRI) (http://www.irri.org/) in the Phillipines and the International Maize and Wheat Improvement Center (CIMMYT) (http://www.cimmyt.org/). Remarkably, the Green Revolution innovations of the late 20th century reduced the fraction of the world's hungry from half to less than a sixth, even as the population doubled from 3 to 6 billion.

Molecular genetic modification (GM) of crops

A genetic revolution that began in the 1960s led to the development of a new set of methods for modifying plants. Research in the 1950s and 1960s identified the existence of tiny chromosomes, called plasmids, in bacteria that could replicate themselves independently [9]. Other discoveries led to the identification of proteins, called restriction enzymes, that cut the small chromosomes in a way that made it possible to insert a piece of genetic material from a completely different organism, then reseal the plasmid. The new 'recombinant' plasmid could then be reintroduced into a bacterium, where it replicated itself many times over, even as the bacteria multiplied. This amplification of the recombinant plasmids yields enough copies of the gene of interest to permit its sequence analysis and its modification. The techniques of cloning and sequencing DNA underlie today's genomic revolution, in which the genetic information has been decoded for literally hundreds of different organisms, from viruses and bacteria to plants, animals and humans.

Additional techniques were developed for the introduction of genes into plants. These generally use either the soil bacterium *Agrobacterium tumefasciens*, which naturally transfers a segment of DNA into wounded plant cells, or mechanical penetration of plant cells using tiny DNA-coated particles [21]. This combination of techniques has made it possible to introduce into plants genetic material from either the same or a related plant or even an unrelated organism, such as a bacterium or a different species of plant.

Several crop modifications achieved using these methods are now in widespread use. Perhaps the best known of these are crop plants into which a gene from the soil bacterium, *Bacillus thuringiensis*, has been introduced. *B. thuringiensis* has long been used as a biological pesticide because it produces a protein that is toxic to the larvae of certain kinds of insects, but not to animals or people (http://www.extension.umn.edu/distribution/cropsystems/DC7055.html). The gene coding for the toxin is often called 'the Bt gene' for its bacterial origin. The Bt toxin genes, which constitute a family of closely related proteins, have been introduced into several different crops, primarily corn and cotton. In the US and Europe, pest-protected crop varieties are produced almost exclusively by companies such as Monsanto, DuPont and Syngenta. In other parts of the world, including in China and India, such crop modifications are being done by both the public and private research sectors.

Another widely accepted crop modification is the introduction of genes that confer resistance to herbicides. Herbicides are chemical compounds that kill plants by blocking physiological processes that are necessary for plant growth and survival (http://www.hort.wisc.edu/cran/pubs_archive/../HowHerbicideWork.pdf). These are generally processes unique either to all plants or certain kinds of plants. Among the most widely used today are compounds that interfere with the production of amino acids that plants make, but animals do not [22]. Herbicide-tolerant crop plants make it possible to control weeds with an herbicide without damaging the crop and have been derived through natural and induced mutations, as well as by introduction of genes from either bacterial sources or modified genes from plant sources. Today, herbicide-tolerant varieties of many crops, most importantly soybeans and canola, are widely grown.

Papaya ringspot virus-resistant papayas are a remarkable GM achievement that saved the Hawaiian papaya industry [23]. Papaya ringspot virus (PRSV) is a devastating insect-borne viral disease that wiped out the papaya industry on Oahu in the 1950s, forcing its relocation to the Puna district of the big island. By the 1970s, the Puna district was producing 95% of Hawaii's papayas. PRSV was first detected in the Puna district in 1992; by 1995 it was widespread and threatening the industry. However, Dennis Gonsalves and his colleagues at Cornell University began a project in 1985 to introduce a viral gene into papayas based on the observations made in Roger Beachy's group at Washington University that introducing a viral gene could make a plant resistant to the virus from which the gene came [24].

The first transgenic papaya plants expressing a PRSV gene were ready in 1991, small field tests began in 1992 and large-scale field tests began in 1994. Approvals from the Animal Plant Health Inspection Service (APHIS) of US Department of Agriculture (USDA), as well as the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA) for release of the seeds to farmers took another three years, by that time many papaya farmers had gone out of business. Transgenic seeds were released in 1998 and by 2000, the papaya industry had come back to pre-1995 levels. Although it was not known at the time, recent studies have shown that the resistance is attributable to post-transcriptional gene silencing, a process in which a small RNA derived from a double-stranded version of the viral gene transcript initiates the cleavage of invading viral RNA [25]. This remarkable method of crop protection enhances a mechanism present in plants and responsible for protecting the plant from further infection by the same and closely related viruses, much as the development of immunity protects people and animals from reinfection by pathogens.

Adoption of GM crops

Although the use of molecular modification techniques in crop improvement engendered controversy from the beginning, GM crops have experienced unprecedented adoption rates since their initial introduction in 1996. By 2008, the latest year for which statistics are available, roughly 10% of cropland was planted in GM crops [26]. Transgenic crops were grown on more than 300 million acres in 25 countries by more than 13 million farmers, 90% of whom were small-holder, resource-poor farmers. The vast majority of transgenic cropland is devoted to just four transgenic crops: cotton, maize, soybean and canola, but the list of transgenic crops is growing and already includes papaya, tomato, poplar, petunia, sweet pepper, squash, alfalfa and, for the first time in 2008, sugar beet.

Few of the widely anticipated adverse effects have materialized. While some resistance to the Bt toxin has developed, it has not been as rapid as initially feared and second-generation, two-Bt gene strategies to decrease the probability of resistance are already being implemented [27]. Predicted deleterious effects on nontarget organisms, such as monarch butterflies and soil microorganisms have either not been detected at all or are not significant. Moreover, while conventional pesticides use decreases the abundance of beneficial insects, Bt crops do not.

The many studies that have been done to assess the safety of foods containing or consisting of GM crops have reached the conclusion that GM foods are at least as safe as non-GM foods [28]. This is in part because of the close scrutiny paid during product development to the potential for toxicity and allergenicity of the proteins encoded by genes being added.

To date, the unexpected effects have been beneficial. For example, many grains and nuts, including corn and peanuts, are commonly contaminated by mycotoxins, toxic compounds made by fungi that follow boring insects into the plants. Two of these, fumonisins and aflatoxin, are extremely toxic and carcinogenic. Bt corn, however, shows as much as a 90% reduction in mycotoxin levels because the fungi that follow the boring insects into the plants do not get into the Bt plants [29].

As well, there is evidence that planting Bt crops reduces insect pressure in other crops growing nearby. Bt cotton has been widely planted in China. Analysis of the population dynamics of the target pest, the cotton bollworm, showed that Bt cotton not only controls the bollworm on transgenic cotton designed to resist this pest, but also reduces its presence on other host crops and thereby decreases the need for insecticide sprays in general [30].

Future challenges in agriculture

The scientific and technological advances in agriculture of the 19th and 20th centuries have been nothing less than spectacular. Since Malthus' time, the human population has expanded more than sixfold. In the developed world, agriculture has become less labor-intensive and has kept apace of population growth worldwide. Today, less than 1 in 50 citizens of developed countries grows crops or raises animals for food. On the one hand, this means that most people live in cities and find livelihoods that pay higher wages than farming. Those remaining on farms often also work in off-farm jobs, raising average farm income. On the other hand, this means that most citizens of developed countries have little knowledge of what it takes to create the bounty of foods that stock contemporary supermarkets.

Moreover, after a half-century's progress in decreasing the fraction of humanity experiencing hunger from half to less than a sixth, the food crisis and the more recent global financial crisis have again begun to swell the ranks of the hungry [31]. Population experts anticipate the addition of another two to four billion people to the planet's population within the next three to four decades [32]. However, the amount of arable land has not changed appreciably in more than half a century, increasing by only about 10% [33]. And it is not likely to increase much in the future because we are losing it to urbanization, salinization and desertification as fast or faster than we are adding it.

Another variable that is becoming crucial is the availability of fresh water for agriculture. Today, about one-third of the global population lives in arid and semiarid areas, which cover roughly 40% of the land area. Climate scientists predict that in coming decades, average temperatures will increase and dryland area will expand [34]. Even now, inhabitants of arid and semiarid regions of all continents are extracting ground water faster than aquifers can recharge and often from fossil aquifers that do not recharge [35].

Thus the challenges to agriculture in the 21st century are profound: increasing agricultural productivity on land largely already under cultivation at higher temperatures using less water. Can it be done? The truth is, we do not know. The impediments are both biological and cultural.

The major crops that now feed the world – corn, wheat, rice and soy – require a substantial amount of water. For example, producing a kilogram of wheat requires between 500 and 2000 L, largely lost through transpiration [36]. But because half of the grain currently produced worldwide is fed to animals, five to ten times as much water is consumed to produce a kilogram of meat as is required to produce a kilogram of grain.

The optimal growth temperature to produce maximal yields of our major crop plants is determined by the temperature optimum for photosynthesis, the process by which plants convert solar energy into chemical energy, and other physiological processes. It is also determined by the temperature range that supports optimal development of the harvested storage organs (grain, bean and kernel) that accumulate starches, proteins and fats [37]. A recent study reports that yields increase with temperature up to 29°C for corn, 30°C for soybeans and 32°C for cotton, but then decline precipitously at higher temperatures [38]. This study predicts that yields of these crops in their current growing areas will decline by 30–46% by the end of the 21st century under the most moderate climate change scenario and by 63–82% under the most rapid warming scenario.

The expected pressures on water availability and increasing temperatures present crucial challenges to agricultural researchers to increase crop water efficiency and heat tolerance. Whether our current highly productive food and feed crops can be modified and adapted to be even more productive at the higher temperatures expected or at more northern latitudes is simply not known. It would therefore be wise to increase investment in research on alternative forms of agriculture based on plants not now used in agriculture, but capable of growing at higher temperatures and using brackish or salt water for irrigation. Indeed, the array of molecular tools and knowledge available today might make it possible to design a wholly new kind of agriculture for a more arid, hotter world.

But even though the molecular tools, physiological knowledge and genomic information available today are extraordinary, there are also political and cultural barriers to their widespread use. Japan and most European and African countries remain largely opposed to growing GM crops and even, in some countries, importing GM food and feed. Moreover, even where there exists a regulatory framework that supports the testing and introduction of GM crops, the regulatory process is both extended and expensive. These factors have largely eliminated the participation of university and other public sector researchers in molecular crop improvement in many countries around the world. It is difficult to predict the progress that can be made in crop adaptation and improvement without the use of contemporary molecular technology.

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