The Future of Food
Biotechnology Markets and Policies in an International Setting

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Chapter 5

Transcending Transgenics— Are There "Babies In The Bathwater," Or Is That A Dorsal Fin?

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Introduction

Most news headlines and assertions of health and environmental concerns about genetically modified (GM) crops center around transgenic technologies. These technologies involve methods of introducing genes into plants by inserting new DNA rather than the more familiar method of introducing genetic material by pollen and egg fusion in a genetic cross.

Modern biotechnologies can do much more than add new genes, and provide single-gene herbicide tolerance and pest resistance in crops like corn, cotton, soybeans, and canola that constitute the lion's share of commercially successful transgenic technologies developed for agriculture to date (see Marra this volume).[1] These innovations have been successful in their target markets, but they were not intended to solve the myriad problems of farmers around the world; except in the minds of the most naïve promoters of the new science, they were never anything other than a simple first generation.

These technologies are still in their early days, with real opportunities for non-scientists (the public, primary producers, and policymakers) to articulate desirable future trajectories and help the scientific community change the way science evolves and interfaces with people's lives. Further, a corresponding opportunity exists for modifying the political and economic landscape—especially in relation to intellectual property rights (IPR)—to encourage fair play and transparency in this pursuit (see Nottenburg, Pardey, and Wright 2001 and this volume).

Crop breeders find transgenic technologies attractive because they make it possible, in principle, to incorporate into plants yield-increasing or nutrient-enhancing traits that would be slow, expensive, or impossible to introduce by conventional means. Most of agriculture is far from the idyllic pursuit of life on the land as envisioned by many urban dwellers; much of it is a hard slog, in a less than benign environment, and typically burdened by debt. Crop production occurs in complex agroecologies, and each farmer's field is different, with challenges that are unpredictable and unique to their circumstances. Rainfall can be excessive (causing waterlogging) or deficient (causing drought if extreme); it varies from year to year and can fall too late or too early in any given year. Most of the world's agricultural soils are either too acidic, too basic, have insufficient nutrients for uptake by plants, or have elevated amounts of salts or metals like aluminum that are toxic to most plants.

Improved crop management practices can alleviate these problems to some extent, but improved crop varieties also have a big role to play. The work of crop breeders is crucial for increasing yields through a stream of improved crop varieties more resistant to drought, waterlogging, and elevated levels of toxic metals or salts; more tolerant to cold; and more robust in their defenses against ever-evolving pests and diseases that overcome previous forms of bred-in resistance. Simply maintaining the historically high yields some now experience is a daunting task. Despite the smugness of those who claim that Malthusian doom has been averted, the natural resource base is dwindling, populations are growing, and the standard of living demanded or desired by burgeoning populations is rising.

The future of crop improvement and plant breeding could be much more exciting and productive than simply servicing the treadmill of current needs. We could make a quantum leap, integrating science with societies, economies, environments, and agricultures. With a new toolkit—both technical and intellectual—breeders could make major contributions to breeding and combining crops and livestock and their associated biota into complex and robust systems. But first, the current vitriol and debate must be transcended so that a shared vision can be devised and ultimately endorsed by many parties.

To understand the furor about transgenics, and to see whether there is a gleaming baby in the turbid bathwater of GM agriculture, we must carefully examine current transgenic technology. It is absolutely critical to appreciate the scientific possibilities—the directions these technologies could take—and to clarify the social and economic forces that are acting on them or that could influence their development.

Defining the Terms Defines the Problem

Language is a very powerful tool, but when abused it is a formidable form of social and psychological manipulation because each word and phrase carries with it a world of context and implied meaning. A productive and respectful discussion about new technologies, trends, and policies demands a linguistic common ground.

Attempts to define the very word "transgenic" illustrate the magnitude of the problem. If we try to define transgenic as a process that involves the introduction of "foreign" DNA, and foreign means from another species, then much of the classical wide-hybridization is transgenic. Of course wide-hybridization is commonly used in conventional plant breeding to broaden the diversity of a crop species, which is generally perceived to be a good thing. The interfertile rice species *Oryza rufipogon, Oryza glabberima*, and *Oryza sativa* have been "mined," that is, their respective genomic capabilities to respond to novel challenges have been tapped and combined for marvelous yield increases by neoclassical plant breeding (Xiao et al. 1998).

If transgenic is defined as a process involving DNA from another genus, the same caveats apply; modern wheat is the fusion of three separate genomes from three distinct species and probably genera, and occurred only a few thousand years ago. Modern triticale is a completely synthetic species created by fusing genomes (by familiar means) that had never before been juxtaposed in nature. Many horticultural crops (berries, for instance) are interspecific hybrids. So where is the line drawn? Many hundreds of plant species, including many crops, are naturally infected by and indeed genetically transformed by the DNA of the naturally occurring soil microbe *Agrobacterium tumefaciens*. The DNA of countless plants actually contains bacterial DNA already, with no human intervention whatsoever.

The DNA sequencing of many genomes has revealed that large numbers of genes and associated sequences are virtually identical—indistinguishable—in organisms ranging from microbes to mushrooms to man (not that big a jump considering some people I've known). The line is further blurred considering that it is now technically feasible for genetic engineers to produce transgenic plants that have only plant DNA introduced into them, with no nonplant DNA sequences. Are these plants transgenic?

When faced with these facts, the debate nonetheless continues in many quarters but shifts its goalposts, and redefines itself as a preference for low versus high technology options, progressing to the issue of whether and to what degree human "intervention" is appropriate in agriculture(a slippery slope considering that all of agriculture is the product of human artifice, intervention, and ingenuity. This trend to object based on the type of technology in question tends to tar transgenics or GM crops—and increasingly any laboratory-based science—with an apparently and implicitly unsavory brush of high technology, at the same time leaving much of modern plant improvement alone. Of course the countless technologies associated with farming, and even more so the processing and provision of food and fiber to consumers, are rarely part of the dialogue.

After all, even the humble hoe or plough, while primitive, invariably derive from sophisticated mining and smelting of ores and alloying, casting, working, and machining of the resulting metals. Many state that the track record for safety or utility of a particular technology renders it acceptable. This is not the whole story, however, as metal-working, besides its very real good in the form of ploughs and construction tools, has been necessary for virtually all weapons as well, from swords and armor to guns and tanks—hardly a benign core technology. Is the issue really track records, or is it just familiarity? Is it the technology, the use of the technology, or more likely the provenance and control of the technology and whether it is perceived to serve a public good. Or are its real benefits preserved for minority interests? Those against swords are rarely against ploughshares, although both depend on similar underlying technologies. Who is using the technology seems to determine much of its acceptability, and this is the crux of the current crisis.

These logical conundra help expose the real interests or misconceptions behind the sometimes vague language and concerns associated with agricultural technologies, and more specifically the interventions of molecular biology. Protests about food safety and environmental concerns could perhaps be better focused on the underlying bone of contention—the control of technology.

"Natural" Is "Good"

Organic, to most people, is equated with natural, and natural is associated with good. The most virulent diseases and plagues that kill millions and devastate landscapes and crops are 100 percent natural, but they are not considered good. Consider smallpox, influenza, polio, HIV, rice blast fungus, plague locusts, and cholera. Consider the deadly natural toxins curare, botulism, diptheria, and so on. Or consider the insidious bacterial agents such as anthrax—a lethal natural candidate for a biological warfare agent.

We must also consider the apparently benign. The wonderful caterpillar-killing, spore-forming bacterium *Bacillus thuringiensis (Bt)*, is used worldwide by the organic agriculture community as a live formulation on many thousands—perhaps millions—of acres to kill myriad lepidopteran organisms, some of them pests. This living soup of trillions of bacteria, each encoding perhaps a few thousand genes of unknown function, is considered "familiar" and "natural" to spray on plants to decimate legions of feeding insect pests. Why is this? Have carefully monitored field trials been done over dozens of years to ensure safety? Have international guidelines for use of the live bacterium been developed and harmonized by supranational bodies, enforced by national legislation? Have stringent quality-control standards been imposed and allergenicity tests mandated? No. Familiarity and accessibility exempt these agricultural practices from such scrutiny: "It doesn't seem to screw things up too badly, anyone can buy a bag of it, and besides—it's natural!" However, as more is learned about these organisms assumed relationships begin to fall apart.

This *Bt* bacterium is closely related to the causative agent of deadly anthrax (*Bacillus anthracis,* a biological warfare agent banned by the United Nations Convention on Biological Weapons) and to food poisoning (*Bacillus cereus*). Some scientists consider these bacteria to be the same species (Helgason et al. 2000). Yet assurances of product and human safety are completely missing in the artisanal applications of these billions of living *Bt* bacteria onto crop plants that are then sold at a premium, since they're organic, in many markets. Are these unacceptable risks? Apparently not. And yet when high technology is used to remove the actual active ingredient—the *Bt* crystal-forming protein toxin—and introduce this into crop plants in a lasting form free of the thousands of other potentially dangerous genes, it is decried by many as a loathsome and unwelcome innovation. Again, is it really the high technology intervention that creates the fear and loathing? Or is it the provenance of the intervention? Authorities fail to regulate countless familiar activities that are far more likely to create problems, such as the potential contamination of organic *Bt* spores with deadly food toxins or lethal pathogens.

The GM debate has been derailed by the very language used. It has little to do with technology. Perhaps if public agencies (departments of agriculture or other entities) rather than large multinational corporations had conducted the first commercial releases of transgenic food crops and their introduction to the food chain the outcry that has dominated the press and industrial and scientific activities would not have reached fever pitch, preventing constructive dialogue.

It seems that the issue must be defined based on whether it impinges on a feeling of acceptability. Acceptability is associated with a comfort-zone that is established by familiarity and by perceived accountability, but is rarely the subject of critical evaluation. Public agencies are rarely more accountable than many in the private sector, which is accountable to the market itself: if the product or process is unacceptable, it doesn't sell (unless the market itself is manipulated). Furthermore, legal and financial liabilities associated with nonperformance or improper performance of products and processes can force adherence to regulatory strictures. And fiduciary and management accountability to shareholders affords an opportunity to scrutinize private-sector behavior. Few of these mechanisms are in place to ensure that the public sector adheres to public- good criteria. Crucially there are few clearly articulated definitions of public good criteria to adhere to, nor frameworks against which to evaluate such behavior.

This is seen in the recent tendency of the public sector to behave in a private-good manner (such as through exclusive or short-sighted patent licensing and by conducting contract research that is not subject to oversight). Ironically, these actions have come in response to demands that the public interest requires the public sector to adhere more closely to supposed private-sector models, especially in control of technology. That said, it really is perception that matters, and this includes the perception that public good is really being provided by public agencies, along with the unspoken corollary in many minds, that the private sector is not concerned with public goods—an unfortunate connection.

Few of even the most ardent critics of "big agriculture" have serious reservations about the value of modest-sized private firms providing farm-level innovations. Small to medium-sized enterprises thus have a potentially enormous role in providing effective R&D and delivery in a package that is acceptable to virtually all observers. It is the "smallness" that engenders trust; the decision makers are face-to-face with the outcomes of their decisions and the risks they take are first and foremost on their own heads. The trend in recent years to consolidate and vertically integrate these entities must be examined and the reasons for this action seriously challenged.

If acceptability of the delivery mechanism is paramount, technologies that promote acceptable mechanisms must be encouraged, along with the legal and business instruments that encourage the decentralized innovative process. Technologies are not neutral; barriers to entry, including intellectual property restrictions, financial capital requirements, context effectiveness, cultural perceptions, market aesthetics, and technological interdependencies, are often intrinsic to particular technologies. And, of course, the design and delivery of new technologies reflect the dominant social and economic forces at work.

In a society characterized by information overload and rapid innovation, even scientists (including myself) are struck by feelings of powerlessness. This issue is at the heart of debates about GM agriculture—not the technology except as an instrument of such disenfranchisement. With this in mind, current and future technologies should be viewed with some detachment: It is important to grasp what they are now, what they involve, what is in the pipeline, and most importantly whether or how technologies can be crafted to cope with the issues at hand—trust, provenance, access, and responsibility to societies and environments.

New Meta-Technologies

Sentinel Plants and Bioindicators

Often, the most robust and sustainable solutions to agricultural problems are initiated and implemented by the very people experiencing the problem—the farmers. These solutions often manifest not in genetic changes but in management changes, such as amended irrigation, fertilization, and plant protection protocols; altered planting regimes; intercropping; and rotations. However, for each of these interventions the managers require sufficient, accurate, and timely information about the challenges and the opportunities for response. One of the greatest untapped opportunities in genetics in agriculture is to increase and improve the information provided to farmers by using the most sensitive biological and chemical sensors known.

These are not silicon devices or expensive neutron probes allied to computers and custom software. They are the plants themselves. Plants have extraordinary capabilities to sense virtually all of the key abiotic and biotic challenges that limit agricultural production and sustainability. However, we don't know how to listen to them well enough, or they don't know how to speak. There are many examples of farm managers planting indicator crops to forewarn of impending diseases or of other stresses. Vineyard managers around the world use rosebushes as sensitive indicators of the fungi that can cause serious loss to grape production; the rose shows symptoms before the vines are damaged, allowing a timely and cost-effective prophylactic regime. Can organisms themselves be used as "instruments"? Can generic methods harness the exquisitely sensitive and specific molecular sensing mechanisms of plants to tell farmers the condition of their fields, their soils, their ecologies, and their crops? Can these be developed to provide timely cues that lend themselves to creative changes in farm management practices? Absolutely.

Envision harnessing the natural ability of a plant to detect trace elements, and converting that detection in the plant to a visual cue that a farmer or agronomist can act upon in a creative manner. Perhaps the plant is engineered to produce a color that is characteristic of the levels of a crucial trace nutrient. A smattering of these plants around a field would then provide a powerful visual signal for farmers to either avoid areas that cannot support the growth of their crops, or to improve the soils with just that cost-effective nutrient and not a wasteful excess of nutrients that are uneconomic, and polluting. Even the most obvious nutrient of all—water—is often not present in absolutely clear quantities. Can reports on water tables, on nitrogen form and concentration, on latent pathogens, even on the crops' own efficiency of using available nutrients be developed? Almost certainly. Can the sensory cues—colors, shapes, or even smells—be harnessed to allow managers to clearly and unambiguously identify opportunities and challenges? Yes.

As biochemical pathways for pigment synthesis in plants become more clearly known, the opportunities for introducing, modifying, or activating these pathways and their genes in particular plants become correspondingly more realistic. Coupling the production of visible pigments in the correct locations with the intrinsic capability of plants to sense and measure their environment— behaving as biological sensors to indicate particular desired parameters—is also becoming feasible. Methods such as micro-array based expression profiling could monitor the transcription of genes that respond to measurement challenges, and isolate and fuse the corresponding promoter to the indicator genes.

If the biological instrument is being used to monitor the presence or level of an abiotic or biotic constraint, the engineering can be readily performed in a noncrop species, to produce what my friend Peter Kenmore at the Food and Agriculture Organization of the United Nations (FAO) likes to call a "sentinel plant," basically a living instrument that relays useful information to a farmer about the condition of her crop or cropping system.[2] The sentinel plant can then be placed in various locations throughout the field, but need not be harvested or consumed. This, of course, leaves the crop unmodified, but allows farmers to use the information to better manage their fields. The sentinel plant is rather similar to the fungal-sensitive rosebush—it doesn't appear in the wine, but makes the farming of the grapes more productive.

If however, the farmer wishes to measure the response to stresses or constraints—for instance, nutrient use efficiency—the crop itself becomes the candidate for bioindicator modification. In this scenario, the effectiveness of nitrogen fixation by soil rhizobia or the health or stress level of the crop can be measured, and farmers can take steps to ameliorate the problems.

The bioindicator approach is also compatible with genetic improvement of the crop. One can set the parameters of a classical plant breeding scheme in which the reporter (or indicator plant's signals) determines the best genetic combinations. After achieving these improvements, the bioindicator (or reporter locus on the plant's genome) could be crossed out, or left in if determined to be benign and acceptable.

Unfortunately, the compelling but simplistic economics of ownership tend to create a culture that imposes solutions in the form of a genetically improved crop (by conventional or nontraditional means), which is sold as seed and requires management regimes to bring the best out of this improved variety. This has been effective in many cases, but it will take creative entrepreneurship and business thinking to secure a revenue stream from a living, self-replicating instrument that costs next to nothing to propagate and very little to actually use, but which could cost a great deal to develop. Revenue from recurrent sales of improved seeds is often seen as the bedrock of capital recovery and hence is crucial to encouraging investment in research to develop new plant biotechnologies.

The combination of high costs and a preoccupation with serving markets in the industrialized word has offered little incentive for scientists to develop these tools, and there are substantial entry barriers presented by intellectual property and financial capital restrictions. Exhortation and inspiration must go hand in hand with improved policy and strategy to foster the inventive spirit that will make innovations possible and deliverable. If the public sector, or small- medium-sized enterprises, were to take the initiative on this issue, progress could be very rapid.

Homologous Allelic Recombination (or Replacement) Technologies (HARTs)

All current methods of plant transformation (transgenesis) are only capable of introducing additional DNA into the genome. They are not capable of removing or specifically altering sequences that are already in place. In genetics terminology, these methods can only introduce a dominant trait. Current methods basically overlay the expression patterns of a transgene on the intrinsic expression of the recipient genome. While techniques such as RNA-mediated gene silencing (broadly encompassing antisense and cosuppression technologies) can effectively "turn off" resident genes of known sequence, this capability is still dominant, and always leaves a "footprint" (that is, new sequences that had not previously been present in the genome). Further, genetic circuitry is so complex that functions are often redundant and silencing one gene does not always silence the trait.

Current commercial transformation techniques for plants typically result in diverse and unpredictable insertion sites into genomes. This situation causes extreme variability in performance of newly introduced traits between lines within the same plant species, making it necessary to generate a large number of primary transgenic events, further involving considerable and expensive effort to rogue these aberrant lines to find only those with stable and acceptable levels of expression of the new gene(s). This logistical requirement makes the process of creating a commercially viable transgenic crop line slower, more cumbersome, and more expensive than it would otherwise be.

Transgenic technology development is still quite primitive, reflecting an inability to understand and harness the natural processes of DNA repair and recombination by which plants routinely and precisely replace or recombine alleles. Alleles are variant forms of the same gene or DNA sequences, and can be considered the cause of intraspecies diversity that plant breeders typically try to optimize.

The most desirable situation for those using genetics to improve crop genomes would be to use homologous recombination to specifically amend the sequence of a particular gene or controlling DNA so that the plant remains in all other ways in its original genetic condition, save for the one subtle change introduced. There would be no need *a priori* for a footprint to be left behind, nor for most of the associated challenges of current trangenics to apply. In short, the desired improvement is brought about with the smallest alteration conceivable, and knowledge about the implications of the change —and the possibility of avoiding unwanted side effects) is maximized.

If a plant's genome were modified with a form of site-directed change that left only a minor allelic variation, it could be sensibly argued that the resulting line was in no way transgenic. The substantial savings in time and money by circumventing the need for adherence to regulatory guidelines developed for conventional transgenics could help lower entry barriers to smaller players in biotechnology, including research and development (R&D) entities in public and private sectors of the developing world. Currently the costs of taking a single product through the regulatory gauntlet imposed by most governments is so high that only comparatively high-margin applications are being pursued, and typically only by large companies. This is a terrible waste of opportunity.

In the baker's yeast *Saccharomyces cerevisiae*, achieving homologous recombination in laboratory conditions is routine. It is also manageable in mammalian cells, with some technical difficulties still to be overcome. Homologous recombination, and its sister technology, site-directed mutagenesis, in which an altered sequence of DNA (or RNA) is used as a template by the natural repair processes to substitute or recombine one allele for another, will almost certainly be developed over the next few years. These technologies, collectively, can be called homologous allelic recombination (or replacement) technologies (HARTs). When they emerge, they will spell the single greatest technical breakthrough since DNA transformation of plants. With HARTs, a modified plant can be, in every way, absolutely identical to its precursor or mother plant with only the most subtle and precise modification.

In fact, until HARTs become available as an experimental tool in plants, much of genomics, the broad catchword used to raise huge amounts of money from unwary investors, is really the "emperor's new sequence." How can scientists formulate a hypothesis about the function of a gene based on information from genomic sequencing or expression patterns and reasonably test that hypothesis? With HARTs, comparative genomics can give rise to precise experimental tests of these hypotheses. Imagine that in comparing sequences around quantitative trait loci of two rice varieties it emerges that a subtle allelic variation—perhaps a DNA sequence change of only a few bases in the gene encoding a regulator—seems to correlate with an important trait. How does one test this? Currently scientists have only correlation—no cause-and-effect relationships—and when moving such alleles around by classical genetics (crossing plants) they get not only babies and the bathwater, but also the bathroom, the whole house, and the neighborhood. Classical genetic crosses, even when followed by exhaustive (and exhausting) back-crosses to clean up and restore the original recurrent genotype, still bring in millions of base pairs of DNA. This encompasses hundreds of variants of genes and nongene sequences, any one of which could be responsible for the observed difference. It is unclear whether critics of transgenesis who use the unfamiliarity of "new" sequences as the lynchpin for their concern know the enormous volume and extent of uncharacterized allelic variation being introduced wholesale by classical plant breeding.

The advent of HARTs in a widely useable fashion would be highly important to anyone wishing to use modern science to improve the performance of agricultural systems through genetics. And it would greatly reduce the entry barrier to diverse innovators. How likely is it to happen and what stands in the way?

A few methods—most of which have been patented, which is not to say unavailable—have achieved a modest frequency of site-directed mutagenesis, site-specific integration (less interesting), or limited forms of homologous recombination. The status quo of site-directed mutagenesis is not yet exciting, but is farthest along (I half-jokingly call the current stage of the technology "site-suggested mutagenesis"). The scientific community's understanding of natural recombination processes is, however, growing rapidly; with the study of *Arabidopsis* biology and genetics, the toolkit to explore such fundamental biological processes is becoming more sophisticated and effective. Modest infusions of private capital into research toward harnessing recombination in plants may well be happening, and clearly private funding of public research—with concomitant control or influence in many cases—is now the norm. It is only a matter of time until HARTs are developed as powerful tools. But this very increase in private interest among the multinationals, the same companies that have been the source of the current generation of field releases, does not necessarily bode well for either the broad availability of the tool or for improved public perception of the craft of modern agricultural genetics. The multinationals need and should have the tools, but should they be the owners, the developers, or the arbiters of their availability?

In a sense, the use of HARTs would be "stealth genetics," undetectable except in its outcomes. When HARTs are achieved, critics doubtless will bemoan the absence of the very footprint (genetic flotsam) that they currently decry. However, these technologies would certainly meet and exceed the requirements and concerns expressed in all the technical criticisms of transgenesis.

Among the intriguing implications of using HARTs are the intellectual property and business challenges associated with an innovation that is virtually undetectable or indistinguishable from other materials, and whose creation may be dependent on process rather than a material difference. The regulatory frameworks currently in place are certainly inadequate to guide the informed deployment of plants (or other organisms) altered by HARTs, unless these are exempt from such oversight.

From a point of democratizing the ability to experiment with information gleaned from genomic analysis, HARTs could be one of this century's great achievements for agricultural research worldwide. But this suite of technologies is vulnerable to being withheld from routine use by onerous or unwise intellectual property terms. Keeping in mind Thomas Jefferson's idea of using a formal grant of intellectual property rights to balance social benefit with private gain, a cogent argument can be made that HARTs for agriculture and medicine would qualify as a unique public good.

Genetic Use Restriction Technologies (GURTs)

The concept of revenue streams through recurrent sales is dogma in the agricultural genetics industries. The track record of hybrid maize is often held up as an example of how the inability to plant-back without losing varietal character has allowed a productive industry to develop based on secure and predictable sales. Citing examples of vegetable seeds that have emerged from the effective use of hybrids, it is persuasively argued that the reliable revenue streams derived from recurrent seed sales have stimulated investment into genetic research to improve the maize crop. The argument hinges on the necessity of recovering the substantial financial investment in high-risk research and the significant delays between the inception of a technological intervention and the delivery of a saleable product.

As a result, methods have been developed to extend the concept of recurrent purchasing to crops that hitherto were not subject to hybrid technologies. In March 1998, U.S. patent number 5,723,765 was granted jointly to the U.S. Department of Agriculture and Delta and Pine Land Company. This patent, called "control of gene expression," soon attracted remarkable attention through an ambitious press campaign conducted by a few concerned activist groups, notably RAFI (Rural Advancement Foundation International, recently renamed the ETC Group), which coined the expression "terminator technology."

The United Nations Convention on Biological Diversity commissioned a substantial review of the technology and its implications (UNEP/CBD/SBSTTA 1999). The Expert Group that prepared the UN report, of which I was author-in-chief, noted that genetic use restriction technologies (GURTs,) could be described as those that could be used to restrict the propagation of the plant itself (V-GURTs, or variety-specific GURTs) and those that would limit the impermissible use of an associated added-value trait (T-GURTs, or trait-specific GURTs). These had very different implications, and needed to be considered separately.

While one of the classes of the technology, V-GURTs, was in principle capable of limiting the germination ability of a second generation of seeds, earning the label terminator, the other class, T-GURTs, could conceivably be an effective tool to put the ability to control transgene expression in the hands of farmers—a necessary step for many socially and environmentally context-dependent applications. However, both technologies were reviled in the press, with the T-GURTs referred to, albeit less evocatively, as "traitor technology." Although the possible use of V-GURTs technology to restrict the potential effects of gene flow in field populations was noted (by making plants carrying the trait or pollinated with the genes encoding the trait unable to germinate), the distinction made by the press was largely nonexistent.

More than the first generation technology (a cumbersome multigene system that had not then, nor has now been reduced to practice) or the principle of recurrent seed purchase (hybrid maize and vegetables and seedless fruit already exemplified that without serious reservations in most quarters), the outrage was largely focused on the anticipated use of this type of technology to further dominate what was being perceived as an already-too-concentrated power base.

The End Run

Rather than struggling to prevent onerous mechanisms designed to ensure recovery of large financial outlays for research and product development, could we rather invent and provide methodologies and policies that would allow technological innovation to be successful without such capital outlays? Could we look at lowering the entry barriers for innovation rather than developing mechanisms that would entrench or at best stifle the status quo?

This approach would identify the underlying reasons that certain technologies are emerging (in this case, the need for recovery of vast sums needed to innovate) and conceive of ways of making those reasons irrelevant (making it cheaper to innovate).

Apomixis—The Germinator

Perhaps the most remarkable example of this positive approach is apomixis, wittily dubbed "the germinator" by Calestous Juma (1999). While some argue that the highest priority for saving the planet is managing population growth through human birth control ("sex without seeds"), others add that a complementary and equally essential innovation will be a revolution in agriculture: apomixis—"seeds without sex." Many plants in nature can reproduce through seeds, but without involving any sexual fusion of sperm and egg cells. This phenomenon, seen prominently in dandelions on most front lawns, allows a genetic makeup that is well adapted for a particular use or environment to breed true and not segregate and squander the optimum condition.

Few agriculturally relevant plants are naturally apomictic. From the thousands of edible plants that could have become the bedrock of modern agriculture, our farmer forebears chose those that seemed to improve over time. Plants that segregated variation were also those that were not apomictic, or not fully so. Today's curious cross-section of flowering plants that serve as our food, fiber, feed, and fuel plants are not capable of the natural process that would allow them to "fix and maintain" the genetic makeup that allows their best performance in a particular environment and to persist with just that makeup. However, many weeds and weedy plants have maintained this capacity, capturing a reproductive strategy that would be perfect for much of the world's agriculture, were it available.

Typically, when most flowering plants reproduce, the pollen, which contains the paternal genome contribution, must fuse with the egg cell containing the maternal genome. That pollen can come from the same plant or another; if it is usually from the same plant, it results in inbreeding. Crops such as rice, wheat, and barley are typically inbred and do not naturally show much hybridity. If, however, the pollination proclivities can be controlled physically or genetically, it is possible, albeit unwieldy, to encourage even these selfing plants to produce hybrids.

The phenomenon of heterosis, often called "hybrid vigor," has been associated with significant increases in productivity in certain crops, most notably maize and rice. More than half of China's rice production is credited to hybrids, which yield substantially more than their inbred parents. Virtually all of the maize production in the United States is from hybrid maize. This phenomenon of heterosis depends on producing plants that have very different (that is, heterozygous) genotypes that can in a sense provide synergism—the resulting whole being greater than the sum of its parts. The problem, of course, is that when a hybrid is produced through normal sexual reproduction, it does not breed true. Thus, bringing a maternal and paternal genome together by genetic crossing produces an ephemeral result that typically must be recreated each generation. For a plant breeding company, this entails extraordinary logistical and cost burdens; for the farmer it requires seasonal seed purchases at prices substantially higher than those of open pollinated or self-pollinated varieties. If one could capture the genetic benefits of heterosis and combine them with the extraordinary logistical benefits of apomixis—being able to "freeze" or fix any genetic combination and have it breed true without requiring pollination of the egg cell—both plant breeding and farming could become much more productive.

The extraordinary progress in the last 10 years in understanding the molecular and cellular events that underlie the sexual process in plants, notably *Arabidopsis*, suggests that the time is ripe to harness apomixis for world agriculture. Excellent reviews of apomixis have been published, most notably that by Grossniklaus, Nogler, and van Dijk (2001) and the current state of apomixis is well reviewed in the companion meeting report from Como (Spillane, Vielle-Calzada, and Grossniklaus 2001).

The Impacts of Apomixis

The impacts of apomixis must guide its development. These impacts range from the development of propagation methods for root and tuber crops such as cassava, potatoes, and yams that could dramatically improve the food security options for the poorest people, to hybrid technologies for new breeds of cereal grain crops. These and other anticipated impacts have been exhaustively reviewed elsewhere (Jefferson 1994; Jefferson and Bicknell 1996). However the most poorly articulated impact, yet possibly the most revolutionary, is not on crops, but on the ability of disenfranchised people to innovate on their own behalf.

The Challenge of Delivery—Pulling All the Pieces Together

Is apomixis really on the horizon? Will the momentum of science in academia, industry, and the international agricultural community eventually produce a useable form of apomixis that achieves even a fraction of its potential, in a timely manner? Ensuring delivery of apomixis to those whose lives will depend on it, will require a concerted, strategic, and proactive initiative unprecedented in agriculture, but with parallels in health sciences and engineering.

The suite of ancillary enabling technologies necessary to implement the trait in numerous crops also must be made available, and these technologies must be tuned for the circumstances of the crops, economies, environments, and societies in which they will be applied. Further, they must be delivered with the licenses necessary to practice and in a policy framework that can encourage fair play and equitable access to the fruits of the technology. This is not currently the case.

Targeting the Whole Package

A highly focused, intellectual property (IP) driven initiative is required to proactively provide freedom to operate for all the critical bottleneck technologies. The absence of any one of these tools for a particular crop or group of innovators could halt progress. But wholesale in-licensing of technologies that are on the verge of obsolescence is not the answer. We need to devlop new technologies that meet stringent guidelines. Almost all of the existing plant biotechnologies have emerged piecemeal from academic observations over the last 20 years, but some are only now emerging with patent protection. The bespoke invention of new enabling technologies has not been done with any vigor or seriousness in international agriculture, even in the private sector, where priorities are shaped by the pressures of coping with low-margin products, that have high development costs and long lead times.

Transformation methodology. To be improved, the apomictic trait must be understood, introduced, and modified within many varieties of each species. Many crops of the developing world have abysmal transformation systems often being developed and practiced by niche-scientists with varying skills. We need new approaches that can work in a "platform-independent" manner and freedom to operate on all these methodologies.

Gene control methodology (T-GURTs). Switching apomixis on and off is critical in many applications, but it must be done with cost-effective, environmentally, and socially acceptable compounds, and with the approval of regulatory authorities. These technologies must be readily accessible to allow different forecast implementations of apomixis to be tested and evaluated.

Homologous recombination (HARTs). Apomixis must be precise, stable, penetrant, and ultimately nontransgenic. Regulatory hurdles are not to be underestimated. The tools to test candidates, and ultimately to amend genetic constitution in diverse crops, are simply not available. If candidate loci emerge from ongoing genomics analysis, they must be tested; without HARTs, scientists are in a frustrating position of having access to dominant gain-of-function analyses only. HARTs are the key to making the whole toolbox work in the developing world.

Genotyping and genomic analysis technologies—Diversity Array Technology (DaRT). Cost-effective techniques to monitor and target plant breeding opportunities and to evaluate germplasm conservation strategies will be crucial. Molecular markers for analyzing genetic diversity will be essential to wisely using this diversity and to understanding relatedness and distinctness of materials for conservation. In spite of its promise, genomics, at least sequence-based genomics, costs far too much and its throughput is too low to apply to most crops of the developing world. Substantial breakthroughs in cost and throughput are required to allow local-scale investigation and are not married to DNA sequence determination; the transition from DNA sequence to phenotype ultimately requires experimental verification of hypothesis, and this bottleneck remains irrespective of the amount of DNA sequence information to hand. Thus DNA sequence information independent methods that allow rapid, cost-effective introgression and analysis of candidate genetic material into advanced crop and livestock lines really are an absolutely essential tool. Such methods are on the horizon (Jaccoud et al. 2001), and when combined with apomixis tools (or used to develop them) will be formidable additions to the plant breeders' arsenal

Conclusion

Achieving food security and adequate nutrition in a sustainable manner is arguably the greatest challenge of this century for the developing world. The solution lies in galvanizing the capabilities of those whose lives are most affected by these challenges to develop the solutions. Top-down imposition of silver bullets will not work—that is a simple matter of logic. However innovative science and policy can help to craft the meta-technologies to enable those experiencing problems to creatively solve them.

If R&D is too expensive, we must make it cheaper. We must counter the current skew of new technologies toward rich markets and simple problems. If innovative potential is centralized we must decentralize it. We must identify opportunities to engage entrepreneurism in achieving local solutions to the myriad distinct problems in agriculture. Unlike pharmaceutical medicine, which deals predominantly with one genome—the human—agriculture deals with dozens of primary genomes (crops and livestock) and thousands of secondary genomes (pests, beneficials, and so on) in a nonhomeostatic environment (that is, the completely variable agroecosystem). Society needs some different technological and intellectual paradigms to deal with this challenge. This includes creating a new hybrid: Technologies that are accessible and adaptable, disseminated by intellectual property tools that guarantee access, not obstacles.

If HARTs and apomixis, and ideally apomixis by HARTs, can be developed and provided at reasonable costs, then virtually any innovators with a knowledge of their local market and environment can develop nontransgenic products (by current definitions) that will presumably not have to pass through the onerous regulatory regimes. If HARTs become a routine tool, any hypothesis derived from the genomic information that is rapidly accumulating can be cheaply and readily tested, and the product would likely be nontransgenic. Genomic information would indeed become a public good.

If experimental technologies lend themselves to local-scale analysis, and if the tools are dramatically cheaper, diverse and robust private- and public-sector entities can creatively service countless modest-margin markets and create exciting new local-level opportunities.

Notes

1. For a summary of some of the plant and animal biotechnologies currently in the research pipeline, see Pew Initiative on Food and Biotechnology (2001).

2. Kenmore, Director of the Global IPM Facility based at the Food and Agriculture Organization of the United Nations (FAO) is one of the most eloquent exponents of farmer field schools and improved heuristics in integrated pest management, and has had a major impact in IPM adoption in rice and in other crucial crops.

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