Plant Domestication, the Brave *Old* World of Genetic Modification

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Abstract

The genetic improvement of crop plants via the newer techniques of biotechnology to produce "genetically modified" crops is a significant driver of progress in agriculture. However, progress has not been unimpeded: various controversies swirl around the benefits, uniqueness, supposed risks and other aspects of "GMOs", or genetically modified organisms—which, as we explain, is a meaningless "category"—and the foods derived from them. In order to resolve the conundrums posed by those issues, it is important to understand the pedigree of genetic modification, which had its inception in the domestication of plants. In this chapter, we briefly introduce the crucial determinants of the "domestication syndrome" for cereals and legumes—that is, loss of seed shattering and reduced seed dormancy—and how it evolved through the ages into contemporary "genetic modification". We argue that the application of genetic engineering to crops within a few years brought a wave of improved domestication traits. Moreover, contrary to most of the early domestication traits, some of these novel traits are advantageous to the crop and not just to humans. The other chapters in this volume discuss current developments in technology, the promise of modern molecular genetic engineering, and the legal and regulatory landscape.

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1. INTRODUCTION

Worldwide, farmers are becoming an ever-smaller fraction of the population, and most city dwellers do not know where their food comes from, the technology involved, or the labour it requires to obtain it. And if they know little about the techniques, technologies and tenuousness of farming, they know even less about its history.

A critical part of that history, which was in effect the first step in genetic manipulation, old and new, was the domestication of plants, which humans have long depended upon for food, feed, fibre, fuel, ornamental flowers and beverages such as wine, beer, tea and coffee, and juices from fruits and vegetables. Since early domestication, there has been a seamless continuum of genetic improvement of crop plants, culminating in far more rapid, precise and predictable modern molecular “genetic engineering” (GE) over the past half century.

The latter has elicited a great deal of unscientific commentary, which frequently includes concerns about “tampering with Nature” or “playing God”, as well as claims that the supposedly “natural” organisms are really better anyway—tastier heirloom tomatoes, healthier ancient grains and so on. Such claims show a lack of appreciation of the evolution of crop plants over millennia and their genetic modification by a seamless continuum of techniques.

2. THE “DOMESTICATION SYNDROME”

Domestication, the process that transforms a wild plant into a crop, is achieved by the selection (either conscious or as a by-product of farming practices) of traits advantageous to humans (for general references, see Harlan, 1992; Meyer, DuVal, & Jensen, 2012; Meyer & Purugganan, 2013; Zohary & Hopf, 2000). It is marked by a plant's stable acquisition (and therefore inheritance by its progeny) of a suite of traits, or characteristics, which are often shared across many species. (Reflecting the essential link between phenotype and genotype, the selection for and introduction of new heritable traits is, of course, accompanied by changes in DNA.)

The sum of all the traits is often referred to as “domestication syndrome”, because it is, in a sense, a complex “illness” that usually makes the crop unable to survive without human care. The reason for this behaviour is evident from the fact that the most commonly selected traits of the syndrome, particularly for grains and pulses, are *loss of seed dispersal* (Arnaud, Lawrenson, Østergaard, & Sablowski, 2011; Dong et al., 2014; Funatsuki et al., 2014; Konishi et al., 2006; Li, Zhou, & Sang, 2006; Lin et al., 2012; Pourkheirandish et al., 2015; Zhou et al., 2012) exemplified in Fig. 1 for rice and *reduced seed dormancy* (Liu et al., 2015; Lush & Evans, 1980; Sugimoto et al., 2010) exemplified for maize in Fig. 2.

The impacts of those traits on the crop are critical. When seeds are not dispersed but are retained in tight groups (in an ear or a pod) on the mother plant, they have a difficult time reaching the ground. Even if they do, once germinated they produce seedlings that are very close to one other and experience strong competition for nutrients, light and water (an example of which is shown in Fig. 3), which causes most individuals to

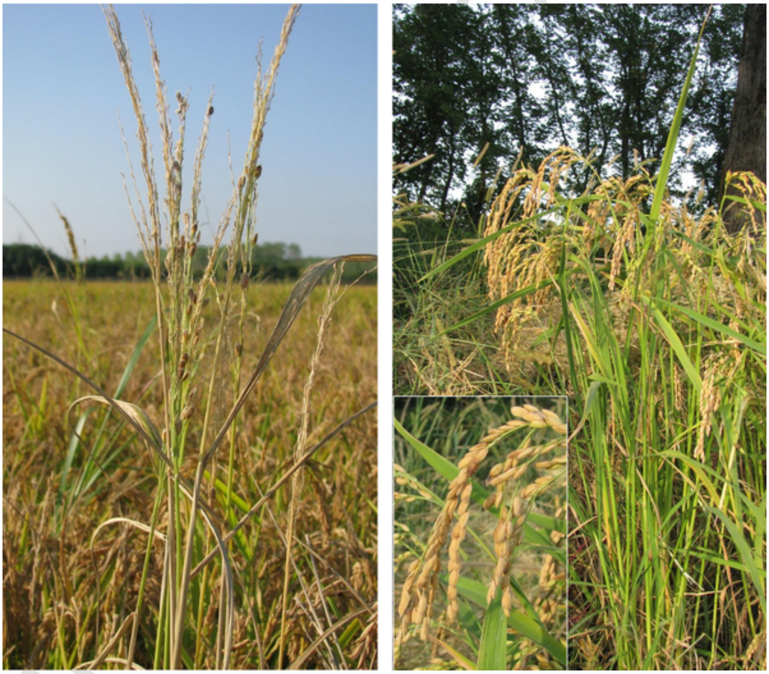

Fig. 1. Seed dispersal. Shortly before harvest, seed dispersal is almost completed in some panicles of red rice (*left*), which is a form of weedy, semi-wild rice. Cultivated rice (*right*), on the contrary, retains all the seeds on the panicle and requires a harsh treatment (threshing) for the detachment of the seeds from the mother plant. The *inset* shows an enlargement showing no gaps in between seeds within the panicle. Pictures were taken in a cultivated field near Milan (Italy).

Fig. 2. Reduced seed dormancy. A maize cob that was partly buried in a field at harvest (late September) demonstrates that maize seeds have little dormancy when placed in favourable conditions. The part of the cob that was buried shows extensive and synchronous germination even if the seeds attained maturity just a few weeks before. Wild cereals in the same conditions, on the contrary, stay dormant in the soil for many months.

die before producing any offspring. Moreover, the reduced seed dormancy promotes germination soon after seed maturity is attained, which often means during an unfavourable season (e.g. just before an extended drought period) or at the wrong place (on the ear itself). The combination of the two key domestication traits is thus almost always lethal to the plant in wild environments (although their effects are compensated for during the farming of crop plants), which is why most crop plants are rarely found outside of cultivated fields.

Other traits commonly selected during domestications include changes in shape or size, timing of flowering, and nutrient and toxin content of the edible parts; these, in turn, affect appearance, reproductive strategies, edibility, resistance to pests and, most important, yield. Depending on the specific plant or its use, many other traits also could be selected for, such as colour, flavour, increased winter hardiness and seedlessness. More recently, resistance to herbicides or pests has been obtained by various means.

The domestication of a plant usually entails only a few crucial mutations, so domestication did (and still does to a significant extent) exploit spontaneous changes in the genetic material and their subsequent selection in new, useful combinations. Genetic modification (in a broad, generic sense) is therefore intrinsic to agriculture because crops would not exist without it. (Readers willing to delve into the scientific literature of old and new domestications are referred to Pigna & Morandini, 2017).

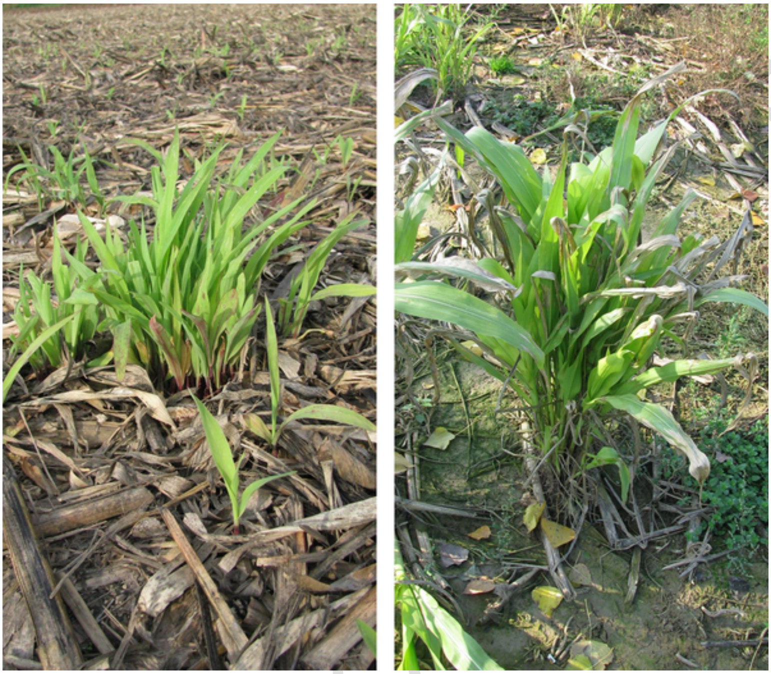

Fig. 3. The combined effect of the two main domestication trait. Voluntary maize seedlings (*left*) sprouted in October in a maize field, only a few days after harvest. The extreme high density and the patchiness are the obvious result of combining the lack of seed dispersal with the reduced seed dormancy. The high density results in strong competition for light, water and nutrients, further slowing growth at a time of the year that is already challenging for a cold-sensitive crop such as maize. After a few weeks (*right*), plants in similar situation have grown further, but are already showing some leaves burned by the low temperatures and will never make it to even produce flowers, let alone viable seeds, in temperate climates because they are soon going to be killed. The combination of the two domestication traits is thus a sort of "synthetic lethal" genotype for this crop in wild, temperate environments.

3. THE MODERN ERA

During the past century, to shorten the time required to identify and introduce useful traits, scientists and plant breeders have developed a panoply of techniques, including the treatment of seeds with radiation or mutagenic chemicals in order to increase significantly the frequency of mutations, and the screening of large numbers of plants with automated and sophisticated analyses. More recently, several powerful molecular techniques for precise site-directed mutagenesis, gene deletion/inactivation, and gene replacement or insertion in genomes have become available. These tools have markedly accelerated crop improvement and development.

Consider, for example, herbicide tolerance (HT), which simplifies weed management and, in certain cases, allows the control of parasitic weeds that can be serious pests. This successful trait has been achieved not only by moving genes from one organism to another via molecular techniques (a process sometimes called "transgenesis") but also through spontaneous mutation and random and site-directed mutagenesis. In 2016 alone, transgenic HT crops were cultivated on 161.9 million hectares or 87% of the 185.1 million hectares of transgenic crops planted globally. *Non*transgenic HT crops—the most important of which are rice, maize, soybean, sunflower and lentil—are also grown on many millions of hectares worldwide (Tan, Evans, Dahmer, Singh, & Shaner, 2005).

For about a century, plant breeders have performed "wide cross" hybridizations, in which hundreds or thousands of genes are moved across what were once considered "natural breeding boundaries", giving rise to plant varieties that cannot and do not occur spontaneously in nature (Fuentes, Stegemann, Golczyk, et al., 2014; Goodman, Hauptli, Crossway, & Knauf, 1987; Mason & Batley, 2015; Randhawa, Bona, & Graf, 2015; Sharma, 1995). In these hybridizations between different species or genera, the parental plants may be sufficiently compatible to produce a viable zygote that will not, however, develop into a fertile plant. To overcome this obstacle, scientists have devised mechanical and biochemical ways to "rescue" the embryos and produce viable, fertile plants from them. Commercial crops derived from wide crosses include common varieties of tomato, potato, oat, rice, wheat, corn and pumpkin, among others. Illustrating the continuum of genetic modification that exists, the products of wide crosses might well be called "nonmolecular transgenics".

Thus, attempts to create meaningful categories of "GMOs", "transgenics", and the like, particularly for purposes of regulatory review or labelling, are fraught, and shed more heat than light (Miller, 2014).

The products of genetic modification, whatever the technique(s) used, are not wholly without problems, but they are not referable to the technology—except perhaps in the sense that the premolecular methods are imprecise and often introduce unwanted genetic changes. A good example is the backdrop to the last major crop epidemic in the United States, which occurred in 1970: A fungus that causes a disease called Southern corn leaf blight claimed approximately 15% of the corn crop, costing farmers to lose 20 million metric tons worth about a billion dollars (Levings, 1990). The culprit was the relative imprecision of older techniques of genetic modification. For several years, most of the corn in the country had been grown from hybrid lines that contained a trait called "Texas cytoplasm male sterility". The extensive use of male sterility obviates the need to remove plants' tassels mechanically or by hand in order to produce hybrid seed, but unknown to plant breeders, those hybrid varieties were more sensitive to Southern corn leaf blight, and 1970 offered climatic conditions (warm and wet) especially favourable to the fungus (Levings, 1990). When genetic changes are introduced with more precise molecular genetic modification techniques, by contrast, the number of genes moved or altered is small, the predictability of the final plant is greater and the likelihood of unwanted changes is less.

A common generic problem with certain crops is gene flow between the domesticated crop and wild or weedy relatives. This happens, for example, with herbicide-tolerant crops, whether they are transgenic or crafted by mutagenesis. Indeed, resistance to the herbicide imidazolinone has moved from cultivated rice to weedy red rice in many places, including Costa Rica, Brazil, the United States and Italy (Busconi, Rossi, Lorenzoni, Baldi, & Fogher, 2012; Gressel & Valverde, 2009). Similarly, the continued use of any pesticide (herbicide, insecticide, fungicide, etc.) or other mean of selection will eventually favour resistant individuals, if given enough time and a sufficient number of individuals.

Thus, the emergence of herbicide-resistant weeds is a predictable result of selection pressure, especially in the absence of good agronomic practices such as crop rotation or the switching of active herbicidal agents. However, although gene flow that spreads herbicide resistance does increase the fitness of weeds, it does so, for that trait, only in the fields. It is therefore not an ecological or safety problem, but an agronomic one.

In fact, although extensive gene flow between HT crops and weedy relatives may reduce the usefulness of the specific herbicide, it does not affect wild environments because herbicides are employed mainly on cultivated fields and, to a lesser extent, on other areas managed by humans (e.g. roadsides and golf courses). In this case, therefore, gene flow does not make the plant more fit in the wild, and, since the trait comes from a crop, gene flow is very likely to confer a *dis*advantage to any recipient plant in the wild because of the genetic burden of all the domestication alleles that are transferred along with the resistance.

Transgenic approaches have been developed to mitigate gene flow from crops (whether for HT or other traits). This is achieved by linking the specific trait to a "mitigator" gene, a gene that is integral to domestication (e.g. conferring loss of shattering or reduced seed dormancy) and which is therefore already present in crops but which is missing in wild or weedy relatives. By tightly linking the two genes, it is possible to reduce the fitness of individuals and prevent their thriving in the wild if gene flow has occurred. Such mitigation is only achievable using molecular genetic engineering techniques (Al-Ahmad, Galili, & Gressel, 2005; Al-Ahmad & Gressel, 2006; Rose et al., 2009).

GE herbicide-resistant plants make possible the use of no-till farming techniques, in which the soil is not ploughed, which reduces soil erosion, runoff of agricultural chemicals, and fuel consumption and carbon emissions by mechanized farm equipment. In 2014 alone, this was equivalent to removing 22.4 billion kg of carbon dioxide from the atmosphere or to removing 10 million cars from the road for 1 year (Barfoot & Brookes, 2016).

The use of modern genetic techniques to improve plants also both enhances sustainability and food security. The United Nations' Food and Agriculture Organization estimates that some 20%–40% of global crop totals are lost annually due to disease and pests. Much of these losses are preventable, and resistance to insect and viral pests has been among plant biotechnology's most striking success stories.

The common bacterium *Bacillus thuringiensis* (*Bt*) has played an important role in agriculture and in the development of GE crop plants. The insecticidal activity of certain proteins in these bacteria has made them an important pest control tool over the past century. Paradoxically, while the use of the intact bacteria as a natural biopesticide sprayed on crops is widely accepted and approved for conventional and organic applications, the engineering of *Bt* genes into major crops has been more controversial—due largely to organized, self-interested opposition to genetic engineering in general.

Since 1996 various recombinant DNA-modified plants have been crafted to contain short sequences of genes from *Bt* to express the crystal proteins that are toxic to certain insect pests (Koch et al., 2015). The plants synthesize the proteins and thereby protect themselves from insects without any external spraying with *B. thuringiensis*. *Bt* crops are protected specifically against the European corn borer, southwestern corn borer, tobacco budworm, cotton bollworm, pink bollworm or Colorado potato beetle. More than 90% of corn and cotton cultivated in the United States are now recombinant *Bt* varieties.

Because GE crops require less pesticide sprays, farmers and their families are at lower risk of poisoning as a result of handling them in large quantities. From 1996 to 2014, the cultivation of GE crops has reduced pesticide spraying by 581 million kg (− 8.2%), equal to the total amount of pesticide active ingredient applied to crops in China for more than a year (Barfoot & Brookes, 2016). This has decreased the environmental impact associated with herbicide and insecticide use on the area planted to recombinant DNA-modified crops by 18.5%. A second-order benefit of reduced insect damage to crops is lower levels of specific mycotoxins in *Bt* corn, which means fewer birth defects such as spina bifida, and less toxicity to livestock (Wu, 2006).

By the mid-1990s, papaya ringspot virus, which devastates the trees and for which there is no cure, was laying waste to Hawaii's papaya industry. American scientists produced two varieties of papayas resistant to the virus via an ingenious strategy (Tripathi, Suzuki, & Gonsalves, 2007). They modified the papaya trees with the addition to the genome of a gene that expresses a coat protein of the virus, the presence of which interferes with viral propagation after infection.

Those papaya varieties saved Hawaii's papaya industry, its second most important crop (after pineapple). Similar commercialized products include virus-resistant squash and potatoes.

It must be stressed that it is difficult to obtain insect- or virus-resistant varieties, as well as many other traits, by conventional means and, when achieved, the new variety is normally the outcome of a random process. Moreover, the presence of concomitant undesirable genetic changes could cause the kinds of problems described earlier for US corn farmers afflicted with Southern corn leaf blight in 1970. By contrast, molecular genetic engineering techniques are versatile tools that precisely, predictably and relatively easily make possible the creation of plants resistant to pests and disease.

Genetic engineering provides consumer-friendly as well as agronomically important traits. Commercialized products include GE potato and apple varieties that are bruise resistant because the enzymes that mediate bruising have been downregulated, reducing the high percentage of waste for those crops (Healy, 2015). The potatoes also contain much less asparagine, a chemical that is converted to acrylamide, a probable carcinogen, when heated to high temperatures.

The domestication of many crops has required thousands of generations for the selection of desirable traits in the farmers' fields and for the genetic material expressing those traits to become fixed within crop genomes. With the benefit of long experience, the time required to domesticate a species has shortened, with several recognizable phases. The first one is a fairly rapid fixation of a few key traits because of strong selection by farmers, then diffusion of the crop to several places together with a long period of minor alterations and variety diversification.

In the second phase, often the crop experiences yield stasis due to inefficient selection. Traits such as fruit colour are easy to select, segregate and multiply in a new breed by farmers, but higher-yielding individuals are more difficult to identify in the absence of easily visible markers, and their identity is more difficult to preserve. Such superior genotypes are present in the population but remain at low frequency because seeds are propagated in bulk. This means that it takes a long time for such traits to undergo positive selection and to become sufficiently frequent in the population to show their effect.

By contrast, the use of modern genetic engineering techniques has allowed wider benefits to more farmers: the access to new, superior genotypes that usually provide large yield increases. (In the case of hybrid maize a fivefold increase compared to open-pollinated varieties is a common outcome.) The development of such genotypes would be extremely difficult or impossible to simple farmers, because the actual "breeding", or genetic modification, requires complex know-how, advanced tools and large investments in time, materials and, therefore, money. This is now most often performed by specialists working in large companies—which may be the source of much of the ideological opposition to modern genetic engineering—rather than by the farmers themselves. However, the benefits of the use of the new techniques have been widely distributed; in fact, over the past 20 years, the cumulative financial benefits from recombinant DNA-modified plants have been equally divided between farmers in industrialized and developed countries (Barfoot & Brookes, 2016).

The present phase, which began with the application of genetics, breeding, sterile tissue culture and more recently, molecular biology, has improved the yields and the pest and disease resistance of several crops far beyond expectations.

4. REALIZING GENETIC ENGINEERING'S POTENTIAL

We now have a far deeper understanding of plant growth, physiology, biochemistry and development than ever before, and that knowledge and the availability of new techniques are being exploited to improve our crops more precisely and predictably, via the transfer and manipulation of genes. This last domestication phase represents an open-ended process and holds great promise for the creation of novel crops and the incremental improvement of existing ones. Various aspects of this knowledge and new technologies are explored in the following chapters.

Agrobacterium is well known for its capacity to transfer specific fragments of DNA (transferred DNA or T-DNA) into plant cells, leading to the formation of tumours (crown galls) by *Agrobacterium tumefaciens* and to abundant root growth (hairy roots) by *Agrobacterium rhizogenes*. The discovery of this natural plant transformation system about a century ago, which can stably introduce foreign DNA into plants, has led to a revolution in agriculture. The Chapter by Otten explains how Agrobacterium, a natural genetic engineer, became a tool for modern agriculture.

In spite of their enormous contribution to mankind, biotech crops continue to face excessive, discriminatory regulatory scrutiny. In the chapter by Arujanan and Teng, the global status of biotech crops, labelling regimes and other challenges to biotech crops are discussed.

The principle of proportionality, which embodies concepts of fairness, equity and consistency, is fundamental not only to government regulation but also to human rights and national and international law. In the following chapter, Bartholomaeus explains why current regulatory burdens on recombinant DNA technology and the newer biotechnologies are applied in a discriminatory way, are disproportionate to the known (lack of) plausible food safety risks and are ignorant of the broader knowledge of natural plant genome plasticity.

Bees, which play an important role in the pollination of a wide range of plants, are likely to encounter genetically modified (GM) crops during their foraging period—especially insect-resistant crops, which have been cultivated worldwide. It is important, therefore, to assess potential impacts of these crops on the nontarget organism honey bee (*Apis mellifera* L.), the most important pollinator species worldwide. By examining the available scientific literature, Ricroch et al. conclude in the next chapter, that the studied protease inhibitors, Cry proteins, RNAi and herbicide-tolerance proteins do not negatively affect the survival of honey bees and have no potential sublethal effect in controlled laboratory conditions or in actual or simulated field trials.

Plant-based expression systems that produce protein-based therapeutic molecules offer several production advantages: low-cost, rapidity, scalability and a significantly lower chance of contamination with prion or mammalian viruses. In the chapter by Chen, the current status and recent advancement of such systems, important clinical products and challenges and future directions.

Genome editing with engineered nucleases (e.g. CRISPR-Cas9, TALENs) represents a highly precise and efficient tool to generate useful novel phenotypes in crops by base additions, deletions, gene replacement or transgene insertion. These techniques generate phenotypic variation in plants that can be indistinguishable from those obtained through natural means or conventional mutagenesis. In the chapter by Pfeiffer et al., the authors discuss issues surrounding the regulatory status of plants edited by engineered nucleases.

In the next chapter, Tani et al. discuss how intense breeding over the past centuries has eroded genetic diversity. Heritable epigenetic variation based on chromatin variation that does not involve alterations in DNA sequence can expand the sources of phenotypic diversity and affect important agronomical traits. Hence, epigenetic variation and the emerging field of epi-breeding can be exploited towards crop improvement in the context of enhancing yield, quality and adaptation to the ongoing climatic changes.

Mora-Oberlaender and colleagues describe in the following chapter the path followed by Colombia for the deployment of GE crops in agriculture. Colombia participated in the formulation of international regulatory policies such as the Cartagena protocol and established a national framework to deal with environmental release of GE crops and their use as food/feed. Within this framework, events for several crops (maize, cotton, flowers and soybeans) have been authorized for cultivation, while there are 104 events from 7 crops approved for food use since 2003 and 59 for feed. While the national framework is still far from a scientifically sound, risk-based approach, the experience gained in Columbia can be of value for other developing and developed countries.

The chapter deals also with the fact that none of the approved events were created within the country, despite the presence of several research groups, because of constraints, some of which are related to Intellectual Property Rights. The authors therefore discuss how public research labs should deal with a heavily patented landscape and how available technologies may lead to more effective product development by local groups, for instance by focusing on species of importance to the national agriculture, using varieties adapted to local conditions and through the deployment of agbiogenerics, that is GE crop events equivalent to a brand-name product which are developed by competitors after the patent protections expire. However, the case of Golden rice testifies that constraints other than IP rights are a major obstacle.

In the concluding chapter, Farouki, a philosopher and historian of science, presents a brief history of the way fear and mistrust about science and technology have been built over the past few decades. She analyses the attacks on new biotechnologies in the context of two complementary phenomena: the suspicion that surrounds everything that is related to food, and the questioning of scientific knowledge, method and truth in the intellectual postmodern sphere.

5. CONCLUSION

There is a long, venerable and seamless continuum of agricultural advances that began with the domestication of plants and has continued with incremental refinements as our experience and knowledge have accumulated and new technologies have become available. Transgenesis and genome-editing techniques have great potential and less risk of unintended effects when compared to spontaneous mutation or random mutagenesis. We need further advances to ensure that our food supply has sufficient resilience—the ability to recover from or adapt to adversity—in the face of the stresses of weather, pestilence and disease.

However, many of those advances—the use and diffusion of the newest technologies for genetic improvement, in particular, many of which are discussed elsewhere in this volume—are being hindered by extrascientific factors. These include government overregulation and antagonism from activists opposed to modern agriculture (for the various reasons discussed earlier) and industries with competing financial interests (e.g. organic agriculture). An important element of these problems is the myth that "GMOs" are a genuine "category" with unique characteristics (Tagliabue, 2016).

If we are to unleash the ingenuity of plant scientists in order to make farming more resilient and to improve food security for a growing world population, we will need enlightened public policy that takes into consideration the seamless continuum from domestication to 21st century genetic engineering. This must include sweeping regulatory reform to make regulation scientifically defensible and risk based. Many scientists have made credible proposals to achieve this (Conko, Kershen, Miller, & Parrott, 2016; McHughen, 2012; Potrykus, 2013), but as yet, there is nary a hint of that on the political horizon.

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