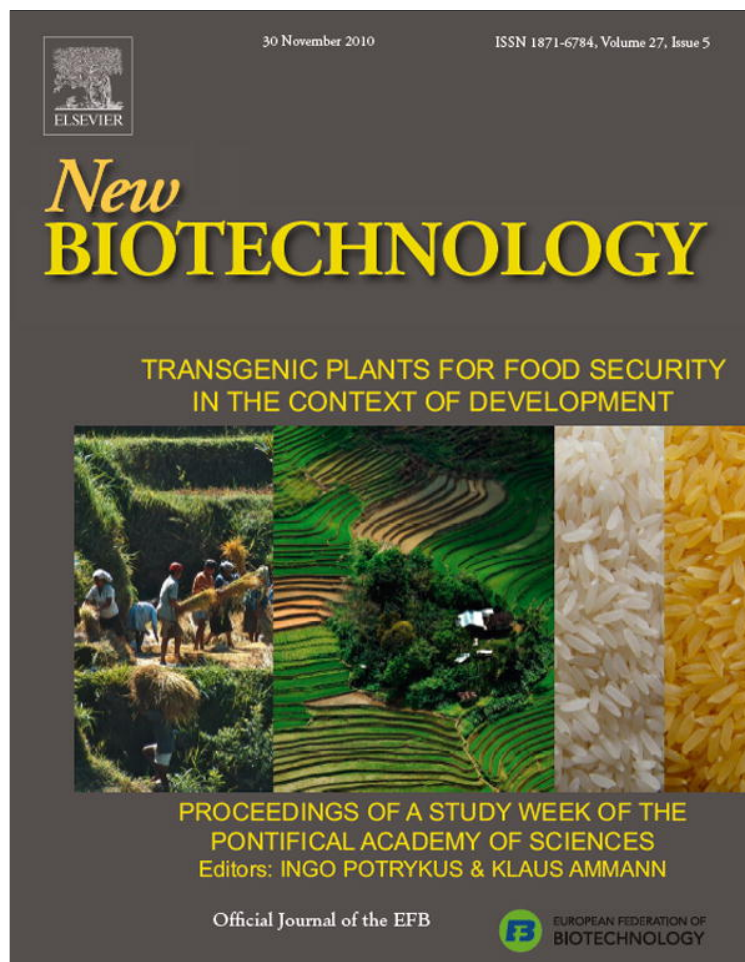


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Genetically modified myths and realities

Review

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Myths abound when it comes to GE crops. At their worst, myths play an active role in discouraging the use of GE to solve problems that afflict humankind, such as malnutrition and birth defects. Of all the various myths, two have been particularly important in preventing the use of GE maize in its areas of origin. The first is that transgenic maize will contaminate and destroy land races, thus destroying biodiversity and its associated cultural traditions. This myth totally ignores the fact that the gene flow that has taken place between maize and its progenitor, between the land races, and between land races and modern hybrids, has not led to any dire consequences. The second myth is that crops are natural and have not been modified by humans, or if they have, that plant breeding does not alter DNA. This myth ignores the fact that for the most part, it is impossible to alter the appearance of crops without changing the DNA. In fact, DNA movement within the crop genome is normal and its movement leads to double-strand DNA repair, with results like those found around transgene insertion sites. In addition, plants have ways to create novel genes. These changes help plants adapt to evolution and to human selection. The net result is that changes similar to what happens during the production of engineered plants takes place anyway in plant genomes.

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Introduction

“And all who told it added something new, and all who heard it made enlargements, too”. (Alexander Pope).

As noted above by Alexander Pope, certain topics are particularly prone to distortions as they are repeated. The topic of genetic engineering in agriculture is probably the one topic that has most lent itself to misinformation over the past decade. The following

excerpts from websites illustrate the extent and nature of the myths surrounding GE (genetically engineered) crops:

“The Microbial Ecology in Health and Disease journal reported in 1998 that gene technology may be implicated in the resurgence of infectious diseases.”

(<http://www.raw-wisdom.com/50harmful>, 8 Dec 2009)

“A number of studies over the past decade have revealed that genetically engineered foods can pose serious risks to humans, domesticated animals, wildlife and the environment.”

E-mail address: wparrott@gmail.com, wparrott@uga.edu.

(<http://truefoodnow.org/campaigns/genetically-engineered-foods/>, 16 Dec 2009)

"The introduction of genetically modified organisms (GMOs) by choice or by accident grossly undermines sustainable agriculture and in so doing, severely limits the choice of food we can eat."

(<http://www.greenpeace.org/international/campaigns/genetic-engineering/hands-off-our-rice>, 16 Dec 2009)

"Our country's children are fed inadequately tested and unlabeled genetically engineered foods in their school meal programs"

(http://www.sierraclub.org/biotech/school_lunch.asp, 17 Dec 2009)

"Latest GMO Research: Decreased Fertility, Immunological Alterations and Allergies"

(<http://www.naturalnews.com/025001.html>, 17 Dec 2009)

"The proof is obvious that one of the major reasons of the bees' decline is by the ingestion of GMO proteins."

(<http://www.infowars.com/death-of-the-bees-gmo-crops-and-the-decline-of-bee-colonies-in-north-america/>, 17 Dec 2009)

"If the corn gene that creates Bt-toxin were to transfer into gut bacteria . . . it might turn our intestinal flora into living pesticide factories."

(<http://www.seedsofdeception.com/Public/GeneticRoulette/ExcerptfromIntroduction/index.cfm>). See rebuttal to this particular point at <http://academicsreview.org/reviewed-content/genetic-roulette/section-5/5-7-bt-genes-and-gut-survival/>.

The existing GE myths are numerous and widespread, and they cover the gamut of topics from health and safety to various aspects of environmental safety. In as much as there are time and space limitations, only two myths will be covered in detail. These two myths are particularly pernicious, as they prevent the deployment of GE crops in areas where they are most needed. They therefore serve to perpetuate conditions that may lead to chronic malnutrition and extraordinary rates of birth defects among the population.

The great maize myth: transgenic maize in its center of origin will destroy it via contamination

As background information, maize originated in southern Mexico [1]. Today, 11 million maize farmers plant 6 million ha of maize

and support a population of 77 million. The average farm size is 3.5 ha, of which 1.50 ha are planted with maize [2]. The central Andean region of South America is a secondary center of maize diversification. This region has about 7 million farmers on 3 million ha that support 16 million inhabitants. Maize yields average about a ton per ha [2].

Agroecologically, traditional maize production in Mesoamerica was very effective when the population was low. Today, the system is not meeting the food needs of the population. The population has tripled in the past 50 years, forcing the land to be subdivided into ever-smaller parcels with each generation. In 1964, there were 321,000 parcels in the Guatemalan highlands. By 1996, the number had increased to 667,000 in the same land area [2]. A yield of ~1500 kg/ha is considered good; yet such a yield is barely ~1/6 of maize yields in the USA. More worrisome is the fact that ~50% of children under 5 are malnourished [3], in part owing to the chronic food insufficiency derived from low yields and small parcel sizes.

The second limitation associated with maize production in Mesoamerica is the prevalence of growth of *Fusarium* spp. and subsequent fumonisin production [4,5] on corn cobs, which follows feeding damage by caterpillars [6–8]. Fumonisin is a carcinogen which is also associated with neural tube birth defects (NTDs) owing to its ability to interfere with sphingolipid metabolism, and hence, folic acid [9–12]. Fumonisin is almost ubiquitous in corn products in the region [4,13–15]. It is therefore not surprising that the region manifests some of the highest rates of NTDs in the world [16], surpassing 115 cases of anencephaly, spina bifida, or encephalocele per 10,000 births, as compared to the world average of about 15 cases per 10,000 (Fig. 1) (Dr Julio Cabrera, Guatemala City, pers. comm.).

The bottom line is that there is a real cost in terms of human health that is associated with the current maize production system. Yet, both yield loss, and particularly, fumonisin production, could be attenuated through the use of insect-resistant maize. Maize transgenic for the Bt gene has been known to lower fumonisin production under several, although not all, circumstances [7,17–20]. Thus, the use of Bt maize would be a simple solution to help address some of the most pressing issues associated with maize production.

Despite the obvious advantages of deploying Bt maize from a humanitarian point of view, there is fierce opposition to the release of GE maize in its center of origin. The arguments are that GE would at best 'contaminate' or at worst, displace, the existing genetic diversity of maize. In addition, there are claims that GE maize would have cultural consequences:



FIGURE 1

Examples of suspected fumonisin-associated birth defects: anencephaly, spina bifida and encephalocele. All are from one summer in one hospital in Guatemala. Photos courtesy of Dr Julio Cabrera.

“There are over 59 known races and thousands of varieties, which will be inevitably contaminated.”

(<http://endefensadelmaiz.org/No-to-transgenic-maize.html>, 17 Dec 2009)

“Scientists worry that the genes could spread through the region’s corn population reducing its genetic diversity.”

(http://www.historycommons.org/timeline.jsp?seeds_crops=-seeds_cropsCorn&timeline=seeds_tm1n, 20 Dec 2009)

“The introduction of genetically engineered varieties also threatens the indigenous cultures and the very knowledge that indigenous peoples have developed for millennia. Genetic contamination of maize threatens the food sovereignty for hundreds of millions of people that rely on maize as their primary source of food.”

(<http://www.globalexchange.org/countries/americas/mexico/news/gmo100101.html>, 17 Dec 2009)

“transgenes might threaten the character or continuance of the Mexican maize landraces. They might thus alter the Mexican diet and the global fate of corn itself”

(<http://www.theotherjournal.com/print.php?id=874>, 21 Dec 2009)

Reports of transgenes in Mexican maize are routinely made [21,22] and rebutted [23,24]. It is probably fair to say that if transgenes are not yet in maize, it is just a matter of time before they are. Regardless of whether or not transgenes have been introgressed into native maize varieties, there is no question that genes flow between maize varieties and landraces. Thus, the issue is not about whether there will be gene flow, but rather about the consequences of such flow.

It is possible to examine the consequences of gene flow by studying maize production in its historical context. First, maize and its progenitor, teosinte, have grown sympatrically for millennia. In some regions, maize has evolved a gene to limit crosses between maize and teosinte; in others, there are no crossing barriers [25], so a low level of gene flow between the two does occur [26] (Fig. 2). The point is that despite the gene flow with each other, neither maize nor teosinte have been damaged or have lost their identities.

The same is true of the various land races. Historically, they have been planted contiguously (Fig. 3), and they readily cross pollinate (Fig. 4). The point again is that these varieties have coexisted for centuries, and despite their intercrossing, have not lost their identity.

Finally, improved maize cultivars and hybrids have been grown in the region for decades now. There is evidence that genes from modern hybrids have been introgressed into the traditional land races [27], *but again, the land races have not perished, nor have there been cultural consequences*. In fact, the greatest threat to the maintenance of land races does not come from introgression of genes, but rather from migration of farmers from the field to the city [28], or economic diversification that lessens farmers’ dependence on maize [29].

On the basis of the fact that there has been gene flow between teosinte, traditional varieties and modern hybrids, it becomes possible to predict the consequences of transgene flow. The topic



FIGURE 2

A maize–teosinte hybrid growing in a Mexican maize field. Photo courtesy of Raúl Coronado.

has been considered previously. The following conclusion is from the findings of the Commission for Environmental Cooperation [30]:

“16. There is no reason to expect that a transgene would have any greater or lesser effect on the genetic diversity of landraces or teosinte than other genes from similarly used modern cultivars. The scientific definition of genetic diversity is the sum of all of the variants of each gene in the gene pool of a given population, variety, or species. The maize gene pool represents tens of thousands of genes, many of which vary within and among popula-



FIGURE 3

White, black and yellow maize drying on a Guatemalan rooftop after harvest.



FIGURE 4

Maize from the Guatemalan highlands, showing that cross pollination takes place naturally between the landraces. Photos courtesy of Eduardo Roesch.

tions. Transgenes are unlikely to displace more than a tiny fraction of the native gene pool, if any, because maize is an outcrossing plant with very high rates of genetic recombination. Instead, transgenes would be added to the dynamic mix of genes that are already present in landraces, including conventional genes from modern cultivars. Thus, the introgression of a few individual transgenes is unlikely to have any major biological effect on genetic diversity in maize landraces."

In summary, there is sufficient experience to state that, by itself, gene flow from transgenic maize will not have the destructive effect predicted by those who oppose GE maize. Any claims to the contrary are not consistent with the available evidence and thus must be considered in the realm of myths.

What is the origin of the great maize myth? There are undoubtedly numerous motivations, combined with a general lack of knowledge on maize genetics and cultivation. First, implicit in the concept that a novel gene introgressed into a land race constitutes 'contamination' implies that land races are somehow genetically defined, static entities. They are not. Whereas land races have recognizable phenotypes, they are genetically dynamic. As mentioned previously, there is gene flow among land races planted adjacently, and farmers exchange seed among themselves, further contributing to gene flow. However, gene flow is countered by selection – farmers participate actively in selecting for the desired phenotypes [29,31,32]. Thus land races are the product of continuous crossing and selection that maintains the phenotype while continuously selecting for the most adapted types for each region. New traits that are considered desirable by the farmers will be maintained; the rest are discarded.

The starting misconception: the myth of natural food

The second concept that is implied by the use of the term 'contamination' is that today's food crops are natural. The perception is that our crops' ancestors were found in the wild, and brought into cultivation. Other than the fact they are now cultivated, they have remained in their original, pristine state. Transgenes thus contaminate them; much like industrial effluent can contaminate and ruin a natural lake.

Few people realize the extent to which today's crops have been modified during the domestication process. It was Charles Darwin who pointed out in his *Origin of the Species* that our domesticated crops have been so altered by breeding and selection, that at times it can be difficult to recognize their wild progenitors. Maize is an extreme example of Darwin's observation, as cobs of teosinte bear little resemblance to those of modern maize (Fig. 5). Thus, there is very little that is natural about our current crops.

However, what makes Darwin's observation so relevant to GE is that, barring a few cases that involve epigenetics, *it is impossible to change the appearance of a plant without changing its DNA*. Yet, the perception remains that breeding does not alter DNA [33]:

"Insertion of DNA can cause deletions and rearrangements of the original DNA at the insertion site. This information helps us understand that GE is significantly different from conventional breeding techniques."

To really evaluate the differences between conventional breeding and GE, it is necessary to evaluate the changes at the DNA level that take place during breeding and selection.



FIGURE 5

A teosinte cob, showing the extent of changes that had to take place during domestication to produce modern maize. Photo courtesy of Raúl Coronado.

Mutation breeding is the most obvious example of a methodology known to alter DNA. There are 2543 known crop varieties developed from mutation breeding (FAO/IAEA database <http://www-infocris.iaea.org/MVD/>). Yet very few of these have been studied to determine the change at the DNA level.

However, mutations from ionizing radiation have been studied most extensively in *Arabidopsis*, and these probably represent the type of changes that take place in crop plants. Deletions ranging from 300 bp to 8 kb are probably the most common result [34]. Small inversions are also possible from mutagenesis. Null alleles have been characterized for chalcone flavanone isomerase and dihydroflavonol 4-reductase. The first contained a loss of 4 bp along with a 1.5-kb inversion within the gene, and an insertion of 272 bp that were originally 38 cM away. The second also has an inversion of the genomic region, with 52 bp deleted at one end and 7.4 kb at the other [35]. Thus, it is clear that changes brought about by ionizing-radiation-mutagenesis exhibit the same features as do transgene insertions. The latter can result in deletions that range from 1 to 825 bp, along with larger duplications and insertions [36].

Naturally occurring DNA segments also get inserted into crop genomes. It is a feature of plant genomes that they are rife with DNA insertions of various types. Plant genomes are primarily composed of retrotransposons [37]. These are DNA elements that get transcribed into messenger RNA which gets reverse-transcribed into DNA copies which get inserted elsewhere in the genome. It can be inferred that retrotransposons are actively moving in crops, as their RNA appears in EST libraries. However, it is only now that genomic technologies are advancing to a point where genomes can be evaluated for active retrotransposition. Although the data are still very limited, an example has already been found in rice variety 'Nipponbare,' which contains a retrotransposon that still moves in the genome [38].

In addition, plant genomes have transposable elements. Unlike retrotransposons, transposable elements excise from the genome and reinsert themselves elsewhere in the genome, without going through an RNA intermediate. Transposable elements were first discovered in some experimental maize inbreds, but active elements were thought to be absent from varieties of maize and other crops used in agriculture. As detection methodologies have improved, and more transposable elements have been discovered, that view has changed. For example, active Ping elements and their derivatives have been found in 'Gimbozu,' a rice variety that is ancestral to many modern rice cultivars. The transposition rate in Gimbozu is 49–63 new insertions per plant per generation, a rate that is representative of what historically took place in farmers' fields. By contrast, the rate of new insertions in its derivative cultivar, 'Nipponbare,' is only about one new insertion per three plants per generation [39], perhaps because breeders have selected for greater phenotypic stability.

Over time, other types of DNA move between cell organelles as well. Lough *et al.* [40] used *in situ* hybridization to illustrate that mitochondrial sequences have inserted themselves into different chromosomes in different maize hybrids over time. Likewise, Huang *et al.* [41] developed transplastomic tobacco, with chloroplasts transgenic for a gene for kanamycin resistance, driven by a nuclear promoter. Thus, the frequency of transfer to the nucleus could be monitored by the presence of kanamycin-resistant pro-

geny, which is 1 per 11,231 gametes. Huang *et al.* [42] had previously determined that the DNA fragments that move from the chloroplast to the nucleus range in size from 6 to 22 kb.

Biologically, the excisions of transposons and the integration of DNA segments all lead to double-stranded DNA breaks that must be repaired. For example, spontaneous 60–880-bp deletions in the waxy locus of maize acquired from 1 to 131 bp of filler DNA, with the filler sequences frequently being homologous to sequences near the deletion endpoint [43]. In all cases, the filler DNA is derived from the normal double-stranded break repair mechanisms of plants [44,45]. Therefore, the filler DNA that is added during the repair of spontaneous double-stranded DNA breaks is identical in origin to that which is found many times in the T-DNA/plant DNA junctions. Filler DNA, up to 51 bp in length, is homologous to sequences near the T-DNA border or the plant DNA border [46,47]. In the end, the repair of double-stranded DNA breaks does not discriminate between inserts of DNA and movement of endogenous DNA elements [48]. Such double-stranded DNA break repairs, and their associated deletions and additions of DNA, are so common that they may even contribute to changes in plant genome size [46,49].

To summarize up to this point, any changes other than insertions that take place at the DNA level are due to the same repair mechanisms that normally mediate DNA double-strand break repair, and thus are in no way unique to transgenic plants. Nevertheless, the fact remains that GE crops do have exogenous DNA, and this DNA is operating in a novel background. To properly evaluate the significance of a novel gene, it is first important to consider that there is a core set of about 13,300 genes necessary for angiosperms. From there, different genes are either amplified in copy number or created in different plant families as these evolve and adapt to their environments and growth habits [50].

The process of gene duplication and creation continues to this day. For example, glyphosate-resistant amaranth arose over the past decade. Resistant plants can have up to 160 more copies of the EPSPS enzyme gene compared to susceptible types, and these genes have moved to all its chromosomes [51]. Alternatively, retrotransposons can capture exons from other genes, and assemble them into novel combinations never before seen. For example, the *Wp* mutation in soybean appeared in Illinois in 1987. It was noticed because the seed were 22% larger and had 4% more protein, while the flower color changed to a very pale pink. The mutation is due to retrotransposon that inserted itself into one of the chalcone synthase genes. This particular retrotransposon has captured five exons from four different genes, and these are transcribed into a novel mRNA [52,53].

The above is an example of a retrogene. Of 898 retrogenes identified in rice, 55% appear to be functional, and about 35% are chimeric in nature, in that they have components from different genes in novel combinations [54]. *The point is that there is little difference, if any, between an entirely novel retrogene being created in a crop, or a transgene being inserted into it.* In contrast to a transgene, a retrogene is almost impossible to detect in the absence of advanced genomic technologies.

All these examples illustrate that DNA in crop plants is dynamic; it changes in response to human selection and other evolutionary forces, such that novel variability is created along the way. The realization that DNA is so changeable does not come as a surprise.

Previously, Rasmusson and Philips [55] realized that modern barley cultivars had more genetic variability than their ancestors, and surmised that new variation must have been created during the past century of breeding efforts. Likewise, McClintock had predicted that plant genomes were particularly prone to change during periods of stress [56]. However, these early visionaries lacked the necessary tools to test their hypotheses.

Today, a wealth of information is starting to come in from genomics projects, and it is becoming evident that, if anything, plant genomes are even more dynamic than originally envisioned. Maize, more than any other crop, has turned out to have more genetic variability than any other eukaryotic species that has been studied to date. A comparison between 'B73' and 'Mo17,' the two inbreds most commonly used to produce hybrids revealed several hundred examples of genes that are present in different numbers in the two inbreds, along with several thousand DNA sequences that are present in one inbred but not in the other, and which contain hundreds of genes [57]! A comparison between B73 and 'Palomero Toluqueño,' a Mexican landrace, revealed that the

genome of the latter is 22% smaller than that of B73 [58]. These examples serve to illustrate the amount of variability that maize can tolerate and still be maize.

It is not surprising then, that gene expression profiles are consistent with the expectations derived from highly variable plant genomes, namely that the use of transgenics yields less variability than the use of other breeding technologies. Gene expression profiles from mutagenized rice plants showed more differences than transgenic plants did when each was compared to its parental variety [59]. The same results were obtained when expression profiles were compared for transgenic wheat and their conventionally bred, non-transgenic counterparts [60,61].

To summarize, the current model that is emerging depicts plant genomes as dynamic entities that respond to environmental stimuli. Under this model, change is the norm, not the exception. Thus, the assertion that the plant breeding process is not like the transformation process must also be considered a myth. The only difference between the two is the time scale.

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