



The Genetic Engineering of Food and the Failure of Science – Part 1: The Development of a Flawed Enterprise

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Abstract. A major conflict is developing in science over transgenic foods. Food, feed, and fiber products derived from transgenic agricultural crops are presented here as a different case from industrial and pharmaceutical crop transgenics and should be parsed from the larger transgenics industry for comprehensive re-evaluation and market roll-back. Reviewed is the development of the crop transgenics industry; the early influence of the biotechnology industry over the US federal regulatory agencies in the context of the development of minimal regulation; the basic technology of plant transgenics; the main transgenic crops, traits, and producing countries; consumer resistance to transgenic foods; industry problems with shrinking investments; the worldwide promotion of transgenic crops; and ecological issues of transgenic crops. Flaws in the one gene–one protein model, the foundation of transgenics, are reviewed in the context of the recent and ongoing restructuring of the science of genetics. Research on the mutational consequences of plant transgenics and its phenotypic ramifications such as allergens and novel proteins is discussed. Major research findings and ‘red flag’ incidents in the history of transgenic foods and feeds are reviewed that reflect the flaws in the genetic foundations of transgenics.

Introduction

A major conflict is imminent in science. On the one side are scientists, universities and corporations who have invested nearly 25 years and tens of billions of dollars in the genetic engineering of organisms (transgenics), mostly bacteria and plants, for food, pharmaceutical, and industrial uses. On the other side is a flood of evidence that food plant transgenics – not bacterial or pharmaceutical plant transgenics – is fatally flawed and has been resting on a theoretical foundation that has crumbled away as the science of genetics reinvents itself. Adding to this side is a worldwide grass-roots movement opposed to genetically engineered foods.

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It is important to parse out the specific problem area – food, feed, and fiber crop transgenics – from the rest of the transgenics industry. The investment of fortunes and careers in transgenics is not all under threat, in this author’s view, only that of food, feed, and fiber crops. This parsing would leave bacterial and pharmaceutical crop transgenics intact (with provisos, below), which very likely constitute the majority of scientists and corporate resources invested in transgenics. Calls for the rolling back of food transgenics therefore should not be seen as a threat to the entire industry. However, owing to the primacy of food and to the decades of investment of both scientific careers as well as dollars into crop transgenics, this emerging conflict has enormous consequences and stands to become a major development in the history of science.

Society is currently in a watershed era as to whether future world food is produced predominantly via patented transgenic crops, largely untested as to their long-term health or ecological effects, or whether food production is based on crops whose genetic integrity is intact, having been subject exclusively to the intra-genus and intra-family plant breeding methods of many millennia, and whose resultant proteins are consistent with our own co-evolved genetic, proteomic, and physiological systems.

Underpinning the development of the transgenic foods situation have been the major changes that have taken place in the relationship between research universities and private industry since the early 1980s, characterized by increased bilateral dependence, networking of scientists from the two sectors, and commercialization of university research (Leydesdorff and Etzkowitz, 2001; Bok, 2003), a dynamic commonly referred to by the term ‘academic capitalism’ (Slaughter and Rhoades, 2004). Sociologists, among other academics, have for some time raised questions about the university science community’s merging into the ‘knowledge economy’, with intellectual property ownership at its center (Press and Washburn, 2000; Kleinman, 2003; Krinsky, 2003; Etzkowitz, 2005; Welsh and Glenna, 2007), and many have lamented the replacing or subsuming of the older communal norms of science as set down by Robert Merton and the ‘science for the public good’ of Vannevar Bush (which will be discussed in Part 2).

In this two-part paper, I will describe how the worst fears of the critics of academic capitalism, fears that the potential loss of scientific direction and integrity that comes with proprietary-centric science could lead to significantly negative developments for the public, have come to pass in the arena of transgenic foods. This is a story of how a grand scientific vision, plant transgenics, a science that its developers believed would vastly improve the world food supply while at the same time generating huge profits, blinded many of those scientist-developers to the increasingly serious flaws in the basic model, mechanics, and end-products of the enterprise.

Why the distinction between traditional agricultural crops (food, feed, fiber) and pharmaceutical crops and bacterial transgenics? First, bacterial genetics are in a simpler class than those of higher plants and animals, and bacterial transgenics, with a few exceptions such as an early fatal disaster involving the nutritional supplement L-tryptophan (Smith, 2007), has been a success.

Pharmaceutical crops are more problematic than bacterial-derived products, yet I believe that a benefit–risk analysis justifies their use, with restrictions on cultivation, transport, and storage. Genes for the production of pharmaceutical compounds have been engineered into crops such as corn and rice. These crops, often clumsily called ‘pharm-crops’, are a different case than transgenic food crops, since the pharmaceu-

tical process generally involves producing and isolating a single or few compound(s) which can then be tested for purity and dispensed using a system which has a clear paper trail (prescriptions), should any problems arise. Current opposition to pharmaceutical crops has to do with them being cultivated in traditional open crop fields, which can lead to contamination via pharmaceutical-laden pollen or seeds, as well as issues having to do with post-harvest contamination of foods in various transport and storage systems.

A plant food product, in contrast to a pharmaceutical crop product, consists of hundreds of different compounds, all or most of which are eaten by the consumer. A food product – for example, a wine grape, a fresh tomato, or a grain of wheat – can be seen as a ‘symphony’ of compounds that make up the potential gustatory and nutritive experience. In the case of transgenic foods, one or more of this collection of compounds may be ‘rogue’, novel, or misformed proteins, inadvertently produced in the transgenics process, and which may be allergenic or toxic, as discussed later in this paper. Under the current system of oversight, transgenic foods during the crop development and subsequent stages are inadequately checked for these compounds, and are dispensed in a system that is largely untraceable if there are health problems amongst consumers.

The inadequate regulation of the cultivation and post-harvest management of pharmaceutical crops has been a serious failure at the US federal level (Earthjustice, 2006). Pharmaceutical crops *must* be grown in contained enclosures like greenhouses and must be transported and stored by exclusively non-agricultural systems in order to eliminate risk of contamination of foods and feeds with pharmaceutical grains. Anything short of these controls is unacceptable.

In the early stages of the development of crop transgenics in the 1980s, thorough scientific scrutiny of this truly radical technology would likely, in this author’s opinion, have led to restrictions on cultivation and marketing of transgenic products, and may have resulted in non-approval altogether. A central factor in this failure has been the early influence of the biotechnology industry, better termed dominion, over the highest levels of the federal regulatory agencies, which led to a ‘hands-off’ policy regarding regulation of transgenic foods. Instead of (actually in spite of, as discussed later) a period of scientific scrutiny early in the evolution of transgenic crops to determine their safety and integrity, these crops were given the green light, resulting in the investment of billions of dollars and thousands of professional careers worldwide. Many countries have either modeled their transgenic foods regulatory system partly or wholly on that of the US, or depended on the US regulatory system as a sanctioning entity for the approval of transgenic crops.

This early industry pressure and science community compliance for a premature green light for transgenic crops is now coming back to bite the industry and the science community, and bite them very seriously. This paper, in two parts, discusses how this situation developed, the nature of the problem, and proposes an alternative in the form of an agroecology-based foundation to world food production.

Development of the Agricultural Transgenics Enterprise

The discovery in the mid-1970s (Van Larebeke et al., 1975) of the ability of the bacterium *Agrobacterium tumefaciens* to insert its own DNA into a host plant’s genome and ‘hijack’ the plant’s metabolic machinery for the bacteria’s own use started a rev-

olution in the genetic manipulation of plants. Since then scientists have developed techniques to harness *Agrobacterium's* DNA insertion machinery to insert genes of the engineer's choice into plants in order to get plants to produce certain compounds or express certain traits. Genes have been snipped from microbes, plants, and even animals via restriction enzyme technology and spliced into the plant genome in order to create new traits like herbicide or insect resistance.

This process, variously referred to as recombinant DNA (rDNA) technology, as well as transgenics or plant transformation, is generally referred to in lay terms as genetic engineering or genetic modification. It produces transgenic crops and foods, popularly called genetically modified organisms, or GMOs.

The growth of the transgenics enterprise has been streamlined by decisions throughout the 1980s and 1990s from the US Supreme Court as well as the US Patent and Trademark Office that supported the patenting of genes and biological processes. The landmark *Diamond v. Chakrabarty* decision in 1980, which held that regular utility patents could be granted for inventions involving living organisms, laid the legal groundwork for developing transgenics as a commercial enterprise.

Traits that have been genetically engineered into crop plants and approved for the US market are (data are up to 2006, taken from Lopez Villar et al., 2007): herbicide resistance (corn, soy, cotton, canola, rice, alfalfa, beet, flax), insect resistance (corn, cotton, potato, tomato), sterile pollen (corn, chicory [radicchio]), virus resistance (papaya, squash, plum), delayed ripening (tomato), altered oil (canola, soy) or protein (corn) composition, and reduced nicotine tobacco. The Monsanto Corporation accounts for some 90% of transgenic traits around the world.

First planted in 1996, soy, corn, canola, and cotton accounted for nearly 100% of the world's 80 million hectares of transgenic crops in 2006 (1.5% of total world crop acreage). The main two transgenic traits are resistance to glyphosate herbicide (approximately 70% of acreage), most of which consists of crops resistant to Monsanto's Roundup® (a proprietary version of glyphosate); and insect resistance in which the plant systemically produces an insecticide derived from the Cry gene of the bacterium *Bacillus thuringiensis*, known as Bt (20% of total acreage). About 10% of acreage consists of corn and cotton varieties in which the two traits are combined (stacked) in the same plant. Until 2004, nearly all transgenic crop acreage has been in four countries – the US, Canada, Argentina, and Brazil. Brazil and Argentina have seen enormous growth in glyphosate-resistant transgenic soybean production, mostly for export to China for livestock feed.

Contrary to popular belief, yields of the major transgenic crops have been shown to be no higher than and sometimes significantly below those of non-transgenic crops, with net returns and profits commonly lower (Myerson, 1997; Qaim and Zilberman, 2003; Benbrook, 2004; Josta et al., 2008). The incentive for using transgenic crops is reported to be 'the convenience effect' of reducing labor costs, with the greatest cost reductions on larger farms (Seedquest, 2000; Fernandez-Cornejo, J. and W. McBride. 2002; Lopez Villar et al., 2007).

Consumer resistance to transgenic foods in the developed countries (Mcinerney et al., 2004) has made for financial problems and reduced investment in the crop transgenics segment of the biotechnology industry (Baue, 2003). The biotechnology industry (of which the transgenic crops sector is just one part), currently worth some \$75 billion (Caruso, 2007a), lost 'a staggering' \$57.7 billion over the period 1994–2004, according to a study by a leading investment consulting firm (Robinson, 2004). According to the Wall Street Journal \$100 billion has been invested in biotechnology

related to genetic engineering and \$40 billion has been lost (Hamilton, 2004). One report states that because of resistance to transgenic products in world markets, the introduction of transgenic wheat (which has not yet been approved) would reduce US wheat exports by 25–50% and cause a reduction in prices of up to 33% (Wisner, 2005).

The transgenic crops industry, with the help of the US government, is aggressively promoting its crop products worldwide (Lopez Villar et al., 2007). In 2003 the Bush administration filed an injunction against the World Trade Organization after the European Commission refused to accept transgenic food from the US (Becker and Barboza, 2003). Developing countries have been targeted by both biotechnology companies and the US government. The George W. Bush administration's top trade official, Robert Zoellick has bluntly criticized developing nations who have refused to accept US transgenic foods (McInerney et al., 2004).

Illustrative is the Monsanto Corporation's global marketing vision from a 2005 company document: 'full adoption of GM crops globally would result in income gains of US\$210 billion per year within the next decade, with the largest potential gains occurring in developing countries at a rate of 2.1 percent gross national product per year' (Lopez Villar et al., 2007).

Much of this push is being done with the help of US foreign aid agencies such as the US Agency for International Development (USAID) as well as well-endowed NGOs such as the Rockefeller and Gates Foundations (African Centre for Biosafety, 2007; Ho, 2007; Lopez Villar et al., 2007). USAID is mandated to partner with US biotechnology corporations to promote the companies' crops in developing countries (Brenner, 2004).

India has been the target of a major transgenic crops campaign (Lopez Villar et al., 2007). The large-scale transfer of capital-intensive crop systems, especially transgenic cotton, to peasant farmers in India has taken the form of a 'fad' or 'stampede' (Stone, 2007), and has led to a farmer debt crisis that has been associated with subsequent mass suicides of indebted farmers (Stone, 2002; Chaudhary, 2007). Thailand (Eyre, 2007) and Indonesia (*Jakarta Post*, 2007) have seen intense promotion of transgenic crops by foreign by both US companies and the US government, and it was in Indonesia that the Monsanto Corporation broke US anti-corruption laws by paying out nearly \$1 million in bribes in order to circumvent environmental regulations governing the planting of transgenic cotton (Guerin, 2005). According to agrarian leaders in Mexico, farmers and agricultural extension services in that country are being pressured to grow transgenic crops (Prensa Latina, 2007). Eastern Europe has been targeted as fertile ground for transgenic crop business (Merrett, 2007). Africa is the focal point of a major push by the crop biotechnology industry (Lopez Villar et al., 2007). According to one South Africa-based consultant 'African governments are facing enormous pressure to endorse and adopt genetically modified crops' (Fig, 2007).

Regulation

No better example of the foundational close relationship of the biotechnology industry with the highest levels of the US federal government is that of the Monsanto Corporation's legendary influence in Washington, as described in Jeffrey Smith's 2003 book *Seeds of Deception* (Smith, 2003). Under the Reagan and G.H.W. Bush administrations of the 1980s, Monsanto, according to the New York Times, created

'support for biotechnology at the highest U.S. policy levels' (Eichenwald and Kolata, 2001) right up to the White House, and developed a 'revolving door' strategy between the highest executive-related positions at Monsanto and the top positions of the federal regulatory agencies. This pattern continued through the Clinton and G.W. Bush administrations, in which the latter hired a former Calgene (transgenic crop company bought by Monsanto) board of directors member, Ann Veneman, as Secretary of Agriculture. Wrote *The New York Times* on Monsanto's power over federal regulations during the G.H.W. Bush presidency:

What Monsanto wished for from Washington, Monsanto and – by extension, the biotechnology industry – got. If the company's strategy demanded regulations, rules favored by the industry were adopted. When the company abruptly decided that it needed to throw off the regulations and speed its foods to market, the White House quickly ushered through an unusually generous policy of self-policing (Eichenwald, 2001).

The biotechnology industry lobbied to have foods derived from genetically engineered plants classified as no different from food from conventionally bred plants. This was known as the policy, or doctrine, of 'substantial equivalence'. There was resistance, however, from scientists within the FDA to the policy of non-regulation and substantial equivalence of transgenic foods. A 2004 paper (Freese and Schubert, 2004) showed that there were internal FDA memos documenting an overwhelming consensus among the agency's scientists that transgenic crops can have unpredictable, hard-to-detect side-effects – allergens, toxins, nutritional effects, new diseases. They had urged their superiors to require long-term studies. According to the authors of the paper, these communications were ignored.

The biotechnology industry essentially won the battle for non-regulation of transgenic foods when in 1992 the FDA released a policy statement on transgenic foods via the *US Federal Register*, the standard protocol for setting federal regulatory policy: 'The agency is not aware of any information showing that foods derived by these new methods differ from other foods in any meaningful or uniform way' (57 FR 22991 [1992-05-29]). The main elements of the regulatory framework are essentially voluntary. Companies that wish to release a genetically engineered food onto the market decide whether or not to consult with the federal agencies, and decide what scientific data to submit. The FDA does not test the products for safety (Mellon and Rissler, 2003). The regulators rely 'almost exclusively on information provided by the biotech crop developer, and those data are not published in journals or subjected to peer review' (Friends of the Earth, 2004).

To accommodate the new transgenic crops and products, the Reagan and G.H.W. Bush administrations fit them, albeit with a high degree of contortion, into the existing regulatory framework of the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), and the US Department of Agriculture (USDA). Explicitly avoided was the creation of any new regulatory legislation. This was part of a movement to deregulate commerce, overseen by Vice President Dan Quayle and the Council on Competitiveness. An example of the contortion that was needed is that of the USDA's role. At that agency, genetically modified crops were classed as potential 'plant pests'. Companies wishing to disseminate transgenic plant material need only to jump the rather ludicrous regulatory hoop of showing that their crop is not a plant pest.

In the US, there is no requirement to label foods that contain transgenic ingredients, with the exception of certified organic foods. By law (USDA National Organic Program) certified organic foods cannot include compounds from transgenic organisms. However, genetic contamination of organic crops via pollination from transgenic crops on neighboring farms is an issue. A significant part of the consistent 20% per year growth of organics since the early 1990s has been shown to be consumer desire to avoid transgenic foods (Lotter, 2003).

In addition to allowing consumer choice, labeling is important in epidemiological analyses if food safety problems occur. However, grass-roots efforts to legislate product labeling and environmental regulation of transgenic foods and crops, with the exception of organics, have in general been unsuccessful in the US. A failed 2002 campaign in Oregon to require labeling of foods containing transgenic components was a bell-wether for other efforts. The biotechnology and grocery industries funded the pro-transgenics (anti-labeling) opposition with over \$5 million, many times more than proponents could muster, and the ballot initiative lost by a wide majority. Similar efforts in California, Washington and Colorado were not successful.

Successes in legislated opposition to transgenic crop production have been relatively small scale, such as a campaign to ban the growing of transgenic crops in Mendocino County California, which won a surprising ballot victory in 2004. Of similar campaigns in five other California counties, only one, Marin County, passed. Efforts to regulate the cultivation of transgenic crops in the state of North Dakota failed. The only other successes have been pockets of legislation that have emerged in counties and townships in regions such as New England.

As one group reported in 2006 on efforts to regulate transgenic crop production: 'While there are some state and regional groups trying to organize and educate farmers, few people attend the meetings and those who do tend to be polarized. The discussion seems to be dominated by agribusiness and the state legislators whose hands they have tied' (Freeman, 2005). This is in contrast with Europe, where public opinion polls show that 70% of the population opposes transgenic foods (Ryan, 2007), whereas in the US that number is less than half, 29% (Mellman Group, 2006). More than 170 European regions and 4,500 smaller zones, over a third of EU territory, belong to the 'GMO Free European Regions' set up in Florence in 2005 (Burcher and Ho, 2007).

A federal court in Hawaii ruled in 2006 that the USDA issued permits illegally for the cultivation of pharmaceutical crops (Earthjustice, 2006). In 2007, a federal judge in California ruled that the USDA violated the law by failing to adequately assess possible environmental impacts before approving Monsanto's transgenic Roundup-Ready® alfalfa (Pollack, 2007). Reflecting on these decisions and on the lack of oversight from either the federal regulatory bodies or the scientific community, one professor of plant breeding at the University of California, whose research examines gene flow from transgenic crops and non-transgenic crops and wild relatives, made the comment that: 'The most effective oversight of the consequences of transgenic crops has come from the judicial branch of government' (Paul Gepps, personal communication, 2007).

Ecological and Agro-ecological Issues

Ecological and agro-ecological issues are a substantial concern with transgenic crops. The use of glyphosate herbicide on major crops in the US has increased 15-fold since the introduction of glyphosate-resistant crops in 1994 (Lopez-Villar and Freese, 2008). The development of glyphosate-resistant weeds as a result of selection pressure from intensive use of the herbicide in herbicide-resistant crops has become a very serious concern (Owen and Zelaya, 2005; Carolina-Virginia Farmer, 2007). By 2007, seven US weed species (Plant Management Network, 2007), and in Argentina 11 species (Benbrook, 2005), had developed glyphosate resistance. Additional issues of concern are pest resistance to Bt in Bt crops (Tabashnik et al., 2003), secondary pest outbreaks in Bt crops (Wang et al., 2006; Ghosh, 2007), the negative effects of Bt crops on beneficial and neutral arthropods and on soil flora (Flores et al., 2005; Hillbeck and Schmidt, 2006), and the effects of Bt toxins on aquatic ecosystems draining agricultural areas (Rosi-Marshall et al., 2007).

Pollen migration and seed escape from grain transportation resulting in gene flow from transgenic crops to non-transgenic crops and to wild relatives of transgenic crops are issues of substantial concern (Chapela and Quist, 2001; Eastham and Sweet, 2002; Mellon and Rissler, 2003; Yoshimura et al., 2006; Caruso, 2007b; Heinemann, 2007; Dalton, 2008). Such transgene transfer and introgression has led to stable incorporation (six years) of herbicide resistance transgenes into wild or weedy relatives and to herbicide-resistant hybrid weeds (Légère, 2005; Warwick et al., 2007) as well as Bt-expressing hybrid plants in the wild (Vacher et al., 2004). Contamination of non-transgenic certified seed by transgenic seed in crops in which transgenic varieties have been developed is widespread in North America (Marvier and Van Acker, 2005). One study found that 32 out of 33 non-transgenic certified canola seed lots were contaminated with transgenic canola (Friesen et al., 2003).

Transgene contamination of native Mexican corn by transgenic corn is now well established (Dalton, 2008). The transgenic crop science community appears to be egregiously indifferent to such transgene spread in the center of origin and diversity of corn, as indicated by a 2002 document signed by over 100 scientists from that community, which states: 'It is important to recognize that the kind of gene flow alleged in the Nature paper is both inevitable and welcome' (Prakash, 2002). (The *Nature* paper, in which Chapela and Quist first report transgene spread to native Mexican corn, is discussed in Part 2.)

The Crop Transgenics Model

The central doctrine of genetic engineering has been the 'one gene-one protein' model (Gibbs, 2003), which, in its simplest form, posits that each gene in the organism's genome governs the production of a single protein or a single process involving just a few proteins. Insert a gene into a plant, turn it on with a promoter, and the plant's biochemical machinery is instructed to produce a specific protein or execute a single process. It was believed to be an elegant and precise model and it excited many scientists and entrepreneurs with the vision of developing a plethora of crops with patented transgenes for feeding the world and making a profit at the same time. With the discovery of *Agrobacterium's* ability to transfer selected genes into plants, the perfect tool for the transgenics enterprise vision was in place, and *Agrobacterium* has since become the work-horse of the plant genetic engineering industry.

Agrobacterium uses a self-replicating circular packet of genes known as a plasmid to transfer part of its DNA to the plant it infects. Scientists discovered that they could ‘disarm’ *Agrobacterium* by deleting its tumor-inducing genes while keeping its ability to transfer DNA via the plasmid. Via the use of restriction and ligation enzymes and other methods, the gene (transgene) that the engineer wants to splice into the plant is introduced into *Agrobacterium*. To verify the transfer of the main transgene, a second gene sequence for antibiotic resistance is included in the transferring plasmid. After infection with *Agrobacterium*, the host plant material is dosed with an antibiotic and only the cells with the transgene packet survive.

A third gene sequence, known as the promoter, needed to turn on the main transgene once it is in the genome of the host plant, is included in the plasmid vector. The tool used for this in virtually all plant transgenics is the CaMV35S promoter, a DNA sequence from the cauliflower mosaic virus, which assures that the transgene will be expressed in all of the host plant cells. Each of these three sequences in the transgene packet, the main transgene, the antibiotic resistance gene, and the viral promoter gene are important in food safety and gene-flow issues of transgenic crops, discussed later.

An alternative to using *Agrobacterium* for delivering the transgene package is particle bombardment, or the ‘gene gun’ method. This technique has come into commercial use predominantly for crops that are not easily infected with *Agrobacterium*. Small particles of metal such as gold are coated with the plasmid DNA packet and are ‘shot’ into the plant, incorporating the transgenes into the plant chromosome. This method has important mutational consequences in the transgenics process, discussed below.

The host plant tissue that is exposed to the transgene-carrying *Agrobacterium* consists of undifferentiated cells or callus tissue. After transfer of the transgene packet and exposure to the antibiotic, each individual cell has a unique arrangement of genes, depending on where and how the transgene packet was inserted, which is random and largely beyond the control of the engineer. Each of those cells is multiplied, and with the help of plant growth regulator applications, is stimulated to differentiate into a plant. Thousands of plants develop, each from an individually transformed cell, and each with its unique gene pattern. Each plant is known as an *event* with a specific event identity. Seed from each of these plant transformation events can potentially give rise to a *line* of the crop. The transgenic line is then cross-bred with existing varieties of the crop until all of the traits desired are incorporated, including the transgenic trait. For example, the Dekalb corn variety DKC60-12 contains Monsanto’s YieldGard® trait for resistance to corn root-worm. YieldGard was bred from the MON863 (discussed later) transgene event in which the Bt insecticide transgene, the CryIA(b) endotoxin, was engineered. A number of seed companies have licensed the YieldGard trait, and the trait can be used in seed for different climate zones. One variety might be for tropical conditions and another for growing in Canada, but both will have the Bt transgene via the MON863 event.

A significant characteristic of the plant transformation process stands out. The placement of the transgene packet in the target plant chromosome is highly imprecise and random. Each plant transformation event, which originates from a single cell, is genetically unique (thus the nomenclature ‘event’). A plant transformation event is virtually impossible to replicate in terms of the nature of the genetic pattern in the host plant genome.

Flaws in the Crop Transgenics Model

The fatal blow to the one gene–one protein model, the underpinning of the crop transgenics enterprise, came in 2003 with the now legendary surprise results, indeed shocking results, of the human genome project, in which the entirety of genes in the human genome were counted and characterized via computerized gene sequencing. While the one gene–one protein doctrine had taken numerous blows in the scientific literature during the 1990s, indicating that it might have serious flaws, it was the human gene count which has done the fatal damage to the model. The result showed that the number of genes in the human genome was vastly lower than had been believed by scientists – about 27 000 – far fewer than the 1–2 million proteins in the human body. The results have completely undermined the foundation of the one gene–one protein doctrine.

A 2007 report (ENCODE Project Consortium, 2007) on the results of the Human Genome Project from the US National Human Genome Research Institute, a large-scale, four-year international collaboration (35 groups from 80 organizations from around the world), essentially puts the final nail in the coffin of the one gene–one protein doctrine. A New York Times article on the report writes:

To their surprise, researchers found that the human genome [and therefore the genome of any higher organism, like a plant] might not be a ‘tidy collection of independent genes’ after all... *Instead, genes appear to operate in a complex network, and interact and overlap with one another and with other components in ways not yet fully understood.* According to the institute, these findings will challenge scientists ‘to rethink some long-held views about what genes are and what they do’ (Caruso, 2007a; emphasis added).

The mechanisms of dysfunction in the plant transgenics process were elucidated in a 2006 review article ‘The mutational consequences of plant transformation’ (Latham et al., 2006), published in the *Journal of Biomedicine and Biotechnology* by scientists in the UK. It was this paper which, for this author, put in place the last piece of the puzzle whose picture showed indisputably that the process of genetic engineering of food crops is deeply flawed, and that the science community had failed to correct the situation before consumers worldwide were made the subjects of the largest diet experiment in history.

In the paper, the authors examine the evidence from various published reports that mutations which occur in the process of transgene insertion include deletions and rearrangements of host chromosomal DNA as well as introduction of superfluous DNA. Two different classes of mutations are discussed in the paper: insertion site mutations and genome-wide mutations, which occur in both the *Agrobacterium* and particle bombardment method of transgene insertion.

Analysis shows that *Agrobacterium*-mediated gene transfer ‘appear[s] to be associated with large-scale rearrangement or deletion of plant chromosomal DNA’ and that ‘insertion of superfluous DNA is also a consistent feature of *Agrobacterium* insertion sites’; while with particle bombardment, ‘[o]nly a handful of studies have provided detailed data on the chromosomal mutations resulting from particle bombardment insertion... it appears that transgene integration resulting from particle bombardment is usually or always accompanied by substantial disruption of plant DNA and insertion of superfluous DNA’. And that ‘insertion of multiple copies (often more than 40) of delivered DNA, sometimes interspersed with fragments of plant DNA, appears to be the norm’.

On genome-wide mutations (mutations away from the site of insertion of the transgene package): [Research] results are broadly consistent. They suggest that plant transformation procedures typically introduce many hundreds to thousands of genome-wide mutations into the DNA of transgenic plants’.

The authors conclude that, ‘The sequence of a functional transgene insertion site resulting from particle bombardment has therefore never been definitively compared to its undisrupted site of insertion, either in the scientific literature or in applications submitted to US regulators’; and ‘Even with the limited information currently available it is clear that plant transformation is rarely, if ever, precise and that this lack of precision may cause many of the frequent unexpected phenotypes that characterise plant transformation and that pose a significant biosafety risk’.

Red Flag Events in the History of Plant Transgenics

Despite the mutation problems with plant transgenics, thorough studies on the toxicology of transgenic foods are few. Domingo surveyed the literature on toxicology studies in a 2007 review article in *Critical Reviews in Food Science and Nutrition*, and wrote that it is ‘quite amazing to note’ the paucity of toxicology studies on transgenic foods, and asks ‘where is the scientific evidence showing that GM plants/food are toxicologically safe, as assumed by the biotechnology companies involved in commercial GM foods?’ (Domingo, 2007).

With the collapse of the one gene–one protein doctrine, and with the perspective of the mutational consequences of plant genetic engineering, the numerous ‘red flag’ incidents in the history of crop genetic engineering may begin to make sense. Many of these were incidents that, by themselves, should have put the scientific community on alert and put the entire process under intense scientific scrutiny. Other than a few scientists who tried to wake-up the scientific and consumer communities to this issue, this scrutiny has never occurred in the US.

- In the mid-1990s, Pioneer Hi-Bred seed company attempted to engineer a soybean with a better protein complement by inserting a gene from the Brazil nut into the soy genome (Nordlee et al., 1996). While it was known that a small percentage of people sometimes experience lethal allergic reactions to the Brazil nut, the chances that out of the hundreds of proteins in the Brazil nut the one transferred to soy would produce this reaction was considered to be very small. Inexplicably, it was found that the transgenic soy indeed contained the Brazil nut allergen. The project was shelved.
- In 1999, Starlink[®] corn, a variety with the Bt insecticide transgene, was released on the market, approved only for animal feed, as it contains a highly stable and allergenic protein that is difficult to break down in the mammalian digestive system. Insufficient protocols for separating feed corn from food corn resulted in contamination of food corn with Starlink corn. Unknown numbers of consumers, probably in the thousands, were sickened due to allergic reactions to the proteins. The Starlink incident underlines several points.
 - Separation of feed from food grain in the commodity stream from field to consumer is difficult. This point has been re-emphasized by the 2006 incident in which transgenic ‘Liberty Link’ rice, unapproved for human consumption, was found in food rice. The incident has so far cost US rice farmers over \$150 million in lost exports (Marvier, 2007). A USDA

investigation was unable to determine the source of the contamination (Weiss, 2007).

- A very small percentage contamination of food by unapproved transgenic varieties can lead to mass food-poisoning outbreaks as a result of allergic reactions to transgenic crops;
- Food contamination-caused epidemics can go undetected due to the lack of labeling and epidemiological protocols such as systematic collection of data on human food-allergy incidents (Smith, 2007).
- Horizontal transfer of transgenes to other organisms has been found, most significantly to bacteria within the mammalian gut. The CaMV promoter gene that is included in the transgene package is important in facilitating horizontal transfer and has been found to be active in human enterocyte-like cells (Myhre et al., 2006). A UK experiment showed that transgenic DNA can survive digestion and transfer to bacteria DNA in the human gut (Smith, 2007). Several studies have shown horizontal transfer of transgenes to occur in test animals fed transgenic foods (Latham and Steinbrecher, 2004; Traavik and Heinemann, 2007). The other gene in the package, the antibiotic resistance gene, is of particular concern given the possible development of antibiotic resistant enteric bacteria. Genetic engineers had made the assumption, without adequate experimental verification, that DNA does not survive the early stages of digestion.

Viral horizontal transfer of transgenes is an issue of concern. In a commentary on a recent paper in *Molecular Plant Pathology* by Latham and Wilson (2007), one analyst states 'concerns have focused on the now well-established fact that viruses recombine with viral transgenes.... Recombination may allow novel viruses to be created and such viruses are known to be an important source of disease outbreaks' (Bioscience Resource Project, 2007).

- A UK laboratory's annual food-allergy tests (n = 4500) show soy allergies jumped 50% after the introduction of transgenic soy to the market (Smith, 2007). In the US, no systematic monitoring system exists for such potential problems (Traavik and Heinemann, 2007), although it is known that food allergies have 'spiked' in recent years (Sheehan, 2006). Protocols currently used to screen for allergenicity of transgenic foods have been shown likely to be insufficient, even if screening is limited to proteins expressed by the transgene only (Kleter and Peijnenburg, 2002). These protocols do not include screening of proteins and protein fragments generated by gene sequences subject to mutations that occur in the transgenics process.
- In the late 1990s, one of Europe's top transgenics scientists, Arpad Pusztai, found that the *process* of genetic engineering of potato introduced fundamental changes to the extent that when the potatoes were fed to test rats they developed potentially precancerous cell growth in the digestive tract; it inhibited development of the brain, liver, and testicles; they developed partial atrophy of the liver, enlarged pancreas and intestines, and immune system damage. Pusztai's termination from his senior position and the subsequent controversy is discussed in Part 2. His paper in *The Lancet*, reporting the results, remains a landmark in food transgenics (Ewen and Pusztai, 1999).
- In 1997 an experiment in which a gene for red color was engineered into petunia went awry when subsequent generations of the transgenic petunia lost their color. Gene silencing, a complex, genetically and proteomically signifi-

cant and little understood process, was implicated and is now acknowledged as a common occurrence in transgenics (Metzlaff et al., 1997). In this case, easily observed features were the subject of gene silencing. The extent to which gene silencing has occurred in transgenic crops is largely unknown. This is especially worrisome for features that are not obvious, such as for nutritional components.

- There are reports from India of the deaths of hundreds of livestock in a number of incidents, all after traditional grazing of post-harvest cotton fields, in this case newly introduced transgenic Bt cotton (Ho, 2006; Mohabbat, 2007). Bt corn has also been implicated in mass allergic reactions in humans to wind-blown pollen from the transgenic crop in the Philippines. The victims blood turned up antibodies to the Bt toxin (Aglionby, 2004). There are reports from India that Bt cotton is associated with allergic reactions in cotton handlers (Gupta et al., 2005).
- Separate groups in Spain, France, India and Italy (Collonier et al., 2003; Hernández et al., 2003; Singh et al., 2007; Rosati et al., 2008) report that transgenic crops are prone to genetic instability. The transgenes in commercial corn varieties and soy varieties, when analyzed by DNA sequencing, were in each case different from the ones described by the company of ownership when they were released. Genetic rearrangements involving the CaMV 35S promoter gene, known to be a 'hotspot' are purported to be the cause. In two cases, scrambling of the genome beyond the transgene insert occurred. The instability finding may put into perspective the incidents of livestock poisoning and mass human allergic reactions. These types of incidents have not been reported in the US, and it may be genetic instability that is responsible for the discrepancy. Such genetic instability would yield different proteomic patterns between the initial introduction of a transgenic line (event) into a crop breeding program to the final release, such as a crop variety developed for the Philippines or one from an Indian branch of a biotechnology firm. There appears to be no research on this issue.
- In a highly significant development, a 10-year Australian project to engineer resistance to a weevil pest into peas showed that allergenic proteins were produced in the transgenic pea and that, as with Pusztai's work on potato, the *process* of genetic engineering caused the problem (Prescott et al., 2005). This research is a major red flag for a couple of reasons, the first of which is that it comes from a top-flight genetic engineering group. Secondly, the mechanism for the creation of the allergenic protein is considered a new dysfunction in plant transgenics. In this case, a common process known as glycosylation, in which a sugar is attached to a protein, malfunctions. Glycosylation occurs relatively late in the sequence from the gene insertion event to eventual protein expression in the transgenic pea. The dysfunctional glycosylation process generates allergenic proteins which, in the current mode of testing transgenic foods, is by-passed and would not be identified. There may be a number of other transgenic foods on the market with this problem.
- In a 2008 report (Velimirov et al., 2008) of research commissioned by the Austrian government, a long-term animal feeding experiment showed significant reproductive problems in transgenic corn-fed rats when all groups were subjected to multiple birth cycles, a regimen that has not hitherto been examined in feeding studies comparing transgenic and non-transgenic foods.

The Austrian research may highlight unpublished (in peer reviewed journals) but widely disseminated (Ermakova, 2006a, 2006b; Ermakova and Barskov, 2006) experimental results of Russian neuroscientist Irina Ermakova of the Russian Academy of Sciences, in which rats fed diets containing transgenic soy had significant reproductive problems. The controversy over her purportedly biased treatment by editors and authors of a critique in the journal *Nature* is discussed in Part 2.

- Immune system disturbances (Malatesta et al., 2002; Finamore et al., 2008) and hepatorenal toxicity (Seralini et al., 2007) have been reported in transgenic grain-fed test animals in feeding studies.
- Proteomic analysis (Zolla et al., 2008) has shown that, compared with the genetically identical corn line minus the transgene package, the transgenic line showed that 43 proteins had been up- or down-regulated. The authors state that this may be the basis for determining non-substantial equivalence.

Veteran transgenics researcher Arpad Puzstai summed up the body of research done on the health effects of transgenic foods: 'A consistent feature of all the studies done, published or unpublished... indicates major problems with changes in the immune status of animals fed on various GM crops/foods' (Smith, 2007).

Commenting on the lack of safety data on transgenic foods in the *Journal of Medicinal Food*, David Schubert, head of the Cellular Neurobiology Laboratory at the Salk Institute in California, wrote in 2008:

There are, in fact, no data comparing the food safety profiles of GM versus conventional breeding, and the ubiquitous argument that 'since there is no evidence that GM products make people sick, they are safe' is both illogical and false. There are, again, simply no data or even valid assays to support this contention. Without proper epidemiological studies, most types of harm will not be detected, and no such studies have been conducted (Schubert, 2008).

Conclusion

The hasty transition of the radically new technology of crop transgenics from the research and development stage to commercialization, in which products of the young industry have permeated global food markets, has resulted in what may turn out to be the largest diet experiment in history. This problem is limited to transgenic foods and should not affect bacterial and pharmaceutical crop transgenics, with the proviso that pharmaceutical crops be grown in enclosures which prevent pollen escape and be transported and stored in systems which do not transport or store food grains at any time.

The lack of oversight that has led to the transgenic foods situation has been a major failure of US's science leadership. This paper has reviewed the major points in the history of these failures, from allowing biotechnology industry domination of US federal regulatory bodies overseeing transgenic products, to a lack of response to 'red flag' incidents and research findings on transgenic crops and foods, to failure to adequately analyze and characterize the genetic and phenotypic integrity of transgenic products. Part 2 of this paper reviews the major factors in the failure of science to oversee transgenics, and discusses the agro-ecological alternative to transgenics as a

foundation for building world food security, on top of which can rest non-transgenic biotechnologies and tried-and-true Green Revolution methods.

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