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The Growth of Genetically Modified Foods

Even before they Arrived on Consumers' Plates, they Showed Great Promise—and Attracted Great Opposition

One morning in May 1994, a pair of letters rolled off a fax machine in the offices of Calgene, a start-up company located in Davis, California, amid the lush agricultural country of the Central Valley. The letters came from the federal Food and Drug Administration (FDA), and they granted regulatory approval for Calgene's first product, a genetically modified tomato. Anticipating this decision, company officials had already laid in a supply of their new Flavr Savr variety, which combined vine-ripened taste with firmness for ease in transport. Three days later, the tomatoes went on sale at a local supermarket. Each Flavr Savr tomato carried a label, while bright-red brochures promised "Summertime Taste...Year Round!"

The company's marketing efforts immediately ran headfirst into Jeremy Rifkin, a long-standing scourge of biotechnology. Vowing to fight a "tomato war," he declared that Americans were "moving in the direction of organic, healthy, sustainable foods" and had no interest in "gene-spliced tomatoes." In an interview, he threatened to "picket markets, hand out notices to consumers, and organize 'tomato dumpings' and boycotts." His Pure Food Campaign had chapters around the country that were ready to follow his lead.

The day the Flavr Savr tomatoes went on sale, Pure Food activists arrived, carrying a cardboard coffin and tossing in tomatoes of their own. This protest only attracted more Customers: The day after the demonstration, the store sold twice as many. For the first time, a gene-spliced food had been offered for sale to the public—and the public had liked it. This was a hopeful step for scientists working in the new technology of genetic engineering, which promised to change the basic characteristics of foodstuffs.

Throughout recorded history, farmers and agronomists have been improving their crops with the conventional methods of plant breeding. Cross-pollination, grafting, and other techniques have yielded countless new varieties of agricultural products with larger yields, hardiness, disease resistance, and other desirable characteristics. During the 1960s Norman Borlaug launched the Green Revolution, which greatly reduced hunger in Third World countries, by creating high-yielding varieties of wheat and rice.

Generic engineering has greatly expanded the potential benefits of plant science, making Borlaug (the 1970 Nobel Peace Prize laureate) one of its most enthusiastic proponents. Yet the need for caution has increased as well, for genetic engineering differs from earlier methods as much as synthetic fabrics differ from linen. It involves nothing less than introducing new genes into crops, thereby touching the most basic processes of life. No standard program of cross-breeding can add fish genes to corn, but such modifications would be straightforward in today's labs.

The process by which traits are transmitted from parent to child has long been a subject for speculation and research. Aristotle suggested that the blood carried hereditary information, a notion that was widely accepted in the West for 2,000 years. By the end of the seventeenth century, following the development of microscopes, Aristotle's theory had been disproved, as ova and sperm cells were identified in humans and animals. In the 1860s the Austrian monk Gregor Mendel performed the first systematic research on plant genetics with his famous studies of garden peas. His work introduced the concept of the gene as a unit of heredity, as when we speak of "a gene for blue eyes." Still, although scientists spoke of genes as if they actually existed, no one knew what they were made of or how they worked.

In 1868 the German chemist Friedrich Meischer discovered the substance we now call DNA, but he and his successors did not appreciate that it had anything to do with heredity. Meanwhile, microscopists identified the cell structures called chromosomes, which got their name because they strongly absorbed the dyes that made cell structures visible. By the end of that century, chromosomes had been identified

with heredity in both plants and animals. However, geneticists believed that they encoded their genetic information in protein molecules, not DNA. They were aware that DNA existed within chromosomes, but it appeared to have too simple a structure to carry the vast amount of information that was needed to produce the enormous diversity of nature. Scientists thought DNA merely provided structural support for the information-carrying proteins.

In 1944 Oswald Avery tentatively identified DNA as the true carrier of molecular information. Alfred Hershey confirmed this in 1952. Now the roles of protein and DNA within a chromosome reversed, with proteins in the structural role. Less than a year later, James Watson and Francis Crick determined DNA's molecular shape as a double helix.

Researchers now declared that a gene is a length of DNA that carries a code for producing a particular type of protein molecule, such as a hormone or enzyme. Many such genes, strung together, make up a chromosome. A revolution in science ensued as researchers solved the genetic code. Crick summarized the findings in 1966. He gave a succinct table that showed how DNA could carry specific information, as if with letters of the alphabet, that combined to determine specific proteins that a cell would produce.

Yet, despite all these advances, scientists could only describe what was going on inside cells; they had no way to intervene directly on a molecular level. The art of gene-splicing, which drew on basic research in molecular biology, dates from 1972. In that year Stanley Cohen and Herbert Boyer introduced a set of techniques that made it possible to cut and splice strands of DNA with much the same facility as when editing a movie in Hollywood. Boyer and Cohen succeeded in adding specific new genes to bacteria, something that had never been done before. Although their methods worked only with microorganisms, the principles behind them applied to plants and animals as well.

When Boyer and Cohen added new genes to bacteria and yeast, they introduced techniques that soon turned these microbes into hormone factories. Insulin, used by diabetics, had been available for decades, but only as an extract from the pancreases of slaughtered hogs and cattle. Genetic engineering offered a much neater approach. Human genes for insulin, spliced into bacteria, led to production of a form of this hormone that was specifically tailored for use in people. It won FDA approval in 1982.

Similar work yielded increased quantities of human growth hormone, which, if administered in childhood, enabled dwarfs to grow to normal size. The only source had been the pituitary glands of cadavers, and the available supply sufficed to treat only about a third of the children who needed it. Then in 1985 the FDA granted approval to a gene-spliced variety from Genentech, produced by bacteria. Very soon the supply was more than adequate.

Gene-splicing technology entered the food industry with a new way of producing rennet, an enzyme that curdles milk to form curds and whey. Rennet had previously been taken from calves' stomachs, but during the late 1980s researchers at Pfizer, a pharmaceutical firm, isolated the gene for making rennet from a calf and inserted it into bacteria. The FDA granted approval to rennet from this source in March 1990. Less than five years later, two-thirds of the cheese produced in the U.S. was being made with rennet from genetically modified bacteria. Monsanto followed in 1994 with bovine growth hormone (BGH), which farmers could inject into cows using hypodermic needles. This boosted their milk output. Critics warned of hormones in the milk supply and of possible harm to cows, but dairies embraced BGH and, for the most part, the public accepted it as well.

In all these applications, though, only bacteria or yeast received the new genes. Humans did not consume these microbes directly, only the chemicals they produced. But geneticists were strongly interested in creating plants with inserted genes. Such genetic manipulations might, for example, add vitamins or other nutrients to fruit or grains. New genes might also enable plants to manufacture their own pesticides as they grow or improve their tolerance to salt so they could grow in soil of poor quality.

One problem was that gene-splicing methods that worked with bacteria did not work with plant cells. Bacteria have thin cell walls that can be made permeable through treatment with dilute calcium chloride, allowing the cells to take up DNA. Plants, on the other hand, have thick cellulose walls that form strong barriers. Scientists nevertheless found ways to penetrate those barriers. One important key lay in a type of

plant disease called crown gall. This amounts to a botanical cancer in which a gall—a mass of tumorous tissue—forms at the crown, or base, of the stem.

Crown gall had drawn attention for many years because it caused crop losses in grapes, cherries, and ornamental plants. As early as 1907 researchers at the U.S. Department of Agriculture had shown that it was caused by a bacterium that took the name *Agrobacterium tumefaciens*, “tumor-making farm bacterium.” In 1974, at Belgium’s University of Ghent, the biologists Jozef Schell and Marc Van Montagu showed that virulent strains of *A. tumefaciens* contained large loops of DNA, called plasmids, within their cells. Two years later, at the University of Washington, Mary-Dell Chilton headed a group of investigators that went further. They learned that a portion of one plasmid, long enough to hold about 20 genes, caused a crown gall infection by inserting itself into the nucleus of a plant cell and integrating with its chromosomes. This amounted to a natural form of gene splicing. Could it be harnessed?

The answer was yes, as the bacterium soon proved to be adaptable for use by researchers. Other geneticists deleted the tumor-causing genes from the plasmid while retaining its ability to be inserted and to function within a plant cell. The injected portion now could serve as a gene carrier, with new genes being spliced into its length. Schell and Van Montagu at Ghent, Chilton at Washington, and a third group at Monsanto all obtained this result. Their basic techniques were in print by 1983, providing a foundation for the development of gene-spliced plants.

Other scientists introduced different methods, which were useful for splicing genes into plants that did not respond to *A. tumefaciens*. In 1984 Ingo Potrykus, working in Basel, Switzerland, found enzymes that made the thick walls of plant cells permeable. This opened the door to the use of gene-splicing techniques that had worked with bacteria. John Sanford of Cornell University followed in 1987 by inventing a “gene gun,” which resembled a sawed-off shotgun. It fired microscopic pellets of tungsten or gold that had been coated with DNA, directly shooting new genes into the nuclei of cells.

Venture capitalists began to fund start-up companies in this new field. Calgene, one of the first, built offices and research labs near the University of California at Davis, where advanced work in agriculture was a specialty. Roger Salquist, Calgene’s CEO, initially envisioned transgenic cotton that could survive the application of bromine-based pesticides. Farmers then could apply these chemicals without fear of harming their crops. William Hiatt, his chief scientist, was also interested in tomatoes.

Most supermarket tomatoes are picked while still hard and green and then are reddened artificially by exposing them to ethylene gas. Such “gassed green” tomatoes have been standard for several decades because they are firm enough to survive shipment from farms, which often are thousands of miles from the cities where people buy them. However, they must be harvested too early to develop their true taste.

As tomatoes ripen on the vine, they also soften, because of the action of an enzyme called polygalacturonase, or PG. Hiatt believed that if he could prevent production of PG within the fruit, he could grow vine-ripened variants that would be firm enough to transport. After isolating the gene that produces PG, Hiatt succeeded in canceling its effects by adding an “anti-sense,” or mirror-image, copy. Belinda Martineau, a Calgene scientist who worked closely with Hiatt, describes the new gene as amounting to a standard PG gene that was “flipped upside down and backward.” Salquist later dubbed it the Flavr Savr gene.

Hiatt started working on high-tech tomatoes in 1984. He harvested his initial crop, grown in a greenhouse, during 1988 and conducted the simple experiment of placing a few of his tomatoes in a room with some fresh-picked standard ones. Three or four weeks later, the regular tomatoes had shriveled and were beginning to rot, while the Flavr Savrs still looked fresh and appetizing. With long life now complementing its prospect of good taste and firmness for ship-ability, Salquist had good reason to think that his company held the tomato of the future. He applied for FDA approval of the Flavr Savrs.

The regulatory process took several years and was open to the public. Jeremy Rifkin participated as a highly interested observer and showed that he was no blind oppositionist but rather was a knowledgeable critic. The Calgene staff had hoped to win a favorable FDA “advisory opinion,” based on the fact that the Flavr Savr gene added nothing new to its tomatoes but merely canceled out the existing PG gene. Rifkin insisted, and the FDA agreed, that regulations called for a more demanding “food additive petition.” This

issue arose because gene-splicing technology introduced some potentially serious risks.

In every gene-spliced organism, whether a bacterium, yeast, or tomato, the process of adding genes was, and still is, highly inefficient. Standard laboratory techniques were applied to a large number of individual cells, of which only a few took up the new genes. Even fewer did so in ways that enabled them to function and multiply. Hence it was necessary to screen out the tiny fraction of properly transformed cells from the overwhelming majority that were useless. The usual approach was to add not only the desired gene—for example, the Flavr Savr—but a second gene that conferred resistance to an antibiotic no longer widely used, such as kanamycin. The complete set of cells used in the experiment was then treated with this antibiotic, and only those whose DNA had been properly transformed could survive. These cells could grow and multiply to give as many copies as necessary.

It was not hard to see how antibiotic resistance in the Flavr Savr tomatoes might cause problems. The gene for resistance, spliced within that tomato, led to the synthesis of a protein molecule that rendered kanamycin ineffective. If that molecule could pass from the digestive tract into the human bloodstream, it might cause problems for the few patients who were still taking kanamycin to fight an infection. In addition, the human intestine held populations of potentially infectious bacteria of the genus *Streptococcus* that might acquire the modified cells' resistance.

The Calgene group had been aware of these issues from the outset and had tried to address them with experiments and citations of others' work. Spurred by questions from the FDA, some of which reflected the views of Rifkin, these scientists did more. They succeeded in showing that once a genetically modified tomato was eaten, the protein molecule that conferred resistance was rapidly digested and rendered ineffective. Whole genes were broken down in similar fashion.

In addition, plenty of kanamycin-resistant bacteria already existed in nature, ready to transfer genes to *Streptococcus* if they had not done so already. For this reason, Calgene researchers concluded that the added risk from Flavr Savr tomatoes was negligible. The FDA agreed and granted its approval.

Now Calgene was up against the really difficult part of the tomato problem: making a profit. The Flavr Savrs proved to be popular, with customers paying up to two dollars per pound for their freshness and taste. Unfortunately, production costs were as high as ten dollars a pound for the fruit that got to market. They were grown in a limited number of areas, where storms and heat waves could take a heavy toll. The Flavr Savr gene did indeed make the tomatoes firmer, but experience showed that they were still too soft to withstand the harsh handling that gassed green varieties stood up to. Whole truckloads of the new tomatoes turned to puree.

As losses mounted, Calgene stayed afloat for a time by issuing new stock. This gave only temporary support, and in 1996 the company sold out to Monsanto. That company had no intention of entering the grocery business. Rather, it prized Calgene's broad patent on anti-sense genes, which applied not only to tomatoes but to gene-spliced food plants in general. This meant that anyone who wanted to use the anti-sense approach to cancel the workings of a gene, in any plant used for food, would have to pay royalties or licensing fees to Monsanto.

Fees and licenses were not all Monsanto hoped to get from its acquisition of Calgene. Monsanto was a major producer of herbicides and other agricultural chemicals, and it saw an opportunity to boost sales of these products. Among its biggest sellers was Roundup, a powerful weed killer with an excellent safety record. Roundup works by disrupting the action of an enzyme that is found in plants but not in humans. Unfortunately, its effects can be indiscriminate, killing the crop along with the weeds. For this reason, farmers sprayed Roundup on their fields while the seeds were still in the ground but switched to less powerful herbicides as the seedlings began to emerge. Monsanto knew that growers would use more Roundup if they had crops that were resistant to its effects. The company introduced a resistant soybean called Roundup Ready in 1988 and later developed resistant strains of wheat.

As its next step, Monsanto hoped to create seeds that could make their own pesticides. To do this, it took advantage of a common soil bacterium, *Bacillus thuringiensis*. This microorganism produces substances known as Bt toxins that are deadly to insects but harmless to humans because they are destroyed within

seconds by acids in the digestive tract. Since Bt toxins are natural products, they are popular with organic farmers. Scientists at Monsanto extracted the gene for a particular Bt toxin from *B. thuringiensis*, transferred copies of it into its plants using *Agrobacterium*, and came up with seeds for corn, and later for cotton, that could produce their own Bt insecticides. Unlike Roundup Ready, which was designed to increase the use of a Monsanto herbicide, these genetically modified seeds promised to greatly reduce pesticide use.

Other companies pursued similar strategies. For example, AgrEvo had its own powerful herbicide, Liberty, which killed plants by disrupting their ability to use nitrates from the soil. A technology devised in Belgium conferred resistance to Liberty in food crops. This led to the development of a transgenic Liberty-resistant canola, whose seeds are an important source of vegetable oil.

The companies spent several years pushing their crops through the regulatory process to win approval for commercial use by farmers. The first such plantings took place during 1996. Monsanto remained in the forefront, offering Roundup Ready versions of soybeans, cotton, and canola, as well as YeildGard corn, which resisted the European corn borer, and NewLeaf potatoes, which were protected against the Colorado potato beetle. Novartis introduced its own corn, which also produced Bt insecticides to fight the corn borer.

Environmental groups, notably Greenpeace, soon called the new products “Frankenfoods.” The arguments they brought up in this case merited, and got, strict attention. Allergies were one major source of concern, and systematic methods were put in place to guard against this risk. Scientists avoided transplanting, any genes from major sources of severe allergens, such as peanuts. Furthermore, they checked every protein molecule produced by their genetically modified plants against a list of 500 common allergens. Any close chemical similarity raised a red flag.

The allergy issue was in the forefront during 2000 amid assertions that a gene-spliced corn called StarLink, approved for use as animal feed only, had contaminated tacos and other corn products. StarLink contains a Bt gene with which it manufactures an insecticide called Cry9C. This particular toxin is not digested as quickly by humans as other Bt pesticides, and the Environmental Protection Agency (EPA) thought the body might have more time to treat it as an allergen.

In September 2000 a genetic testing laboratory found StarLink genes in tacos manufactured by Kraft Foods. This prompted a number of companies to examine their products made from corn or corn flour. In all, nearly 300 food items that may have contained StarLink corn were recalled by manufacturers. The media went into a frenzy; Greenpeace and similar groups had a field day, and some 50 people claimed that they had become sick by eating corn that contained StarLink. At this point the Centers for Disease Control entered the controversy, conducting sensitive blood tests on a number of these patients. None of them showed antibodies to Cry9C, which would have appeared if this substance had indeed caused an allergic reaction. Whatever had made them ill, it StarLink.

Around the same time, Bt insecticides gave rise to controversy about the prospect that pollen carrying Bt genes might prove deadly to certain insects. At Cornell University, the entomologist John Losey raised the specter of danger to monarch butterflies. Losey had fed monarch caterpillars with milkweed leaves dusted with pollen from a type of *Bt* corn, and many of the caterpillars died. The results seemed alarming, but advocates of gene-splicing noted that the experiments amounted to forcing insects to eat insecticide. To these people at least, the high death rate was hardly a surprise.

New research then gave results that were far more reassuring. The EPA established a maximum safe density for *Bt* pollen grains, and milkweed plants growing near cornfields showed levels far below this threshold. The purported danger to monarchs proved to arise from only one strain of *Bt* corn, with other varieties being safe, and this strain was withdrawn from sale. Zigfridas Vaituzis, director of the EPA group that had conducted the studies, told *Scientific American* in 2001 that “the weight of the evidence suggests Bt corn pollen in the field does not pose a hazard to monarch larvae.”

Even if pollen from genetically modified plants did not threaten butterflies, however, it still posed a different risk, one that could ultimately make the weed problem even worse. Under this scenario, gene-spliced crops resistant to powerful herbicides such as Roundup or Liberty might pollinate and fertilize similar plants that were growing in the wild. These would already possess the hardiness of weeds and hence could grow into

superweeds, kudzu-like intruders that would be immune to attack by the strongest agricultural chemicals.

This issue was particularly serious and took several years to resolve. At London's Imperial College, Mick Crawley directed a study in which nearly 50 plots of ground were sown with transgenic crops, allowing them to interbreed freely with wild types. He found not only that this created no superweeds, but that the gene-spliced crops died off within a few years, crowded out by the hardier wild varieties.

As these reassurances came to light, plantings of transgenic crops took off. During 2002 some 34 percent of America's corn, 71 percent of its cotton, and 75 percent of its soybeans were genetically modified. Canada, Australia, Argentina, China, India, and Indonesia also embraced this technology. No health risks were identified, and evidence mounted of economic and environmental benefits. In China, for example, plantings of *Bt* cotton boosted yields, cut production costs, and chopped the use of pesticides to barely one-sixth its former level. This virtually eliminated farmers' complaints of headaches, nausea, skin pain, and digestive problems that had resulted from application of toxic chemicals.

Despite all this, genetically modified foods have been far from universally accepted, particularly in wealthier countries. The reaction differs greatly from one part of the world to the next. While most Americans and Canadians accept the principle of allowing producers to prove the safety of their genetically modified plants, the European Union has gone so far as to institute a general moratorium on commercial cultivation of all such crops.

Why have transgenic crops encountered vastly different receptions in Europe and America? Old-fashioned protectionism for European farmers certainly plays a role. So does simple America-bashing, which always goes over well with Europeans when they are not having a war. But there are deeper reasons at work.

In the United States, regulatory approvals come from the FDA, the EPA, and the Department of Agriculture. All three have long-standing records of successful regulation, and their open procedures have made them broadly trusted. By contrast European regulatory agencies hold much less esteem among the general public, with only multinational companies such as Monsanto reaping greater disdain. This results in part from repeated regulatory failures, still fresh in mind, that placed public life and health at risk. The sleep-inducing drug Thalidomide, for example, was legal in Europe for several years until it was shown in 1962 to cause birth defects. In America a more cautious FDA withheld its approval (though it was a close enough call that Congress decided to strengthen the FDA's drug-licensing powers.) In the 1980s Britain saw widespread outbreaks of mad-cow disease in cattle that had eaten food supplements containing meat and bone meal from infected sheep. Many people ate meat from these sick cows, and more than a hundred of them died from Creutzfeldt-Jakob disease, a horrifying and incurable illness, before the British government took belated and drastic action in the late 1990s by destroying large numbers of cows that were at risk.

With attempts at science-based regulation in public disfavor, people turned instead to environmental groups. These activists strongly supported the "precautionary principle." The 1982 World Charter for Nature, issued by the United Nations, incorporated this principle, stating that "where potential adverse effects are not fully understood, the activities should not proceed." The journal *Science* commented that "if interpreted literally, no new technology could meet this requirement." Nevertheless, the 1992 Treaty on European Union established this principle as the basis for European environmental law. It has little if any legal standing in the U.S., but it leaves Europe's critics of transgenic technology free to spin out novel scenarios of risk, and Europe's regulators are now seeking to regain public favor by following the environmentalists. They view genetic methods as new and inadequately tested, posing not only known hazards but unknown ones as well, and therefore meriting the deepest distrust.

To be sure, Europe has no crying need for biotechnology. As in America, its people are well fed and its farmers receive generous subsidies. Wealthy European countries are inclined to see farming as a traditional cultural activity, like folk dancing, that deserves preservation, rather than as a productive economic activity whose efficiency should be maximized. European consumers thus have the luxury of dismissing products such as Roundup Ready as merely a ploy to sell more chemicals. In Africa, though, transgenic foods can make a much greater difference. The Kenyan plant scientist Florence Wambugu views Roundup Ready crops

as a godsend: “We could liberate so many people if our crops were resistant to herbicides that we could then spray on the surrounding weeds. Weeding enslaves Africans; it keeps children from school.”

Even so, many farmers in Africa are not free to plant transgenic crops. Their governments seek to earn hard currency through exports of foodstuffs to Europe, and European agencies refuse to accept foods that have been genetically modified. In 2002 Zimbabwe and Zambia rejected American donations of genetically modified food even though some people in those countries were reduced to eating leaves. The reason lay in their concern that American genes would contaminate the local crops; the markets in Europe were to be protected at all costs.

Amid such determined resistance, advocates of transgenic foods will strengthen their hand if they can offer crops that carry direct benefits for consumers rather than for farmers. In fact, such a product already exists: A “golden rice” that contains beta carotene, which the body converts into vitamin A. For lack of this vitamin, more than a million children in the Third World die each year, while another third of a million go blind. The new rice, announced in 1999, represents the work of the research pioneer Ingo Potrykus, along with Peter Beyer of Germany’s University of Freiburg. The Rockefeller Foundation funded their work, in which they modified the gene assembly of conventional rice by splicing in genes from the daffodil plant that produce beta carotene.

Elsewhere, an international consortium is developing a genetically modified variety of corn that clones itself instead of cross-pollinating freely with other plants. This promises to eliminate the necessity of buying new seed each year to ensure a pure strain, a benefit that could prove invaluable to Third World farmers. Gene splicers can also find hope in the recent experience of China, which has made a strong commitment to transgenic research. Its first genetically modified product, a *Bt*-producing cotton, was planted commercially for the first time in 1997, when the rest of the world already had 2.5 million acres of such cotton in cultivation. In 2001 China’s *Bt* cotton fields covered some five million acres, nearly as much as the rest of the world combined. Now Chinese scientists are developing genetically modified strains of rice that could eventually feed billions of people.

With transgenic crops already so widespread, it seems unlikely that anything like a European-style ban will be enacted in the countries that are already enjoying the technology’s benefits. Yet one unfortunate incident could be enough to reverse the trend and slow or stop the spread of genetic modification to other crops. Proponents, therefore, must not only continue to exercise the most extreme caution to reassure consumers; they must also find ways to sell genetic modification as a positive good instead of a necessary evil.

Gene-spliced crops make farming easier, safer, and more productive, but except for the abortive experiment with Flavr Savr tomatoes, they have not, thus far, offered anything consumers can see or taste. When that day comes, Americans and perhaps even Europeans may put genetically modified foods in their shopping carts with no more trepidation than they attach to tangelos or seedless oranges.