Chapter 1

The Birth of Synthetic Biology and the Genetic Mode of Production

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Biology is as important as the sciences of lifeless matter, and biotechnology will in the long run be more important than mechanical and chemical engineering.[1]

Julian Huxley, 1936

Nearly 400 years ago, the English scientist-philosopher Francis Bacon envisioned a time when the plants and animals on the earth were the starting materials for refashioning biological life forms according to human design.[2] To a degree, agricultural scientists have been fulfilling Bacon's prophecy through crossbreeding of crops and animals. We have seen the results of these genetic experiments in the highly developed domesticated varieties of corn and tomato plants, which have evolved from wild relatives of these plants that would today seem unsuitable to our palette. For example, the North American subsidiary of the Swiss agri-biotechnology company Syngenta recently announced the result of years of consumer research and crossbreeding in its five pound seedless, miniature spherical watermelon.[3]

With crossbreeding, scientists were limited in how much they could modify plants and animals. They could only combine the traits of somewhat similar species with compatible DNA through grafting and cross-fertilization. However, thirty years ago, Bacon's vision that science would eventually exploit the biological resources of the planet

Genetically Engineered Crops

doi:10.1300/5880_01

the way it had learned to transform the earth's natural ores, such as copper and iron, to create the industrial revolution, seemed within grasp. In 1973 Stanley Cohen, Herbert Boyer, and others developed recombinant DNA (rDNA) molecules[4] and the following year demonstrated the expression of foreign genes implanted in a bacterium by rDNA methods.[5] These discoveries prepared the way for transporting genes from biological organisms of distant phyla. Thus, the concept of crossing species barriers was introduced. DNA molecules, the fundamental units of inherited traits, could now be redistributed or repositioned according to the desires of the gene engineers.

This chapter discusses the early and later developments in a new field of applied molecular genetics, including the birth of an academic–industrial complex based on the potential of gene splicing, the role of gene technology as a new mode of production in agriculture, drugs, and therapeutics, and the marketing of biotechnology as a green revolution in agricultural genetics.

BIOTECHNOLOGY: EVOLUTION OR REVOLUTION?

Robert Bud has traced the roots of modern biotechnology to zymotechnics, or the fermentation industries in Europe.[6] According to Bud's in-depth review of the history, Karl Ereky, a Hungarian agricultural engineer who worked on the production of food animals, coined the term "biotechnology" in 1917. "His notion of biotechnology was a conception that food animals like the pig were machines converting inputs into human protein."[7] Ereky described a pig as a "Biotechnologische Arbeitsmachine."

Historian Bud viewed the change from classical breeding to modern GE of crops and microbes as a change of degree and not of kind. However, there are reasons for characterizing the tools of molecular genetics as fostering a revolution (abrupt and discontinuous change) in biology. I once characterized it in the following way:

> The discovery of the fungibility of genes forces us to make the next frame shift in our concepts of life. We can no longer accept uncritically the aphorism that "like begets like." It cannot be said that a pig's snout is uniquely of a pig and that there is some-

> thing we call "pigness" that is trapped in the evolutionary construct of the pig family of animals. These so-called species demarcations have been transcended by the discovery that genes can be shifted from organism to organism and with these shifts in genes the phenotypic properties of living forms on the planet can be rearranged as Bacon had foreseen.[8]

In 1984, the U.S. Office of Technology Assessment (OTA) defined biotechnology as "any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals or to develop micro-organisms for specific uses."[9] The OTA distinguished between new and old biotechnology. Modern (post-1973) or new biotechnology is based on a set of techniques for undertaking "precision" genetic and cell engineering that include uses of rDNA, cell fusion, monoclonal antibodies, tissue culture technology, and novel bioprocessing methods. The OTA emphasized the historical continuum between old and new uses of biological organisms for practical purposes.

Three discoveries are central to the development of new biotechnology as distinguished from traditional fermentation engineering, and cross breeding of animals and crops. These include the discovery of new classes of enzymes, DNA sequencing, and methods of transposing genes within and across species.

A group of enzymes called restriction enzymes were found to cut DNA at predictable sites. These enzymes initially gave scientists the tools to isolate DNA sequences that could be reintegrated into other organisms. Another group of enzymes called ligases were found to seal the ends of DNA molecules. The ligases are the "chemical glue" that give scientists the ability to splice together segments of DNA from different biological organisms. Finally, an enzyme called reverse transcriptase transcribes single-stranded messenger RNA into double-stranded DNA. Mammalian genes contain noncoding regions of DNA that are split off from the gene when messenger RNA is formed. Prior to the discovery of reverse transcriptase independently by Howard Temin and David Baltimore in 1970, it was believed that the transformation from DNA to RNA was not reversible.[10]

A second core discovery central to biotechnology's development was gene sequencing. This is the process by which the precise nucleotide components of a gene are determined. Gene sequencing is

essential to understand which segments of DNA correspond with specific proteins, or how the coding and noncoding regions of DNA differ. Scientists can derive the amino acid sequence from the DNA sequence, but as of yet cannot predict the three-dimensional structure and function of the protein from the gene sequence. According to Gilbert, new theoretical breakthroughs will be required to make that happen. "It is here that a theoretical biology will emerge. It will be a science of pattern recognition—extracting from the genetic sequence the identity of human genes, their interrelationships, and their control elements. This information will be used to predict how the genes and their proteins function."[11]

The third set of discoveries central to the new field of biotechnology are methods for transporting segments of DNA across biological systems. Even prior to the Cohen-Boyer experiments, Paul Berg created recombinant DNA molecules constructed from viruses, which, because they naturally infect cells, can unload their DNA into the cell's chromosome.[12] Simpler, more efficient methods for transporting DNA used circular segments of DNA called plasmids. The plasmids can be cut into segments and can be attached to a foreign piece of DNA, and the spliced segments are annealed at the ends to reestablish the circular plasmid suitable for activation of its genetic components in the cell. Other methods of transporting DNA molecules, where naked DNA is delivered by physical mechanisms to the cell's chromosome, include microinjection or micropropulsion (gene gun).

DNA alone, without the apparatus of the cell, cannot synthesize anything or even replicate itself. Cells provide the environment and biological mechanisms within which the chemical structure of DNA can be "read" and translated into instructions, serving as signals to the cell to undertake the process of protein synthesis. In his *Harper's* essay, titled "Unraveling the DNA Myth," Barry Commoner noted: "Genetic information arises not from DNA alone but through its essential collaboration with protein enzymes."[13] The new gene engineers have learned how to intervene in and co-collaborate with the cellular machinery. In 1980, an editorial/commentary in *Nature* stated: "Genetic manipulation is used by the biotechnologist to enhance the natural genetic repertoire of microorganisms."[14] This was indeed Bacon's vision of expanding the biodiversity of life through human invention.

The cell is the protein factory. The DNA in the cell provides the chemical template for protein production. In the new field of molecular biotechnology, scientists can bring foreign DNA segments into organisms and activate the cellular "production apparatus" to synthesize a protein that the cell(s) had not synthesized before.

FIRST-GENERATION FEARS ABOUT GENE SPLICING: LABORATORY HAZARDS

Concurrent to the discoveries that made the front pages of the national daily newspapers and popular science magazines were expressions of concern about the potential risks of GE. A group of scientists asked: Would these new set of techniques produce organisms that can unexpectedly create harm? The first voices of caution came from young scientists who were poised to apply the new techniques in their own work. They cosigned letters in leading science journals and organized symposia to consider the potential or speculative hazards associated with transplanting genes from mammalian cells (eukaryotes) to bacteria (prokaryotes).

The cautions first raised by scientists soon turned into public debates in dozens of communities where laboratories were being built to accommodate the new U.S. National Institutes of Health containment guidelines for rDNA molecule research. Scientists who viewed the rDNA techniques as a new frontier in biology were fearful of overreaction by the government, which might proscribe or delay fruitful lines of inquiry. The confluence of new science and new fears provided the grist for extensive print media coverage of genetics. There were events that stoked the flames of publicity such as the International Conference at Asilomar, California; the Cambridge, Massachusetts rDNA debates; meetings of the National Institutes of Health Recombinant DNA Molecule Advisory Committee; and U.S. congressional hearings between 1977 and 1980 on the dozen active bills that would regulate gene-splicing experiments. Public fears about the inadvertent release of rDNA organisms were met with unrestrained claims of medical and commercial benefits that the new research methods would bring. The commercial possibilities of rDNA were manifestly obvious to the young scientists who embraced the new research program. The expression "cloning scarce proteins" was among

the first clues for potential commercial application. This was a no-brainer for anyone following the science.

By 1974 it was demonstrated that toad genes could be incorporated and expressed in a bacterium.[15] Since bacteria reproduce rapidly, scientists could exploit their cellular mechanism to copy (clone) and express the foreign gene. Consequently, large volumes of the bacteria can yield large quantities of a foreign protein.

The commercial opportunities of cloning foreign genes into bacteria and scaling up for production of human proteins were of great interest to the pharmaceutical industry. In 1977, at a U.S. National Academy of Sciences symposium on rDNA research, a representative of Eli Lilly and Company cited four classes of human proteins as candidates for large-scale production by rDNA techniques: hormones, coagulation factors, hereditary disease replacement enzymes, and immunological factors.[16]

Applications of rDNA to agriculture were also enthusiastically discussed within a brief period after the science became understood. Extrapolating from ideas of traditional plant and animal breeding, scientists began thinking of biological systems as having interchangeable parts, where desirable characteristics could be transferred from one species to another, somewhat like moving Lego™ blocks. Thus, molecular plant scientists began planning research to move nitrogen-fixing genes from bacteria to plants so the latter could become auto-nitrogenous. Four other agricultural applications highlighted in a 1977 National Academy Forum were enhancing photosynthesis and increasing the efficiency of CO_2 fixation, biological pest control, fuel production through bioconversion, and plant breeding.[17] A quarter century after those predictions were made, rDNA applications in biological pest controls and plant breeding have spawned dozens of commercial products such as insect-resistant and herbicide-tolerant crops, including *Bt* corn and glyphosate-tolerant soybeans.[18]

Those outside of the scientific community were distrustful of scientists serving as their own gatekeepers, while the scientists themselves could see it no other way. Citizen groups harkened back to the nuclear industry where well-paid atomic scientists underestimated the risks of radiation hazards. Both the novelty and the perceived powers of rDNA technology created a buzz in business and among public-interest communities but for different reasons. Ironically, the contro-

versy over gene splicing and its accompanying media publicity did not drive away the venture capitalists. Rather, it seemed to pique the interest of investors who demonstrated enthusiasm for becoming players in the very early stages of the technological breakthroughs.[19] As Martin Kenney noted: "Curiously, the debate and publicity about health and safety issues actually attracted the attention of venture capitalists, the potential financial backers; it may also have discouraged established pharmaceutical firms from capturing the technology."[20]

EMERGING INDUSTRIAL SECTORS

The methods described in the aforementioned section defined a new mode of protein production. Within a very short time after the Cohen-Boyer discovery, scientists understood the commercial applications of applied molecular genetics and communicated these to the business sector. Academic biologists, responding to new liberal patent regulations and federal technology transfer inducements for universities, developed for-profit partnerships with companies or set up their own venture capital firms. There were four companies dedicated to biotechnology in the 1970s: Cetus, Biogen, Genex, and Genentech. The period between 1980 and 1984 saw a rapid growth and expansion of the biotechnology business. Over thirty new firms were established in 1980. Nearly seventy more were added in 1981 and twenty-two in 1982.[21] A report by the OTA cited more than 400 dedicated biotechnology companies in operation and 70 major corporations which had invested in biotechnology by 1988.[22]

By 1981, the biotechnology market was worth about $25 million, mostly for reagents and contract research. The biotech market was projected to reach $20 billion by 1990 and jump to $30-34 billion by 2000. The actual growth of biotechnology fell far short of the early estimates with revenues in 1989 at $1.5 billion almost exclusively from pharmaceuticals and diagnostics. In 1992 the revenues from agricultural biotechnology products grew to about $184 million.

By the mid-1980s about 10 percent of the 500 largest U.S. companies reported that they were investing in biotechnology.[23] These companies were from five major commercial sectors: pharmaceuticals, agriculture, environmental, therapeutics, and industrial. The latter included the production of new materials and energy from biomass.

The first major drug to come out of rDNA biotechnology was human insulin. It was marketed in the United States in 1982 and was expected to replace bovine and porcine insulin, which were manufactured by extracting and purifying the protein from the pancreases of cows and pigs.

Toward the end of the 1980s, in addition to insulin, four other proteins produced from GE cells had been approved by the U.S. Food and Drug Administration (FDA). They included human growth hormone, hepatitis B vaccine, alpha interferon (an antiviral agent), and tissue plasminogen activator (tPA), an agent that reduces blood clots. Throughout the 1990s the therapeutic biotechnology companies brought scores of products to clinical trials including anticancer therapies, vaccines, early diagnostic screening tools, and viral vectors designed for human gene therapy.

The agricultural sector embraced biotechnology somewhat more cautiously as debates about releasing GE plants and microorganisms into the environment persisted. The Monsanto Corporation was the first major established company to develop in-house research programs in biotechnology starting as early as 1978. Four years later it was spending about 28 percent of its total R&D budget on biotechnology.[24]

In 1983 the first engineered plant (petunia) was grown using biotechnology. Two years later the first field tests were begun for plants resistant to insects, viruses, and bacteria. By 1986 the Environmental Protection Agency (EPA) approved the release of the first transgenic crop, a gene-altered tobacco plant. This was also the year that the federal government approved the Coordinated Framework for regulation of biotechnology, which allocated agency responsibility among the EPA, the Department of Agriculture (USDA), and the FDA for different aspects of genetically modified organisms and products developed from them. The new framework was introduced without enacting new laws.

From the mid-1980s through the mid-1990s, extensive field trials for transgenic plants were carried out. The USDA and EPA approved more than 2,500 field trials between 1987 and 1995. A little more than 800 of these trials were for herbicide-resistant crops, about 700 for insect resistance, about 600 for plant quality (such as value-added properties), and nearly 400 for disease resistance. By the mid-1990s

the first commercial biotech plants entered the marketplace. In 2001 significant percentages of the U.S. production of cotton (69 percent), soybeans (68 percent), canola (55 percent), and corn (26 percent) consisted of genetically modified varieties that were either insect- or herbicide resistant.

The science media echoed the boundless enthusiasm of the investment community that GE crops would revolutionize agriculture by creating more food, a cleaner environment, and more wealth. GE crops were dubbed as the next "Green Revolution." A 1991 report from the World Bank captured the sense of optimism regarding GE plants.

> The great appeal of these techniques is that they can be used to improve the tolerance of both crops and animals to particular stresses, pests, and pathogens, and to increase the efficiency with which plants and livestock use limiting nutrients. They also hold out the promise of relieving the present biological constraints to higher yields. In countries where the new technologies are applied the results should be increased agricultural production, improved comparative advantage in the production of some commodities, new opportunities for the use of marginal lands and a reduced need for agrochemicals.[25]

Between 1996 and 2002 the global acreage planted with GE crops increased from 4.25 million acres to 146.8 million acres, a 35-fold increase. The acreage devoted to transgenic crops represented about 51 percent of the total agricultural acreage. Nearly 100 million acres of transgenic crops were planted in the United States during 2002, an increase of about 15 million acres over the previous year. The estimated global area devoted to GM crops for 2004 was 200 million acres, up from 167 acres in 2003. The number of countries growing transgenic crops also steadily increased from six in 1996, nine in 1998, twelve in 1999, and sixteen and seventeen in 2002 and 2004 respectively. Monsanto's genetically modified seeds accounted for about 118 million acres of transgenic crops or about 81 percent of the world acreage planted with GE products in 2002.

Many European farmers were opposed to GE crops. Nevertheless, the European Community approved the sale of GE soybeans in the 1990s. In total, there were eighteen biotech food products approved

by the European Union (EU) prior to June 1999. Since that year there has been a de facto moratorium on additional approvals pending the passage of new regulations. One of Europe's traditionally large U.S. imports affected by the moratorium is corn. Exports of corn from the United States to Europe nosedived from 1.5 million metric tons in 1998 to 23,000 metric tons in 2003.

The EU is developing new labeling and GE food traceability requirements for biotechnology food products and animal feed. Under its preliminary provisions, even highly refined products such as corn and soybean oil, and animal feed produced from biotechnology crops, would have to be labeled. The passage of the new labeling and traceability rules has been linked to the lifting of the EU moratorium.

The acreage dedicated to transgenic crops also increased in the developing countries, which grew from 14 to 27 percent of the global acreage between 1997 and 2002. The developing nations with the largest acreage of transgenic crops in 2004 were Argentina (16.2 million hectares), Brazil (5.0 million hectares), and China (3.7 million hectares). Four crops that dominated the transgenic varieties planted in 2002 are soybeans, corn, cotton and canola, with soybeans (herbicide tolerant) occupying 62 percent of the global acreage.

SECOND-GENERATION CONTROVERSIES: ENVIRONMENTAL RELEASES OF GEOS

During the 1970s, the public angst about rDNA focused mainly on laboratory hazards of genetically modified organisms. The debates were about containment levels, siting of laboratories, worker health and safety, and proscribed experiments. Commercialization had begun but on a small scale. By the 1980s agrochemical companies and small biotech start-ups were beginning to file applications to field-test GE crops, rDNA-produced veterinary hormones, and genetically engineered microorganisms (GEOs). The environmental release of GE fish was also being considered. The second-generation rDNA controversies were about products, rather than techniques, specifically about large-scale releases of GEOs into the environment and their impacts on ecosystems, and on the human health effects of GE crops and rDNA-derived animal hormones.

Three agricultural products introduced during the 1980s and early 1990s, ice-minus bacteria, slow-ripening tomatoes, and recombinant bovine growth hormone (rBGH), were among the first commercialized organisms involving rDNA technology. Ice-minus bacteria, a genetically modified strain of *Pseudomonas syringae,* were the first gene-engineered product released into the environment. After five years of regulatory review, lawsuits, and community protests in Monterey, California, this soil bacterium with its ice-nucleation gene excised was field-tested in northern California in 1987. Ice-minus was designed to be sprayed on crops in the frostbelt when temperatures fell to a few degrees below freezing to prevent damage from ice crystallization. The company that developed ice-minus, Advanced Genetic Resources, merged with DNA Plant Technology in 1989. Research on the genetically modified form of *P. syringae* was halted by the company in 1990.[26]

The Flav'r Savr tomato was a GE product developed in response to consumer interests for a tomato picked ripe from the vine, rather than green, that could still be transported without losing its firmness and freshness. The genetic technology that made this possible is known as "antisense." It involves reversing a DNA sequence in the plant. The chemical ethylene, produced naturally by plants, is an essential part of the ripening process. Plants that exhibit lower levels of ethylene are otherwise the same except that they ripen more slowly. By applying the antisense technology to the gene that synthesizes ethylene, scientists were able to reduce the rate of ethylene produced in the plant. In laboratory trials, delaying ethylene synthesis allowed the tomato to remain firm for as much as six weeks longer than non-transgenic tomatoes. The Flavr Savr tomato was designed to increase consumer use of tomatoes during the off-season and became the first transgenic whole-food product introduced on the market.

In May 1994 the FDA issued a finding that the Flavr Savr tomato was as safe as traditionally bred varieties. It also approved, as a food additive in the tomato, the marker enzyme for the resistance to the antibiotic kanamycin. The gene for that enzyme is part of the genetic alteration of the tomato. Under its policy of "substantial equivalence" the FDA did not require any special labeling of the tomato because it argued that the Flavr Savr maintained the essential characteristics of traditionally bred tomatoes.

There was scarcely a public debate over the marketing of the GE tomato per se, in large part because no new proteins were added to it, although, there was some concern about the spread of antibiotic resistance markers in fresh produce. In addition, the introduction of the first fresh food GE product raised the specter that "genes from different food sources, exchanged and rearranged, might alter the quality, toxicity or nutritional value of food sources."[27]

The Flavr Savr(™) tomato proved to be largely unsuccessful as a consumer product. It was introduced at a time when new foreign nontransgenic hothouse tomato varieties successfully entered the market at competitive prices. Some also attribute the limited commercial success of the Flavr Savr(™) to the fact that the antisense technology was initially used on a poor variety of tomato. By 1995 transgenic delayed-ripening tomatoes had been granted nonregulated status by the USDA. Many of the new transgenic varieties were used primarily for processing. Other tomato varieties were developed with thicker skin, altered pectin, and increased lycopene content.

The third of the first three new rDNA products generated the largest public reaction. Recombinant bovine growth hormone (rBGH) is a veterinary product whose development closely resembles human protein products. The gene for the animal hormone is transferred to a bacterium, which is then grown in large fermentation tanks and induced to express the hormone.

Cows injected with rBGH will increase their lactation and produce 15 to 20 percent more milk. Critics of rBGH cited increased cases of mastitis in cows, the inhumane treatment of animals who are chemically lactated, and uncertainty over the relationship between rBGH and the production of Insulin Growth Factor (a potentially dangerous side product). Moreover, groups such as the Consumers Union and small farmer organizations argued that consumers would receive no benefit from this product. Also, the benefits would accrue disproportionately to large highly mechanized dairy farms.

The ecological side of the second-generation controversies over rDNA technology included the extent to which transgenic crops released into the environment would (1) invade natural habitats through accelerated germination, root growth, and dispersal by acquiring resistance to biotic and abiotic stressers; (2) transfer herbicide tolerance traits from domesticated crops to weeds;[28] (3) reinforce the increased

use of chemical herbicides adding to the human and wildlife toxic load;[29] (4) support the use of monocultural herbicide applications increasing the probability of weed resistance; (5) accelerate the growth of resistant traits in insects; (6) harm nontarget insects from the pesticidal properties of the plant; (7) result in the loss of genetic diversity.[30]

The release of transgenic animals into the natural environment also became a contested issue when proposals were made to the U.S. federal government for restocking rivers with genetically modified salmon, enlarged by growth hormone genes.

Bacillus thuriengensis (*Bt*) is a natural bacterium known to be effective against certain insects (lepidoptera) because of its toxic proteins. Some ecologists and environmentalists argued that the overuse of *Bt* would accelerate the onset of resistant strains. They cited evidence that more than 500 species of pests have developed resistance to conventional pesticides.[31]

By the mid-1990s the print media in the United States began reporting research results that confirmed some of the environmental concerns raised by natural resource ecologists. For example, *The New York Times* reported in March 1996: "A field study has shown that a gene inserted into a crop plant can easily be transferred to a close relative, highlighting potentially unseen consequences of the genetic engineering of plants. . . ."[32] Four years later the same paper ran the headline "New study links biotech corn to butterfly deaths" referring to the corn pollen with *Bt* toxins that can be carried to milkweeds, plants that are the food sources for Monarch butterfly *(Danaus plexippus)* caterpillars.[33] The *Times* referred to a field study in which scientists observed the toxic effects of pollen from transgenic plants on milkweed-feeding Monarch larvae.[34] This study came after a series of investigations involving pollen and Monarch butterflies began at Cornell University in 1999. After depositing *Bt* corn pollen on milkweeds and exposing them to Monarch larvae, Losey and his colleagues observed the toxic effects.[35] Although the results of these studies did demonstrate that *Bt* corn pollen could be toxic to Monarch larvae, it did not stop the planting of *Bt* corn. Instead, regulators were more attentive to the concentration of *Bt* pollen and effects on nontarget insects. U.S. regulators promoted the use of buffer zones to separate planted areas from sensitive species.

THIRD-GENERATION BIOTECH CONTROVERSIES: GLOBALIZATION

After almost a decade of negotiations on international trade liberalization, on January 1, 1995 the World Trade Organization (WTO) became a formalized part of the new economic order, receiving support from over 100 nations. It was the culmination of treaties such as the General Agreement on Tariffs and Trade (GATT) and the North American Free Trade Act (NAFTA). The single term that describes this multilateral effort to eliminate trade barriers and create permeable borders for commerce, investment, and, some would say, labor, is "globalization."

While free marketers throughout the world rallied around this concept, many grassroots organizations, unions, agricultural collectives, and small farmers began to question the equity of the radical rearrangement of market flows. Large multinational corporations, operating under enormous economies of scale and low resource labor costs from plants located in developing countries, were poised to drive out local entrepreneurs.

The first products of agricultural biotechnology were reaching the marketplace during the period that globalization was taking hold. The lens of globalization was turned on biotechnology. Many of the critics of globalization chose GE crops as their first example of the downsides of a global market system.

Europe had experienced some severe food contamination crises in the late 1990s including outbreaks of mad cow and hoof and mouth diseases. When U.S. GE crops were ready for European markets, many states wanted more extensive testing and demonstrable proof that these products were safe. In the United Kingdom there was a protracted public controversy involving Arpad Puzstai, a respected scientist working at the Rowett Research Institute in Aberdeen, Scotland, with 270 scientific publications on his resume, who reported that he found intestinal changes in rats fed on GE potatoes.[36] Puzstai's work was actively discredited by other scientists in the United Kingdom and he was relieved of his position at the institute, but the controversy over his findings continued after he published his study in *The Lancet* on October 16, 1999.[37] Meanwhile, U.S. biotech companies who

were seeking foreign markets for their transgenic seeds were finding it increasingly difficult to turn Europe into a biotech importer.

Anti-biotech activists formed alliances with anti-free trade activists. Their common concern was that several major chemical–agricultural corporations were gaining a world monopoly over GE seeds. These transnational agribusinesses sought open trade barriers so they could sell seeds cheaply to European farmers. Because the seeds were linked to certain chemical inputs such as herbicides, they could also expand their global herbicide markets. Anti-free trade activists observed U.S. chemical companies investing heavily in biotechnology while buying up seed companies to develop a global distribution network. According to agricultural expert Charles Benbrook, the developing nations in Africa were less than enthusiastic about the first-generation GE crops "created to make pest management simpler on America's large, mechanized farms."[38]

When the biotechnology industry was criticized for ignoring the needs of developing countries and expanding intellectual property ownership over biological entities, the industry released a GE product designed to turn the tide of public opinion, "Golden Rice," a strain of rice that contains beta carotene, which the body turns into vitamin A. People who are deficient in vitamin A from lack of leafy green vegetables and carrots are at risk of becoming blind. The biotech industry supported a research program to develop beta-carotene rice that would provide a person sufficient amount of vitamin A to prevent blindness. Thus, in lieu of addressing the problem of vitamin deficiency by enriching the diversity of the diet in developing countries, the approach chosen through the "genetic mode of production" was to create a single crop with all the essential amino acids and micronutrients. Early prototypes of "Golden Rice" had levels of beta carotene that were too low to reduce blindness when individuals were consuming normal diets of rice. While the media made it sound like we had turned the corner in preventing blindness from vitamin-A deficiency, there was still considerable R&D development left to increase the expression of beta carotene and to assess the acceptability of the orange-colored rice in the developing world where people prize white rice.

Golden Rice sparked a lively debate over biotech's role in improving the quality of life in developing countries. Critics of Golden Rice pointed to the complex set of reasons why the rural poor in the devel-

oping world go hungry including poor soil fertility, lack of inexpensive seeds, inferior infrastructure for transporting food and supplies, and lack of agricultural technology. They dismissed the single product solution to rural poverty.

In May 2003 U.S. trade representatives petitioned the WTO to declare illegal the de facto moratorium adopted by the EU on approving new GE crops under the new international trade agreements. The WTO convened a dispute resolution panel in early 2006 to hear the U.S. petition, which claimed $300 million in lost exports resulting from the GE moratorium The WTO resolution panel declared that the EU moratorium was not justified, but since the de jure moratorium was over it took no action. In another action, the U.S. president sent a message to developing nations that America would link foreign aid to a nation's policy on GE foods. In essence, developing nations that refused GE crops in aid would not get privileged foreign aid status. This came in the aftermath of Zambia's 2002 rejection of shipments of U.S. food aid containing GE corn. The Bush administration rebuked those opposed to GE products as "undermining efforts to fight hunger in Africa."[39]

Efforts by the U.S biotech companies and trade representatives to make Europe GE friendly according to American standards had not succeeded by late 2003. In July 2003 the European Parliament approved legislation requiring strict labels for goods made with genetically altered ingredients. This action is consistent with the EU's desire for a standard for labeling and traceability. "This legislation also ensures that genetically modified . . . foodstuffs like grains will be traced from the moment of their inception to their arrival in the European Union through the processing stage and into the supermarket."[40] American farmers and grain processors, who wish to export to European markets, would have to separate GE from non-GE seed to comply with the labeling provision. In another setback for the biotechnology sector, the Cartagena Protocol on Biosafety, first agreed upon by 130 nations in January 2000, came into effect in September 2003 after being formally ratified by the fiftieth state.[41] By July 2006, the Congo became the 134th signatory nation to ratify the biosafety convention. According to the Cartagena Protocol, countries can bar the imports of GE entities (seeds, crops, microbes, or animals) if they believe it would

threaten their environment. Like the European Parliament decision, the Cartagena Protocol also calls for labeling of GE products.

CONCLUSION

The biotechnology revolution has passed its thirtieth anniversary, if we mark its beginning with the publication of the first plasmid-mediated gene transplantation experiment. Like other industrial revolutions, it is premised on new forms of production. Scientists have learned the secrets behind the system under which living cells produce proteins and have commandeered that system to either replicate scarce products of nature or to synthesize new ones. GE is as much a revolution in molecular genetics as it is in biology as a whole. Thirty years ago, biology became transformed in ways that chemistry and physics had years before. In Barry Commoner's words: "Biology once was regarded as a languid, largely descriptive discipline, a passive science that was content, for much of its history, merely to observe the natural world rather than change it. No longer."[42]

Since genes are transferable across living things, they can be reassigned to new cellular factories. Thus, a protein typically synthesized in a human cell can be produced more efficiently and in greater quantities in a plant cell. Agriculture becomes a new production system for human proteins called biopharmaceuticals supplanting human tissue culture production.[43]

The "genetic mode of production" has given rise to new products, new methods of producing old products, and new delivery systems (such as vaccines delivered through crops). Moreover, it has created a bridge between universities, small start-up companies, and multinational corporations.

Nearly two decades ago, in his book *Biotechnology: The University-Industry Complex,* Martin Kenney questioned whether biotechnology will survive as a freestanding industry or whether it will provide the tools for and be absorbed by traditional industries.[44] In fact both these developments have taken place. Traditional industries have incorporated the tools of biotechnology into their production and/or service systems. At the same time GE techniques have spawned a new information-based industrial sector. In this sense biotechnology is like the computer revolution. It is both a freestanding industrial

sector and a set of tools that have been integrated into other sectors. The most visible signs of the new industry are to be seen in the field of pharmaceuticals and agriculture. Other applications, especially in the field of biomaterials, are also likely to evolve although outside of the intense media limelight. According to the leading trade organization, the Biotechnology Industry Organization (BIO), in 2003 there were 1,457 biotechnology companies in the United States; 342 are publicly held. According to BIO, the revenues in this sector reached $34.8 billion in 2001.[45] According to the twentieth-anniversary edition of *Beyond Borders: The Global Biotechnology Report 2006*, Ernst and Young report that revenues of publicly traded biotechnology companies reached $63.1 billion in 2005, the highest in its thirty-year history.

Previous technological revolutions in the twentieth century, such as the invention of plastics, microelectronics, and computers, have sold themselves. Biotechnology has met numerous forms of public opposition at the outset, and as it matures, it will carry new moral dilemmas and force adjustments within civil society. With the benefits of hindsight we will also be in a better position to distinguish between exaggerated claims and ideologically based criticisms of this new industry, the benefits and liabilities of which have thus far been largely assessed by a prospective rather than a retrospective analysis.

NOTES

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Chapter 1

The Birth of Synthetic Biology and the Genetic Mode of Production

Sheldon Krimsky

Biology is as important as the sciences of lifeless matter, and biotechnology will in the long run be more important than mechanical and chemical engineering.[1]

Julian Huxley, 1936

Nearly 400 years ago, the English scientist-philosopher Francis Bacon envisioned a time when the plants and animals on the earth were the starting materials for refashioning biological life forms according to human design.[2] To a degree, agricultural scientists have been fulfilling Bacon's prophecy through crossbreeding of crops and animals. We have seen the results of these genetic experiments in the highly developed domesticated varieties of corn and tomato plants, which have evolved from wild relatives of these plants that would today seem unsuitable to our palette. For example, the North American subsidiary of the Swiss agri-biotechnology company Syngenta recently announced the result of years of consumer research and crossbreeding in its five pound seedless, miniature spherical watermelon.[3]

With crossbreeding, scientists were limited in how much they could modify plants and animals. They could only combine the traits of somewhat similar species with compatible DNA through grafting and cross-fertilization. However, thirty years ago, Bacon's vision that science would eventually exploit the biological resources of the planet

Genetically Engineered Crops

doi:10.1300/5880_01

the way it had learned to transform the earth's natural ores, such as copper and iron, to create the industrial revolution, seemed within grasp. In 1973 Stanley Cohen, Herbert Boyer, and others developed recombinant DNA (rDNA) molecules[4] and the following year demonstrated the expression of foreign genes implanted in a bacterium by rDNA methods.[5] These discoveries prepared the way for transporting genes from biological organisms of distant phyla. Thus, the concept of crossing species barriers was introduced. DNA molecules, the fundamental units of inherited traits, could now be redistributed or repositioned according to the desires of the gene engineers.

This chapter discusses the early and later developments in a new field of applied molecular genetics, including the birth of an academic–industrial complex based on the potential of gene splicing, the role of gene technology as a new mode of production in agriculture, drugs, and therapeutics, and the marketing of biotechnology as a green revolution in agricultural genetics.

BIOTECHNOLOGY: EVOLUTION OR REVOLUTION?

Robert Bud has traced the roots of modern biotechnology to zymotechnics, or the fermentation industries in Europe.[6] According to Bud's in-depth review of the history, Karl Ereky, a Hungarian agricultural engineer who worked on the production of food animals, coined the term "biotechnology" in 1917. "His notion of biotechnology was a conception that food animals like the pig were machines converting inputs into human protein."[7] Ereky described a pig as a "Biotechnologische Arbeitsmachine."

Historian Bud viewed the change from classical breeding to modern GE of crops and microbes as a change of degree and not of kind. However, there are reasons for characterizing the tools of molecular genetics as fostering a revolution (abrupt and discontinuous change) in biology. I once characterized it in the following way:

> The discovery of the fungibility of genes forces us to make the next frame shift in our concepts of life. We can no longer accept uncritically the aphorism that "like begets like." It cannot be said that a pig's snout is uniquely of a pig and that there is some-

> thing we call "pigness" that is trapped in the evolutionary construct of the pig family of animals. These so-called species demarcations have been transcended by the discovery that genes can be shifted from organism to organism and with these shifts in genes the phenotypic properties of living forms on the planet can be rearranged as Bacon had foreseen.[8]

In 1984, the U.S. Office of Technology Assessment (OTA) defined biotechnology as "any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals or to develop micro-organisms for specific uses."[9] The OTA distinguished between new and old biotechnology. Modern (post-1973) or new biotechnology is based on a set of techniques for undertaking "precision" genetic and cell engineering that include uses of rDNA, cell fusion, monoclonal antibodies, tissue culture technology, and novel bioprocessing methods. The OTA emphasized the historical continuum between old and new uses of biological organisms for practical purposes.

Three discoveries are central to the development of new biotechnology as distinguished from traditional fermentation engineering, and cross breeding of animals and crops. These include the discovery of new classes of enzymes, DNA sequencing, and methods of transposing genes within and across species.

A group of enzymes called restriction enzymes were found to cut DNA at predictable sites. These enzymes initially gave scientists the tools to isolate DNA sequences that could be reintegrated into other organisms. Another group of enzymes called ligases were found to seal the ends of DNA molecules. The ligases are the "chemical glue" that give scientists the ability to splice together segments of DNA from different biological organisms. Finally, an enzyme called reverse transcriptase transcribes single-stranded messenger RNA into double-stranded DNA. Mammalian genes contain noncoding regions of DNA that are split off from the gene when messenger RNA is formed. Prior to the discovery of reverse transcriptase independently by Howard Temin and David Baltimore in 1970, it was believed that the transformation from DNA to RNA was not reversible.[10]

A second core discovery central to biotechnology's development was gene sequencing. This is the process by which the precise nucleotide components of a gene are determined. Gene sequencing is

essential to understand which segments of DNA correspond with specific proteins, or how the coding and noncoding regions of DNA differ. Scientists can derive the amino acid sequence from the DNA sequence, but as of yet cannot predict the three-dimensional structure and function of the protein from the gene sequence. According to Gilbert, new theoretical breakthroughs will be required to make that happen. "It is here that a theoretical biology will emerge. It will be a science of pattern recognition—extracting from the genetic sequence the identity of human genes, their interrelationships, and their control elements. This information will be used to predict how the genes and their proteins function."[11]

The third set of discoveries central to the new field of biotechnology are methods for transporting segments of DNA across biological systems. Even prior to the Cohen-Boyer experiments, Paul Berg created recombinant DNA molecules constructed from viruses, which, because they naturally infect cells, can unload their DNA into the cell's chromosome.[12] Simpler, more efficient methods for transporting DNA used circular segments of DNA called plasmids. The plasmids can be cut into segments and can be attached to a foreign piece of DNA, and the spliced segments are annealed at the ends to reestablish the circular plasmid suitable for activation of its genetic components in the cell. Other methods of transporting DNA molecules, where naked DNA is delivered by physical mechanisms to the cell's chromosome, include microinjection or micropropulsion (gene gun).

DNA alone, without the apparatus of the cell, cannot synthesize anything or even replicate itself. Cells provide the environment and biological mechanisms within which the chemical structure of DNA can be "read" and translated into instructions, serving as signals to the cell to undertake the process of protein synthesis. In his *Harper's* essay, titled "Unraveling the DNA Myth," Barry Commoner noted: "Genetic information arises not from DNA alone but through its essential collaboration with protein enzymes."[13] The new gene engineers have learned how to intervene in and co-collaborate with the cellular machinery. In 1980, an editorial/commentary in *Nature* stated: "Genetic manipulation is used by the biotechnologist to enhance the natural genetic repertoire of microorganisms."[14] This was indeed Bacon's vision of expanding the biodiversity of life through human invention.

The cell is the protein factory. The DNA in the cell provides the chemical template for protein production. In the new field of molecular biotechnology, scientists can bring foreign DNA segments into organisms and activate the cellular "production apparatus" to synthesize a protein that the cell(s) had not synthesized before.

FIRST-GENERATION FEARS ABOUT GENE SPLICING: LABORATORY HAZARDS

Concurrent to the discoveries that made the front pages of the national daily newspapers and popular science magazines were expressions of concern about the potential risks of GE. A group of scientists asked: Would these new set of techniques produce organisms that can unexpectedly create harm? The first voices of caution came from young scientists who were poised to apply the new techniques in their own work. They cosigned letters in leading science journals and organized symposia to consider the potential or speculative hazards associated with transplanting genes from mammalian cells (eukaryotes) to bacteria (prokaryotes).

The cautions first raised by scientists soon turned into public debates in dozens of communities where laboratories were being built to accommodate the new U.S. National Institutes of Health containment guidelines for rDNA molecule research. Scientists who viewed the rDNA techniques as a new frontier in biology were fearful of overreaction by the government, which might proscribe or delay fruitful lines of inquiry. The confluence of new science and new fears provided the grist for extensive print media coverage of genetics. There were events that stoked the flames of publicity such as the International Conference at Asilomar, California; the Cambridge, Massachusetts rDNA debates; meetings of the National Institutes of Health Recombinant DNA Molecule Advisory Committee; and U.S. congressional hearings between 1977 and 1980 on the dozen active bills that would regulate gene-splicing experiments. Public fears about the inadvertent release of rDNA organisms were met with unrestrained claims of medical and commercial benefits that the new research methods would bring. The commercial possibilities of rDNA were manifestly obvious to the young scientists who embraced the new research program. The expression "cloning scarce proteins" was among

the first clues for potential commercial application. This was a no-brainer for anyone following the science.

By 1974 it was demonstrated that toad genes could be incorporated and expressed in a bacterium.[15] Since bacteria reproduce rapidly, scientists could exploit their cellular mechanism to copy (clone) and express the foreign gene. Consequently, large volumes of the bacteria can yield large quantities of a foreign protein.

The commercial opportunities of cloning foreign genes into bacteria and scaling up for production of human proteins were of great interest to the pharmaceutical industry. In 1977, at a U.S. National Academy of Sciences symposium on rDNA research, a representative of Eli Lilly and Company cited four classes of human proteins as candidates for large-scale production by rDNA techniques: hormones, coagulation factors, hereditary disease replacement enzymes, and immunological factors.[16]

Applications of rDNA to agriculture were also enthusiastically discussed within a brief period after the science became understood. Extrapolating from ideas of traditional plant and animal breeding, scientists began thinking of biological systems as having interchangeable parts, where desirable characteristics could be transferred from one species to another, somewhat like moving Lego™ blocks. Thus, molecular plant scientists began planning research to move nitrogen-fixing genes from bacteria to plants so the latter could become auto-nitrogenous. Four other agricultural applications highlighted in a 1977 National Academy Forum were enhancing photosynthesis and increasing the efficiency of CO_2 fixation, biological pest control, fuel production through bioconversion, and plant breeding.[17] A quarter century after those predictions were made, rDNA applications in biological pest controls and plant breeding have spawned dozens of commercial products such as insect-resistant and herbicide-tolerant crops, including *Bt* corn and glyphosate-tolerant soybeans.[18]

Those outside of the scientific community were distrustful of scientists serving as their own gatekeepers, while the scientists themselves could see it no other way. Citizen groups harkened back to the nuclear industry where well-paid atomic scientists underestimated the risks of radiation hazards. Both the novelty and the perceived powers of rDNA technology created a buzz in business and among public-interest communities but for different reasons. Ironically, the contro-

versy over gene splicing and its accompanying media publicity did not drive away the venture capitalists. Rather, it seemed to pique the interest of investors who demonstrated enthusiasm for becoming players in the very early stages of the technological breakthroughs.[19] As Martin Kenney noted: "Curiously, the debate and publicity about health and safety issues actually attracted the attention of venture capitalists, the potential financial backers; it may also have discouraged established pharmaceutical firms from capturing the technology."[20]

EMERGING INDUSTRIAL SECTORS

The methods described in the aforementioned section defined a new mode of protein production. Within a very short time after the Cohen-Boyer discovery, scientists understood the commercial applications of applied molecular genetics and communicated these to the business sector. Academic biologists, responding to new liberal patent regulations and federal technology transfer inducements for universities, developed for-profit partnerships with companies or set up their own venture capital firms. There were four companies dedicated to biotechnology in the 1970s: Cetus, Biogen, Genex, and Genentech. The period between 1980 and 1984 saw a rapid growth and expansion of the biotechnology business. Over thirty new firms were established in 1980. Nearly seventy more were added in 1981 and twenty-two in 1982.[21] A report by the OTA cited more than 400 dedicated biotechnology companies in operation and 70 major corporations which had invested in biotechnology by 1988.[22]

By 1981, the biotechnology market was worth about $25 million, mostly for reagents and contract research. The biotech market was projected to reach $20 billion by 1990 and jump to $30-34 billion by 2000. The actual growth of biotechnology fell far short of the early estimates with revenues in 1989 at $1.5 billion almost exclusively from pharmaceuticals and diagnostics. In 1992 the revenues from agricultural biotechnology products grew to about $184 million.

By the mid-1980s about 10 percent of the 500 largest U.S. companies reported that they were investing in biotechnology.[23] These companies were from five major commercial sectors: pharmaceuticals, agriculture, environmental, therapeutics, and industrial. The latter included the production of new materials and energy from biomass.

The first major drug to come out of rDNA biotechnology was human insulin. It was marketed in the United States in 1982 and was expected to replace bovine and porcine insulin, which were manufactured by extracting and purifying the protein from the pancreases of cows and pigs.

Toward the end of the 1980s, in addition to insulin, four other proteins produced from GE cells had been approved by the U.S. Food and Drug Administration (FDA). They included human growth hormone, hepatitis B vaccine, alpha interferon (an antiviral agent), and tissue plasminogen activator (tPA), an agent that reduces blood clots. Throughout the 1990s the therapeutic biotechnology companies brought scores of products to clinical trials including anticancer therapies, vaccines, early diagnostic screening tools, and viral vectors designed for human gene therapy.

The agricultural sector embraced biotechnology somewhat more cautiously as debates about releasing GE plants and microorganisms into the environment persisted. The Monsanto Corporation was the first major established company to develop in-house research programs in biotechnology starting as early as 1978. Four years later it was spending about 28 percent of its total R&D budget on biotechnology.[24]

In 1983 the first engineered plant (petunia) was grown using biotechnology. Two years later the first field tests were begun for plants resistant to insects, viruses, and bacteria. By 1986 the Environmental Protection Agency (EPA) approved the release of the first transgenic crop, a gene-altered tobacco plant. This was also the year that the federal government approved the Coordinated Framework for regulation of biotechnology, which allocated agency responsibility among the EPA, the Department of Agriculture (USDA), and the FDA for different aspects of genetically modified organisms and products developed from them. The new framework was introduced without enacting new laws.

From the mid-1980s through the mid-1990s, extensive field trials for transgenic plants were carried out. The USDA and EPA approved more than 2,500 field trials between 1987 and 1995. A little more than 800 of these trials were for herbicide-resistant crops, about 700 for insect resistance, about 600 for plant quality (such as value-added properties), and nearly 400 for disease resistance. By the mid-1990s

the first commercial biotech plants entered the marketplace. In 2001 significant percentages of the U.S. production of cotton (69 percent), soybeans (68 percent), canola (55 percent), and corn (26 percent) consisted of genetically modified varieties that were either insect- or herbicide resistant.

The science media echoed the boundless enthusiasm of the investment community that GE crops would revolutionize agriculture by creating more food, a cleaner environment, and more wealth. GE crops were dubbed as the next "Green Revolution." A 1991 report from the World Bank captured the sense of optimism regarding GE plants.

> The great appeal of these techniques is that they can be used to improve the tolerance of both crops and animals to particular stresses, pests, and pathogens, and to increase the efficiency with which plants and livestock use limiting nutrients. They also hold out the promise of relieving the present biological constraints to higher yields. In countries where the new technologies are applied the results should be increased agricultural production, improved comparative advantage in the production of some commodities, new opportunities for the use of marginal lands and a reduced need for agrochemicals.[25]

Between 1996 and 2002 the global acreage planted with GE crops increased from 4.25 million acres to 146.8 million acres, a 35-fold increase. The acreage devoted to transgenic crops represented about 51 percent of the total agricultural acreage. Nearly 100 million acres of transgenic crops were planted in the United States during 2002, an increase of about 15 million acres over the previous year. The estimated global area devoted to GM crops for 2004 was 200 million acres, up from 167 acres in 2003. The number of countries growing transgenic crops also steadily increased from six in 1996, nine in 1998, twelve in 1999, and sixteen and seventeen in 2002 and 2004 respectively. Monsanto's genetically modified seeds accounted for about 118 million acres of transgenic crops or about 81 percent of the world acreage planted with GE products in 2002.

Many European farmers were opposed to GE crops. Nevertheless, the European Community approved the sale of GE soybeans in the 1990s. In total, there were eighteen biotech food products approved

by the European Union (EU) prior to June 1999. Since that year there has been a de facto moratorium on additional approvals pending the passage of new regulations. One of Europe's traditionally large U.S. imports affected by the moratorium is corn. Exports of corn from the United States to Europe nosedived from 1.5 million metric tons in 1998 to 23,000 metric tons in 2003.

The EU is developing new labeling and GE food traceability requirements for biotechnology food products and animal feed. Under its preliminary provisions, even highly refined products such as corn and soybean oil, and animal feed produced from biotechnology crops, would have to be labeled. The passage of the new labeling and traceability rules has been linked to the lifting of the EU moratorium.

The acreage dedicated to transgenic crops also increased in the developing countries, which grew from 14 to 27 percent of the global acreage between 1997 and 2002. The developing nations with the largest acreage of transgenic crops in 2004 were Argentina (16.2 million hectares), Brazil (5.0 million hectares), and China (3.7 million hectares). Four crops that dominated the transgenic varieties planted in 2002 are soybeans, corn, cotton and canola, with soybeans (herbicide tolerant) occupying 62 percent of the global acreage.

SECOND-GENERATION CONTROVERSIES: ENVIRONMENTAL RELEASES OF GEOS

During the 1970s, the public angst about rDNA focused mainly on laboratory hazards of genetically modified organisms. The debates were about containment levels, siting of laboratories, worker health and safety, and proscribed experiments. Commercialization had begun but on a small scale. By the 1980s agrochemical companies and small biotech start-ups were beginning to file applications to field-test GE crops, rDNA-produced veterinary hormones, and genetically engineered microorganisms (GEOs). The environmental release of GE fish was also being considered. The second-generation rDNA controversies were about products, rather than techniques, specifically about large-scale releases of GEOs into the environment and their impacts on ecosystems, and on the human health effects of GE crops and rDNA-derived animal hormones.

Three agricultural products introduced during the 1980s and early 1990s, ice-minus bacteria, slow-ripening tomatoes, and recombinant bovine growth hormone (rBGH), were among the first commercialized organisms involving rDNA technology. Ice-minus bacteria, a genetically modified strain of *Pseudomonas syringae,* were the first gene-engineered product released into the environment. After five years of regulatory review, lawsuits, and community protests in Monterey, California, this soil bacterium with its ice-nucleation gene excised was field-tested in northern California in 1987. Ice-minus was designed to be sprayed on crops in the frostbelt when temperatures fell to a few degrees below freezing to prevent damage from ice crystallization. The company that developed ice-minus, Advanced Genetic Resources, merged with DNA Plant Technology in 1989. Research on the genetically modified form of *P. syringae* was halted by the company in 1990.[26]

The Flav'r Savr tomato was a GE product developed in response to consumer interests for a tomato picked ripe from the vine, rather than green, that could still be transported without losing its firmness and freshness. The genetic technology that made this possible is known as "antisense." It involves reversing a DNA sequence in the plant. The chemical ethylene, produced naturally by plants, is an essential part of the ripening process. Plants that exhibit lower levels of ethylene are otherwise the same except that they ripen more slowly. By applying the antisense technology to the gene that synthesizes ethylene, scientists were able to reduce the rate of ethylene produced in the plant. In laboratory trials, delaying ethylene synthesis allowed the tomato to remain firm for as much as six weeks longer than non-transgenic tomatoes. The Flavr Savr tomato was designed to increase consumer use of tomatoes during the off-season and became the first transgenic whole-food product introduced on the market.

In May 1994 the FDA issued a finding that the Flavr Savr tomato was as safe as traditionally bred varieties. It also approved, as a food additive in the tomato, the marker enzyme for the resistance to the antibiotic kanamycin. The gene for that enzyme is part of the genetic alteration of the tomato. Under its policy of "substantial equivalence" the FDA did not require any special labeling of the tomato because it argued that the Flavr Savr maintained the essential characteristics of traditionally bred tomatoes.

There was scarcely a public debate over the marketing of the GE tomato per se, in large part because no new proteins were added to it, although, there was some concern about the spread of antibiotic resistance markers in fresh produce. In addition, the introduction of the first fresh food GE product raised the specter that "genes from different food sources, exchanged and rearranged, might alter the quality, toxicity or nutritional value of food sources."[27]

The Flavr Savr(™) tomato proved to be largely unsuccessful as a consumer product. It was introduced at a time when new foreign nontransgenic hothouse tomato varieties successfully entered the market at competitive prices. Some also attribute the limited commercial success of the Flavr Savr(™) to the fact that the antisense technology was initially used on a poor variety of tomato. By 1995 transgenic delayed-ripening tomatoes had been granted nonregulated status by the USDA. Many of the new transgenic varieties were used primarily for processing. Other tomato varieties were developed with thicker skin, altered pectin, and increased lycopene content.

The third of the first three new rDNA products generated the largest public reaction. Recombinant bovine growth hormone (rBGH) is a veterinary product whose development closely resembles human protein products. The gene for the animal hormone is transferred to a bacterium, which is then grown in large fermentation tanks and induced to express the hormone.

Cows injected with rBGH will increase their lactation and produce 15 to 20 percent more milk. Critics of rBGH cited increased cases of mastitis in cows, the inhumane treatment of animals who are chemically lactated, and uncertainty over the relationship between rBGH and the production of Insulin Growth Factor (a potentially dangerous side product). Moreover, groups such as the Consumers Union and small farmer organizations argued that consumers would receive no benefit from this product. Also, the benefits would accrue disproportionately to large highly mechanized dairy farms.

The ecological side of the second-generation controversies over rDNA technology included the extent to which transgenic crops released into the environment would (1) invade natural habitats through accelerated germination, root growth, and dispersal by acquiring resistance to biotic and abiotic stressers; (2) transfer herbicide tolerance traits from domesticated crops to weeds;[28] (3) reinforce the increased

use of chemical herbicides adding to the human and wildlife toxic load;[29] (4) support the use of monocultural herbicide applications increasing the probability of weed resistance; (5) accelerate the growth of resistant traits in insects; (6) harm nontarget insects from the pesticidal properties of the plant; (7) result in the loss of genetic diversity.[30]

The release of transgenic animals into the natural environment also became a contested issue when proposals were made to the U.S. federal government for restocking rivers with genetically modified salmon, enlarged by growth hormone genes.

Bacillus thuriengensis (*Bt*) is a natural bacterium known to be effective against certain insects (lepidoptera) because of its toxic proteins. Some ecologists and environmentalists argued that the overuse of *Bt* would accelerate the onset of resistant strains. They cited evidence that more than 500 species of pests have developed resistance to conventional pesticides.[31]

By the mid-1990s the print media in the United States began reporting research results that confirmed some of the environmental concerns raised by natural resource ecologists. For example, *The New York Times* reported in March 1996: "A field study has shown that a gene inserted into a crop plant can easily be transferred to a close relative, highlighting potentially unseen consequences of the genetic engineering of plants. . . ."[32] Four years later the same paper ran the headline "New study links biotech corn to butterfly deaths" referring to the corn pollen with *Bt* toxins that can be carried to milkweeds, plants that are the food sources for Monarch butterfly *(Danaus plexippus)* caterpillars.[33] The *Times* referred to a field study in which scientists observed the toxic effects of pollen from transgenic plants on milkweed-feeding Monarch larvae.[34] This study came after a series of investigations involving pollen and Monarch butterflies began at Cornell University in 1999. After depositing *Bt* corn pollen on milkweeds and exposing them to Monarch larvae, Losey and his colleagues observed the toxic effects.[35] Although the results of these studies did demonstrate that *Bt* corn pollen could be toxic to Monarch larvae, it did not stop the planting of *Bt* corn. Instead, regulators were more attentive to the concentration of *Bt* pollen and effects on nontarget insects. U.S. regulators promoted the use of buffer zones to separate planted areas from sensitive species.

THIRD-GENERATION BIOTECH CONTROVERSIES: GLOBALIZATION

After almost a decade of negotiations on international trade liberalization, on January 1, 1995 the World Trade Organization (WTO) became a formalized part of the new economic order, receiving support from over 100 nations. It was the culmination of treaties such as the General Agreement on Tariffs and Trade (GATT) and the North American Free Trade Act (NAFTA). The single term that describes this multilateral effort to eliminate trade barriers and create permeable borders for commerce, investment, and, some would say, labor, is "globalization."

While free marketers throughout the world rallied around this concept, many grassroots organizations, unions, agricultural collectives, and small farmers began to question the equity of the radical rearrangement of market flows. Large multinational corporations, operating under enormous economies of scale and low resource labor costs from plants located in developing countries, were poised to drive out local entrepreneurs.

The first products of agricultural biotechnology were reaching the marketplace during the period that globalization was taking hold. The lens of globalization was turned on biotechnology. Many of the critics of globalization chose GE crops as their first example of the downsides of a global market system.

Europe had experienced some severe food contamination crises in the late 1990s including outbreaks of mad cow and hoof and mouth diseases. When U.S. GE crops were ready for European markets, many states wanted more extensive testing and demonstrable proof that these products were safe. In the United Kingdom there was a protracted public controversy involving Arpad Puzstai, a respected scientist working at the Rowett Research Institute in Aberdeen, Scotland, with 270 scientific publications on his resume, who reported that he found intestinal changes in rats fed on GE potatoes.[36] Puzstai's work was actively discredited by other scientists in the United Kingdom and he was relieved of his position at the institute, but the controversy over his findings continued after he published his study in *The Lancet* on October 16, 1999.[37] Meanwhile, U.S. biotech companies who

were seeking foreign markets for their transgenic seeds were finding it increasingly difficult to turn Europe into a biotech importer.

Anti-biotech activists formed alliances with anti-free trade activists. Their common concern was that several major chemical–agricultural corporations were gaining a world monopoly over GE seeds. These transnational agribusinesses sought open trade barriers so they could sell seeds cheaply to European farmers. Because the seeds were linked to certain chemical inputs such as herbicides, they could also expand their global herbicide markets. Anti-free trade activists observed U.S. chemical companies investing heavily in biotechnology while buying up seed companies to develop a global distribution network. According to agricultural expert Charles Benbrook, the developing nations in Africa were less than enthusiastic about the first-generation GE crops "created to make pest management simpler on America's large, mechanized farms."[38]

When the biotechnology industry was criticized for ignoring the needs of developing countries and expanding intellectual property ownership over biological entities, the industry released a GE product designed to turn the tide of public opinion, "Golden Rice," a strain of rice that contains beta carotene, which the body turns into vitamin A. People who are deficient in vitamin A from lack of leafy green vegetables and carrots are at risk of becoming blind. The biotech industry supported a research program to develop beta-carotene rice that would provide a person sufficient amount of vitamin A to prevent blindness. Thus, in lieu of addressing the problem of vitamin deficiency by enriching the diversity of the diet in developing countries, the approach chosen through the "genetic mode of production" was to create a single crop with all the essential amino acids and micronutrients. Early prototypes of "Golden Rice" had levels of beta carotene that were too low to reduce blindness when individuals were consuming normal diets of rice. While the media made it sound like we had turned the corner in preventing blindness from vitamin-A deficiency, there was still considerable R&D development left to increase the expression of beta carotene and to assess the acceptability of the orange-colored rice in the developing world where people prize white rice.

Golden Rice sparked a lively debate over biotech's role in improving the quality of life in developing countries. Critics of Golden Rice pointed to the complex set of reasons why the rural poor in the devel-

oping world go hungry including poor soil fertility, lack of inexpensive seeds, inferior infrastructure for transporting food and supplies, and lack of agricultural technology. They dismissed the single product solution to rural poverty.

In May 2003 U.S. trade representatives petitioned the WTO to declare illegal the de facto moratorium adopted by the EU on approving new GE crops under the new international trade agreements. The WTO convened a dispute resolution panel in early 2006 to hear the U.S. petition, which claimed $300 million in lost exports resulting from the GE moratorium The WTO resolution panel declared that the EU moratorium was not justified, but since the de jure moratorium was over it took no action. In another action, the U.S. president sent a message to developing nations that America would link foreign aid to a nation's policy on GE foods. In essence, developing nations that refused GE crops in aid would not get privileged foreign aid status. This came in the aftermath of Zambia's 2002 rejection of shipments of U.S. food aid containing GE corn. The Bush administration rebuked those opposed to GE products as "undermining efforts to fight hunger in Africa."[39]

Efforts by the U.S biotech companies and trade representatives to make Europe GE friendly according to American standards had not succeeded by late 2003. In July 2003 the European Parliament approved legislation requiring strict labels for goods made with genetically altered ingredients. This action is consistent with the EU's desire for a standard for labeling and traceability. "This legislation also ensures that genetically modified . . . foodstuffs like grains will be traced from the moment of their inception to their arrival in the European Union through the processing stage and into the supermarket."[40] American farmers and grain processors, who wish to export to European markets, would have to separate GE from non-GE seed to comply with the labeling provision. In another setback for the biotechnology sector, the Cartagena Protocol on Biosafety, first agreed upon by 130 nations in January 2000, came into effect in September 2003 after being formally ratified by the fiftieth state.[41] By July 2006, the Congo became the 134th signatory nation to ratify the biosafety convention. According to the Cartagena Protocol, countries can bar the imports of GE entities (seeds, crops, microbes, or animals) if they believe it would

threaten their environment. Like the European Parliament decision, the Cartagena Protocol also calls for labeling of GE products.

CONCLUSION

The biotechnology revolution has passed its thirtieth anniversary, if we mark its beginning with the publication of the first plasmid-mediated gene transplantation experiment. Like other industrial revolutions, it is premised on new forms of production. Scientists have learned the secrets behind the system under which living cells produce proteins and have commandeered that system to either replicate scarce products of nature or to synthesize new ones. GE is as much a revolution in molecular genetics as it is in biology as a whole. Thirty years ago, biology became transformed in ways that chemistry and physics had years before. In Barry Commoner's words: "Biology once was regarded as a languid, largely descriptive discipline, a passive science that was content, for much of its history, merely to observe the natural world rather than change it. No longer."[42]

Since genes are transferable across living things, they can be reassigned to new cellular factories. Thus, a protein typically synthesized in a human cell can be produced more efficiently and in greater quantities in a plant cell. Agriculture becomes a new production system for human proteins called biopharmaceuticals supplanting human tissue culture production.[43]

The "genetic mode of production" has given rise to new products, new methods of producing old products, and new delivery systems (such as vaccines delivered through crops). Moreover, it has created a bridge between universities, small start-up companies, and multinational corporations.

Nearly two decades ago, in his book *Biotechnology: The University-Industry Complex,* Martin Kenney questioned whether biotechnology will survive as a freestanding industry or whether it will provide the tools for and be absorbed by traditional industries.[44] In fact both these developments have taken place. Traditional industries have incorporated the tools of biotechnology into their production and/or service systems. At the same time GE techniques have spawned a new information-based industrial sector. In this sense biotechnology is like the computer revolution. It is both a freestanding industrial

sector and a set of tools that have been integrated into other sectors. The most visible signs of the new industry are to be seen in the field of pharmaceuticals and agriculture. Other applications, especially in the field of biomaterials, are also likely to evolve although outside of the intense media limelight. According to the leading trade organization, the Biotechnology Industry Organization (BIO), in 2003 there were 1,457 biotechnology companies in the United States; 342 are publicly held. According to BIO, the revenues in this sector reached $34.8 billion in 2001.[45] According to the twentieth-anniversary edition of *Beyond Borders: The Global Biotechnology Report 2006,* Ernst and Young report that revenues of publicly traded biotechnology companies reached $63.1 billion in 2005, the highest in its thirty-year history.

Previous technological revolutions in the twentieth century, such as the invention of plastics, microelectronics, and computers, have sold themselves. Biotechnology has met numerous forms of public opposition at the outset, and as it matures, it will carry new moral dilemmas and force adjustments within civil society. With the benefits of hindsight we will also be in a better position to distinguish between exaggerated claims and ideologically based criticisms of this new industry, the benefits and liabilities of which have thus far been largely assessed by a prospective rather than a retrospective analysis.

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