Chapter 6

Agriculture

"Biotechnology has been a vital part of human activity for many thousands of years. In all probability the first biotechnologists were Neolithic men and women who may well have preferred the taste of fermented cereals to raw groin."

Industrial Biotechnology Association
Biotechnology. . . in Perspective

"I suspect that virtually all of our current policy thinking about agriculture is very near in time to being totally irrelevant. Major crops such as corn and wheat could see thousandfold increases in yield through genetic manipulation. '

Terry Sharrer
Smithsonian Institution curator of agriculture

CONTENTS

Boxes

Figures

Tables

Chapter 6
Agriculture

INTRODUCTION

Biotechnology has the potential **to** be the latest in a series of technologies that have led **to astonishing increases in** productivity of world agriculture in recent decades. Since 1948, for example, the widespread use of fertilizers, synthetic chemical pesticides, and high-yielding varieties of major grain crops have produced yield increases in the United States of about 2-percent per acre annually. The use of farm machinery of steadily increasing power has led to a sharp decrease in labor needed to farm an acre of land. Since 1940, labor requirements in the United States have decreased 75 percent, while output per acre has doubled. The decreasing amount of labor required to produce increasing amounts of products has allowed farm size to increase about three fold over the years, while the total number of farms declined. Total harvested acreage in the United States, however, has remained relatively constant at approximately 340 million acres. Access to farm equipment, better seeds, and other inputs has led to productivity gains in other major agricultural exporting nations as well (6, 11, 51).

Until about 10 years ago, U.S. agricultural research was directed toward maximizing yield—the quantity of production per acre. But, to compete with agricultural producers in developing countries where land and labor are cheap and to compete with producers in developed countries with access to sophisticated technology, U.S. farmers will have to produce their crops more efficiently. Today there is increased interest in the development of technologies that will help to reduce the cost of agricultural production (42). There is also research in the development of new, higher value-added products. Biotechnology can contribute to agriculture in each of these ways:

- The application of biotechnology to agriculture can result in further gains in yield. Some examples include new animal health care products, new plants that are more resistant to environmental stresses (e.g., frost or drought), or the use of new reproductive technologies to develop higher producing dairy cows.
- Biotechnology can also contribute to productivity by lowering the cost. of agricultural inputs. For example, plants that are resistant to pests may require less treatment with chemical pesticides resulting in savings in chemicals and labor costs.
- There is also the potential for the development of higher quality foods and new higher value--added products to meet the needs of consumers and food processors. These include lower fat meats, oilseeds with altered fat content, or vegetables with a longer shelf life.
- It is also hoped that biotechnology will contribute to the development of environmentally benign methods of managing weeds and insect pests through such new products as pest resistant crops.

Biotechnology is being applied to agriculture by new firms dedicated to the use of biotechnology and by well-established firms adapting biotechnology to their existing research programs. The potential products vary considerably, from agricultural inputs (e.g., seeds and pesticides) to veterinary diagnostics and therapeutics, to food processing enzymes, to products with improved food processing qualities. Animal health products are often manufactured by pharmaceutical firms, since there are strong similarities in the research required for developing human drugs, vaccines, and diagnostics and those products intended for livestock. Established research-based seed companies are expanding into biotechnology, while small, new firms attempt to develop products in this area as well. Both small dedicated biotechnology firms (DBCs) and established agrochemical firms are exploring biotechnological approaches to pesticides (25).

Investment in biotechnology, by both small and large firms, depends on the potential for the development of commercial products based on research and development (R&D). The potential for profiting from these new products depends on a variety of factors, such as the potential size of the market for the products and the rate at which new products and technologies are likely to be adopted, the potential for repeat sales, the existence of regulatory hurdles, and the possibility of public opposition.

Biotechnology applications to agriculture are being explored throughout the world but mainly in

Photo credit: U.S. Department of Agriculture

Cloned strawberry plants in a growth chamber.

developed countries. Although few products are currently available, it is possible to get an indication of activities in different countries through surveys of field tests reviewed by national authorities. The climate for developing agricultural biotechnology varies considerably from country-to-country, depending, especially, on differences in intellectual property protection, regulations, and public perception.

APPLICATIONS OF BIOTECHNOLOGY TO AGRICULTURE

While there are many promising applications of biotechnology to agriculture, biotechnology is neither a panacea nor a replacement for established tools. It provides an additional approach to agricultural problems. For example, leaner meats can be produced by altering animal nutrition, through selective breeding or by the administration of hormones-some of which might be produced through biotechnology. Eventually, transgenic animals that contain less fat may be produced. Ultimately, the best route may be a combination of techniques including biotechnological methods. Similarly, new plants can be produced through selective breeding, cell culture techniques, or through genetic engineering techniques. Genetic engineering extends the range of new traits that may be introduced into a plant to include traits from other species.

The first products being developed are animal diagnostic and therapeutic products that are already on the market and biopesticides, the first of which have won regulatory approval. Transgenic plants are currently being field tested and are likely to be available within a few years. Transgenic animals will first be developed for laboratory uses; technologies for producing transgenic livestock for food will probably not be available until after the turn of the century.

Applications to Animals

Reproductive Technologies

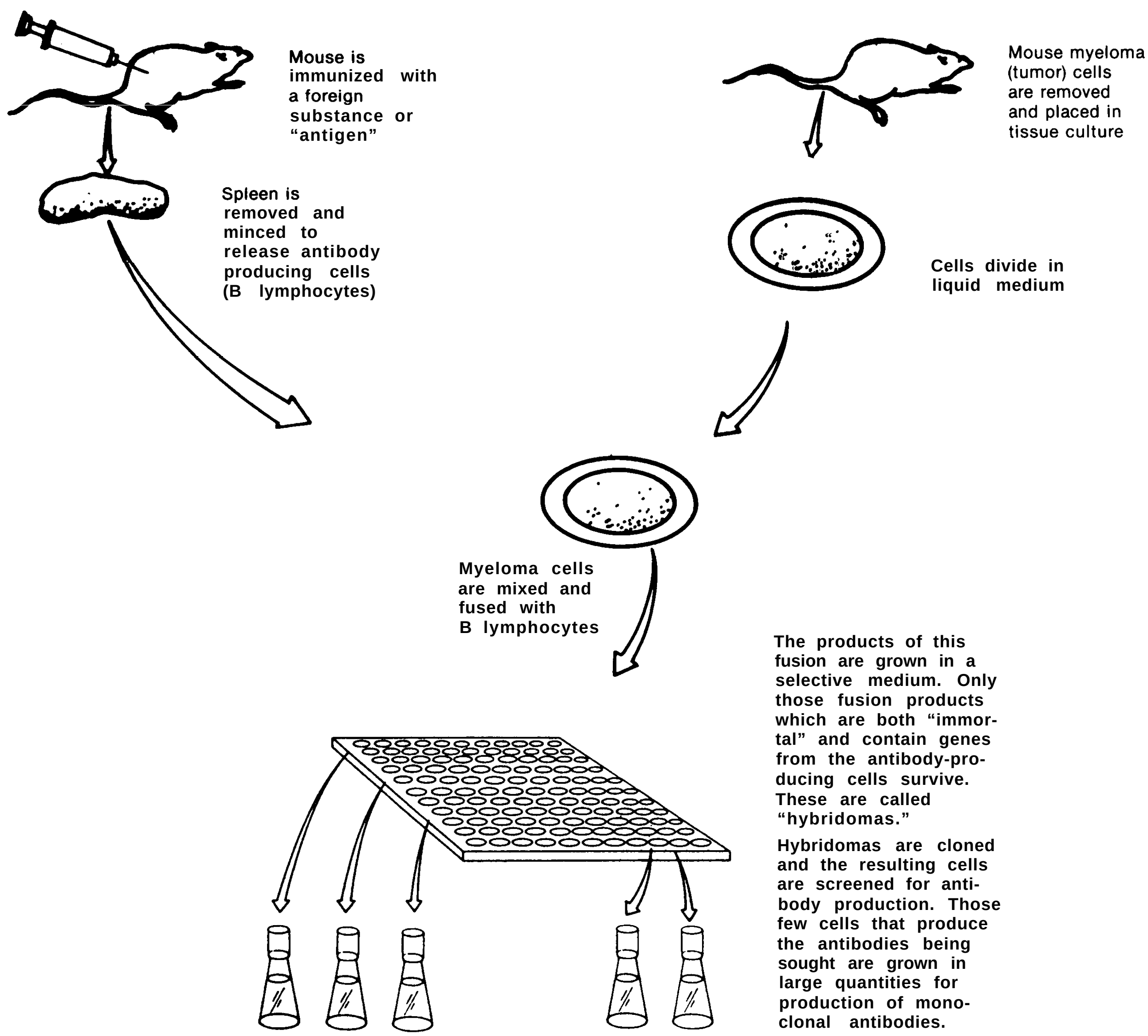
A variety of new reproductive technologies may have an important impact on animal production. Some technologies that do not depend on biotechnology are already in use. Artificial insemination, using semen from genetically superior bulls, is routine in the dairy industry today. Technologies are also available, although none has been widely adopted, that separate sperm to allow sex determination in artificial insemination. Sex selection would be valuable for dairy farmers, for example.

Traits from genetically superior female animals can be propagated using embryo transfer techniques. Cows treated with hormones produce several eggs which are fertilized by artificial insemination, collected, and transferred to surrogates. Laboratory techniques are also available that permit the embryos to be split into multiple, identical copies (43).

Animal Health Products

The application of biotechnology to animal health care products is similar to R&D in health products for humans, and often these products are developed by the same fins. Monoclinal antibodies, for example, may be developed into new diagnostic

Figure 6-l—Preparation of Monoclinal Antibodies



SOURCE: Office of Technology Assessment, 1991.

products for animal diseases just as they are used in tests for human disease (see figure 6-l). New, safer animal vaccines have also been developed. The first genetically engineered vaccine, introduced by Molecular Genetics in 1984, protects against scours (a disease in calves and piglets). A genetically engineered swine pseudorabies vaccine was approved in the United States in 1987, and rabies vaccines are being tested in the United States, Canada, and Europe (12,14,53).

Although the technical possibilities for animal health products may be similar to human products, and the R&D investment required may also be similar, their profitability is not similar. Unlike human health care products, the decision to use animal health care products is essentially a business decision. Animal products do not command prices comparable to those of human health products.

Growth Hormones

Bovine growth hormone, or bovine somatotropin (bST), which stimulates milk production is under development by four U.S. firms. The Food and Drug Administration (FDA) found in 1985 that the milk and meat from treated cows were safe for human consumption, and that finding was confirmed by a committee assembled by the National Institutes of Health (NIH) in 1990. Some farm organizations, however, concerned about the possible toxic effects of BST, its possible rejection by consumers, its effects on animal welfare, and the ultimate effects of increased efficiency of milk production on the survival of marginal dairy farmers, have opposed BST, leading to moratoriums on its use in Wisconsin and Minnesota. Similar concerns have resulted in a moratorium on BST use in the European Community (EC) (7,34).

Animal growth hormones are also being studied as a method to produce leaner meats. The variation in body composition among animals of the same species depends on the growth stage of the animals, their nutritional history, and their genetic base. The production of leaner meats can be accomplished by manipulating these variables through selective breeding, nutrient management, and hormone administration. For example, selective breeding has resulted in the production of modern, leaner hogs. Also, leaner beef has been produced by breeding cattle of larger frame size. The administration of porcine growth hormone, produced through genetic engineering, can speed the growth of hogs, improve feed efficiency, and result in leaner meat (32).

Transgenic Animals

An alternative to treatment with growth hormones is transferring growth hormone genes directly into the genomes of animals, so the additional hormone is supplied endogenously rather than administered by the farmer. Early experiments, however, have shown that simply transferring the genes is not effective, and further fine-tuning of the regulation of the genes' expression is necessary (8). Other genes, such as the human estrogen receptor and insulin-like growth factor, have been transferred to cattle in attempts to produce faster growing animals (8,34). Using transgenic livestock as food, however, is not expected before the end of the century. In the near term, transgenic animals are being developed for nonagricultural purposes, including models for human disease and for use in toxicity testing. For example, one transgenic mouse line produces human sickle cell hemoglobin (40). Other mice, including the frost patented transgenic animal, have been given genes important in cancer development (55). These may eventually be used to identify carcinogens in a shorter the than is now possible and to facilitate studies of oncogenes. Another nonagricultural application of transgenic animals is their use in the production of pharmaceutical proteins. A gene encoding a protein can be transferred to animals that then produce the desired protein in their milk, from which the protein can be purified (30).

Photo credit: Rex Dunham, Auburn University

At top, a transgenic carp containing trout growth hormone gene; bottom, normal carp.

Applications to Plant Agriculture

Microbial Pesticides and Other Micro-organisms

The frost biotechnology-based products for plant agriculture to be commercialized were biopesticides. Many nonengineered biopesticides based on ***Bacillus thuringiensis*** (BT), a bacterium that produces a protein toxic to the larvae of many butterflies and moths, have been in use since the early 1960s (31). Biopesticides, however, represent a tiny fraction of the international pesticide market that is dominated by chemical pesticides (49). Over 600 chemical pesticides have been approved by the Environmental Protection Agency (EPA).

Nonrecombinant biopesticides based on BT have some advantages over chemical pesticides: they are highly toxic to specific pests, leaving humans, crops, wildlife, and beneficial insects unharmed; they do not persist in the environment; and they can be produced using fermentation processes (21,31). But commercial weaknesses have prevented their widespread use. Each pesticide is active against relatively few pests, so the potential market for many pesticides is small. In addition, naturally occurring microbial pesticides often work too slowly and degrade too rapidly in the field. Biotechnology offers a means of addressing these commercial drawbacks. Eventually, more than one pesticidal protein will be engineered into a micro-organism, thereby increasing its host range. The gene for the protein can also be modified, allowing more of the pesticide to be produced and increasing its effectiveness against pests (21). In addition, pesticides can be formulated and delivered to increase their persistence in the environment.

For example, two U.S. firms, Mycogen and Crop Genetics International, are exploring new delivery systems. Mycogen is developing a series of biopesticides designed to protect vegetable crops. Mycogen scientists inserted a gene that encodes a BT toxin into a different bacterium that produces more of the toxin. After the bacteria produce the toxin, the bacteria are killed and treated to fix the cell walls. This leaves a particle containing crystalline toxin within a long-lasting protective coat (47). The dead bacteria are sprayed on plants as a topical insecticide, killing susceptible insects that eat the sprayed plants. Although dead bacteria are not as long lasting as live, reproducing bacteria, the use of killed bacteria makes the regulatory approval process simpler and faster.

Crop Genetics International, Inc. (CGI) has explored a different method of delivering BT toxins. CGI has used micro-organisms called endophytes that live and reproduce inside the vascular system of plants. CGI scientists inserted a gene for a BT toxin into the genome of an endophyte that was then inoculated into seeds. When the seeds were planted the endophytes multiplied inside the plants. The firm has field-tested corn and rice containing an endophyte with a BT gene that protects the plants against the European corn borer and the rice stem borer. The field tests have shown that the endophyte does not survive outside the plant, nor is the endophyte transferred to nearby uninoculated plants. CGI has agreements with four seed companies that plan to use CGI's technology to introduce the endophytes into their existing seed products. The company expects to extend this technology to other major crops (49).

Microbial biopesticides compete in the marketplace with chemical pesticides, and eventually, they will compete with plants that have been made pest resistant through the incorporation of BT genes directly into their genomes. Biopesticides have the advantage of being widely applicable to many varieties without extensive multiyear breeding programs necessary for developing transgenic plants. On the other hand, both the plants containing endophytes and the transgenic plants are resistant to pests without the labor of spraying crops. The pesticide contained in dead bacteria has a strong advantage, however, in its relatively quick regulatory approval time. EPA approved two of Mycogen's recombinant biopesticides in June 1991.

Other useful micro-organisms, such as improved nitrogen-fixing bacteria, are also being field-tested. These bacteria live in nodules on the roots of legumes, such as peas and beans. The bacteria convert nitrogen in the air into a form that the plants can absorb and use. Research is directed at developing strains of bacteria that fix nitrogen more efficiently and that can effectively compete with indigenous soil bacteria in forming nodules thereby being better able to support a healthy crop of legumes (3).

Plant Research

Scientists also use biotechnology as a tool for basic research on plant growth and development. One technique, restriction fragment length polymorphism (RFLP) analysis, shows particular promise in speeding conventional plant breeding and, eventually easing breeding involving complex multigenic traits. An RFLP map consists of a set of cloned deoxyribonucleic acid (DNA) fragments from chromosomal locations throughout a plant's genome. A RFLP marker, or one DNA fragment, can be used as a tool to follow the inheritance of the particular region of the genome in which the marker is located. This procedure can then be used as a guide to selecting plants that possess specific genetic attributes desired in a seed product (see box 6-A).

A good example is the application of RFLP analysis to backcross breeding. Many of the im-

Box 6-A—Plant Genome Projects

To identify and characterize genes that are agriculturally important, the United States and several other countries have begun to fund research on plant genomes. The U.S. Department of Agriculture's (USDA) Plant Genome Mapping Program is the largest of these programs, with a budget of$11 million in research funds for the 1991 fiscal year. Its specific objectives are construction of high-resolution gene maps for those plants species with sufficient background information already available (e.g., tomato, corn, and rice); development of low resolution maps for all major crop species important to the United States (about which little information is available at the moment); high-resolution mapping and sequencing of specific regions of the chromosome for investigating specific genes of economic interest (e.g., hybrid vigor, disease resistance, and drought resistance); and a complete sequencing of ***the Arabidopsis*** genome. In addition, the USDA's Agricultural Research Service has received a $3.7 million appropriation in fiscal year 1991 to manage dissemination of information generated by the program (using such tools as databases and publications). Eventually, it is hoped that the gene maps and sequences will be used to identify and manipulate genes that encode important traits.

The National Science Foundation (NSF), the National Institutes of Health (NIH), and the Department of Energy (DOE) have also funded research on ***Arabidopsis thaliana,*** an agriculturally unimportant member of the mustard family increasingly being used as a model system by plant scientists (just as fruit flies are used by animal geneticists). ***Arabidopsis is*** a small plant with a small genome (about 10 percent that of the human genome), small seeds, and a short life cycle (about 6 weeks). These qualities allow it to be grown in large numbers in greenhouses and rapidly screened for mutations. In addition, DNA can be transferred into ***Arabidopsis*** plants using ***Agrobacterium*** vectors, and viable plants can be regenerated from cultured cells. Scientists can study genes important to plant growth and development, for example, in this small, easily manipulated plant and then apply this new knowledge to agriculturally important crop plants. The NSF is spending $4.4 million in fiscal year 1991 on studies of the ***Arabidopsis*** genome through its existing research programs. The European Community, through its Biotechnology Research for Industrial Development and Growth in Europe (BRIDGE) program, is also funding gene mapping studies on the ***Arabidopsis*** genome, allocating ECU 3 million for 1991-92. The United "Kingdom, in addition to participating in BRIDGE, funds research and postdoctoral fellowships for work on ***Arabidopsis.***

Japan' s Ministry of Education and the Ministry of Agriculture, Forestry, and Fisheries (MAFF) fund studies on plant genomes, particularly rice. The MAFF plans a 10-year project on the rice genome to begin in 1991. The MAFF also plans to construct a rice research facility in Tsukuba, Japan's "Science City."

SOURCES: U.S. Department of Agriculture, 1991; National Science Foundation, 1991; *Kagaku Kogyo Nippo*, Aug. 31, 1990; A. Vassarotti et al., "Genome Research Activities in the EC," *Biofutur*, October 1990, pp. 1-4; "Genome Research," *European Biotechnology Information Service,* vol. 1, No. 17, 1991, p. 17.

provements introduced into modern crop plants originated in related varieties, races, or species. Traditionally, a plant containing one desirable trait, such as disease or pest resistance, was crossed with a plant from a standard line into which the desired trait was being introduced. In backcross breeding, the offspring of this cross (containing the desirable trait) would be grown and crossed again with a plant from the standard line. Offspring from this cross containing the desirable trait would again be crossed with the parent line. After several generations, plants will be obtained that are nearly identical with the original, standard line but which now will contain the desirable trait. RFLP markers can be used to identify offspring that have inherited the desirable trait but that, by chance, also have inherited much of the genome derived from the standard line. One group has estimated, using computer simulation, that this technique can be used in breeding tomatoes, cutting the number of crosses from six to-three (46).

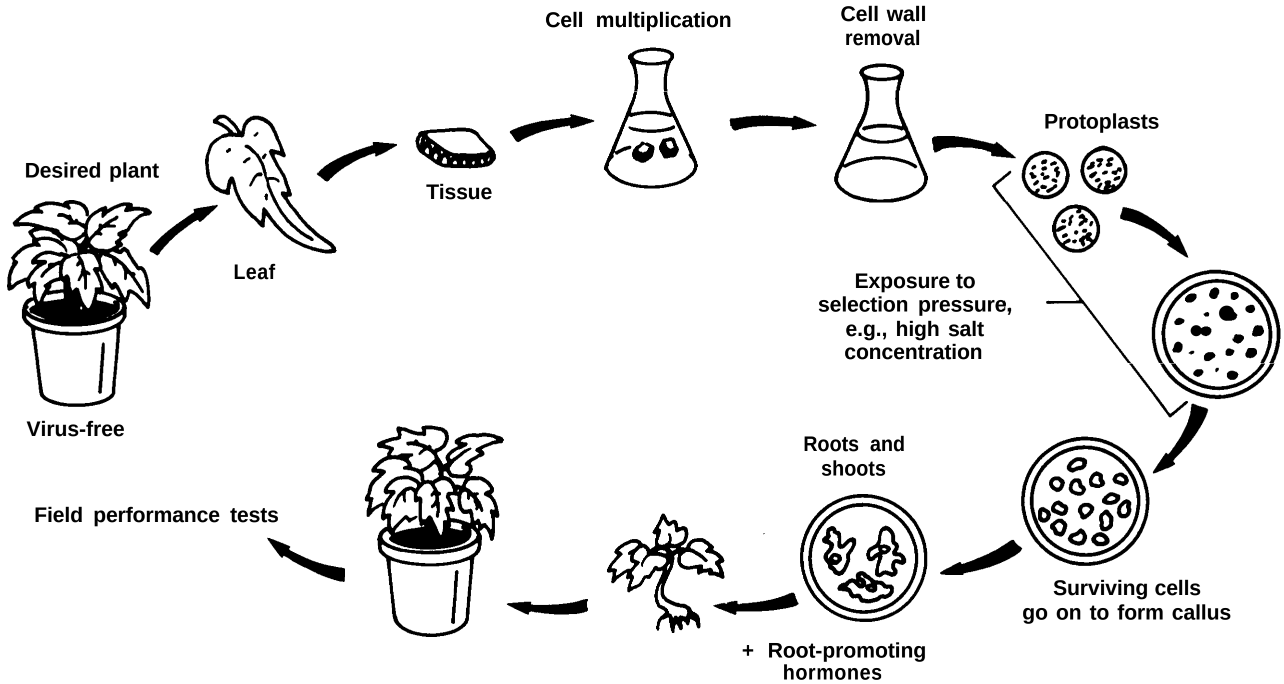
Cell Culture

Plant cells grown in culture can be an alternative source of valuable substances that are now isolated from whole plants. Vanilla, for example, is usually extracted from the beans of the vanilla plant. Vanilla isolated from cultured cells of the vanilla plant can be produced less expensively than traditional vanilla extract, according to a firm that has developed a process for producing vanilla in commercial quantities. Other substances, including pigments and fragrances, have also been isolated from cultured plants cells (9,45).

New plants can also be developed from cultured plant cells (see figure 6-2). Unlike cultured animal cells, some cultured plant cells treated with a mixture of nutrients, minerals, and hormones will

Figure 6-2—Plant Propagation: From Single Cells To Whole Plants

The process of plant regeneration from single cells in culture



The process of plant regeneration from single cells or plant tissue in culture.

SOURCE: Office of Technology Assessment, 1991.

form roots and shoots and grow into viable organisms. Plants derived from these cultured cells may contain mutations resulting in altered traits. These new plants can then be screened for desirable traits. For example, FreshWorld, a joint venture between DuPont and DNA Plant Technology, is selling crisper, sweeter carrots and celery regenerated from cultured cells. DNA Plant Technology is using the same techniques to develop tomatoes having higher solids content—a product useful to food processors. In Japan, a late-maturing variety of rice was developed using these techniques by a joint venture company formed by Mitsubishi Chemical Industries and the Mitsubishi Corp., and a short-stemmed variety was developed by the Mitsui Toatsu Chemical co. (19).

Transgenic Plants

The ability to insert foreign genes into plants, using recombinant DNA (rDNA) methods, provides plant breeders with new strategies for plant modification and improvement. Research and field-testing have recently been dominated by plants exhibiting three kinds of new traits: herbicide resistance, insect resistance, and viral resistance. Altering other plant traits important for plant growth and development, such as those affecting plant tolerance of environmental stress (e.g., drought and salinity) or traits that add to value, often require better understanding of the molecular basis of these traits-many of which may be multigenic and, therefore, more difficult to transfer.

Genes that confer resistance to several classes of herbicides have been isolated and transferred to a number of plants, including tomato, tobacco, cotton, oilseed rape, soybeans, sugar beets, and alfalfa. Herbicides are widely used in agriculture, leading to increased crop yields that result when weeds competing for soil, light, and nutrients are removed. Herbicides also contribute to soil conservation by permitting no-till practices in which weeds are controlled through herbicide use rather than by plowing. The herbicide-resistant gene enables a crop plant to tolerate the toxic effects of a herbicide applied to kill surrounding weeds. Chemicals are currently available to control most weeds, but

Photo credit: Rohm & Haas Co.

Manduca sexta (tobacco hornworm) larva at work. The moth will consume 95 percent of its entire life cycle's food supply while in the larval stage of development. Moth larvae are the most destructive insects to world agriculture and forestry.

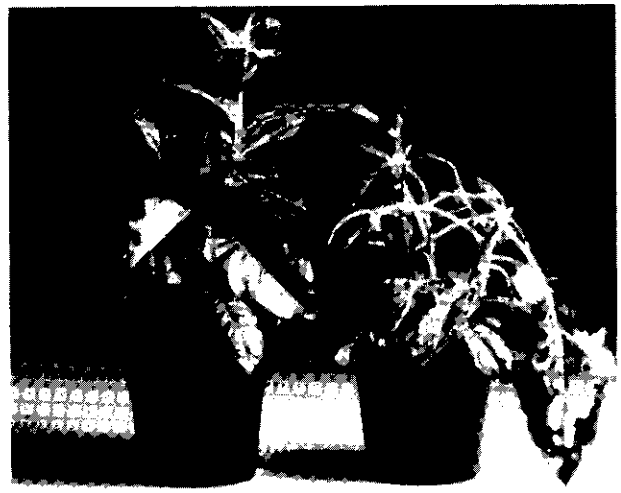


Photo credit: Rohm & Haas Co.

The effects of the BT gene transfer on laboratory tobacco plants can be easily seen in the plant on the left which was infested with 20 tobacco hornworm larvae. Within 40 hours the hornworms were killed by the BT protein in the plant tissue they ingested, leaving the plant virtually undamaged. The other plant, which did not have the gene transfer, shows total destruction by the same number of insects in the same time period.

developing herbicide-resistant plants increases the variety of crops to which a particular chemical may be applied. It is possible that this could lead to increased use of chemical herbicides. However, if troublesome chemicals can be displaced by increasing the use of herbicides that require lower application rates, do not persist in the environment, and have fewer toxic side effects, then there will be an environmental benefit (27).

The first successful transfer of an insect-resistance gene to a plant was done with tobacco by a Belgian firm, Plant Genetic Systems, in 1987 (54). Insect resistance has now been transferred to a number of plant species by transferring genes for pesticidal proteins isolated from BT (31). Because any particular toxin is effective only against specific insects, chemicals may still be necessary for control of multiple pests. Broader spectrum pest control may eventually be achieved by transfers of several insect-resistance genes. It is possible, however, that increased use of plants containing BT toxins will result in BT-resistant pests.

Within the last few years, it has been learned that introducing genes that encode viral proteins can make plants resistant to virus infection(l). Although the mechanism of viral resistance is not well understood, this is an area of active research and field-testing. Its commercial prospects are limited to specific crops in specific regions where viral diseases present a significant problem, such as wheat in the United States and cassava in the tropics.

Traits such as insect or disease resistance can increase the value of plants to farmers. Other new plants are being developed, however, with traits that are not aimed at increased yields or lower input costs for farmers. These traits are intended to meet the needs of food processors and consumers. These new plants have traits that change the nutritional content of a plant, alter its processing qualities, or increase its consumer appeal. For example, genetically engineered tomatoes, developed by Calgene and now being tested, have a gene that interferes with the ripening process that causes tomatoes to become soft. In the future, additional products based on a deeper understanding of molecular mechanisms may be developed. For example, the nutritional content of corn may be enhanced by increasing the amount of the amino acids lysine and methionine in the seeds. Work is underway to produce coffee with lower caffeine content. Oilseeds with higher oil contents, altered ratios of fatty acids (for enhanced nutritional properties), or longer shelf lives will be developed. Genes that control flower colors are being transferred to develop new ornamental. Some of these traits can be modified through traditional breeding programs, but biotechnology can improve the efficiency of making changes and extend the range of possible modifications (5).

Applications to Food Processing

Biotechnology can contribute to food processing in various ways, but most current applications emphasize cost reduction. Biotechnology can be used to improve the production of existing goods currently made using fermentation, such as vitamins and amino acids used as additives in food and animal feed. Biotechnology can also be used for the production of food processing enzymes. One food enzyme, chymosin, used in cheesemaking, was traditionally extracted from calves' stomachs and sold as part of a mixture called remet. Rennet varied in quality from batch-to-batch, and its scarcity led to rising prices in recent years. Researchers at Pfizer, Inc. transferred the gene encoding chymosin to bacteria that could be grown in large fermentation tanks, yielding large amounts of chymosin. The enzyme was approved for food use by the FDA in 1990 (55 Fed. Reg. 10932).

Micro-organisms are widely used in baking and brewing. A baker's yeast altered using biotechnology has been approved for use in the United Kingdom (U.K.). There is also interest in developing genetically engineered micro-organisms for the production of high-value compounds currently isolated from plants. Among these products are dyes, vitamin s, flavors, colors, lipids, steroids, and biopolymers (16,39,44).

The application of biotechnology to food processing has received a great deal of interest in Japan. Japan leads in world production of amino acids and fermented food products. Their expertise in fermentation makes biotechnology a natural extension of their current strength (16).

CASE STUDY: THE SEED INDUSTRY

Whether or how biotechnology is used by a firm depends on a variety of factors, among them:

- ***The potential for profits from the investment. This*** depends on the size of the market, rates of adoption, intellectual property protection, the existence of substitutes, and public acceptance of new products.
- ***The role of R&D in the industry.*** This may depend on competitive pressures to develop new products.
- ***The time it takes to realize a return from such an investment. Anything*** that delays the return on the investment, such as regulations, may inhibit investment. A more detailed description of the seed industry provides an illustration of interplay between the forces that influence the use of biotechnology.

Industry Structure

In 1988, U.S. farmers spent $3.7 billion on seeds (52). The worldwide market has been estimated at $12 billion to $15 billion. But these estimates exclude the extensive informal seed market. Farmers often plant seed saved from a previous harvest or purchase seed from another farmer. Estimates of the total seed market vary considerably, ranging as high as $62 billion (41).

The seed industry has many markets, including those for grass, forage, vegetable, flower, and field seeds, each having its own supply, demand, price, and organizational characteristics. Many seed producers are small firms that grow and distribute common varieties of seed for regional markets. The small firms conduct little or no research, but they effectively market new technologies provided by public or private seed suppliers.

A portion of the seed industry consists of larger firms with resources to invest in the long-term research necessary to produce genetically improved seeds (see table 6-l). These are the firms likely to benefit from the use of biotechnology. For these fins, however, investment in research has historically been less than 5 percent of revenues (13). Today, investment in research is higher; in 1989,

Table 6-l—Major World Seed Firms

Pioneer Hi-Bred International	United States
Sandoz	Switzerland
Ciba-Geigy	Switzerland
DeKalb	UnitedStates
Upjohn	United States
Limagrain	France
Cargill	United States
Volvo	Sweden
Lubrizol	UnitedStates
KwS.	Germany

SOURCE: Office of Technology Assessment, 1991.

Pioneer Hi-Bred International invested 7.6 percent of total revenue in R&D (37). Most seed research is based on selective breeding programs used to develop seeds that are high yielding or have other advantageous traits.

Internationalization and Consolidation

Over the last 30 years, the seed industry has been marked by increasing internationalization. During the 1960s, major U.S. firms began exporting seeds, particularly the better hybrids, into Latin America and Europe. This was followed, in the 1970s, by increasing acquisitions of small firms, as U.S. firms expanded into Europe and large European seed firms invested in the United States. The major firms also developed subsidiaries in Australia and Latin America-especially in Argentina, Brazil, and Mexico. The French firm Limagrain, for example, has subsidiaries in Australia, Brazil, Chile, Germany, Italy, Mexico, Morocco, The Netherlands, Spain, Tunisia, Turkey, and the United States. The U.S. firm Pioneer Hi-Bred International, Inc. sells seed in 80 countries worldwide and has subsidiaries in Argentina, Australia, Austria, Brazil, Canada, France, Germany, India, Italy, Japan, Mexico, the Philippines, Spain, and Thailand (41).

Seed companies were, historically, closely held businesses. Increasingly, however, both small and large seed firms have been acquired, not only by other seed firms but by other major multinational companies. Since the mid-1960s, over 100 seed companies have been acquired by multinational chemical, pharmaceutical, and oil corporations—often those with agricultural chemical subsidiaries. Few major seed companies remain independent: the U.S. firms Pioneer Hi-Bred International, Holden's Foundation Corn Seeds, and DeKalb; the French firm, Limagrain; and the Brazilian firm, Agroceres SA, have managed to continue independently. Other major research-based firms are now subsidiaries of multinational corporations whose main business is not seeds.

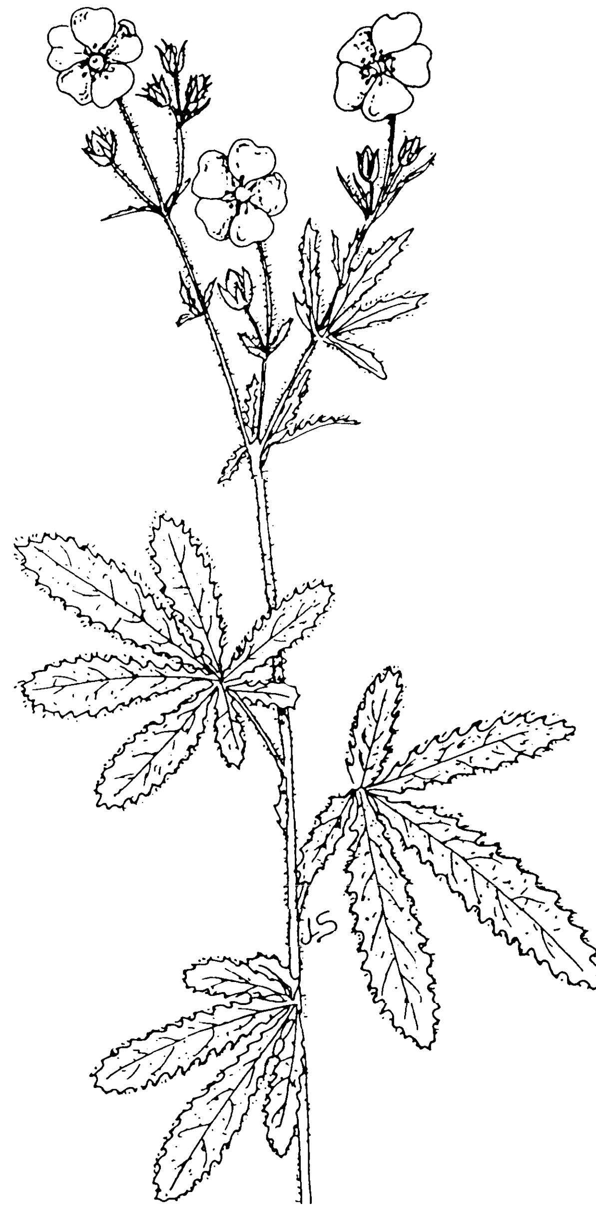


Photo credit: National Agricultural Library

Many of the corporations that chose to invest in seed companies were European firms that lead in world sales of pesticides and fertilizers. The Swiss firm, Ciba-Geigy, for example, acquired the U.S. seed firm, Funk, in 1974. The British chemical firm ICI has acquired six seed companies, including Garst, one of the leading U.S. firms. Rhone-Poulenc has recently acquired five seed firms, including

Clause, an important French company. The U.S. chemical firm Lubrizol owns eight seed firms through its Agrigenetics subsidiary. Corporations best known for producing pharmaceuticals have also invested in seed firms. Upjohn owns Asgrow Seeds, and Sandoz acquired eight seed subsidiaries from 1976 to 1988, including Northrup King and Stauffer Seeds in the United States. There are also examples of major cereal and sugar producers acquiring seed firms. Cargill, the major U.S. food producer, specializes in seeds of corn, wheat, and sunflowers and has subsidiaries in nine countries. Cardo, a major Swedish sugar producer and now a subsidiary of Volvo, has invested heavily in the production of sugar beet seed. More recently, biotechnology firms have begun to acquire seed firms, seeking outlets for their technology. For example, Calgene has purchased Stoneville, and Biotechnica has purchased five regional seed companies (17,20,41).

This recent consolidation has made the research-based sector of the seed industry extremely concentrated. For example, in 1985, four firms supplied 64 percent of corn seed in the United States; Pioneer Hi-Bred, alone, supplied 38 percent. Pioneer also led in providing corn seed in France, where it held 55 percent of the market, followed by Limagrain with 15 percent. In Brazil, 34 percent of corn seed was supplied by Agroceres. In France, sunflower seed sales were dominated by Cargill, which held 75 percent of the market in 1985 (41).

Research in Seeds

Keeping market share requires constant development of new, improved products. For example, in 1989, Pioneer released 24 new corn hybrids. A new hybrid is usually marketed for about 7 or 8 years before it is superseded by improved hybrids. A hybrid's lifetime depends on how unusual it is, how much competition there is (if a market is large, competitors will develop similar hybrids), and how insect and disease pressures change over time. A few exceptional hybrids have been sold for more than 20 years, because they have qualities that make them suitable for a particular region (28). A number of other factors influence the types of research projects that a seed firm may choose to undertake. Among these are: the potential market size, the time it will take to realize a return on investment, the availability of intellectual property protection, and technical constraints.

Hybrid Seed

The research-based sector of the industry grew with the introduction of hybrid corn in the 1920s. Hybrid seeds are the first generation of a cross between two unrelated strains of a plant. Some hybrids have much higher yields than conventional seed and, therefore, command high prices. The high yields more than offset the higher prices firms charge for the seeds.

Hybrids do not breed true. The high yield is obtained only in the first generation. To obtain the high yield, farmers must purchase seed from suppliers each year. In the United States, 95 percent of corn planted each year is grown using seed purchased from seed suppliers. The assurance of repeat business gives seed firms a strong incentive to continue research into better yielding hybrid seeds. Corn, grain sorghum, sunflowers, and some vegetables are typically sold as hybrids (2).

Most other crop species are naturally self-pollinated. For many of them it is difficult to produce hybrid seeds on a large scale for commercial purposes (see box 6-B). Unlike hybrids, self-pollinated varieties breed true. Farmers can choose to buy fresh seed or to plant seed saved from the previous year's harvest with little difference in yield. Although there are advantages to buying fresh seed, which has an assurance of purity and has been cleaned and tested for germination, or seed of a newly available, higher yielding variety, farmers often choose to plant saved seed. As a result, only 35 percent of wheat and 50 percent of cotton seeds are purchased from suppliers each year (2).

Firms do research on self-pollinated crops, but there is much less incentive to invest heavily because the companies cannot capture profits as they can with hybrids. Competition with saved seed also depresses the prices firms can charge for their seed (2,23).

The repeat business associated with hybrid seeds guarantees a sizable market. The market size also depends on how widely the crop plant is grown. Most research, using both biotechnological and traditional approaches, is performed only on those crops that offer markets of sufficient size to enable returns on R&D investment.

Box 6-B—Developing New Hybrids

Some plants readily lend themselves to hybrid production. In corn, for example, the structures that produce pollen, the anthers, are located at the top of the plant on the tassels. If a plant's tassels are physically removed or if a mutant is grown that does not produce pollen, all the eggs will be fertilized by pollen from neighboring plants. By growing plants of one strain of corn near plants that are genetically male-sterile or hand-emasculated, hybrid seed can be obtained

In many plants, however, there are no genetic male-sterile varieties. In addition, many of these plants have small, delicate flowers, and it is difficult and time-consuming to remove anthers by hand. Some chemical treatments are available for producing sterile plants (and have been used in the production of hybrid wheat). For many plants, however, producing hybrids on a commercial scale is not practical.

Recently, however, scientists from a Belgian firm, Plant Genetic Systems NV, collaborating with scientists at UCLA have developed a general method for producing male-sterile varieties. The scientists transferred a gene that prevents anther development into otherwise normal tobacco and oilseed rape plants, resulting in male-sterile plants. The extension of this technology to additional crops has the potential to extend the benefits of hybrid production to other species. It is hoped that some of these new hybrids may show the increases in yield typical of hybrid corn.

SOURCE: C. Mariani et al., "Induction of Male Sterility in Plants by a Chimaeric Ribonuclease Gene," *Nature* vol. 347, 1990, pp. 737-741.

Intellectual Property

To stimulate private-sector research on nonhybrids, Congress passed the Plant Variety Protection Act (PVPA) in 1970. PVPA extends patent-like protection to sexually reproducing plant varieties outside the existing patent system. PVPA is administered by the U.S. Department of Agriculture (USDA) rather than by the U.S. Patent and Trademark Office (PTO). It gives the owner of a protected variety the right to exclude others from selling, reproducing, importing, or exporting the protected variety for 18 years. But, there are two important exceptions: farmers may save or sell seed they have produced themselves for future planting, and researchers, including competitors, may also use protected varieties in their research programs to develop new seed products. A system establishing similar breeders' rights was created in Europe by a 1961 treaty establishing the International Union for the Protection of Plant Varieties (UPOV).

A survey of seed companies, conducted in 1980, reported growth in the number of research programs on nonhybrid crops and increases in total research expenditures on nonhybrid crops after PVPA was enacted in 1970. For example, of the 21 soybean breeding programs the surveyors found existing in 1979, only four had existed before 1970 and some of those were founded with the expectation that PVPA would be enacted. Increases in cereal research were also noted, while forage-breeding programs had increased slightly and seemed to be unaffected by passage of the new law (36).

Seed firms face difficulties enforcing provisions of PVPA. If another firm sells a protected variety, the seed company that owns the variety must find the seed pirate and sue for damages. Although the extent of infringements is unknown, it occurs often enough that seed firms are taking action. Asgrow Seed Co. has found violators advertising Asgrow varieties in local newspapers, but protected seed sold less blatantly, under a new name, is harder to track (24).

PVPA is limited in its protection of products developed using biotechnology. It extends protection to a single variety only. Today, utility patents may also be obtained for plants and plant parts as a result of a 1985 Supreme Court ruling (10). Utility patents offer broader protection than does PVPA; there is no farmer or research exemption. Finns have filed patent applications for, among other things, DNA sequences, plant cells, gene isolation processes, DNA transfer processes, whole plants, and other plant parts. Questions remain, however, about the scope of patent coverage, and in the absence of new legislation they will be answered as the courts resolve disputes (31).

In Europe, intellectual property protection for plants remains confined to protection for plant varieties established by UPOV, although DNA sequences, plasmids, and plant cells are patentable. Plant and animal varieties are generally excluded from patent protection in European countries. Patent laws in Australia and Japan, on the other hand, do not exclude plants and animals (4).

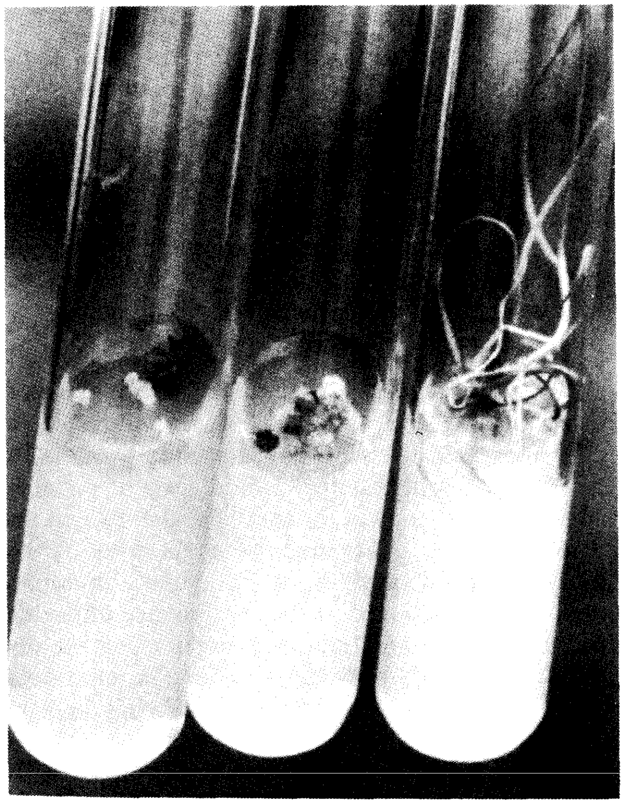


Photo credit: Diversity, Genetic Resources Communications Systems, Inc.

Plant culture.

Regulations

In conventional plant breeding programs, potentially useful new traits are bred into plants that have other important agronomic traits, and the plants are then field tested in different climates. The most successful varieties are then bred for several years to produce commercial volumes of seed. This process, from the initial breeding to product introduction, takes 10 to 15 years (5). For genetically engineered plants, this process is lengthened because of requirements for field testing to demonstrate safety. In addition, firms have to obtain regulatory clearance before marketing a new product. These increases in the time it takes to develop new products have their greatest impact on cash-starved, small fins. It is also unclear how the FDA will evaluate food plants, although the FDA has made clear its intention to use its existing authority under the Food, Drug, and Cosmetic Act (15,48).

Regulations on field testing genetically modified plants are particularly strict in northern Europe, due to adverse public opinion. In Japan, regulations for field-testing genetically modified plants were issued by the Ministry of Agriculture, Forestry, and Fisheries in the summer of 1989, but, so far, only a single test has been reported.

Technical Constraints

Technical constraints have, over the last several years, limited the ability of seed firms to apply biotechnology to the most valuable potential projects. Of the plants that have been field-tested in the United States, the vast majority have been vegetable crops altered to make them herbicide, insect, or virus resistant. There has been heavy emphasis on applying biotechnology to vegetables, because they are the easiest crops into which to transfer DNA. The most widely used method of transferring DNA into plant cells depends on the use of an infectious bacteria, ***Agrobacterium tumefaciens,*** which, on infection, transfers DNA into the genome of the plant. Altered forms of the bacteria have been developed that allow researchers to transfer specific DNA fragments that confer useful, new traits into a plant. But, these bacteria do not infect cereal plants (56,57). Only recently have researchers reported a new technique for DNA transfer into plants using a particle delivery, or ballistic, system (22). Three firms have reported the successful application of this technique to corn, followed by regeneration of viable plants with new genes incorporated stably into nuclear DNA. The variety of plants to which biotechnology can be applied will expand in time, but needed gains in transformation efficiency must be made for the true potential of gene-transfer technology to be realized.

The number of traits that researchers alter is also likely to increase. Such qualities as herbicide, insect, and virus resistance are relatively easy to transfer, because they are carried by single genes. Many other important traits, however, are probably affected by multiple genes and are not well-understood genetically or biochemically. Manipulating these traits requires a long-term investment in fundamental plant metabolism research in order to understand the molecular basis of these traits.

The Congress, responding to criticism of the USDA's funding of basic research, has recently increased the USDA's funding for competitive grants (33). The National Research Initiative is being funded at $73 million in fiscal year 1991, and its budget will increase to $500 million in 5 years.

The Response of Firms

In this market, few direct paths are open to firms. A number of companies, both large and small, have been developing plants with improved agronomic traits. For large firms, biotechnology presents an opportunity for growth and a way of protecting market share. Large firms with many popular high-yielding products and established distribution systems can incorporate these new traits into their products. But new dedicated biotechnology firms do not have the same access to quality germplasm or distribution outlets. For them, biotechnology presents growth opportunities, but it is important to develop partnerships with larger firms (38). In some cases, small biotechnology firms have sought eventual outlets for their technology through purchases of small seed firms.

Some small firms survive solely by isolating new genes or developing new technology that can be licensed to larger firms. These alliances, between large and small firms, provide sorely needed financing to small firms while providing large firms with wider access to new technology. But, as large firms develop more in-house expertise, these strategic alliances may become more focused and less available.

Some firms plan to invest in the long-term research necessary to develop plants with improvements in nutritional content or processing qualities. Few firms can afford the substantial investment or the long wait required until this research results in commercial products. In addition, marketing these products presents new challenges. Traditionally, seed companies have generally sold their products to farmers, with little emphasis on the development of plants with traits important to their eventual users. But developing and selling a product with properties of interest to particular end-users (e.g., an oilseed with altered composition making it useful to producers of commercial fried foods), require the development of close working relationships between breeders and end-users (13).

THE INTERNATIONAL CLIMATE FOR AGRICULTURAL BIOTECHNOLOGY

The major food exporting nations consist of a handful of developed countries (see table 6-2). Some developing nations, such as Argentina, Brazil, and Thailand, are also important exporters of grains, feeds, and tropical products. Exports tend to be concentrated among a very few countries: five countries are responsible for over 90 percent of wheat exports; seven for over 90 percent of feed grain exports, such as corn, barley, sorghum, and oats; and four countries account for over 95 percent of soybean and soy product exports. Similarly, the EC and Eastern Europe account for over 85 percent of pork exports, and six countries provide over 80 percent of beef exports (26).

Because biotechnology products for agricultural use are still in development, it is not possible to compare the numbers of products actually manufactured in different countries. Field trials of potential plant products, however, are regulated by national agricultural or environmental authorities. These trials are outdoor tests of genetically modified organisms, conducted to gain experience important for future commercial development or to test the new plant under field conditions. There is no official census of such tests, but the USDA has kept an unofficial tally that gives a rough estimate of activities in different countries (see table 6-3). Unfortunately, little is known about testing in the Third World.

Through the summer of 1990,93 field tests of transgenic plants had been approved in the United States, far more than in any other country. In the EC, 62 tests had been approved, including 28 in France and 12 in Belgium. Canada and Australia, major agricultural exporting nations, had approved 18 and 4 tests, respectively. There is little activity elsewhere. In general, transgenic plants are being developed in nations that are major exporters of agricultural products, with the greatest activity in the United States.

In northern Europe, particularly Germany and Denmark, public concern about possible environmental risks and ethical issues associated with biotechnology has translated into regulations that discourage field testing of genetically engineered organisms. The lack of patent protection for transgenic organisms also tends to inhibit investment in transgenic plants in Europe.

In Japan and other Asian countries, public perception of biotechnology appears to be mixed. The use of biotechnology to produce pharmaceuticals and industrial and food processing enzymes is well accepted, but agricultural applications are less so

Table 6-2—Major Exporters of Basic Agricultural Commodities Traded Worldwide

Wheat	Feed grains	Soybeans and soybean products	Beef	Pork
United States Canada Australia France Argentina	United States Argentina Canada South Africa Thailand Australia France	United States Brazil Argentina European Community	European Community Australia Argentina New Zealand Brazil Canada	European Community Eastern Europe

SOURCE: U.S. Department of Agriculture, *Agricultural Yearbook 1985.*

Table 6-3-Field Tests, by Country (summer 1990)

United States	93
European Community	62*
Canada	18
Australia	4
Argentina	1
Japan	1
Other	8

* 28 in France; 12 in Belgium

NOTE: Because of differences in definitions, some of these statistics for countries outside the United States may include tests of modified micro-organisms as well as transgenic plants, but these tests are relatively few.

SOURCE: U.S. Department of Agriculture, 1991.

(18). In Japan, there has even been an historical aversion to the use of nonengineered microbial pesticides. Their use is permitted but much more strictly regulated than in Europe or the United States. This is partly because BT was originally isolated in Japan as a potent pathogen of silkworms. Although strains nontoxic to silkworms have been developed, the use of BT in Japan was banned until 1971, and the first permits for its use were not granted until 1982. It is thought that the stringency of the regulations has inhibited corporate interest and investment in the development and improvement of biopesticides in Japan (50). Japanese surveys have also reported concern about environmental releases and food uses of transgenic plants and animals (29). A survey of Japanese businesses found that only 38 percent of the 66 responding agricultural firms considered biotechnology decidedly or fairly important for their company's future; in contrast, 89 percent of manufacturers of drugs and diagnostics took that position (35).

SUMMARY

Like other technical innovations, biotechnology has the potential to improve the productivity of agriculture by increasing yields, decreasing costs, and providing new products. Applications include animal health products, hormones, transgenic animals, biopesticides, and transgenic plants. Surveys of field tests of transgenic plants reviewed by national authorities show that the United States leads in this activity, followed by the EC (especially France), and then by Canada. Activity is greatest in countries that have access to biotechnology research, that are leading agricultural producers, and where there is little public concern about the applications of biotechnology to agriculture.

In the seed industry, research investment has traditionally been heaviest in crops sold as hybrids, particularly corn, because these crops offer the most opportunities for profit. But corn, the crop that has drawn the most research in the past, has not been amenable to biotechnological manipulation until recently. Therefore, research has focused on crops and traits that are easier to manipulate. As technical roadblocks are lifted, research is likely to increase on other crops and on more complex traits. Other roadblocks exist:

- More basic research is needed on fundamental plant biochemistry, genetics, and physiology—in addition to plant biotechnology. This research would help in identifying and manipulating genes involved in producing complex traits of agricultural importance. Congress has begun to address the need for basic research by increasing funding for competitive grants administered by the USDA.
- The FDA has given industry little indication of its approach concerning food safety of genetically modified plants, making it difficult for industry to plan commercial introduction of new foods.
- Intellectual property protection is lacking for plants and animals in Europe and in less developed countries.

Currently, small dedicated biotechnology firms are isolating genes, developing new techniques, and working with larger firms to commercialize their technology. A number of small firms are also acquiring small seed firms as future outlets for their technology. Large seed firms and agrochemical firms are building in-house expertise and exploring technology through their relationships with small firms.

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