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The Evolution and Development of Biotechnology

A Revolutionary Force in American Agriculture

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The Evolution and Development of Biotechnology: A Revolutionary Force in American Agriculture. By Joel Schor, Agriculture and Rural Economy Division, Economic Research Service, U.S. Department of Agriculture. Staff Report No. AGES 9424.

Abstract

Techniques of gene transfer are revolutionizing agricultural research and development. Within the past 15 years, a merging of science and technology and of the university research system with private industry has resulted in new products and applications. Problems have arisen such as patenting of living processes, maintaining academic freedom, determining strategies for risk assessment, furthering consolidation of agriculture, displacing efficient producers, and emerging monopolies. USDA has established review mechanisms to facilitate development of agricultural biotechnology, while protecting public safety and the environment. These include expanded research guidelines, a national infrastructure to identify outdoor test sites, expert reviewers for evaluating proposals, and post-release monitoring of test-site environments.

Keywords: germplasm, hybridization, bioproducts, gene transfer, risk assessment, patents

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Summary

Gene manipulation for plant and animal improvement through simple selection is centuries old. New techniques of gene transfer, however, are revolutionizing agricultural research and development. Within the past 15 years, a new binding of science, technology, the university research system, and private industry has resulted in new products and applications entering the marketplace. Problems and concerns have also arisen, such as patenting of living processes and genes, maintaining academic freedom of inquiry, determining models for risk assessment, further consolidation of agricultural production, and displacement of some efficient smaller producers. In the next decade, the momentum of biotechnology will likely reach even greater acceleration and significance.

This volume focuses on the evolution of biotechnology, from the basic scientific research and germplasm accumulation that preceded it, to the current state of affairs and implications for policymakers. The report places science, as it relates to agriculture, in historical perspective, with a final chapter on the evolving process of regulation. The new technology is producing disruptive changes abroad and may do so in the United States, not only in terms of production and marketing, but also within the social fabric of U.S. rural communities. For example, the substitution of high-fructose corn syrup (HFCS) for cane sugar as a sweetening agent has required substantial economic adjustment to some Third World countries, and the development of bovine somatotropin (bST) in the United States has economists predicting substantial reductions in the number of dairy farmers. bST promises to increase milk production dramatically per individual cow.

While contemporary gene manipulation in the test tube is seen as the essence of biotechnology, the foundation of the science was laid 120 years ago with the discovery of nucleic acids. The centuries-old practice of simple selection of superior seed and animals has evolved into the more sophisticated techniques of cross-breeding, grafting, hybridization, and population studies by modern plant breeders.

By 1930, the manipulation of viable germplasm by scientists within the land-grant system produced a breakthrough in agricultural productivity. The success of hybrid corn caused a great surge in agricultural research and helped the commercial and industrial world to take advantage of the science of biotechnology and to deliver its products to the public.

Biotechnology makes great advances possible, but also poses challenges to the industry and society. Considerable consolidation has occurred in the seed industry as large input suppliers have absorbed smaller suppliers and biotechnology startup companies. A convergence has also occurred among pharmaceutical corporations and universities external to the land-grant community. Such consolidations may transfer some managerial aspects of farming to the input supplier. For example, industry could present the farmer with packaged programs of altered seed, fertilizer, irrigation equipment, and harvesting devices which, being closely linked, limit the farmer's options in seeking alternate supplies. A related question deals with the status of middle-size farms (gross sales of $100,000-$250,000). Can those farmers remain

competitive if advances in biotechnology raise the cost of inputs?

Biotechnology also introduces some risk for society. The patenting of living processes and of "proprietary" genes is without precedent. Drawing a fair and equitable line to benefit the public as well as the scientists and companies implementing the research, while preserving a wide margin of safety, remains a central and difficult issue.

Risk assessment has been a major regulatory concern. Although altered bacteria can be equipped with genes that self-destruct, they can never be recalled to the laboratory once released into the environment. That is why the National Institutes of Health and other Government agencies, including the U.S. Department of Agriculture, have a responsibility to ensure safety in research and in product development. An elaborate structure has evolved and continues to be modified to adjust changing research needs to new realities while minimizing risk.

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Introduction: Is Biotechnology Really New?

Historians of agriculture have pointed to the revolution in agricultural productivity throughout the world in the past two decades as proof of the effectiveness of agricultural science and technology (Rasmussen, 1982, pp. 82-3; Schlebecker, 1975, pp. 295-320).[1] Sustaining the food increases made possible by the Green Revolution remains a concern of many governments and international agencies. This study describes recent developments in the laboratory and draws on history to illustrate contemporary trends in biotechnology.

Germplasm is the base of the new science. As used here, the term "germplasm" refers to the hereditary material of any living organism, or group of organisms, that determines their characteristics. For example, there is the germplasm of an apple tree, or the germplasm of all Granny Smith apple trees, or the germplasm of all Washington State apple trees. Also, if the hereditary materials in any bit of germplasm are the product of nature, the work of a plant breeder, or the results of a molecular biologist's gene-splicing experiment they are called germplasm. Regardless of its form, germplasm is a combination of genes. There are combinations of genes in every cell of every plant or animal, because in each cell is a copy of every gene that characterizes that organism. The actual number of genes in any given cell is less significant than those that are "expressed." It is very difficult to determine which genes are responsible for a particular trait. Traits are governed by hundreds or thousands of genes working in concert. It is not presently possible to obtain a numerical figure which corresponds to a value for germplasm (Witt, 1985, pp. 9-10).

Germplasm, as the material for biotechnology, has taken on a new importance and value beyond its role as the scientific foundation of biotechnology. In addition to the scientific foundation of biotechnology, this report examines the historical accumulation of germplasm,

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[1]Full titles of works cited are listed in the References section at the end of each chapter.

the effect of hybridization, and the evolution of patent-like protection of living things. The commercialization of biotechnology and its effects are rather recent, scattered throughout agriculture, and a complex subject to analyze. Accordingly, this report takes more of a topical rather than a chronological approach.

Progress and development in the theories that led to the present understanding of the mechanics of heredity have been uneven and complex. No one field of research can claim monopoly, and knowledge appeared frequently from unlikely sources. Contributions from numerous researchers over the past 120 years advanced knowledge. The scientists involved were usually connected with universities or in medical research. The research was regarded as "basic" and remained rather secluded as late as the 1960's. By then, it had become clear to researchers that the new reductionist view of heredity—based on the critical function of storage and transmission of information within the molecules of DNA—had triumphed, and many began to redirect their research to that view. A group of prominent scientists, the molecular biologists, emerged. Thirty years ago, the field of study was called biochemistry. Today, the term "molecular biology" is becoming prominent. The distinction between the two disciplines continues to remain blurred, although it has become clearer over the past decade. Biochemists and molecular biologists now study at different levels of organization.

Biotechnology in agriculture began 80 years ago when Erwin Frink Smith and Charles Orrin Townsend, both with USDA, observed the naturally occurring genetic mutation in plants induced by bacteria, but failed to fully recognize the significance of their observation. This came much later, and Deoxyribonucleic Acid (DNA) has only recently swept the public at large. The rapidity of new discoveries, the claims of young corporations seeking grants, and media hyperbole have also contributed to the investment excitement.

The new techniques of gene transfer have been used to produce new plant and animal genotypes. Gregor Mendel made plant and animal breeders aware of genes. Frederick Meischer discovered the nucleic acids that Watson and Crick mapped out years later. Erwin Frink Smith studied naturally occurring genetic transfers produced by agrobacter bacteria in trees early in this century. None of these scientists, however, could successfully manipulate genes external to the plant and animal systems that contained them. But, direct genetic transfer through protoplast fusions and recombinant DNA insertions is now commonplace. Science has progressed to the cellular and molecular level of the genome (the genes that compose the living organism). Gene frequencies are being altered with surgical precision. New plant and animal varieties will be engineered, and many anticipate a "new industrial revolution [author's emphasis] in agriculture" (Kloppenburg, 1985, p. 296). Science is able not only to create new organisms in a test tube, but also to obtain wide extra-species combinations, such as placing human hormones into petunias. It is possible to speed the time factor, which has constrained plant and animal breeders working with whole organisms.

The manipulation of microbial genomes by agricultural scientists can be used by industry in agrochemical and veterinary pharmaceutical production. Biotechnology has altered boundaries between academic disciplines and between academia and the business world. Molecular

biology/biochemistry now involves plant and animal breeding. Research outside land-grant universities is now of interest to agriculture. Plant breeding and biological science share the same technology with agrochemical firms.

Experimentation in the early 1970's removed the science from its academic cloister. Although research continued at the university as before, it became clear that genetic transfers could be accomplished easily in conventional laboratories, that a limitless number of bioproduct applications were possible, and that the financial rewards from the end products could be substantial. The science became a technology and soon gave rise to a new industry. Expectations for large profits produced a number of small biotechnology "startup" companies, which were often unions of university-trained scientists and venture capitalists. Large amounts of working capital have been invested by corporations engaged in applied uses and in product development. A unique aspect of this new technology has been its near total dependence on university research. Martin Kenney, of Cornell University, states, "In no other fledgling industry have university scientists played such an all-encompassing role" (Kenney, 1986, p. 4). The original intimacy with academia has continued, producing new relationships between the university, public research, and private enterprise.

The question of the intent of the new biotechnological research generates controversy. Work at USDA's experiment station in Beltsville, MD, is not tied to the needs of a few specific client interests, so scientists there can concentrate on fundamental discovery and knowledge. This process is critical because the full identification of genes and the effects of their transfer are largely unknown. Filling in these gaps will become the scientists' contribution.

Basic research is usually more expensive in total cost than applied testing. The private sector historically has preferred to leave the basic work alone. However, the research in this expanding field is becoming increasingly privatized. An effect of early fervor within the university community was the loss of faculty and graduate students to private industry once scientific breakthroughs had occurred. Increasing acceptance of contracts and joint ventures between universities and private firms has made it more financially rewarding for professors to stay at their posts. A second area of tension is patents and the free transmission of ideas and the sharing of knowledge. A balance must be found for science to move forward.

Cell fusion and gene insertion techniques, most notably the well-known Cohen-Boyer breakthrough of the early 1970's, led to investment of large amounts of venture capital in many small "startup" biotechnology companies. A few companies, such as Genentech, are now becoming corporate leaders. Another aspect of this process is the absorption of the startup companies into multinational corporations. Capital-rich multinational corporations have purchased seed companies and biotechnology research outfits and issued contracts to universities for training graduate students, to consolidate their efforts and to position themselves to make the greatest possible gain. They also possess the regulatory experience, legal talent, and political power necessary to protect and advance their interests (Doyle, 1985, p. 112).

In addition to the exterior changes associated with this new technology, there exists a new interior framework that must be placed in historical perspective. That framework consists of major scientific revolutions that have occurred in this century: the splitting of the atom and its results, discovery of the importance of vitamins and minerals in nutrition, the cathode-ray/ computer and its application, the development of space technology, and the new recombinant DNA biotechnology. The overall effect of the first four revolutions led to the expanding knowledge base, which has made the genetic transfer technology simple and easy to perform by large numbers of skilled technicians.

Companies anxious to protect newly developed bioproducts sought the expansion of patent rights and became involved in litigation and lobbying for Federal legislation. New concepts of patent protection have recently emerged, such as transformed bacteria (containing proprietary genes), which can break down compounds in crude petroleum to help clean up an oil spill. Product protection is not new to agriculture, but protection for living processes is virtually without precedent.

Client-oriented research or private sector research is conducted to make profits, preferably in the short term. Product development and protection may conflict with environmental and other concerns. For example, will new herbicide-resistant plants be more or less reliant on chemicals in agricultural production? Likewise, questions have been raised about the efficacy of growing acid-rain-resistant trout in lieu of eliminating the air pollutants responsible for fish kills.

The risks of experimentation are being studied and assessed by public boards, such as that now functioning at the National Institutes of Health (NIH). The NIH guidelines for biotechnology research have been widely copied by other developed nations and are being applied to agricultural research and development. Similar guidelines, voluntary in nature, have been in effect for several years within USDA. USDA has created an Agricultural Biotechnology Research Advisory Committee (ABRAC) to exercise oversight functions and develop new guidelines for environmental release of altered substances. The ABRAC debates and decisions are scrutinized by outside observers anxious to apply the results within the contexts of their own countries.

Who benefits from research? That question has already been raised in the United Nations. In 1983, the Food and Agriculture Organization of the United Nations witnessed a furious debate on this question. Third World nations complained of a stranglehold by Western seed companies on the world's plant and genetic resources, regardless of where they were found. Their fear is that biotechnology companies will engineer crops to be sold as a package of inputs available only from them. The familiar phrase is heard, "we give them our plants, then they sell the seed back to us."

The seed trade industry plays a central role in restructuring research from the public to the private sector. Biotechnology, in the economic sense, is the latest layer of multinational corporate consolidation, involving the acquisition of seed companies, particularly companies

with plant-breeding capabilities. The seed and the undifferentiated animal cells will act as the vehicles for many applications of biotechnology.

Biotechnology is a mobile technology. It can easily move from region to region and across national boundaries. The research is frequently decentralized in many small companies and laboratories under contract from multinational corporations. Other multinational corporations have invested in their own inhouse biotechnology research units. Biotechnology is only now beginning to reach the public eye.

Many environmental concerns have arisen over the consequences to human life of altering the genetic content of the genome, especially in the view of our planet as a self-sustaining, interdependent system. While the word "biohazard," introduced by scientists, has become a commonplace term, few people know that some of the new biotech research has been quarantined on the grounds of safety. Many aspects of the technology have become insulated from the public in the interest of national security. Despite some controversies, biotechnology currently exists in an optimistic phase. No serious accidents have occurred, nor have there been recorded adverse effects.

The alteration of the seed, first through unregulated biological manipulation and, today, under legal protection, is the starting point for the biotech revolution. Before hybridization, seeds possessed the attributes of free goods, imported, exchanged, or sold inexpensively to farmers through seed improvement societies or through State experiment stations. Development of the biologically sterile hybrid facilitated the entry of farm supply companies into plant breeding and other living processes. It is helpful to trace the early accumulation and improvement of seed. Seeds constitute the foundation of plant germplasm on which plant biotechnology rests. Agriculture underwent a revolutionary transformation after hybridization that has led not only to the commodification of seed, but also to expansion of the agricultural input industry to such an extent that it now appears to control much of American agriculture. Today's altered seed requires most other inputs, such as certain herbicides, for best results. Altered livestock also require special chemicals and feeds for best growth.

A significant difference between biotechnology and the technologies that preceded it is the time between a discovery and the opportunity for commercial application. There is often no time lag. Research can flow from the university research center almost immediately to the corporate boardroom. The time in which product applications are conceived, researched, and produced for marketing is compressed, although products will continue to be developed in the long term as well as the short term. Regulatory application and testing are also reduced to facilitate product introduction. However, care is exercised and risks are being assessed in granting permission to release novel organisms into the environment. These factors contribute to the excitement about the new technology.

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Through the Laboratory Historically: The Empirical Basis

Biotechnology includes any technique that uses living organisms or processes to make or modify products, to improve plants or animals, or to develop micro-organisms for specific uses.[2] It focuses on two powerful molecular genetic techniques: induced recombinant deoxyribonucleic acid (rDNA) and cell fusion. Using these technologies, scientists can visualize the gene, allowing them to isolate, clone, and study its structure. Such knowledge and skills give scientists much greater control over biological systems, conferring the potential for significant improvement in the production of plants and animals (U.S. Congress, Office of Technology Assessment, 1986, p. 31). The key word is "technique." It allows a scientist to obtain greater understanding and control over the process of evolution. How and when these techniques came into being and their consequences constitute appropriate historical questions.

Biochemical/Biological Origins

The revolution now in progress began with Swiss scientist, Frederick Meischer (1844-1895) who, in 1869, discovered the nucleic acids (Chargaff, 1971, 1978, pp. 107-108; 1971, p. 638).[3] His writings did not attract much attention.

Using first the nuclei of white blood cells and later the spermatozoa of the Rhine salmon, he isolated DNA. Meischer himself recognized the significance of his discovery, and it was soon followed by the discovery of ribonucleic acid (RNA), produced from constituent DNA in the laboratory of Hoppe-Seyler in Tubingen, Germany. Nevertheless, 75 years passed before the importance of his work began to be recognized. All the chemical substances that constituted the DNA and RNA macromolecule needed to be identified. Their biological functions as carriers of genetic information, their species-specific character, and their detailed structure had to be determined (Chargaff, 1971, p. 638).

Physiological chemistry, as it was called in the 19th and early 20th centuries, was the original domain of nucleic acids, which was taken over later by organic chemistry, and then by biochemistry. By the end of the first stage of the chemistry research, the qualitative composition of nucleic acids was known. Although scientists knew that DNA and RNA were found in all living cells, they did not comprehend the actual structure and function of the molecules. The realization that chemical substances might be responsible for controlling the

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[2]This statement is the broadest of three current definitions. Biotechnology is viewed as aiding animal and human medicine, waste and pollution management, advanced plant breeding, mineral leaching, enhanced oil recovery, diagnostics, and the development of analytic equipment. A second definition places biotechnology in the field of genetic engineering. In this view, biotechnological processes are intended to modify biological systems, regardless of their eventual utility. The basic premise is that biotechnology can be used as much for assisting scientific inquiry as for developing products. The third, or commercial, view, derived from trade publications, is that of "application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services" (Lappe, 1984, pp. 42-43).

[3]The historical explanation of DNA is summarized from this source.

basic biological characteristics of an organism became accepted by the mid-1920's. The key discovery came in 1927/28 from the observations of a British pathologist, Frederick Griffith, who was treating pneumonia patients. One of his patients carried several types of pneumonia-causing organisms instead of a single strain, which was generally accepted as the cause for the illness. The patient's illness seemed to change during the course of the disease. Griffith devised a test to determine whether such a bacterium could change from one type to another. He injected disease-producing (virulent) and nondisease producing (avirulent) cells into mice. The mice received what Griffith believed to be innocuous amounts of dead virulent cells and live avirulent ones. Nevertheless, the animals with both micro-organisms died almost as promptly as those receiving the live, disease-producing cells alone. Thus, the dead, virulent cells had transferred a lethal biological quality to normally nonpathogenic pneumococcal bacteria (Lappe, 1984, pp. 13-14).

Griffith, therefore, had evidence that a chemical substance had transformed a benign bacterium into a pathogenic one. This finding created a resurgence of scientific interest and, by 1930, many believed that a transforming principle was involved. However, the nucleic acids were ignored and attention fell upon other substances (Chargaff, 1971, p. 639).

Oswald Theodore Avery (1877-1955) and coworkers at the Rockefeller Institute published an article in 1944 on the transformation of one pneumococcal-type bacteria into another. The article concluded that a nucleic acid was in fact the agent of transfer. The transformation represented a permanently inheritable alteration of a cell. They were the first to identify the chemical nature of the substance responsible for the change. Their discovery appeared to foreshadow a chemistry of heredity and made probable the nucleic acid character of the gene (Chargaff, 1971, p. 639).

Chargaff surmised there should exist demonstrable chemical differences between deoxyribonucleic acids, since different DNA types exhibited different biological activities. He discovered the ratios in which these constituent amino acids occurred and correctly formulated the notion of base-pairing or complementarity in the way amino acids unite with each other (Lappe, 1984, p. 15).

Studies of viruses and bacteriophages, principally Escherichia coli phages, contributed to the current understanding of recombinant DNA. Experiments by Delbruck and Luria, S.S. Cohen, and Hershey yielded simple and perceivable systems of viruses. They demonstrated that the proliferation of bacterial viruses in the infected bacterial cell was affected solely through the DNA of the phages. These results confirmed Avery's previous seminal observations (Chargaff, 1971, p. 640).

Erwin F. Smith and Charles O. Townsend, working for USDA, made a remarkable discovery in 1907 that contributed to the genetic line of knowledge in agriculture (Lappe, Appendix E). The potential for genetically engineering plants came from controlling organisms that had solved the problem themselves. The key breakthrough was the discovery that plants are commonly altered genetically in nature in much the same way that bacterial chromosomes can

be integrated with the DNA's of viruses. For plants, a common soil bacterium, Agrobacterium tumefaciens, inserts foreign genes that then produce RNA and proteins totally outside the genetic code of the plant itself (Lappe, Appendix E).

The researchers observed the formation of a growth or plant tumor called a crown gall on a plant at the site of a fresh wound that had been invaded by the A. tumefaciens. Although Smith and Townsend were unaware that they were observing a natural DNA transfer, they were on the right track. Their research was guided by the idea that the cancers they were inducing in plants were related to those in human beings and in animals. For many years, interest in this research was sustained by the American Medical Association, which awarded Smith its certificate of honor, and by the National Institutes of Health, which continued to subsidize his research (Bailey, 1920, p.415; Smith Papers, Box 1, National Agricultural Library, 1991). Smith stated, "My concept is this, that fundamentally plants and animals are alike, that physical and chemical laws apply equally, that is uniformly, to all living things, and hence that discoveries relative to the fundamental cell-mechanics of animals apply equally to plants, and vice versa"(Smith, *Scientific American, Supplement*, p. 42). Smith then advanced his hypothesis that plant cancers and, by inference, those in animal species, were caused by parasites that remained unidentified.

This simple mechanism was incompletely understood in the early 20th century. Today, agrobacter bacteria are used routinely to effect a controlled genetic transfer. The scientist deletes the genes that cause the crown gall disease and substitutes other genes to study.

Researchers still had to identify the molecular structure of DNA and RNA, which produce enzymes that generate the proteins of the cell. The actual mapping of the molecule in accordance with the biochemical evidence accumulated over the past 100 years was accomplished by such pioneers as Watson and Crick, Monod and Jacob, Holley, Nirenberg, and Linus Pauling. By the 1950's, the belief that DNA was the carrier of biological hereditary information was accepted widely among scientists (Chargaff, 1971, p. 640).

The x-ray diffraction work on DNA by Wilkins in London and Chargaff in New York, led Crick and Watson, in 1953, to the accurate construction of the double helix of two intertwined DNA strands held together by specific hydrogen bonds, those predicted by the principles of base-pairing. The model suggested a possible pathway for nature to bring about the replication of the DNA molecule, with the conservation of its innate biological information, based on its nucleotide sequence. Francis Crick brought forward his "Central Dogma" of molecular biology: genetic information moves from DNA to RNA to protein, and thus, directs all vital functions (Chargaff, 1971, p. 641; Kloppenburg, 1985, p. 298).

The double helix structure of DNA helps explain how the copying process works. The pairing between the nucleotide bases is fairly weak, so that the process of cell division causes the DNA to "unzip" down the middle. The result is a pair of separate strands of DNA, each with a series of unpaired bases searching for replacement complementary bases. Since base components will join only with specific component amino acids, each strand serves as a

template, and the end result is the formation of two identical RNA molecules (Elkington, 1985, p. 19).[4]

How are the instructions within this molecular code to be decoded? The decoding or gene expression involves two key steps: transcription and translation. In transcription, the DNA double helix is unzipped near the target gene and a single-stranded strip of messenger ribonucleic acid (mRNA) is synthesized. This mRNA strip is then released from the section of unzipped DNA that it has been copying and is used by the cell's protein factories, the ribosomes, to produce the desired protein. This process is called translation. In the first stage of the division, the genetic message is copied, while in the second stage, the resulting copy is translated into the language of proteins.

Each protein is composed of amino acids. There are 20 different types of amino acids in living organisms, and each amino acid is coded for by three base pairs, called a triplet. Once the protein has performed its task, both it and the mRNA are dissipated and are no longer essential to the chemical process.

There are important differences between the genetic mechanisms of higher organisms (eukaryotes, for example, animals, plants, yeasts, and molds) and lower organisms (prokaryotes, for example, bacteria). The eukaryotic cells possess a cell nucleus containing a number of chromosomes, while the prokaryotic cells have no nucleus and only a single large chromosome which floats freely in the cell. The latter also possess small rings of DNA called plasmids.

Bacteria, with about 1,000 genes, constitute a simpler system to utilize than human cells, which may contain as many as a million genes. However, the structure of bacteria imposes limitations because these micro-organisms cannot add vital sugar groups onto commercially attractive molecules like yeasts. The sugar groups facilitate fermentation.

Proteins produced by transcription and translation perform most of the cell's basic functions. The most diverse kind of proteins are made of enzymes, which act as catalysts to initiate and speed biological reactions. A second group of proteins is used to build cell membranes, and a third group, including hormones, regulates cell functions. Other proteins, like hemoglobin, transport oxygen from the lungs to every cell in the body.

The genetic code remains universal to all organisms. A key technique of biotechnology involves coaxing DNA from one organism to express itself in a totally different organism. This mechanism has made the entire field of genetic engineering possible. Expression can occur when embryonic cell nuclei are fused, agrobacter bacteria transfer a known gene into a plant cell, or a retrovirus performs the transfer in animal cells.

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[4]I am indebted to this author for the simple, yet accurate, description of the information capacity of DNA and for his characterization of transfers, vectors, methods, and cloning.

Yet there are important differences in the way DNA molecules of different species code the start and stop signals that control gene expression. The genetic engineer must hunt for the appropriate signals to insert at the beginning and end of a DNA sequence that has been transferred into a foreign host.

Early in the 1960's, scientists discovered the methods of natural transfer between bacteria. This work was pioneering because it led to many of the current techniques. One method utilizes bacteriophages or viruses that infect bacteria. These phages inject DNA into bacterial hosts, which then pass it forward to future generations as part of the parent DNA. This viral DNA occasionally becomes active and produces new viral particles that burst forth from the host, often carrying particles of the bacterium's DNA with it. Thus, when the fugitive particles infect different bacteria, they may bring along genes from their previous host.

Another route involves direct transfer of genes through "conjugation." One bacterium attaches a small projection to the surface of a second bacterium, and another small projection to the surface of a third bacterium. The DNA passes through the projections from the donor to the recipient with the first bacterium serving as an intermediary. The transfer is made to the bacterial plasmids, not to the bacterial chromosomes. The plasmids are so small that they can pass into and out of cells with relative ease. Once the process was understood, phages and plasmids became the focus of those trying to transfer particular bacterial genes.

Bacterial Breakthrough and Commercialization

Bacteria prove able, much more so than human cells, to cope with intruding DNA. They possess a range of restriction enzymes that chop the DNA molecules where specific sequences of nucleotides are found, enabling them to slice up the intruder while leaving their own DNA intact. A laboratory accident led Salvador Luria to this extraordinary discovery. He discovered the enzymes that splice DNA when he broke a test tube containing one bacterium and borrowed another which contained a culture of a different strain. Herbert Boyer, Stanley Cohen, and Paul Berg enlarged upon Luria's work. In 1973, they spliced a DNA sequence from one organism into bacterial plasmid DNA, and then inserted the plasmid into an E. coli bacterium where it was multiplied and successfully expressed. The commercial importance of this achievement was described in the U.S. Patent No. 4,237,244 issued to them in 1980 for their "Process for Producing Biologically Functional Molecular Chimeras":

> The ability of genes derived from totally different biological classes to be replicated and be expressed in a particular micro-organism permits the attainment of interspecies genetic recombination. Thus, it becomes practical to introduce into a particular micro-organism functions which are indigenous to other classes of organisms (Kloppenburg, 1985, p. 299).

Controlled mutation at the molecular level remained elusive until Cohen and Boyer's successful development of practical procedures in 1973. From that date, events moved rapidly. A rat insulin gene was soon cloned and, 4 years later, the first human insulin made by rDNA

technology entered clinical trials. The convergence of basic and applied research in biotechnology became evident. Large chemical firms recruited the scientific expertise necessary for product development from academe, since the skills did not exist, at first, in corporate labs (Kloppenburg, 1985, pp. 301-302).

Financial incentives were offered to attract genetic engineers, and venture capital was abundant for biotechnology entrepreneurs. In 1976, Herbert Boyer and Robert Swanson founded Genentech, one of the first of over 110 similar companies founded during 1976-84 devoted to commercializing the advances in genetic technology. Venture capital and university scientists founded Agrigenetics, Advanced Genetic Sciences, DNA Plant Technology Corporation, Hybridtech, Molecular Genetics, and Repligen. These firms began to offer stock to the public and had accumulated $2.5 billion in investment funds by 1984 (Kloppenburg, 1985, p. 302).

Restriction enzymes, or endonucleases, are the "scissors" used by genetic engineers to open plasmids and insert foreign DNA. Another group, the ligases, are the "paste" used to glue the molecule back together again. If a nucleotide sequence occurs only once on a plasmid, then the appropriate restriction enzyme will open up the plasmid only once. If it occurs a number of times, the DNA will be broken into several pieces.

By the late 1970's, scores of restriction enzymes had been isolated from bacteria. New companies were set up to hunt for and market these enzymes as tools of the biotechnology trade. The cloning of DNA, involving producing a large quantity of a given DNA molecule by inserting it into a host bacterium, became increasingly routine. Large amounts of purified hormones and new drugs became a reality as a result. The first successful cloning took place in 1973, followed the next year by the first expression (visible alteration) of a gene cloned from a different species of bacteria (Elkington, 1985, p. 22).

Once inside the host cells, the rDNA plasmids replicate themselves again and again. They also replicate lengths of foreign DNA which have been spliced into them. Because the restriction enzymes have cut out various different DNA sequences, only a few of the plasmids will reproduce the desired DNA fragment.

The task of finding and tracking the target sequences remained. One widely used method involved a plasmid called pBR 322. Its virtue lay in its relatively small number of bases (4,300) and in the fact that it contained genes which made its host cell resistant to two antibiotics, tetracycline and ampicillin. If foreign DNA entered either of these genes, then the specific resistance it conferred was lost. The resulting clones could be of three distinct types. One would be resistant to both antibiotics, showing that the plasmid had been inserted unchanged. A second type would be resistant to just one antibiotic, indicating that a plasmid carrying foreign DNA had been inserted. And the third variety would show no resistance to either antibiotic, showing that the plasmid had not been accepted by the host cell. This system could quickly identify clones that accepted the foreign DNA (Elkington, 1985, p. 22).

In 1981, almost 80 years after Smith's study of crown gall disease, scientists finally discovered how to use agrobacter bacteria to successfully insert additional bits of DNA into the Ti plasmid of the plant cells, and to obtain a mature plant. By the end of 1982, genes for at least three foreign proteins were being introduced into plant cells, one from bacteria, one from mammalian cells, and one from plants. When the genetic engineering was successful, the inserted material became a permanent part of the plant's seed, hence, it could be propagated. These experiments made possible the insertion of other genes that would become commercially important. For example, new plant lines could then be created (Lappe, Appendix E.)

Other methods of gene transfer have also come into use. One involves the direct addition of DNA preparations to developing plant embryos during critical periods after pollination. Another approach, favored by the Chinese, applies DNA to cotton embryos which permits selection of genetically altered and more vigorous crop lines. A third approach to plant engineering involves direct manipulation of chromosomes (a synthetic insemination without sperm cells) to induce parthenogenesis and thereby fix desirable traits.

Institutional Mechanisms for the Development of Biotechnology

German universities were the pioneering centers for the early discoveries in the 19th century. As biochemistry evolved, it took root in England at Cambridge University and in the United States within the medical colleges. Pressure to support medical knowledge with a stronger scientific background led to a restructuring of medicine from 1900 to 1930. Biochemistry proved to be a discipline that supplied the medical profession with a more scientific foundation. In American as well as European universities, the biochemists' professional role became teaching medical students and training medical graduates in clinical investigation. Biochemists depended on clinicians for financial and political support, and clinicians depended on biochemists for training and new diagnostic techniques. The biochemists also performed limited, practical research on vitamins in human nutrition (Kenney, 1986, p. 23).[5]

The Office of Scientific Research and Development (OSRD) was created during the early 1940's to advise the military, most notably to perform the Manhattan Project. Biological and medical sciences were organized under the Committee on Medical Research (CMR), which allocated funds for projects to aid the war effort. Although the physicists received the bulk of funds, CMR spent $25 million, over a fifth of which went to malaria research. Successes from these efforts produced a generation of wonder drugs that demonstrated the high value of biochemical research and provided a powerful impetus for continuing such research after the war.

Administrators, such as Vannevar Bush of OSRD and James Conant of CMR, were

[5]I am indebted to Kenney and Elkington for the discussion of the institutional mechanism that perpetuated DNA research.

determined after the war to form a national science agency that would be insulated from political manipulation. They proposed that all Federal funds be directed through a National Science Foundation (NSF) in hopes that science would become self-governing and autonomous. The Truman administration gave medical and public health research national priority. In the 2 years preceding the war, the National Institutes of Health (NIH) budget was about $700,000, with less than a third of that amount awarded in research grants. Private foundations during these years gave $4.7 million for medical research. Aside from a small cancer research program, the Federal medical effort was confined to animal diseases and carried out by USDA. The early work on cancer or crown gall in plants carried out by Erwin Frink Smith in USDA facilities was funded in part by a private foundation, the American Cancer Society.

The NSF was founded and research funds allocated to it in 1950, and a national medical research policy began to evolve. The Federal Government would support both basic and targeted research through NIH. The primary mission of the agency would be the conquest of specific diseases. Federal grants would also support targeted research through agencies with missions aimed at particular problems, and it would support basic, nontargeted biological and biomedical research through NSF. In this essential framework, biochemistry/molecular biology expanded.

NIH-funded research reached the $1-billion level by 1967, an amount which meant that money for virtually every discipline had increased. During the same period, a number of molecular biologists received prizes, and cancer research became increasingly linked to DNA research. The comprehension of DNA progressed rapidly because of the cancer funds available. The search for a cancer cure became the primary justification for molecular biological/biochemical research.

In postwar science, both NSF and NIH funds were allocated to investigators on a competitive basis. Most grants were evaluated on a peer review basis and awarded to the most successful professors. These professors recruited more graduate students and postdoctoral researchers to work on their projects, enlarging the centers for expertise or research empires.

The research fund flow became a continuing concern of scientists, and a suitable framework for protecting the process developed. Before World War II, NIH had conducted its research in-house but, thereafter, the agency became an extramural funding agency as well. The competitive grants programs ensured that the better equipped research facilities would obtain the bulk of the funds. From 1972 to 1981, the top 20 institutions received 51 percent or more of the total extramural funds. A series of causes, probably including the peer review system, the annual Federal budget cycle, and others, combined to produce a tendency toward short-term projects. The grant application process could also be time consuming, taking as much as 30 percent of the research time (Kenney, 1986, p. 10). These developments tended to concentrate research at a small number of institutions and contributed to its increased cost.

The scale of NIH and NSF funding facilitated development of a large medical research base

Table 1--Funding of NIH viral oncology (cancer) program

Year	Funding level	Year	Funding level
	Million dollars		*Million dollars*
1965	10.0	1976	101.6
1966	18.6	1977	100.2
1967	19.1	1978	106.7
1968	19.5	1979	110.5
1969	19.2	1980	106.3
1970	21.2	1981	94.6
1971	36.1	1982	87.5
1972	48.2	1983	86.4
1973	64.5	1984	93.3
1974	81.6	1985*	106.7
1975	86.5		

*Funding levels increased thereafter. The National Cancer Institute at NIH, which accounts for the vast majority of cancer funding reported figures as follows: 1987-$134 mil; 1988-$145 mil; 1989-$152.6 mil; 1990-$160.3 mil; 1991-$174.0 mil; 1992-$169.2 mil. Courtesy NCI Budget Office. Source: (Kenny, p. 17).

in the United States and made possible construction of laboratories and research complexes (table 1). The grants process enabled the construction of private organizations such as the Sidney Farber Cancer Institute with its research teams, labs, and grant-writing specialists. The perpetuation of the system was checked in some measure by the requirement that results be publicized to justify refunding. Peer review guaranteed that information flowed within the academic community.

Although competition has been endemic in public research, it is by no means the only driving force. Competition is balanced by the desire to know among those doing the actual investigations. Competition intensified when it became clear that scientists were close to actually mapping the DNA macromolecule. Nevertheless, even during the final phase of discovery, information was shared freely among researchers. The tradition of sharing has undergone a constriction since then.

There is no clear line of DNA research in agriculture, despite the early experimentation of Erwin Frink Smith with crown gall. Smith undertook his investigation during the period of expansion into research which had been initiated by Secretary of Agriculture James Wilson.

Chronology, Part I:
Conventional Biotechnology

1770 Benjamin Franklin sends seeds from Europe (the first soybeans) to colony of Pennsylvania.

1827 President John Quincy Adams instructs consular officers to ship to the United States any useful plants.

1839 Congress appropriates $1,000 fo the Seed Distribution Program, administered by the U.S. Patent Office. Free seed dispersal becomes a popular program until 1924.

1859 Charles Darwin publishes "On the Origin of Species" in London.

1862 The organic act formally establishing the USDA calls for the collection and distribution of exotic seed.

1865 Gregor Mendel presents his laws of heredity to the Natural Sciences Society, in Brunn, Austria. His discovery is ignored.

1869 Swiss scientist Frederick Meischer discovers DNA.

1870 Navel orange is introduced into the United States from Brazil.

1883 The term "germplasm" is coined by German scientist August Weismann.
American Seed Trade Association (ASTA) is founded.

1897 The Congressional Seed Distribution Program reaches its apex.

1900 Science of genetics is born with rediscovery of Mendel's works by Hugo De Vries and others.

1906 The term "genetics" is coined.
Experiments with crown gall disease in plants are underway by Erwin Frink Smith of USDA. Smith is observing naturally occurring gene transfers via bacteria, but he is unaware of the implications of his observations.

1909 The term "gene" is coined and replaces Mendel's term "factors."

1916 George Harrison Shull, corn breeder and genetics professor, begins publication of "Genetics."

Continued--

Chronology, Part I:
Conventional Biotechnology--continued

1918 Donald Jones, contemporary of Shull, invents the "double-cross" (crossing of two single crosses) that renders hybrid corn useful for practical application.

1926 Henry Agard Wallace, future Secretary of Agriculture, founds the Hi-Bred Company, a hybrid corn-seed producer which later becomes Pioneer Hi-Bred International, the largest seed company in the world.

1930 Congress passes the Plant Patent Act, which recognizes the rights of plant breeders for the first time.

1936 USDA Yearbooks of 1936 and 1937 not only sound the first alarm over the loss of important germplasm, but also are the first and the last effort to catalog the genetic diversity available in the United States.

1940 Oswald Avery discovers the "transforming factor" or isolates DNA for the first time.

1947 Geneticist Barbara McClintock discovers that genes possess the ability to move on the chromosome and peform new functions. Scientific community fails to recognize the importance of her discovery.

1953 James Watson and Francis Crick describe the double helical structure of DNA.

1957 The term "agribusiness" is coined by Ray Goldberg of the Harvard Business School.

1958 The National Seed Storage Laboratory (NSSL), the first long-term facility of its kind, opens in Ft. Collins, Colorado.

1961 The International Union for the Protection of New Varieties of Plants (UPOV) is negotiated in Paris, France. The goal of the "Convention of Paris" is to make uniform plant breeders' rights legislation throughout the world.

1970 The Southern Corn Leaf Blight sweeps across the South, destroying 15 percent of the U.S. corn crop.
Congress enacts the Plant Variety Protection Act (PVPA) to extend patent protection to plant varieties reproduced sexually by seed.

1972 The National Academy of Sciences releases its report "Genetic Vulnerability of Plants," which is publicized in the mass media.

Wilson authorized the USDA purchase of a 300-acre experimental farm in Arlington, VA, in 1901 (now site of the Pentagon) and, in 1910, a 475-acre compound for animal and dairy research at Beltsville, MD (Kerr, p. 40).

Cancer research on animals at USDA was small, compared with allocations for biomedical research through NIH and NSF. Yet, a second stream of research expertise that was to merge into present agricultural biotechnology existed since the turn of the century. This was the tradition of genetic improvement through animal semen and plant seed that has formed the cornerstone of land-grant/experiment station research. The plant breeder has been the most visible achiever. The plant breeders, agronomists, and other applied biologists were largely unaffected as the biogenetic and related fields expanded during the 1950's. Genetic research, which produced the new, revolutionary techniques for manipulation of genes at the cellular level and through the plant plasmid, made DNA research possible not only at the top universities, but also at the land-grant/experiment station institutions, though the latter were slower to become involved. Discoveries made outside of the land-grant institutions in the 1960's in cutting, splicing, and constructing DNA sequences in vitro led, in the 1970's, to attempts to reintroduce DNA into living organisms (Kenney, 1986, p. 22).

The Boyer-Cohen experiment, performed in 1973, is considered the event that began the economic development of biotechnology processes. Boyer not only founded his own biotechnology company, Genentech, but his experiment raised the question of the risks from biotechnology. Boyer and Cohen demonstrated that they could move genes from organism to organism so simply that even high school students could do it (Kenney, 1986, p. 23). They did so by fusing the nuclei of living cells. A new industry was born, along with a new necessity for regulatory mechanisms to safeguard the environment and public health.

The Work and Continuing Effects of the Medical Research Council Laboratory of Molecular Biology

As scientists gravitated toward private companies or created their own, basic research continued within public facilities, becoming increasingly sophisticated with the expanded knowledge base. Foremost among the public institutions was the Medical Research Council Laboratory of Molecular Biology (LMB) associated with the Cambridge University Medical School and located near Cambridge, England (Elkington, 1985, pp. 25-30). Established in 1947, the LMB became a pioneer and home for a succession of Nobel laureates. Here, the final mapping of the double helical structure of DNA occurred, in 1953, by Watson and Crick, concluding the quest begun by Meischer in 1869. The x-ray diffraction techniques, developed in the same year by John Kendrew and Max Perutz, greatly simplified the determination of protein molecules and amino acids. By using heavy metals in his analytical technique, Kendrew could determine structures of still larger molecules. He determined the structure of myoglobin, a protein that stores oxygen in muscle tissue, and Perutz did the same for hemoglobin. For this achievement, they received the Nobel Prize in chemistry in 1962. Since then, many more proteins have been mapped out.

The final description of DNA created excitement among scientists, similar to that of the Manhattan Project shortly before the development of the nuclear bomb. Investigations led to discoveries by Crick and Sidney Brenner of the triplet nature of the genetic code and to messenger RNA, the derivative of DNA. Simultaneously, at the Cambridge University Department of Biochemistry, Frederick Sanger worked to determine the chemical formulas of protein molecules. Sanger succeeded in determining the sequence of amino acids in the insulin molecule, for which he was awarded the 1958 Nobel Prize for Chemistry. These discoveries were cumulative in their overall effects. The new methods for determining structure, coupled with advances in microbial genetics and biochemistry, were merged into the field of molecular biology. Thereupon, the Medical Research Center decided to combine Perutz's and Sanger's efforts into a single new laboratory, the LMB, which was expanded in 1962 to include the existing biochemical and biological facilities. The merger of facilities reflected symbolically the origins of molecular biology in biology and in biochemistry.

The discovery of new methods in turn led to fresh approaches and to still newer methods by which the knowledge base grew rapidly. At LMB, Sanger discovered a way to determine the sequence of bases along nucleic acids that allowed genes to be mapped out, making possible a new approach to genetics. Before this breakthrough, geneticists could only infer the structure of genes from actual crosses. Sanger's methods allowed scientists to use direct chemical analysis. These methods have now been universally adopted. Nearly 2 million nucleotide sequences are now known, including the complete sequences of some viruses.

Discoveries at LMB challenged other groups of scientists working in the United States in the same area. Choh Li's group at the University of California, Berkeley, determined the structure of the pituitary hormone ACTH. Vincent du Vigneaud did the same for the simple molecules, oxytocin and vasopressin, which he went on to synthesize. Oxytocin, the first hormone synthesized, brought him the Nobel Prize in 1955. Li isolated human growth hormone in 1956, and in 1970, he synthesized it from 256 amino acids.

Summary

The discovery and mapping of rDNA took a long, circuitous path through physiological chemistry, organic chemistry, biochemistry, and molecular biology. In agriculture, the early experiments of Smith were germane to DNA research, but were not focused on discerning the actual mechanics of heredity. Early curiosities, such as the agrobacter bacteria investigated by Smith and the Griffiths phenomenon, constituted the first puzzles which, now that rDNA is better understood, have contributed to the international efforts in research currently underway. While the initial experiments were performed with public funds and by the land-grant system as well as by biochemistry and molecular biology departments of other major private universities, no group of institutions were the sole founders. The Cohen-Boyer genetic experiments in 1973 led directly to the current pursuit of genetic transfer in both higher and lower organisms by genetic engineers in commercial and university labs.

Large pharmaceutical firms with animal divisions, such as Lilly and Merck, were quick to

grasp the importance of product development in agriculture and in veterinary medicine. A wide array of low-volume/high-value products, from pharmaceuticals such as hormones, insulins, interferons, vaccines, and antibiotics to specialty chemicals such as food additives, enzymes, pheromones, amino acids, and pesticides, are being created and sold. Other active properties of micro-organisms are also of interest, such as designed plant symbiotic microbes with enhanced nitrogen fixation capabilities and frost inhibition effects. Engineered micro-organisms are expected to be used in mineral leaching in mining, in facilitating oil recovery, in degrading pollutants and toxic wastes, and in transforming biomass feedstocks into substrates for the production of commodity chemicals and single-cell proteins (Kloppenburg, 1985, p. 299).

Plants, animals, and humans have become the material of the genetic engineer as well. Techniques of superovulation and embryo transfer are changing the genetic composition of dairy herds and other animals, while scientists look forward to designing new breeds using the new genetic information obtained through cell fusion techniques. Chimeras and transgenic livestock (animals produced by interspecies crossing or acquisition of new genes to the germline) are perceived as the first proofs of modification and as indications of what lies ahead. Yet, predictions about the development and use of livestock are difficult. Before gene insertion in farm animals becomes commonplace, scientists must first understand how the inserted genes work, and how promoters and enhancers (DNA segments which regulate genetic activity) will alter gene expression. They must also understand tissue-specific expression of a gene of interest and must isolate and determine the functions of genes that control physiological processes important for production. A greater knowledge of the genome (the total genetic content) of the animals chosen for gene insertion is needed. Each transgenic animal possesses the potential of becoming a new strain. The location of inserted genes needs to be related to the other genes in order for one to understand the effects of repositioning. The stability of gene expression must also be explored. Finally, some feel that the scientist has a responsibility to educate the public and regulatory agencies so that informed decisions about the usefulness of genetically engineered livestock can be made (Rexroad, 1986, p. 128).

Plant breeders are working to incorporate foreign genes into economically important species to improve photosynthesis, stress tolerance, nitrogen fixation, and herbicide resistance. Plant tissue culture offers promise of moving the production of some crops out of the fields and into the factory. Development time of new varieties with these value-added characteristics is likely to be reduced. The broad applications of biotechnology are evident by the large number of products that can be generated. The industrial sectors that will be affected by biotechnology account for a substantial percent of the annual American gross national product. Annual worldwide sales of bioengineered products are estimated to reach $40 billion by the year 2000 (Kloppenburg, 1985, pp. 300-301).

The current trend indicates that the private sector is taking the lead in commercializing research now that the technology has been created and worked out in detail. This process is not unusual. Public knowledge and information becomes a foundation for those with the resources to build an industry of salable products. What perhaps is unique is the

commodification of living processes themselves. Agriculture is being altered by the inputs, such as seeds, animal stocks, fuels, and fertilizers, as well as by the substitutions, like high-fructose corn syrup for cane sugar, new animal feeds, synthetic fuels, and feed stocks, that are created by biotechnology. The transformation is likely to have significant effects on the agricultural sector.

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Seed Research in the Public Sector: Variety Improvement Before 1935

The history of American agriculture began with the cultivation of plant seeds and animals, and with subsequent genetic refinement over the past two centuries. Ours is a world of plant immigrants including maize, beans, and squash brought to North America by the Indians (Rasmussen, 1975, p. 94).[6] Likewise, Native Americans were plant breeders for thousands of years, taking the better seed and mixing it with their neighbors' varieties. Immigrants brought seed with them from other parts of the world until North America possessed tobacco, rice, sugarcane, hemp, melons, fruits, and nuts. Kloppenburg describes the process for plant improvement. A parallel involving animal improvement might also be drawn.

> Absent a total crop failure, they [American farmers] selected the best individual plants to be saved as seed for the subsequent year's planting, a process known now as simple mass selection. Insofar as they augmented their planting stock with seed from other farmers or newly arrived immigrants, they were providing the conditions for natural crossing and the generation of additional variability for successive cycles of selection. Though unaware that they were "breeding," farmers were engaged in building an adapted base of germplasm for American agriculture. (Kloppenburg, 1985, p. 75).

The Accumulation of Germplasm

Biotechnology, no matter how ingenious the genetic manipulation and production of interspecies life forms, will continue to rely on the rich varietal germplasm of plants and animals for its success. The collection and perpetuation of this genetic base has been the work not only of farmers and agricultural societies, but also of public institutions in America, such as the U.S. Department of the Treasury and the U.S. Department of Agriculture (Clay, 1900, p. 642).[7]

Elkannah Watson, founder of the Berkshire Agricultural Society, prevailed upon Secretary of the Treasury William L. Crawford to request foreign consuls and naval officers in 1819 to act as conduits of exotic seed (Baker, and others, 1963, p. 4). Both Thomas Jefferson and

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[6]An indirect result of the Lewis and Clark expedition was the accumulation of germplasm--the Osage orange (which, by midcentury, had become the principal fencing tree), the Oregon grape, the golden currant, the western snowberry bush, varieties of beans, corn, and flowers. The nursery business benefited from these and other seeds, as did agriculture. (See Gates, The Farmers's Age, p. 296; Rasmussen, Yearbook, 1976, pp. 17, 21-22.)

[7]Undoubtedly, the germplasm base of livestock was improved and expanded from 1820 to 1880 (see Rossiter, 1979, p. 8). There were significant losses as well in the early 1800's. For example, the Narragansett pacer, an excellent saddle horse, was bred during the 18th century. It was small, hardy, and noted for its comfortable gait and fleetness. Yet, after the American Revolution, the pacers diminished rapidly in number, and by 1800, the breed was practically extinct. They had been exported to the West Indies, perhaps faster than they were raised (see Bidwell and Falconer, 1985, p. 113).

William Crawford understood the importance of plant collection and species evaluation for the future of the Nation and encouraged acquisition for many years. During this period, germplasm was viewed as a free good. By 1819, a patent act had been in existence for 30 years. However, no legislator presumed the act would be applied to plants (Kloppenburg, 1985, pp. 78-80). The free-good view of germplasm was widely accepted in this country for over 100 years.

One of the first steps toward permanent public intervention in the collection and preservation of germplasm occurred when Crawford decided to issue a circular calling for seeds on March 26, 1819. The circular specified plants that could be useful, were previously uncultivated, or were of superior quality. This action led eventually to a large public commitment to agricultural research and the accumulation of germplasm, which was carried out by USDA.

No expenditures were authorized for seed collections by consuls and naval officers, but a second circular (1827) provided detailed instructions for the preservation and shipping of seed. The Navy proved very cooperative and launched special expeditions for seed gathering. These efforts were facilitated by Henry Ellsworth, Commissioner of Patents during 1836-49, who believed novel plant varieties to be as valuable as new mechanical inventions. First voluntarily, and then with Federal funds, he collected many varieties of plants and seeds that were distributed by members of Congress and agricultural societies (Baker and others, 1963, pp. 4-6).

Ellsworth ensured the success of his program by dispersing exotic varieties of seed on his personal initiative. These varieties were widely distributed to farmers under the postal frank of sympathetic congressmen. Use of the mails for such a purpose was innovative in those days, years before parcel post was established for other items. When Ellsworth left the Patent Office in 1849, 60,000 seed packages were being sent out annually (Baker and others, 1963, p. 6; Paul Gates, 1961, pp. 14-17).[8]

After Ellsworth's retirement, the Patent Office was moved from the U.S. Department of the Treasury to the U.S. Department of the Interior, yet the seed distribution program was unaffected by the change in location to Interior. Ellsworth's successors obtained a growing appropriation for seed collection and distribution. Over 1 million seed packages had been sent out by 1855. A substantial supply of foreign germplasm was obtained and broadly distributed in the United States (Baker and others, 1963, p. 8; Kloppenburg, 1985, p. 8).

The process of species diversification fell also to farmers who molded the genomes into useful forms through trials and species evaluation. Since botanical knowledge was limited, distributing exotic seed to farmers was the best way to develop adapted and improved crop

[8]Ellsworth was fortunate in having Charles L. Fleischmann, a German immigrant, as a coworker. During the 1840's, they collaborated not only in the seed distribution program, but also in efforts to further enlighten Congress on scientific agriculture. Fleischmann also became influential in obtaining Merino sheep and Shorthorn cattle for breeders in the United States.

varieties (Kloppenburg, 1985, pp. 83-84).

Foreign seed provided the opportunity for natural cross-breeding with established varieties so that, even when individual introductions were unsuccessful, they left a useful legacy of genetic variability. Natural cross-breeding made possible the spread of crops to new areas by a few adaptive varieties. From 1839 to 1859, the wheat center (statistically speaking) moved from western Pennsylvania to western Ohio, and the crop took on the resemblance of one native to those newly planted areas after only 20 years. Individual farmers developed improved cultivars, the most famous being Red Fype wheat, Grimm alfalfa, and Rough Purple Chili potato. These plant germplasm sources derived respectively from Poland, Germany, and Panama (Reitz, 1954, p. 108).

By 1800, a group of naturalists recognized that cross-fertilization could be used to produce a new plant variety, and a few of them actually performed the practical application over the next 50 years. These were the men who, as large growers or farm property landlords, formed the backbone of the agricultural societies. They supported agricultural education and research, hoping to increase profits and to raise the status of agriculturalists. The obvious economic motivation was augmented by the interest in science applied to agriculture, which was fostered by the publication, in 1841, of *Organic Chemistry and Its Applications to Agriculture and Physiology*, by Justus Liebig. The work was particularly appealing to growers in the Eastern United States, who were suffering from increasing soil infertility (Rossiter, 1979, pp. xii-xiii, 3). By 1850, private societies and journals were campaigning for elevation of the Patent Office's Agriculture Division to departmental status and for the establishment of agricultural colleges. Over the next decade, several agricultural education institutions were founded: in Michigan, 1857; in Iowa and Minnesota, 1858; in Pennsylvania and Maryland, 1859; and in New York, 1860 (True, 1900, p. 162).

From Seeds to Scientific Agriculture

Lobbying efforts of the agricultural societies and journals succeeded in creating the U.S. Department of Agriculture in 1862. With the South out of the Union and western worries assuaged through passage of the Homestead Act, the Morrill Land-Grant College measure became law. Establishment of many new colleges was delayed by the Civil War, and those which came into existence encountered difficulties. The colleges also experienced tensions between interests that advocated scientific versus practical research. Nevertheless, an institutional foundation had been created in which agriculture and science were joined. A binding of USDA and the new colleges had begun (Eddy, Jr., 1957, pp. 58-66; Kerr, 1987, pp. 9-11).

USDA was created with the idea that the collection and dissemination of germplasm would be a major activity (Baker and others, 1963, p. 14). Isaac Newton, the first Commissioner, authorized expansion of the propagation garden and initiated formal bilateral exchanges of seeds with foreign governments. His efforts were perpetuated by successors. As the population moved westward following the Civil War, interest in crops and varieties suitable to

arid regions of the Great Plains and the Southwest assumed particular importance. From 1860 to 1900, the wheat center again moved west and north from Ohio into Minnesota as well as the Dakotas and Nebraska, which became major producers of newly introduced varieties of wheat. Chinese and African germplasm brought sorghum cultivation into Kansas and Texas, and forages, like Japanese lespedeza and Johnson grass from Africa, facilitated livestock production. The navel orange, sent by the Brazilian consul in 1871, established the basis of the California citrus industry. USDA encouraged trials of virtually every world crop of any economic importance, and remained identified with these efforts until late in the 19th century (Reitz, 1954, p. 253).

Passage of the Hatch Act in 1887, which established State agricultural experiment stations, usually in conjunction with land-grant institutions, facilitated the arrangement of a regular program of plant and seed distribution by USDA. Commissioner Norman Colman expressed the hope that the experiment stations might do the testing and experimental work "for the whole body of agriculturalists" (Kloppenburg, 1985, pp. 91-92). In reality, the relationship between USDA and the experiment stations remained limited, with deference paid to the prerogatives of individual institutions. The experiment stations themselves had limited contact with farmers (Kerr, 1987, pp. 20-21; Marcus, 1985, pp. 216-19).

By 1893, a challenge to the established seed program was given by the Secretary of Agriculture, J. Sterling Morton, who recommended that USDA withdraw from the seed "business" and reduce the budget for germplasm distribution by 75 percent (Kloppenburg, 1985, pp. 91-92). Seeking to bolster the position of the emerging seed industry, Morton stated in his first annual report that the Seed Division had outlived its utility (*Report of the Secretary*, 1893, pp. 20-21; Baker and others, 1963, p. 34). The seed industry he favored consisted of small dealers in vegetable and flower seeds, which found a market among urban dwellers whose numbers were increasing through migration and immigration. Representatives of 34 companies met in New York City in 1883 to form the American Seed Trade Association (ASTA) (Kloppenburg, 1985, p. 99-100; Pieters, 1900, pp. 559-560). However, Morton's clash with Congress over seed distribution was unsuccessful, and since the program was popular with the public, record numbers of seeds were distributed in 1897. USDA seed purchases, through competitive bidding, quality testing, and widespread distribution, ensured a superior product at reasonable cost. The program, by virtue of its popularity, had become an institutional obstacle to the expansion of private enterprise in the seed business. By the end of the 19th century, a State presence was firmly established in the plant sciences, resulting from the collection of germplasm and research, which was not profitable for private industry, but was essential to both agricultural and industrial progress (USDA, *Annual Report*, 1887, pp. 653-654).

Developments in Science

At the turn of the century, developments in science, such as the rediscovery of the Mendelian ratios, transformed plant breeding from a preoccupation of farmers to that of scientists. Concerned about stagnant agricultural productivity from 1900 to 1930, nonfarm business

interests advocated agricultural science and the mechanization of agricultural production. These efforts boosted legislation that provided space for basic agricultural research. Later interventions in agriculture by the New Deal greatly strengthened the capacity for agricultural research (Kloppenburg, 1985, pp. 101-102).

Before leaving office, Morton recommended the use of the new experiment stations, run by scientists, to evaluate seed. Plant introduction activities of the Patent Office and by USDA had transformed many of the world's botanical species into American crops. Continuous infusions of germplasm were necessary as crops spread out or as disease or pests rendered other varieties obsolete. The free seed program was no longer serving the purposes for which it had been initiated. Thus, the new Secretary of Agriculture, James Wilson, sought to uncouple the congressional distribution from the scientific collection, evaluation, and dissemination of foreign germplasm (Kloppenburg, 1985, pp. 102-103).

Wilson established the Seed and Plant Introduction Section within USDA in 1898 to coordinate plant exploration and introduction activities. Professional botanists were employed. The "golden age of plant hunting," initiated with N.E. Hansen's journey to Russia, began in 1898. His was the first of 48 excursions spread over the next 25 years. Most exotic germplasm collected flowed to the experiment stations as Morton had wished, yet substantial portions also went to individual farmers for trial--339,442 packages in 1916 alone. Both the stations and farm experimenters continued to employ the same methods of breeding as before: simple mass selection. The new phenomenon of hybridization as an addition to selection began to arouse interest at the stations about 1890. Worldwide interest in the promise of this new technique prompted the Royal Horticultural Society of England to organize a conference on the subject in July 1899. Notable American agricultural researchers presented at the conference, including H.J. Webber of USDA's Plant Breeding Laboratory, Liberty Hyde Bailey of Cornell University, and W.M. Hays who represented U.S. agricultural experiment stations.

Papers published in 1900 by European botanists, Hugo de Vries, Carl Correns, and Erich Tschermak, confirmed the rules of heredity originally proposed by Mendel. W.J. Spillman, wheat breeder at the Washington State Experiment Station, was also close to an independent "rediscovery"of the Mendelian ratios. His paper in the following year helped ensure rapid acceptance of new theories in the United States. At the second International Conference on Plant Breeding and Hybridization in New York in 1902, William Bateson, who shortly conferred the name genetics upon the new science, advocated hybridization as a means of controlling changes in plants (Mayr, 1982, p. 727). W.A. Orton, a USDA cotton breeder, had just developed a hybrid, wilt-resistant cotton variety (Proceedings, 1905, p. 204). Some scientists began to visualize plant varieties as fluid groups rather than as fixed forms of chance origin. Germplasm was recognized as capable of being molded in a predictable fashion through hybridization. This new notion was very similar to the change in perspective occurring now under the impetus of the biotechnological revolution.

The new vision and excitement gave rise to creation of the American Breeders Association

(ABA) in 1903 by Hays, Bailey, and Webber, acting on the suggestion of Secretary Wilson. Wilson, intent on strengthening the scientific work of USDA, centralized plant-related work in the Bureau of Plant Industry in 1901. As first chairman of the ABA, Hays believed that scientists were on the threshold of controlling the breeding of plants and animals. He called for the active cooperation, through the mechanism of the ABA, of State scientists and private enterprise. This cooperation would become a key issue of agricultural research policy with the development of hybrid corn. Namely, which group was to serve the other? (Kloppenburg, 1985, p. 108).

Agitation among farmers for legislation ensuring high seed quality began during the period of Populist revolt and continued for a generation into the Progressive Era. Farmers had become dissatisfied with the quality of purchased seed. Responding to farmer pressures, 11 States passed laws during 1899-1908 to protect seed quality (Kane, 1964, pp. 161-166). Watson S. Woodruff, president of ASTA, denounced seed legislation as "one of the most serious matters for consideration that our Association has ever had to face" (ASTA, 1910, p. 23). Nevertheless, for the first quarter of this century, the seed lobby was unable to make its influence felt, while the States were free to move deeper into plant breeding. Also, important private interests, such as railroads and banks, favored expansion of public agricultural research (Kloppenburg, 1985, p. 113).

Railroads and much of the banking industry depended on agricultural productivity and total output for revenues. These revenues had risen substantially through increases in cultivated land and application of farm machinery during 1870-1900. After 1900, growth began to slow. The U.S. position in international trade became a concern. Both the national interest and the specialized interest of railroads and banks were perceived as best served by improving the lives of American farmers. Recommendations of the Country Life Commission, organized during this period, relied on the use of science and education to accomplish this task. Adoption of improved farming practices and new technologies was believed to be the best means to expand the commodity volume. The General Education Board (Rockefeller Foundation), encouraged the land-grant institutions to adopt agricultural demonstrations and a systematic approach to extension work (McConnell, 1953, p. 25).

Private firms took the initiative ahead of USDA with their own extension programs, with the railroads being the most active. They used demonstration trains, such as the Burlington and Rock Island (B&RI) "Seed Corn Specials," which stressed use of better plant varieties. During 1904-11, the B&RI trains covered over 35,000 miles, often carrying Iowa State agronomists who lectured farmers at every small town and hamlet connected by track. Demonstration work was initiated among blacks in the South in 1906 by the General Education Board and USDA at Tuskegee Institute, AL, through T.M. Campbell and George Washington Carver. Passage of the Smith-Lever Act in 1914 institutionalized the county agent program into the Federal system, enabling private industry to reduce its educational efforts (Schor, 1982, pp. 32-33; Scott, 1962, pp. 3-8; True, 1928, p. 279).

Completing the Land-Grant Triad: Teaching, Research, and Extension

With the passage of Smith-Lever, the mechanism for the transfer of practical scientific knowledge from the agricultural college and experiment station to the farm, the triad of land-grant education was now complete (Kellogg, 1967, pp. 191-192; McConnell, 1953, p. 32; Schor, 1982, pp. 154-55).

The easier transfer of knowledge was no guarantee of immediate productivity increases. Though farmers were willing to experiment with innovations and new seeds, experiment station research tended to focus more on immediate practical applications than on more theoretical work. The public research was a function of farmer demands, which frequently caused resentment among scientists who felt their potential was being ignored (Kerr, pp. 1987, 48-49; Rosenberg, 1976, p. 156).[9]

Scientists were feeling the constriction of immediate applicability of their research, even before passage of the Smith-Lever Act, and they began lobbying for more freedom of research through the land-grant college association. This effort resulted in the Adams Act (1906), which specifically appropriated funds for original research and empowered the Secretary of Agriculture to ascertain how the money was used. USDA enforced the Adams Act through the Office of Experiment Stations, but change came slowly. Popular pressure for practical results was not easily resisted. One of the hopes expressed for the Smith-Lever Act was the freedom from practical research diversions.

Despite the Smith-Lever Act, though, funds remained short and scientists' efforts were aimed at business interests, from whom support was necessary for additional funds. The tight funding situation was alleviated in 1925 when Federal funds to the experiment stations were tripled by the Purnell Act. These funds were not reserved strictly for basic research, but nevertheless helped to create "significant institutional and financial space . . . for agricultural research which was relatively autonomous" (Kerr, 1987, pp. 68-70; Kloppenburg, 1985, pp. 118-119).

Progress in Experiment Station Research

Even with the research mechanism in place and the opportunity established, the biological sciences were still relatively young. The new science of genetics required further sophistication before findings could be applied to breeding practice. The old method of plant improvement, that of varietal introduction, still prevailed, although by 1905, E.M. East had begun his studies on inheritance at the Connecticut Experiment Station. A visit by M.A. Carleton to Russia early in the century yielded a group of wheats, known as hard wheats, for

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[9]A second generation of scientists employed by the experiment stations were more numerous, sophisticated, and specialized in agricultural disciplines than were their predecessors. This cohort demanded greater research opportunities.

purposes of milling and export. The Karkov variety was growing on over 21 million acres in the United States by 1921 (Galloway, 1912, p. 116; Klose, 1950, p. 43.).

Although the experiment stations still used imports to improve crop varieties, and the farmer continued as before in the plant breeding process, experiment station breeders were also developing more sophisticated techniques. E.M. East discussed the works by well-known naturalists on the transmission of biological traits, and George Shull began studying quantitative inheritance in corn. The practiced method of breeding in 1900 was single-line selection, which was the segregation and reproduction of seed from single plants. The seed was applied through continuous selection to subsequent generations, with attention to the value of the variance revealed in the populations. Usually a plot of 100 plants constituted a standard (Clark, 1937, p. 219). In experiment station research, the method became linked with the Mendelian analysis of hereditary differences, and hybridization became more common in conjunction with selection (Simmonds, 1979, p. 213).[10] Two varieties were crossbred, and new genetic variability was generated by the combination of resultant hereditary characters. Single-line selection was then applied to the progeny of the cross. An important advance was the discovery that characteristics could be transferred from one variety to another by a modification of this approach called a "backcross." Through this technique, an elite variety was crossed with an exotic variety containing genes for resistance to a disease that previously rendered the elite strain susceptible. The progeny of the cross was selected for possession of the characteristic and mated again to the elite variety. The process was repeated until a new variety was created that contained all of the elite characteristics plus disease resistance.

The practical manifestation of Darwinian and Mendelian thought in the backcross method profoundly affected plant breeding. This method proved too time-consuming for most farmers to employ. As the complex nature of the chromosomal basis of heredity became revealed through research, an understanding of such genetic features as linkage, multiple and modifying factors, and factor interactions became necessary for the breeder. The development of sophisticated statistical methods made biostatistics (biometry) vital for the analysis and interpretation of experimental results. Plant breeding became less of an art and more of a science. By 1920, the breeding of rust-resistant wheats involved knowledge not only of the chromosome but of the number of chromosomes and their genomic relationships.

With the new knowledge came a new perception of plants by breeders. The move from selection to hybridization shifted the focus from the whole organism to its constituent genetic parts, that is, upon one gene rather than upon the whole plant. The breeder now wanted exotic germplasm with specific genetic traits that could be transferred to established varieties. The new view became important in the development of plant breeding in this country. The breeder's task shifted from adaptation of elite germplasm from other countries to improving established varieties through incorporation of exotic characters.

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[10]The definition of hybrid evolved in meaning from simple cross-breeding or sexual combination of two varieties of plant or animal to a combination of two inbred lines, as in "hybrid corn," after 1935.

Plants originally considered of no intrinsic value became very important if they possessed certain desirable characteristics. Plant exploration continued as before throughout the 1930's. The new collection, however, tended to be described in terms of particular characteristics of germplasm. That is, the collectors preferred useful genes over useful plants. The introduced-strain method of producing new varieties gradually began to yield to the hybridization method. Experiment stations continued to promote distribution of new varieties to farmers. The Wisconsin Experiment Station established a State Cooperative Experiment Association of about 1,500 university graduates who in 1910 agreed to multiply and disseminate newly released varieties. Their organization became a model for the "crop improvement associations" created during 1915-30. Such associations were closely allied to the colleges and experiment stations. A legal framework of "seed certification" provided for inspection and regulation of seed production. The college-grown seed varieties thus became available as certified seed and served agriculture well.

Public Research and the Private Sector

Seed companies were deliberately absent from these associations as part of experiment station policy. Private companies were free to purchase certified seed from crop improvement association growers. But public breeders were unwilling to allow seed companies to become the exclusive conduit for dissemination of their work to the farming community. Public breeders were actually setting the benchmarks of quality. The association of "certification" with "quality" tended to level prices among different varieties. Certified seed reduced the possibilities for product differentiation.

Since the new breeding techniques came from publicly sponsored research, the crop improvement associations established the International Crop Improvement Association (ICIA) in 1919 to protect the interests of seed growers on a national level. ICIA possessed an influence sufficient to counter that of ASTA. If private companies wanted to pursue the new methods, they would have to obtain breeders from the public sector. Without legal protection for newly developed varieties, there would be difficulty obtaining adequate returns on research investment. The seed companies were locked into a subordinate position in the seed industry. Their position grew worse during the 1930's as farmers reduced their purchased inputs further during the Depression (*ASTA*, 1934, p. 56). Subsidized seed distribution during the Depression came from grain handlers rather than from seed dealers.

Plant Research and the Depression

Although advances in plant breeding were being made from 1900 to 1934, there was no dramatic rise in productivity. The new varieties, while not generally raising average yields, were facilitating the movement into new areas, such as wheat into Kansas, Colorado, and Oklahoma, cotton into the Texas High Plains, rice into Louisiana, and soybeans into the Midwest. Nearly 40 million new acres were brought into cultivation after 1917 in response to rising prices and the production drive by cooperative extension services (Saloutos, 1982, p. 3). Problems of disease necessitated a search for resistant strains. The effect of plant breeding

merely ensured the maintenance of previous production levels. Also, not all research brought progress.

The benefits from agricultural research were called into question by farmers as high prices for crops began to come down after 1920. Opposition to research reached Congress by 1932, at the height of the Depression. Items in the USDA budget, which appeared earmarked for scientific work, were attacked. Over-production was viewed as a curse created by the scientist. The new Roosevelt administration inherited a budget low in funds for research and was not immediately inclined to increase those funds (Pursell, 1968, p. 231).

The new Secretary of Agriculture, Henry A. Wallace, as a plant breeder, founder of the first hybrid seed-corn company, and editor of the influential journal *Wallace's Farmer*, viewed science as beneficial and as a possible solution to the Nation's agricultural distress. "Give Research a Chance" was written for the *Country Gentlemen*, in which Wallace warned of the consequences if research was neglected (Wallace, 1934b, pp. 5-6, 34, 36). The article moved Congressman James P. Buchanan, Chairman of the House Appropriations Committee and member of the Agriculture Committee, to favor allocations for fundamental research and freedom for Wallace to formulate his own program (Kloppenburg, 1985, p. 137). The Bankhead-Jones Act of 1935 authorized an additional $20 million during 1935-40, for research into the basic problems of agriculture. The act also gave funds for nine regional research centers and strengthened the Extension Service (Kerr, 1987, pp. 217-220).

Breeders could account for the characters of 350 corn genes and could map the location of 100 genes on the chromosome by 1936. The rediscovery of Mendel's theories around 1900 had brought about the promise of a new way to alter plants, and the promise was realized through hybridization by 1935. Once the hybrid became widely accepted as a production success, publicly sponsored research became legitimized and permanent (Jenkins, 1936, pp. 455-522).

From 1935 to 1970, production yields dramatically increased for wheat, cotton, soybeans, and corn. Such production increases rendered New Deal-era programs inadequate to slow the economic consolidation and migration among farmers. Nor could production controls, from the Agricultural Adjustment Administration to the Payment-in-Kind program in 1983, cope successfully with changes derived from the agricultural research centers. Yet, the results of the publicly sponsored research for the good of all, as perceived by plant experts, ensured that plant breeding would no longer remain exclusively within the public sector. Nor could public breeders sustain a disinterested attitude toward their work.

Gradually, the tension between the scientists' desire to pursue basic research and the need to produce results of value to farmers was replaced by a tension between basic research and the need (driven by needs for funds) to produce results of value to seed companies and other private firms that sought to exploit the results of biotechnological research—a tension that continues to the present.

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Biotechnology:
The Parallel and Precedent of Hybrid Corn

Hybrid corn was an important breakthrough for agricultural science. Public science's focus on the hybrid paved the way for private industry seed sales. In a larger sense, publicly sponsored research and development on hybrids created the environment for biotechnology.

Neither public nor commercial breeding had a significant effect upon the varieties grown in American cornfields before 1934. Farmers were the principal breeders. They mixed the varieties at hand (Northern Flint and Southern Dent landraces), which were genetically derived from varieties used by the American Indian. These crosses of two distinct gene pools produced a reservoir of corn germplasm from which a great variety of plants could be extracted. Rigorous mass selection by farmers proved sufficient to produce a large number of varieties exhibiting different characteristics and adaptability to different areas.

Corn expanded in importance from 1866 to 1900. Total acres planted tripled and production quadrupled. Chicago replaced Cincinnati as the primary processor of agricultural and animal products. Corn became a mainstay of the Midwestern economy, increasing interest among both land-grant personnel and commercial seedmen. Railroads, during the first decade of the 1900's, presented farmers with demonstration trains or "seedcorn specials," equipped with displays and plant breeders, and the "corn show" also became popular. The latter were contests in which representatives from experiment stations and college departments of agronomy judged upon the best corn. A complex hierarchy of shows, from the local to the national level, had evolved by 1908. The shows, sponsored by grower associations and companies such as Armour and International Harvester, offered expensive prizes of farm equipment to the winners (Robinson and Knott, 1963; Wallace and Brown, 1956).

The purpose behind the corn shows was to encourage farmers to adopt better varieties by providing tangible examples. The shows were very successful in achieving this end. Winning samples of corn received high prices as seedstock (Sprague, 1955, p. 224). Ironically, the success of the education program ultimately led to a reduction in corn yields, because many of the characteristics of the winning corn emphasized aesthetic qualities, traits not necessarily correlated with yield or other economically important characteristics (Hayes, 1963, p. 26).

The shows encouraged farmers to adopt better varieties, but they ultimately encouraged genetic uniformity, which, in this case, reduced vigor. From 1900 to 1935, corn yields gradually declined. Scientists began to recognize this effect after 1910. Yet, the corn shows had developed a momentum among farmers, county agents, and academicians. Breeders took several approaches to reverse the decline, but none proved effective due to the natural outbreeding proclivities of the corn plant. Once a superior variety had been developed, outbreeding with other varieties in the field made it impossible to permanently fix its characteristics. Likewise, inbreeding reduced vigor and yield. Thus an impasse, either apparent or real, in corn breeding had been reached (Simmonds, 1979, p. 152).

One notable achievement in American agriculture during the bleakness of the Depression was the development of hybrid corn. It continues to be considered, by plant scientists and agricultural experts, as one of the most successful examples of applying science to farming.

Production figures for hybrid corn remain impressive. Corn yields increased sharply after hybrid seed became available commercially in the mid-1930's. The shift from open-pollinated to hybrid varieties was completed by Corn Belt farmers in a single decade and, by 1965, over 95 percent of American corn acreage was sown with hybrid seed. Corn output increased by over 2.3 billion bushels from 1930 to 1965. This production increase occurred despite a reduction of over 30 million acres of land on which corn was grown.

Yet, when one considers the broader effects of hybrid research, hidden costs emerge that lead to a changing evaluation of hybrid success. Similar costs apply when assessing agricultural biotechnology (Doyle, 1985, pp. 32-45; Kloppenburg, 1985, p. 145).[11] In assessing the value of hybrid corn, it is necessary also to consider the costs of abandoning productive routes other than the hybrid route in the improvement of corn. Alternatives to hybridization were available. One prominent method was population improvement of the open-pollinated varieties. According to Richard Lewontin, geneticist at Harvard University, immense effort went into obtaining higher yield hybrids. However, "virtually no one has tried to improve the open-pollinated varieties, although scientific evidence shows that if the same effort had been put into such varieties, they would be as good as or better than hybrids by now" (Lewontin, 1982, p. 16). Others believed that hybrids would achieve high-yield levels more quickly than the open-pollinated varieties. The crucial difference between the open-pollinated varieties and the corn hybrids was that the former could be replanted, while the latter could not without considerable yield reduction. The hybrid effectively uncoupled a seed's use value from its exchange value. Open-pollinated varieties yielded seed to the corn farmer, while new hybrid seed had to be purchased every season for best results (Berlan and Lewontin, 1983; Simmonds, 1979, p. 159).[12]

Hybridization boosted the role of private enterprise in plant breeding and seed production. From 1934 to 1944, hybrid seedcorn sales went from zero to over $70 million as a wide variety of new and established companies entered production. Seedcorn became the seed industry's mainstay and, by 1981, accounted for nearly half of the $4 billion in annual American seed company sales (Davenport, 1981, p. 9; Steele, 1978, p. 29).

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[11]I am again indebted to Jack Kloppenburg (pp. 145-210) for the discussion presented in this chapter. It has been condensed, modified, and slightly reworked.

[12]Simmonds argues that the development of hybridization in corn was the result of historical accident, simply that ideas about hybrids developed at the moment at which progress by other methods seemed poor. Thus, hybridization was pursued as the result of objective scientific assessments by individual breeders that this route held out the most promise for gains in productivity. On the other hand, Richard Lewontin and J.P. Berlan maintain that hybrids opened up great profit opportunities and, for this reason, efforts were shifted to the new technique.

Early Discovery of the Hybrid Among Academic Breeders

An American botanist, James Beal of Michigan State University, first used "detasseling" of corn plants to control pollination and produce a hybrid cross. He recorded yield increases as high as 50 percent in 1877, but his work went unnoticed. Cyril G. Hopkins developed an early, pure-line breeding system that established inbred lines in hybrid corn late in the 1890's. Since the hybrid is the result of inbreeding, or self-pollination of the plant, and crossbreeding using inbred lines several generations old, the final product is referred to as the first-generation or single-cross hybrid (Doyle, 1985, p. 37).

Two experiment station researchers, Edward Murray East and George Harrison Shull, set out to overcome the problems associated with inbreeding and yield. In 1905, they discovered that crosses between inbred lines produced heterosis or "hybrid vigor" (Doyle, 1985, p. 37; Schapsmeier, 1968, p. 29).

Another practical problem remained for the scientists. Small hybrids did not offer enough seed. This problem was solved by the double-cross method. In 1917, Donald Jones, a student of East, took the seed of two single-cross hybrids and crossed them with good results. The double-cross produced yields 20-25 percent above the yields produced by open-pollinated varieties, with large, regular kernels that could be used and sold as hybrid seed (Doyle, 1985, p. 38; East and Jones, 1919, pp. 195-210).

From Laboratory Curiosity to Hybrid Power: Pioneer and DeKalb

Some farmers and businessmen, such as Henry A. Wallace of Des Moines and Tom Roberts, the DeKalb County, IA, farm advisor, simultaneously were experimenting with corn breeding. Encouraged by his father, who was to become a Secretary of Agriculture, Henry A. Wallace, a high school student, began to experiment in 1904 (Schapsmeier, 1968, pp. 18-19).[13] After graduation from Iowa State College in 1910, he began writing for *Wallace's Farmer* and followed the work of Shull and East. By 1913, however, he had temporarily abandoned the hybrid quest, concluding that the process was "too laborious." Then came the Jones breakthrough using the double-cross method in 1917. This development encouraged Wallace to use some inbred lines developed by East and others in Connecticut. He crossed these with Midwestern corn varieties and, by 1924, produced the Copper Cross hybrid, which was the first hybrid to be developed for sale in the Iowa Corn Belt. In the first year, his output totaled 15 bushels of seed, which sold for $1 each (Doyle, 1985, pp. 38-39; Schapsmeier, 1968, p. 27).

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[13]In 1904, Dr. Holden, a plant breeder in USDA, gave the young Henry A. Wallace some of his elite corn and asked the youth to ascertain its productive capacity. Wallace discovered that there was no relationship between yield and appearance. Wallace verified that the productive capacity of the plant lay within its kernels, not the appearance. At that time, his experiment had little effect on prevailing beliefs. In asserting that Wallace was "one of the first to recognize the principle of controlled heterosis--the hybrid vigor--for plants other than corn and also for improvement of animals," the Schapsmeiers overstate Wallace's contribution.

The Connecticut work of East and others had a great effect on private breeders Henry Wallace and Eugene Funk, who recognized the commercial promise of the double-cross. On wartime special assignment to USDA in 1917, Funk secured a special appropriation for the establishment of six Federal field stations for research into corn diseases. The first of these field stations was located on Funk Farms. In 1919, Funk set his principal breeder to develop inbred lines in what he hoped would be proprietary hybrids (Crabb, 1947, p. 210).

The Jones double-cross hybrid was not the only method of developing vigor in plants. Another promising method involved production of an improved variety by inbreeding and crossbreeding. This method was a refinement in the open-pollinated approach. It entailed the self-fertilization of plants once or twice, selecting those lines for desired characteristics, intercrossing these superior lines in bulk, and continually repeating the process (Hayes and Garber, 1919, p. 313). This method is what is now called recurrent selection and forms the basis of contemporary methods of population improvement (Hallauer and Miranda, 1981; Kloppenburg, 1985, pp. 164-165; Simmonds, 1979). Unlike the double-cross, the population improvement route results in a superior plant population that replicates the seed, which can then be replanted without loss in vigor.

By 1918, Henry A. Wallace used the influential *Wallace's Farmer* to advocate the double-cross by publicizing and praising scientists who were pursuing hybrid research. Yet, more than media pressure was necessary to make hybridization central to public corn research (Kloppenburg, 1985, p. 105). The principal agronomist at USDA, C.P. Hartley, was opposed to hybrids, as were most researchers at the various experiment stations, while the extension agencies generally favored the corn show as the route of progress. With the election of Warren G. Harding as President in 1920, hybrid research received more favorable treatment within USDA. Henry C. Wallace, Henry A. Wallace's father, was appointed Secretary of Agriculture. Once in office, father deferred to son on the matter of corn breeding conducted by USDA. F.D. Richey was researching hybrids and replaced Hartley as principal Agronomist in Charge of Corn Investigations in 1922. In office less than 2 months, Richey issued a memorandum to researchers urging investigations based on self-fertilized corn lines. Inbreeding projects were expanded, especially in the Corn Belt. The increased hybrid research proved indispensable for development of new plants. The Purnell Act of 1925 gave Richey both the institutional authority and the financial strength to organize his initiative into directed scientific inquiry. Richey appointed a committee to formulate a national corn breeding program in 1925, and the Maize Genetic Cooperative Groups were formally established in 1928. Yet, superior hybrid lines were still not as available as open-pollinated varieties (Crabb, 1947, pp. 247-248; Jenkins, 1937, p. 21; Simmonds, 1979, pp. 147-148).

Ten research leaders, in different locations, were responsible for investigating one of each of the 10 gene linkage groups then known to corn. A wide variety of inbred lines were adapted to different areas, and effective methods of predicting their performance and combining ability were discovered, simplifying the problems of test-crossing and evaluation. Purnell funding allowed Richey to support hybrid development, while bypassing departments within USDA and the land-grant system that resisted the new direction taken by research

(Kloppenburg, 1985, pp. 165-167; Sprague, 1983, p. 61).

Henry A. Wallace established the first seedcorn company in America, Hi-Bred Corn Company, in 1926, later to be renamed the Pioneer Hi-Bred Corn Company. Tom Roberts and Charles Gunn also experimented with hybrid corn lines. They started in 1923 and maintained secrecy for 5 years, while Gunn proceeded with inbred lines. Their secrecy was aimed at upstaging a potential competitor, William Eckhardt, who also had an established seed business in northern Illinois (Crabb, 1947, pp. 157-158; Doyle, 1985, p. 39).

By 1935, public agencies had developed hybrids that produced 10-15 percent higher yields than open-pollinated varieties. These plants were a result of 10 years of intensive research and the application of large human and financial resources. Their evolution also entailed abandoning the open-pollinated approach of plant improvement.

The sale of hybrid seed had begun to prosper by 1935. The DeKalb Agricultural Association sold 15,000 bushels of hybrid seed in 1935, and production of seedcorn increased exponentially during the next few years as DeKalb expanded into other States. By 1940, more than 4 million Corn Belt acres were planted with DeKalb hybrids. One hybrid in that year, DeKalb 404 A, was planted on 2.5 million acres and was credited with advancing the Corn Belt 200 miles to the north. Pioneer and DeKalb, selling through farmer-dealers, became the most powerful companies in the industry for the next 40 years (Doyle, 1985, p. 40).

Only breeders who knew the parent lines and breeding sequence were able to make the high-yielding hybrid. This knowledge was legally protected as a trade secret. More important to the seed company, farmers could not save and replant the seed, because hybrid vigor was lost. Farmers had to purchase new seed every year, and did so willingly, because the yields offset the prices they paid (Doyle, 1985, p. 42).

Gradual acceptance in the 1930's became total adoption in the next decade. One percent of Corn Belt acreage in 1933 went to hybrids. By 1944, the acreage had reached 88 percent. Per-acre yields increased dramatically. The hybrid persisted and went unquestioned until the 1970 blight.

Indirect and Unanticipated Consequences

As agriculture moved from open-pollinated diversity to hybrid lines, the varieties carrying open-pollinated characteristics began to disappear. The genetic base for corn had been narrowed. Many scientists and breeders became concerned, including Henry A. Wallace. Nevertheless, hybridization had initiated a trend that had spread to livestock as well as other crop species (Doyle, 1985, pp. 42-43; Horsfall, 1975, pp. 109-110).

As early as 1920, Wallace became interested in breeding hybrid chickens. His son, Henry B. Wallace, offered hybrid chickens commercially in 1942. DeKalb followed 2 years later with its poultry breeding program and marketed "DeKalb Chix" in 1948. The Pioneer hybrid

"Hy-line" layers were bred for reduced body weight, superior shell strength, size, and egg yield. The broilers were bred for more efficient feed-to-meat conversion, better hatching ability, and superior growth rates. By 1977, more than 1.2 million white-egg and brown-egg laying chickens were produced for about $25 million in net sales. DeKalb applied hybrid techniques to hogs, and Pioneer applied them to cattle. Hybrid crops, however, remained the most lucrative area for both companies. Both companies applied their techniques to other crops, such as sorghum, alfalfa, sunflowers, and cotton (Doyle, 1985, pp. 43-44).

The 1950's and 1960's were decades of large sales of hybrid sorghum, a popular new feed grain first hybridized in Texas in the 1940's. DeKalb initiated its sorghum program in 1956. Farmers accepted the new product more quickly than hybrid corn. By 1960, 70 percent of all sorghum acreage went to hybrid varieties. Pioneer introduced its hybrid lines in the early 1960's and, by 1970, the two firms dominated both hybrid corn and sorghum markets. Pioneer had also begun its hybrid alfalfa program (Doyle, 1985, p. 44).

Wheat was considered for hybridization, yet the nature of the self-pollinating wheat flower made controlled crossbreeding even more difficult than for corn and sorghum. DeKalb began its wheat hybridization program in 1961, however, and Pioneer and other firms followed in 1969. DeKalb invested $25 million over the next 20 years to produce high-yielding varieties, but by 1982, decided to abandon the effort. DeKalb moved into hybrid sunflower breeding in 1979, and Pioneer moved into hybrid cotton in 1975. By the mid-1980's, these two seed industry leaders were selling hybrid seed throughout the world. Thus, hybridization actually revitalized a whole commercial industry based on the seed, created a niche for proprietary rights short of patenting, and gained predominance as the tool of plant science (Doyle, 1985, p. 45). Although the hybrid vogue may have peaked during the 1980's, these effects continue to be felt.

In the 1920's, many experiment stations and land-grant college administrators believed that farmers could produce their own hybrid seed with the support of public agencies, and short courses for farmers interested in breeding hybrids were held in Iowa and Wisconsin (Sprague, 1980, p. 2). Other States adopted a similar support mechanism, and as a result, many farmers were able to produce hybrid seed for themselves and their neighbors. The hybrid seed corn market was no longer in the hands of a few private companies.

As long as hybrid corn derived from publicly developed varieties, which breeders were compelled to use, prices and profits would remain low (Jenkins, 1937, pp. 455-522; Sprague, 1980). Private research programs were expensive and had to compete with public corn breeding programs. One answer for private industry was to place a proprietary designation on the public lines it used for breeding. This approach was taken by the mid-1930's, and one immediate consequence was that hybrid producers restricted information about breeding lines by declaring them trade secrets. A well-known corn breeder, Merle T. Jenkins, complained publicly about such restrictions as early as 1936 in the *Yearbook of Agriculture* (Jenkins, 1937, p. 479).

This trend continued into the 1940's, creating further friction between public and private breeders, each with a different mission and sense of responsibility. Private breeders realized that assuming the task of developing the finished varieties from the public sector would increase profits. The development of efficient methods during 1930-46 made such applied research less expensive and haphazard. In 1942, a seedsman told the North Central Corn Improvement Conference:

> If our experiment stations will devote their energies to the advancement of fundamental research, they have it within their power to provide a basis for future progress in technical and practical corn breeding. . . around which active interest and cooperation of the entire hybrid industry, big and small, can rally and develop (Kloppenburg, 1985, p. 176).

The quotation is important because the same call to deflect public research from competition in product development with the private sector has been advanced ever since. In the 1930's and 1940's, there was no institutional mechanism in place to accomplish this goal. To create it, the America Seed Trade Association (ASTA) initiated the annual "Industry-Research Conference," beginning in 1946, to bring public and private breeders together to exchange views. This process led to the establishment, in 1952, of the Agricultural Research Institute as part of the National Science Foundation. Its charter members came from industry, public research, and Government, and the official purpose was the integration of public and private research. Representatives of private industry also began attending meetings of the International Crop Improvement Association, the American Society of Agronomy, and the American Society for Horticultural Science. These organizations provided institutional forums from which a new relationship gradually emerged. Congress and the public were pushing public research institutions to coordinate their work with private industry to make the best use of public research dollars. Also, scientific disciplines were interested in keeping practitioners in both spheres aware of each other's work (Kerr, 1987, pp. 89-101, passim).

Public plant breeders gradually accepted the reorientation desired by private breeders. The process was accomplished over the ensuing years, but not without some resistance from public breeders who believed that applied research programs of the experiment stations should not be eliminated merely to solve a marketing problem in the seed trade, and that farmers should continue to benefit from public research (Kloppenburg, 1985, p. 178; Porter, 1961, p. 213).

From 1937 to 1941, experiment stations released 336 hybrids. The number fell to 113 during 1942-49, and none were released thereafter (Kloppenburg, 1985, p. 180). Reductions of cultivated varieties had nearly ceased by 1970. Smaller suppliers and individual farmers were left with a declining supply of open-pedigreed public varieties and eventually had to leave the business or become linked with larger firms connected in some way to sources of supply. Few firms could afford the large research programs necessary to maintain the supply. By 1980, eight companies controlled 72 percent of the seed corn market. The public hybrid releases, which had previously acted as a restraining force on market prices, ceased to exist. The

private sector controlled the nature and direction of research.

In the final sense, breeding has value only if the fruits can be applied to production in some way. With the seed companies producing commercial hybrids, private enterprise imposed itself between public research and the seed consumer. The public research product entered into the process only so far as the companies chose to utilize it. Public breeders recognized this and had to adjust their research agendas accordingly. If they had not done so, their research results would probably have gone unused.

The effect of this new relationship was illustrated in corn breeding, which experienced a resurgence in population improvement techniques after 1950. In the 1920's and 1930's, ways to improve plant varieties were through inbreeding and hybridization, but a stabilizing of yields by the late 1940's seemed to indicate the need for other approaches (Hallauer and Miranda, 1981, p. 8; Huey, 1961, p. 11; Sprague, 1983, p. 62; Steele, 1978, p. 32).[14] The narrow pool of elite inbreeds required a boost from open-pollinated populations in order to increase yields. Many sophisticated techniques for the upgrading of open-pollinated populations have evolved since 1950. Again, the prospect of stable, superior commercial corn varieties that farmers could replant was raised. It was suggested that these products could yield as much as the conventional hybrids and were less costly and more reliable in areas of variable conditions. Yet, an alternative approach to the hybrid route was never seriously considered except by developing nations whose farmers could not pay for hybrids. Population improvement continued to be subordinated to the dominant hybrid model. Nevertheless, population improvement made substantial inroads. The technique moved forward and so improved inbreds that, since 1965, single-cross hybrids have replaced the double-cross varieties. Thus, the inbreeding of new hybrids using the population improvement techniques remained a public function, but would not displace the hybrid seed (Zuber and Darrah, 1980, p. 241).

Contributions beyond the essential germplasm and population improvement continued to be made by the public research sector. One contribution was the elimination of manual labor in the corn-detasseling process. In postwar America, labor costs for detasseling increased rapidly. D.F. Jones used the cytoplasmic male sterility factor (CMS) to prevent the outbreeding of hybrids (Jones and Everett, 1949). Jones proposed incorporation of these CMS factors into female parent lines and the incorporation of "restorer" genes into male parents. All female plants produced were sterile, which eliminated the need for manual detasseling. The seed industry adopted the process, and by 1965, nearly all hybrid seed corn production used this technique. Don Duvick, president of Pioneer, estimated that in 1965, over 3 billion plants with the CMS character were grown. This cut the requirement of labor for detasseling by 125,000 workers. The reduction of labor, however, was not accompanied by lower seed prices for farmers.

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[14]Kloppenburg (1985) shows (pp. 164-165) that Jones was aware of the value of the population improvement technique but chose to follow the hybrid approach. Jones knew that the hybridization would lead to commercial application in the short term and became its advocate.

Other Effects

Hybrid corn facilitated the expansion of other branches of the agricultural inputs sector. From the 1940's onward, machinery and agrochemicals accompanied hybrid seed for maximum efficiency and yield. Not only was the machinery tailored to suit the corn, but the corn was bred to suit the picker. By shaping the plant to the machine, breeders facilitated the use of pickers and combines. Thicker stalks reduced lodging, but they also made hand-harvesting more difficult. The number of acres harvested mechanically rose steadily from 1930 to 1950, with the benefits flowing to those farmers able to purchase machinery. Genetic technology was not scale neutral and resulted in the displacement of a large number of hired laborers (Crabb, 1947; Macey and others, 1938).

Before 1945, agrochemicals applied to corn were negligible. Military needs during World War II created a vast fertilizer production capacity, especially for nitrogen. The annual meeting of the American Society of Agronomy (ASA) in 1942 anticipated the problem of surplus fertilizer production. Increasing the farmers' use of commercial nutrients seemed to be the profitable answer. ASA president Richard Bradfield told plant scientists that at least twice as much nitrogen would be available after the war and at far lower prices (Bradfield, 1942, p. 1070).

However, the hybrids used in 1944 were not suited to the different levels of fertility made possible by fertilizer application. They responded by developing weak stalks, and lodging (tendency of the stalk to bend) again became a problem (Steele, 1978, p. 32). During this period, yields had leveled off from overreliance on a narrow range of inbreds. After 1953, the market for hybrid seedcorn was reaching its peak as the amount of corn acreage planted to hybrids topped 90 percent (table 2). Breeders were faced with pressures to put excess fertilizer capacity to use and to address the reality of a maturing seed market (Kloppenburg, 1985, p. 192).

These factors resulted in the new population improvement and inbred extraction programs, which ran throughout the late 1950's and 1960's. As seedcorn sales and use increased and plants were grown closer together, other agrochemicals besides fertilizer were required. Farmers turned to pesticides, fungicides, and herbicides to sustain their yields. The widespread use of these chemicals became a major factor in shaping our present agricultural system and also became a contributor to the growth of the agrochemical industry (Pimentel and others, 1973, pp. 443-449).

The hybrid system included the movement of corn into the rapidly growing livestock feed and fattening industry. Low corn prices facilitated development of large feedlot operations and expanded markets for pork, beef, and poultry meat (Perelman, 1977, p. 45).[15] Likewise, corn

[15]Corn that is used for human consumption has not improved in nutritional quality and protein content. It may actually have declined in food value since the elimination of open-pollinated varieties. Hybrids with improved food quality are available, but such hybrid varieties do not yield as well as standard hybrids and present problems for

Table 2--Development of grain-corn acreage, yield, production, prices, and selected uses, United States

Year	Acreage harvested	Yield per harvested acre	Production	Season average price per bushel	Feed use	Exported	Acres planted to hybrids
	Million acres	*Bushels*	*Million bushels*	*Dollars*	*Constant 1967 dollars*	*-Million bushels-*	*Percent*
1930	85.5	20.5	1,757	.60	1.00	NA	NA	0.1
1935	82.6	24.2	2,091	.66	NA	NA	NA	0.5
1940	76.4	28.9	2,206	.62	1.55	NA	NA	15.0
1945	77.9	33.1	2,577	1.23	1.48	NA	NA	53.0
1950	72.4	38.2	2,764	1.52	1.48	2,482	117	78.0
1955	68.5	42.0	2,873	1.35	1.45	2,366	120	87.0
1960	71.4	54.7	3,907	1.00	1.01	3,092	292	94.0
1965	55.4	74.1	4,103	1.16	1.13	3,362	687	95.+
1970	57.4	72.4	4,152	1.33	1.33	3,570	517	95.+
1975	67.5	86.3	5,829	2.55	1.27	3,570	1,711	95.+
1980	70.1	91.0	6,648	3.27	1.63	4,518	2,355	95.+

NA=Not available.
Sources: U.S. Department of Agriculture, *Agricultural Statistics, 1980*, p. 30; *Agricultural Statistics, 1981*, p. 30; Harvard Business School, 1982; Leath and others, 1982; Sprague, 1967.

exports increased 20 times from 1950 to 1980 (Morgan, 1979). Dramatic corn production increases created the problem of overproduction. Scholars of the agricultural adjustment programs of the New Deal agree that hybrid plantings nullified the effect of production controls on corn acreage after 1940, and encouraged adoption of hybrid seed by farmers (Paarlberg, 1964, p. 675). The link was so direct that Henry A. Wallace, then Secretary of Agriculture, had to answer charges of conflict of interest resulting from his continued association with Pioneer Hi-Bred. The price of a bushel of corn in 1967 constant dollars actually fell after 1940 (table 2). The gains realized by the farmer from increased production

machine harvest. Hence, farmers will not grow them, and seed companies will not produce them.

were largely negated by the added expenses for inputs required by hybrid corn.

Changes in corn culture and widespread adoption of the tractor subjected farmers increasingly to the agricultural treadmill: the cycle of innovation/increased production/depressed prices/further innovation. Farmers on the leading edge of the process survived and prospered, while others experienced a high rate of attrition. The number of farmers in the North Central region, which encompasses the Corn Belt, declined by 35 percent during 1935-60. The number of U.S. farmers (most of them tenants) fell by 62 percent. Regions were affected differently, but corn production has become centralized in the Corn Belt States, of which Illinois and Iowa are the most important producers (Leath and others, 1982, p. 1; Staub and Blase, 1971, p. 120).

Centralization changed farm structure and growing patterns. The early adopters of the new technology absorbed their less innovative neighbors. Specialization created monocultures in certain areas. Many Corn Belt livestock operations were transformed into cash-grain producers. Soybeans, which fixed nitrogen in the soil, initially replaced hay until farmers discovered that with heavy fertilization, continuous corn production was possible. Reliance on continuous plantings of row crops, however, increased soil erosion (Batie and Healy, 1983, pp. 45-53; Ruttan and Sundquist, 1982, p. 83).

Specialization brought additional problems. Continuous row crops exacerbated the problem of soil erosion, and monocultures increased susceptibility to pests and disease, particularly when individual plants were genetically uniform. Hybrid corn, with its narrow genetic base, became increasingly vulnerable to disease. The Southern Leaf Blight made its first appearance in 1970. Corn prices rose 20 percent that year, and losses to consumers and farmers were estimated at $2 billion. Hybridization techniques were found to be the chief cause. Despite the lesson of the blight and the resulting lawsuits by damaged farmers against the seed companies involved, the genetic base of the hybrid, specifically the T-cytoplasm variety, continues to remain narrow (Harlan, 1975, pp. 618-621; Meyers, 1983, p. 17; Sprague, 1972, p. 287; Yarwood, 1970, pp. 218-220; Zuber and Darrah, 1980).

American hybrid technology in corn breeding was transferred to other nations, such as Italy (50 percent of corn crop from two public lines), Mexico, Guatemala, El Salvador, Venezuela, Brazil, Uruguay, Argentina, Costa Rica, Cuba, Colombia, Peru, Chile, and Kenya. Once the hybrid programs were established through the U.S. Agency for International Development and the Rockefeller Foundation, participating countries were obligated to purchase fertilizer and follow established growing methods. The large companies have successfully established themselves in areas where commercial agriculture has provided a market for hybrid corn. Pioneer, for example, markets hybrid corn in over 90 foreign countries and has research centers in 9 of them (Gregg, 1982; Johnson, 1983, p. 157; Mangelsdorf, 1964, p. 46; Sprague, 1967, p. 677).

The hybrid model has played a role in the Green Revolution. American scientists implemented this production method while working in the Rockefeller and Ford

Foundation-funded international agricultural research centers (IARC's). The IARC's are similar to public research agencies in the United States not only in their institutional character, but also in the purpose, orientation, and commitment to client service. The varieties developed by the IARC's followed the pattern established by hybrid corn development in this country, and required the same kinds of plants and inputs (Jennings, 1974, pp. 1085-1088; Plucknett and Smith, 1982, pp. 215-220).

Hybridizing Other Crops

Hybridization has been slow to develop among cereal crops. Costs have been prohibitive for private breeders. The hybrid has had more success with vegetables, particularly the tomato. Discovery and introduction of the cytoplasmic male sterility (CMS) traits, beginning in the 1940's, began a trend in vegetable research. In the early 1950's, a CMS system was applied successfully to sugar beets. For the past three decades, a variety of complex strategies have been used to regulate sexual expression and crossing to produce commercial hybrids in more than 20 species (Frankel, 1983).

Although table 3 shows continued interest in hybridization and commitment of resources, overall progress has been slow. The major trend in horticultural breeding is in the development of hybrids in almost all sexually produced crops (Craig, 1968, p. 246). The economic interests of breeders and the insistence on field uniformity by research engineers and suppliers continue to provide large incentives for hybrid development.

In the 1920's, breeders selected a storm-resistant cotton that held together against the winds on the Texas High Plains. The cotton was responsible for the early success of the mechanical stripper. Plant uniformity of hybrid corn and sugar beets facilitated success of mechanical harvesting. Nonhybrids in beans, tomatoes, lettuce, and many fruits have also been bred for mechanical harvesting. The degree to which a plant can be transformed to fit mechanized specifications is crucial to whether or not the machine can be substituted for hand labor. The union of plant and machine is so well established that the term "phytoengineering" has been coined to refer to it (Wittwer, 1973, p. 69). No estimates have been made of workers displaced by phytoengineering, but the number is assumed to be large. Useful characteristics for machine harvesting include (Kloppenburg, 1985, p. 207):

*Uniform maturity	*Dwarfing determinacy	*Early maturity
*Fruit abscission	*Concentrated fruit set	*Uniform shape of fruit
*Disease resistance	*Blossom abscission	*Uniform plant size
*Fruit resilience	*Slow seed development	*High plant population

The emphasis upon these characteristics limits the achievement of other objectives. Tomato breeder M.A. Stevens stated that the tomato has been bred for disease resistance, while nutritional quality has been an afterthought (Stevens, 1974, p. 87). Mandated nutritional levels in food crops have been resisted by public and private breeders. A 1970 attempt by the Food and Drug Administration to include newly developed varieties within the "generally

Table 3--Selected crops in which hybrid seed is commercially available

Crop	Date hybrid seed available	Hybridization system	Hybrid acreage planted in 1980
	Year	*Type*	*Percent*
Corn	1926	CMS/hand emasculation	99
Sugar beet	1945	CMS	95
Sorghum	1956	CMS	95
Spinach	1956	Dioecy	80
Sunflower	NA	CMS	80
Broccoli	NA	Self incompatibility	62
Onion	1944	CMS	60
Summer squash	NA	Chemical sterilant	58
Cucumber	1961	Gnoecy	41
Cabbage	NA	Self incompatibility	27
Carrot	1969	CMS	5
Cauliflower	NA	Self incompatibility	4
Pepper	NA	Hand emasculation	NA
Tomato	1950	Hand emasculation	NA
Barley	1970	Genetic male sterility	NA
Wheat	1974	CMS/chemical sterilant	NA

NA=Not available.
Source: Kloppenburg, 1985, p. 203.

recognized as safe" (GRAS) classification to prevent decline in nutritional value was dropped after opposition from the plant science community (Doyle, 1985, pp. 148-49; Gabelman, 1975, pp. 248-250).

Hybridization altered the structure of agriculture in corn, influenced the agenda of public research, and removed the farmer from production of the seed to reliance on the commercial firm. Hybridization gave the United States its present corn culture, and is also being expanded through biotechnology. Only the mechanism has changed: new patent protection of living processes has replaced hybridization.

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Legal Protection of Living Processes

The development of hybrid corn not only created vigor in seed corn, but also reinvigorated the seed industry, which became a force in setting the national legislative agenda. The hybrid possesses a built-in protection because only the breeder knows the exact identity of the parent line, which was kept from potential competition as a trade secret. Yet, plants and other food products still remained in the category of free goods that anyone could grow, breed, and improve. Plant breeders were dissatisfied with being unable to patent or receive royalties from their products. During the Depression, Thomas A. Edison urged Congress to extend patent protection to breeders. Edison himself had become involved in some plant research. The 1930 Act protected plants for the first time. After passage of the act, Edison told the New York Times, "Luther Burbank [who had improved about 800 varieties of trees, vegetables, fruits, and flowers] would have been a rich man if he had been protected by such a patent bill" (*New York Times*, May 5, 1930).

Senator Thaddeus Caraway of Arkansas wanted to know precisely the point at which the new plant's identity became the exclusive property of the breeder: "At what stage do they fix their absolute right so that nobody else can further produce [it] or benefit?" The answer offered by a colleague, Clarence Dill of Washington, was that the Patent Office would make the determination, though Dill himself had grave doubts about the constitutionality of the bill. Dill told Caraway that the 17-year protection accorded the breeder acted in the same way as a copyright on which royalties were paid for reproduction or use. Clearly, the senators were well aware that they were involved in a new area of patent protection with which they were unfamiliar and over which they held doubts as to constitutionality (U.S. Congress. House, May 5, 1930, pp. 8391-8392; Senate, May 12, 1930, pp. 8750-8751).

Before 1930, patents for plants were not available in the United States. The legislation was drafted as an amendment to the existing patent laws and introduced in the Senate and House. A minimum of debate characterized the Senate discussions, and despite some objections as to constitutionality, the Senate passed its version on May 12, 1930. A day later, the House took up the Senate bill. With no opportunity for discussion or amendment, the bill was passed by voice vote. Ten days later, it was signed into law by President Hoover (Doyle, 1985, pp. 51-52).

The new law protected only asexually propagated species, those for which budding, grafting, cuttings, and other nonsexual techniques were the means for commercial reproduction. Such crops included most fruits, nuts, and many flowers. The American Seed Trade Association (ASTA) had lobbied to include sexually reproducing species, but legislators were unwilling to provide monopoly control over any food crop. For this reason and because of farmer opposition, the legislators also excluded tuber-propagated species to prevent potatoes from being patentable. USDA had opposed inclusion of sexually reproducing species on the grounds of genetic instability. Paul Stark, a nursery owner and lobbyist who actually drafted the bill, was willing to accept a compromise that allowed limited patents. He advised ASTA's Plant Patent Committee:

> It seemed to be the wise thing to get established the principle that Congress recognized the rights of the plant breeder and originator. Then, in the light of experience, effort could be made to get protection also for the seed propagated by plants which would be much easier after this fundamental principle was established (ASTA, *Proceedings*, 1930, p. 66; Kloppenburg, 1985, p. 219).

Under the terms of the 1930 Act, the patentable products had to be "distinct" and "inherently stable." Seed crops did not possess these qualities. Although fashioned with the breeder in mind, the chief beneficiaries of the legislation were the nursery and flower companies that could obtain patents. Of the more than 5,000 patents granted from 1930 to 1985 for plants such as roses, fruit trees, walnuts, apple trees, lilacs, African violets, mints, and sugarcane, about 70 percent were issued for roses and other flowering plants. Twenty percent were issued for fruits, such as avocados, strawberries, pears, and apples. The rest were issued for poplar trees, evergreens, pecan trees, lawn grasses, and hops. Stark Brothers Nurseries accounts for almost 30 percent of all apple patents, 15 percent of all plum patents, 11 percent of all pecan patents, and 10 percent of all peach patents. Driscoll Strawberry Associates in California holds 30 percent of all strawberry patents, and U.S. Sugar Corporation holds 7 of the 10 patents issued for sugarcane (Doyle, 1985, p. 55).

Other factors after 1940 combined to make private investment in research appealing even though sexually reproducing varieties were excluded under the Plant Patent Act. The rapid growth of State seed certification programs which tested and certified commercial seeds, after World War II, limited price levels throughout the seed market. As profit margins were cut back, some companies established marketing efforts based on uncertified seed displayed with a brand name. This product differentiation proved profitable, and the key to success became a proprietary product coupled with compelling advertising (White, 1959, p. 22). If firms were to avoid violations of the Federal Seed Act of 1939, which prohibited use of synonyms for a single variety, they would have to do research to develop proprietary varieties. By 1950, accumulated knowledge, including new breeding techniques developed at land-grant universities, made the applied work less expensive and results more predictable. Also, a steady stream of germplasm flowed from the public breeders, which, with minor alterations, could become marketable "proprietary" varieties.

A third incentive to private research was the growth of potential markets. Land planted in alfalfa increased from 13 million to 29 million acres during 1939-58, and acreage planted in soybeans increased by 25 million acres. The precedent of hybrid corn encouraged seedmen. Commercial seed enterprises sought to assume functions previously performed by public agricultural science by moving into research and development of private plant varieties during the 1950's. This was especially important to seed companies involved in marketing vegetable, forage, and field crops not amenable to hybridization.

The National Council of Commercial Plant Breeders (NCCPB) was established to promote private breeders' interests in 1954. Its goals were outlined in an address to the Agricultural Research Institute 2 years later by a representative of the NCCPB who complained of

Government breeders "crowding" the commercial breeder, and that public "concentration upon development of new varieties" had produced a competitive situation in which "scientific productivity is not accelerated." Therefore, he reasoned, research for the development of commercial varieties should largely be the responsibility of private firms (Kloppenburg, 1985, p. 222; Quisenberry and others, 1956, pp. 79-80). At issue was the release of finished varieties by public institutions. If the releases were eliminated, private firms with research programs would not only have an advantage over competitors who depended upon the public varieties, but would also be able to influence public research agendas, since basic research in plant variety development had little direct value unless used in applied research.

A second priority of the NCCPB involved efforts to weaken regulatory programs that had disciplined the market and had provided some assurance of quality in commercially available plant varieties. By 1950, many State experiment stations published lists of recommended varieties, and new cultivars were eligible for certification only if they were markedly superior to existing ones. During the late 1950's, the seed industry asserted that certification should be based only on varietal purity and that any determination of quality should be left to the consumer. This approach would remove certification from its association with quality and from its price-leveling effect. It would open up a market based on product differentiation (for example, corn plants with a blue or an orange flower) since the varietal name would be the sole criterion the purchaser would have for distinguishing among different seed varieties. This would facilitate the marketing of privately developed cultivars.

To move public researchers and programs in desired directions, ASTA used the Farm Seed Industry-Research Conference, which was designed, according to a seed executive, to achieve "complete understanding, confidence, and cooperation between science and industry" (Apfelbaum, 1956, p. 58) as a forum. Seed trade members became participants in the annual meetings of the Agricultural Research Institute, the American Society of Agronomy, the International Crop Improvement Association, and the American Society for Horticultural Science. In these proceedings, a division of labor between public and private breeders existed, which was negotiated and renegotiated (Christensen, 1957; Loden, 1963; White, 1959; Porter, 1961).

By the late 1950's, certified seed was losing ground to brandname products for some crops, those not self-fertilizing like wheat and soybeans. Substantial research investments had been made by the big firms associated with hybrid corn and sorghum production. Smaller firms and individual growers found it more difficult to compete and, by 1959, the industry had become more concentrated. The seed department manager of the Tennessee Farmers Cooperative complained that the research giving larger companies their advantage was "nothing more than 'borrowing'. . . what has been developed by USDA and experiment station plant breeders, adding a little private stock in some instances, slapping a fancy label on it, mapping out a Madison Avenue advertising program for it, and putting it on the market" (Little, 1958, p. 131; Porter, 1961, p. 48).

Conditions in the seed industry reflected the changes in agriculture as a whole. Large changes

transforming American farming from a more specialized and highly capitalized business had been accelerating for a decade. Public breeders knew they must adjust to the times. The question of plant breeders' rights arose again but, this time, for sexually reproduced species.

The Convention of Paris for the Protection of New Plant Varieties ratified by European nations in 1961 attempted to provide international uniformity in plant patents, but, paradoxically, it confused the issue of consumer protection. Under the prior European system, seed firms were given patent protection, but new cultivars were required to be superior in order to be sold. Thus, a protection for consumers of seed existed before passage of the Convention of 1961 and the Convention saw no need to address the issue. The American seed industry campaigned for protection without any reference to quality. USDA hoped to ensure consumer protection in plant breeders' rights (PBR) by amending the Federal Seed Act to require compulsory review and registration of all new varieties (Caren, 1964, p. 35). If PBR legislation was to entail a quality control aspect, the seed industry was prepared to resist it (Christensen, 1957, p. 96; Kalton, 1963, pp. 56-57). PBR legislation was justified by seed companies in terms of larger numbers of superior plant varieties derived from increased private investment in breeding, but they opposed institutional mechanisms for ensuring that new varieties would in fact be improvements. To the seed companies, PBR was more marketing than research legislation. The industry also wanted to use PBR as a means to facilitate marketing of proprietary products by preventing public agencies from releasing finished varieties. PBR legislation encouraged private investment in varietal development, making public activities in such applied work seem redundant (Kalton, 1963, p. 49).

Many public breeders accepted the seed industry arguments. They were aware of the significance placed upon "basic" and "applied" research, which indicated the direction of their research. This group believed that basic research meant funding, and funding meant the opportunity to continue experimentation. Many public breeders cooperated as the influence of the input suppliers grew and that of the farmers diminished (Butz, 1960, p. 381; Dorsey, 1976, p. 28; Hanway, 1965, p. 117).

Public breeders' concerns about the impending legislation encompassed protection for publicly developed cultivars, the free flow of germplasm, the use of protected varieties in research, a farmer exemption clause, and for the rights of growers too small to finance breeding programs. In 1967, ASTA supporters introduced an amendment to the original Plant Patent Act to include sexually reproduced plants. The issue came to a head with opposition coalescing from USDA, horticulturalists, the Crop Science Society of America, the Farm Bureau, the land-grant university complex, and small companies without breeding programs (Myers, 1969; U.S.Congress, Senate, 1970). Agriculture Secretary Orville Freeman wrote to John McClellan, Chairman of the Judiciary Committee, stating his objections to the proposed change: "Great difficulty is encountered in keeping a seed-propagated plant true to its original characteristics. Many varieties of crop plants exhibit a change in genetic composition from year to year, so that a variety, in a few years, would no longer even fit the description of the basis on which it was patented" (Doyle, 1985, p. 58). The attempt to expand the 1930 Act failed on this occasion, but the public agencies were persuaded that some form of protection

was inevitable (Kloppenburg, 1985, p. 229; Weiss, 1969, p. 84).

Further meetings were held over the next 2 years by the parties and institutional representatives involved. ASTA drafted legislation known as the Plant Variety Protection Act (PVPA). By its terms, the seed industry would obtain proprietary rights to new varieties, unhampered by considerations of quality. Novelty, uniformity, and stability were to be the sole criteria for patent protection. Public agencies introduced language ensuring that products of their breeding plots were eligible for protection, that farmers could save and replant protected seed and sell to neighbors without infringement, and that protected varieties could be used for research purposes. It was recognized that a system of variety protection would reduce freedom of germplasm exchange (Fortman, 1969; Weiss, 1969).

Once a compromise agreement was reached, the bill went to Congress. In the Senate, testimony took less than an hour, with little opposition. Vegetable canning and freezing interests objected to the legislation. They were concerned that monopoly control of commercial varieties would bring substantial increases in the price of seed.[16] In the House, Rep. Robert Kastenmeier, Democrat from Wisconsin, briefly argued with Agricultural Committee Chairman W. R. Poage, Democrat from Texas, over the issue of inventor concealment. Kastenmeier expressed his concern about increased costs of seed to the farmer, and eventually, to the consumer as well. In the 1980's, the concealment issue would reemerge when it was discovered that publicly funded plant scientists had stopped freely exchanging plant material (Doyle, 1985, pp 308-309). The objections of the canning industry were addressed by excluding six vegetable species from coverage under the act: okra, celery, peppers, tomatoes, carrots, and cucumbers (Plant Variety Protection Act, 84 Stat. 1559, p. 18). Objections of wheat growers for provisions ensuring the maintenance of quality in newly released varieties had no apparent effect on the legislation. President Nixon's new Assistant Secretary for Marketing, Richard Lyng, argued strongly for passage, and according to one observer, "became involved in bureaucratic infighting when the Bureau of the Budget (currently the Office of Management and Budget) threatened to veto the bill" (Doyle, 1985, p. 60, also pp. 62-64; Kloppenburg, 1985, p. 231). The PVPA was enacted on December 24, 1970.

Importance of the Plant Variety Protection Act

If viewed as a marketing act, PVPA was a mechanism for influencing further shifts in public/private divisions of labor in plant-breeding research. Substantial increases have occurred since 1970, both in the number of firms engaged in plant breeding (if not seed

[16]Although spokespersons for the National Farmers Union and smaller companies view the consolidation of the seed industry with concern, pointing to monopolistic tendencies such as the rapid increases in seed prices since 1970, others within the industry find seed companies competitive and domination of the industries by a few companies to be unlikely. However, in the lucrative hybrid corn market, the opportunity for competition is restricted due to the high costs of entry, which pose significant barriers. The total number of seed companies has been declining since 1970, and the trend is predicted to continue (Doyle, 1985, pp. 100-103).

companies) and in absolute expenditures of private funds for research. Although the increases in both areas have been cited by seed industry spokesmen as originating from PVPA, the trends actually began at least a decade before with research on vegetable and forage crops. An examination of increases and shifts in cereals and soybeans reveals the likelihood that such growth in demand would have encouraged greater private investment regardless of PVPA (Kloppenburg, 1985, pp. 232-233). Kloppenburg asserts that research expenditures tended to stabilize after passage of PVPA, with only forages and grasses showing consistent growth (Perrin and others, 1983, p. 29). Thus, the increases in private research because of PVPA appear slight. The conclusion is true for claims of increased choice and better quality. While more choices are available, varieties brought out for sale were not significantly improved (*Industry News*, p. 1051).

The seed industry has unquestionably given farmers more choices, regardless of improvement. Nearly 1,200 certificates of protection had been granted under PVPA by December 31, 1983. The distribution was uneven among the new selections. Five crops accounted for 63 percent of new and protected varieties, half of which were soybean or wheat cultivars. Most private investment was attracted to crops with high potential markets yet to be captured from farmers and public agencies, such as wheat and soybeans, or to crops (peas, beans, and cotton) in industry-dominated markets where varietal competition is more appealing than price competition. Among these crops, the expanded choice was perhaps more apparent than real, representing a genetic "fine-tuning" of elite-adapted varieties (Plant Variety Protection Office, 1984, p. 13). In many instances, private effort went into developing uniqueness/patentability through transfer of noneconomic traits such as flower color. The variety was changed, but not improved. Seed certification officials have noted a trend toward loose and vague variety descriptions resulting from PVPA requirements. Seed company executive Robert Kinsell stated that "it almost seems that we are trying to fill the needs of the law rather than the needs of the public" (Kinsell, 1981, pp. 62, 65).

Farmers have become increasingly concerned and confused by the proliferation of varieties placed on the market. When new patented varieties are nationally advertised, though not necessarily improved, farmers may end up paying more for the same quality seed. Farm organizations such as cooperatives were also hampered by PVPA. In the Delta and Pine Land Company v. Peoples Gin Company, settled in 1982, a Federal district court in Mississippi found an agricultural cooperative in violation of PVPA because it acted as agent for its farmer/members in arranging sales of seed of a ginned cotton crop from one farmer to another (Doyle, 1985, pp. 306-308; U.S. District Court, 1983, pp. 939-945).

Many acquisitions and mergers have taken place within the seed industry since 1970. Many of the companies that acquired seed firms were large, multinational corporations with established agricultural or agrochemical interests. A number of factors contributed to this trend, such as rising commodity prices and export markets of the 1970's, the opportunity to integrate the marketing of agricultural inputs, and passage of PVPA. As part of a large corporate structure, the seed industry now negotiates its interests from a powerful position, a reversal of roles from former times (Roberts, 1979, p. 46).

Among the first to be acquired by the large corporations were the hybrid corn companies, with the exception of the single largest, Pioneer Hi-Bred. Corporations investing in biotechnology acquire marketing networks with such firms, particularly if they possess successful plant breeding programs. Except for Pioneer Hi-Bred, which controls a large percentage of the market, the top 10 companies that account for over 80 percent of the hybrid seedcorn sold in the United States have merged with large corporations (see list).

The argument of industry that PVPA would permit public research stations to direct basic research for plant breeding to important areas that industry did not pursue appears to be true. PVPA reinforced the arguments used by seed companies to encourage public research in areas they desired (Roberts, 1979, p. 215).

Economic incentives, usually in the form of financial grants and contributions, were also used by industry to influence public breeders. Contributions to State agricultural research grew by 63 percent, in constant dollars, from 1966 to 1977. Although private funding is small compared with the total research budget of a land-grant institution, it has greater leverage since so much of the public expenditures goes to fixed items, such as salaries and equipment. Most experiment stations have integrated these grants into existing research programs to avoid disruptions in the overall mission (Kerr, 1987, p. 144; Kloppenburg, 1985, p. 243).

Industry pressure has been successful. A general shift has occurred at State research institutions engaged in forage crop breeding toward the more basic activities of population improvement and germplasm enhancement. The number of finished varieties has been dropping. States have been withdrawing from conventional vegetable breeding and the development of new soybean and wheat varieties. Since 1980, USDA's Agricultural Research Service has been phasing out Federal varietal releases (Leffel, 1981, p. 47; Phillips, 1983, p. 14). The relationship of the land-grant university/experiment station to crop improvement associations ceased to function as a mainstay of the competitive market structure. This occurred despite the fact that public varieties in soybeans, wheat, oats, barley, and rice are still in use (Kloppenburg, 1985, p. 244).

Congress reexamined PVPA in 1980 to determine if any changes should be made. Critics became concerned over the seed industry's concentration as well as the noncompetitive pricing that appeared to be developing. By December 1983, eight corporations, all multinationals, held 35 percent of all PVPA certificates issued. If finished varietal development was left entirely to private industry, public influence over quality would be lost, and small seed companies and individual growers without breeding programs, dependent on public agencies for their products, would have to purchase seed from the multinational corporations. Farmers, as well as small companies, have become much less important in the seed industry. The withdrawal of public agencies from the development and release of cultivars has produced an increase in genetic vulnerability. As early as 1972, the National Academy of Science, in its report *Genetic Vulnerability of Major Crops*, stated that the new law might discourage wheat breeders from developing the genetic diversity concept so necessary in plant pest biological control, merely to satisfy the qualification of uniformity

Selected American seed companies by parent firm

ARCO
- Desert Seed Company

Diamond Shamrock
- Golden Acres Hybrid Seed

Cargill
- ACCO
- Dorman
- PAG
- Paymaster Farms
- Tomco Genetic Giant

Celanese
- Celpril, Inc.
- Moran Seeds
- Joseph Harris Seed Company
- Niagara Farm Seeds

Ciba-Geigy
- Columbiana Farm Seeds
- Funk Seeds International
- Germain's
- Hoffman
- Louisiana Seed Company
- Peterson-Biddick
- Shissler
- Swanson Farms

Lubrizol
- Agricultural Laboratories
- Arkansas Valley Seed
- Jacques Seeds
- Keystone Seed Company
- McCurdy Seed
- Seed Research Associates
- Sun Seeds
- Taylor-Evans
- V.R. Seed
- Colorado Seed
- Gro-Agri
- R.C. Young

Monsanto
- Jacob Hartz Seed Company
- DeKalb Hybrid Wheat
- Farmers Hybrid Company
- Hybritech Seed International

Occidental Petroleum
- Excel Seeds
- East Texas Seed Company
- Missouri Seeds
- Moss Seed Company
- Payne Brothers Seed Company
- Ring Around Products
- Stull Seeds
- West Texas Seed Company

Pfizer
- Clemens Seed Farms
- DeKalb AgResearch (joint venture)
- Jordan Wholesale Company
- Ramsey Seed
- Trojan Seed Company
- Warwick Seeds

Sandoz
- Gallatin Valley Seed Company
- Ladner Beta
- McNair Seeds
- Northrup King
- National N-K
- Pride Seeds
- Rogers Brothers
- Woodside Seed Growers

Shell
- Agripro, Inc.
- H.P. Hybrids
- Nickerson Seed Company
- North American Plant Breeders
- Rudy Patrick
- Tekseed Hybrids

Stauffer
- Stauffer Seeds
- Blaney Farms
- Prairie Valley Seed

Upjohn
- Asgrow Seed Company

W.R. Grace
- Pfister Hybrids
- American Breeders' Service

Source: Doyle, 1985, 100-103; also Kloppenburg, p. 242.

required by the law (Doyle, 1985, p. 68).

The ASTA continued to press for further protection and was successful in having amendments added in late December 1980. These amendments added to the agricultural resource base eligible for private ownership. The language was broadened from specifications, which required detailed alterations, to generalized descriptions of plant varieties protected (U.S, Congress, Plant Variety Protection Act, Amendment, 94 Stat. 3550). Eight months earlier, another decision had far-reaching implications for the patenting of living things.

The Chakrabarty Decision

In 1972, Amanda Chakrabarty, a research scientist with General Electric, filed a U.S. patent application for a genetically engineered bacterium. The action raised legal and ethical questions by scientists and environmentalists regarding the patenting of living micro-organisms. Eight years later, in June 1980, the Supreme Court ruled in favor of Chakrabarty. "The patentee has produced a new bacterium with markedly different characteristics from any found in nature, and one having the potential for significant utility," wrote the court. "His discovery is not nature's handiwork, but his own; accordingly, it is patentable subject matter." In the majority opinion written by Chief Justice Warren Burger, "Congress thus recognized the relevant distinction was not between living and inanimate things, but between products of nature, whether living or not, and human-made inventions" (Witt, 1985, p. 83).

The Supreme Court regarded the bacterium as patentable because it was novel, useful, and had no natural twin. Justice Burger based the Court's ruling on the general patent law, as well as PVPA, to extend plant protection into the world of biotechnology products. Soon after the decision, investment in biotechnology rose substantially, demonstrating the principle that investment follows strong patent protection (Witt, 1985, p. 83). Although the living process in question was a bacterium, the Chakrabarty decision sent the signal for which companies interested in agricultural biotechnology were waiting. Plants, animals, even individual gene sequences could be patented under the same general patent law (35 USC 101 or Section 101) that covered computers, screwdrivers, artificial hearts, and other manmade items. Before Chakrabarty, the Patent Office received 10-20 applications a year in what it specifies as the genetic engineering area. Thereafter, the number increased dramatically. By the end of 1984, more than 2,600 applications were pending. The applications continued to climb, reaching 3,900 by January 1985, 5,773 by January 1986, and 7,821 by August 1987 (Van Horn, 1988; Witt, 1985, p. 83).

After Chakrabarty, PPA and PVPA took on new significance. Under section 101 of PVPA, the distinction between sexual or asexual reproduction became meaningless. Under both PPA and PVPA, the former administered by the Patent Office, the latter by USDA, only single claims are awarded. For each new variety, regardless of the prior technology that created it or the genetic material it possesses, a company must apply for a new claim. If the

item consists of a novel process that introduces foreign genes into crop plants, and if numerous new varieties are produced with it, the patentee must apply for a new claim on each one (Witt, 1985, pp. 83-84).

As a result of Chakrabarty, it is possible to file a single, multiple claim. Multiple claims cover and protect whole plants, parts of plants, and plant processes. According to Anthony Diepenbrock, an expert on plant patents, "you could file for protection of a few varieties of crops, their macro parts (flowers, fruits, seeds, and so on), their micro parts (cells, genes, plasmids, and the like), and whatever novel processes you develop to work with these parts--all using one multiple claim." If awarded this type of claim, the patentee draws a boundary around the given processes and products. Any other corporation that steps over that line, using, making, or selling its own products, can be sued for patent infringement. Enforcement constitutes the most substantive part of Section 101 of PVPA (Witt, 1985, p. 84).

The old limitations under PPA and PVPA permitted researchers to use protected varieties to develop new varieties and granted farmers the right to sell seed to other farmers. As interpreted by the Patent Office, Section 101 not only expanded the reach of protection beyond what PPA and PVPA could offer, but also put enforcement behind its claims. The Patent Office has had no guidance from the court since the Chakrabarty decision. The Supreme Court did not address the issue of whether Section 101 extended to plants. However, Lorance Greenlee, chief patent counsel for Agrigenetics Corporation, stated, "because the Patent Office made clear early on that it would interpret the language in *Chakrabarty* broadly, and because the decision itself put the issue of patenting living organisms to rest, everyone [in the legal community] assumed plants would be acceptable under 101" (Witt, 1985, pp. 84-85).

Under pressure to rule on such sensitive questions, the Patent Office announced a policy of preemption on October 17, 1984. The statement declared that "any subject matter protectable under either the plant patent law or the Plant Variety Protection Act is preempted by that law and cannot be protected under the general patent law." Yet, within the same statement came the words that "the court's discussion of Section 101 of our patent law, and the purposes and effects of the plant patent law and the Plant Variety Protection Act, makes clear that plants are within that subject matter that can be patented under Section 101 of the general patent law." The Patent Office was saying that while Section 101 did apply to plants, it did not want the responsibility of awarding 101 claims for plants, and then at some future date, encounter a court decision that would place the patents in jeopardy (Witt, 1985, p. 85). The overlapping protection provided by the different laws has since raised problems that remain unresolved (*Agronomy Journal*, 1956, p. 603; Kloppenburg, 1985, p. 373).

The greatest concern among plant breeders has arisen over the patenting of processes rather than products. Process patents for breeding techniques have been objectionable to plant breeders for a long time. The American Society of Agronomy criticized Donald F. Jones

Chronology, Part II:
Revolutionary Biotechnology

1970 Plant Variety Protection Act (PVPA) passed. Conferred patent protection to developers of novel, sexually reproduced (by seed) plants. Criteria to be novelty, uniformity, and stability as distinguished from quality.

1971 Consultative Group on International Agricultural Research (CGIAR) established by Rockefeller and Ford Foundations, with other contributors, to sustain the Green Revolution.

1973 Revolutionary biotechnology begins, with the first gene cloned by Stanley Cohen and Herbert Boyer.

1974 First expression of a gene cloned from a different species in bacteria.
Recombinant DNA (rDNA) experiments first discussed in a public forum (Gordon Conference).
International Board for Plant Genetics Resources (IBPGR) created in the Food and Agriculture Organization (FAO) of the United Nations, but constituted as a CGIAR institution.

1975 U.S. guidelines for rDNA research outlined (Asilomar Conference).
First hybridoma (artificially created cancer cells) created.

1976 First firm to exploit rDNA technology founded in the United States (Genentech).
Genetic Manipulation Advisory Group started in United Kingdom.

1978 First product made with rDNA (somatostatin, a protein).
Nobel Prize awarded to Hamilton Smith and Daniel Nathans for discovery of restriction enzymes.
Establishment of new set of NIH guidelines, which relaxed rules for gene transplantation experiments.
Bill to regulate DNA fails in congressional committee.
Recombinant DNA Advisory Committee (RAC) restructured by Secretary of Health, Education and Welfare Califano to expand and broaden its membership.

1979 NIH Director Fredericks established a voluntary compliance program to cover private industry.

1980 *Diamond* v. *Chakrabarty* decision by Supreme Court, permitting patent rights for micro-organisms.
Cohen/Boyer patent submitted for the construction of rDNA.
Amendments to PVPA passed to cover six previously excluded species, despite heated debate for granting proprietary rights over so basic a resource as plant germplasm. PVPA brought into accord with Paris Convention, enabling the United States to become a member of the International Union for the Protection of New Varieties of Plants (UPOV).
United Kingdom stresses biotechnology research and development (Spinks report).
Federal Republic of Germany stresses biotechnology research and development (Leistungsplan).

1980 Initial public offering by Genentech sets Wall Street record for fastest price-per-share increase.
Second major revision of NIH guidelines clears way for most rDNA experiments to be performed at minimal containment requirement.
Charles Weissman (University of Zurich) and Walter Gilbert (Harvard) form Biogen.
Successfully produced bacteria that released interferon, a rare antiviral substance.
rDNA Advisory Committee (RAC) undergoes change in attitude toward regulation that substitutes submission of proof of safety by experimenters to evidence that research was hazardous. Failure to find such evidence brought exemption from the guidelines.

1981 First monoclonal antibody diagnostic kits approved for use in the United States.
First automated gene synthesizer marketed.
Japan stresses biotechnology research and development.
Japan's Ministry of International Trade and Technology declares "The Year of Biotechnology."
France stresses biotechnology research and development (Pelissolo report).
Hoechst/Massachusetts General Hospital agree to 10-year, $70-million collaboration, which involves research in exchange for use of all patents and training of company scientists at Harvard each year.
Initial public offering by Cetus sets Wall Street record for the largest amount of money raised in an initial public offering ($125 million).
Industrial Biotechnology Association founded.
DuPont commits $120 million for life sciences research and development.
More than 80 new biotechnology firms (NBF's) formed by the end of year.

1982 First rDNA animal vaccine (for *colibacillosis*) approved for use in Europe.
First rDNA pharmaceutical product (human insulin) approved for use in the United States and the United Kingdom.
First research and development limited partnership formed for the funding of clinical trials.

1983 First plant gene expressed in a plant of a different species.
$500 million raised in U.S. public markets by new biotechnology firms.

1984 Judge John Sirica postponed the scheduled environmental release of rDNA organisms.
Stanford awarded Cohen/Boyer patent on basic rDNA process.

Source: Lappe, 1984, pp. 50-51; Witt, 1985, pp. 124-26).

and Paul C. Mangelsdorf, in 1956, when they applied for a patent of Jones's fertility restorer system, which made double-cross hybrid production possible without detasseling (Innes, 1982, p. 786). The patent of Agrigenetics for hybrid seed production came under attack in 1982. In the August 26, 1982, issue of *Nature*, N.L. Innes, of the British Association of Plant Breeders, accused the company of appropriating rights that have been the "stock-in-trade of plant breeders for some considerable time and have already been used commercially" (Lamberts and Sneep, 1984, p. 2). In 1984, the European Association for Research on Plant Breeding complained about the fact that certain breeding techniques could be patented altogether and their application not be allowed in the production of new varieties (*Biotechnology Newswatch*, 1984a, p. 3).

In biotechnology, science has increasingly become business, and in this country, restriction on the flow of information has followed. At a seminar on vectors for crop improvement, Dr. Johannes de Wet, of the University of Illinois Genetic Engineering Center, described his use of a new pollen vector. Yet, he refused to answer questions regarding his transformations of tomatoes and sorghum with his technique "upon the advice of patent counsel" (*Biotechnology Newswatch*, 1984a, pp. 1-2; Fox, 1984, pp. 1080-1082). In a decision that may prove to be a precedent, a Federal circuit court denied a pharmaceutical manufacturer the right to use a competitor's patented compound in research (Doyle, 1985, p. 72). It appears that the new synthetic biology is simply a continuation of the trend toward commodification that began with the Plant Patenting Act of 1930.

Given the history of seed patenting, the road appears open for the private control of entire living processes. Questions arise, such as whether food-producing resources should be patented and, if so, whether they should be treated differently from other kinds of patents; whether patents on agricultural supplies, such as pesticides and livestock antibiotics, contribute to the benefit of society; and whether such patents facilitate the economic concentration of power in the food and farm system (Witt, 1985, pp. 86-87). Germplasm can mutate and change, as can the technology that manipulates it. Germplasm normally changes more quickly than the laws designed to govern it. The publicity given genes and transfer technology has generated interest, controversy, and concern for the value of germplasm upon which the technology ultimately is based (Fox, 1984, pp. 1080-1082).

By 1989, the question of patenting plant and animal life had been resolved affirmatively. In the legislative debates on transgenic animals before Congress on September 13, 1989, USDA and industry both embraced the right of industry to patent transgenic farm animals and objected to farmer exemptions for breeding or selling such animals or their offspring (DNX, Inc., 1989, pp. 5-6; Jones, 1988, p. 2).

Biotechnology shifts the economic power in favor of agribusiness and away from the farmer. The fact that genes have become private property should be a part of any discussion of the effects of biotechnology on agriculture.

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The Commercialization of Biotechnology and Its Effects

The success of hybrid corn, followed by new patent protection at the molecular level, has provided an incentive for large capital investment in the new industry. Biotechnology is changing both the agricultural production system and the agricultural research system by providing a common technical base on which the pharmaceutical, chemical, agricultural, and food processing industries can come together. Public institutions that provide research support for agriculture are expanding to provide support for new clients. Other public and private institutions, such as Harvard, MIT, Rockefeller Foundation, Caltech, Scripps Clinic and Research Foundation, and Washington University, have changed focus to enter agriculture. The entire chemical/pharmaceutical industry is mobilizing to participate in the new agricultural revolution. Genetic engineering companies that specifically target agricultural biotechnology have been founded to take advantage of a predicted $50-$100 billion market opportunity (Kenney, 1982, pp. 217-218).

At the end of 1984, according to Marc Lappe, 202 American of 2,484 companies in the Western industrialized nations were developing recombinant-DNA products and supporting the basic industry of biotechnology. Competitive, well-capitalized major companies, such as Genentech, Genex, Cetus, Bethesda Research Laboratories, DuPont, Eli Lilly, International Plant Research Institute, Monsanto, Phillips Petroleum, and Biogen, initially dominated the industry. Throughout the world, major firms are involved in producing feedstuffs, energy-producing feedstuffs, energy products, pharmaceuticals, fragrances, reagents that facilitate diagnosis of disease, and other products where potential markets justify small-scale production. Table 4, compiled by the Office of Technology Assessment (OTA) and adapted by Marc Lappe, displays areas of major interest to American firms. According to Lappe, by 1984, the aggregated investment in human health-related products by Western nations had grown to more than half a billion dollars.

Private researchers are devoting great energy to agriculture and related areas, even more energy than for pharmaceuticals. Market readiness and existing regulatory obstacles seem to be the controlling factors in products selected for development in agriculture. Emphasis on quick returns has led to development of animal vaccines, antibiotics, and growth stimulants in the veterinary health field, and they have come ahead of the time predicted by knowledgeable observers (table 5).

Products for agriculture are being produced ahead of predicted dates and in substantial number. While the biggest rewards may be in the longer term products, such as leaner animals and genetically redesigned plants that fix nitrogen, production of many of the above products is already reaping benefits. The most recent evaluation of potentially available technologies by OTA offers the following scenario: of 57 likely technologies in animal research, 27 were expected to have been available for commercial introduction around 1990, and the remaining 30 between 1990 and 2000. In plant agriculture, 50 of the 90 technologies examined were predicted to be in use around 1990, and the other 40 between 1990 and 2000 (U.S. Congress, Office of Technology Assessment, 1986, p. 299).

Table 4--Major areas of research and development among U.S. biotechnology firms

Research and development areas	Companies engaged in work	Companies specializing in this area[1]
	Number	
Pharmaceuticals	133	70
Animal agriculture	59	5
Plant agriculture	53	16
Specialty chemicals and food	40	8
Commodity chemicals and energy	28	3
Microbial application to the environment	21	6
Electronics	7	2

[1]Companies that list only a single specialty in their prospectus or annual report. (Lappe, pp. 52-53).

Source: Adapted from Table 4 in U.S. Congress, Office of Technology Assessment. *Commercial Biotechnology*, pp. 67-70.

Animal Biotechnology

The pharmaceutical industry was among the first to realize the potentials of biotechnology for improving health care for animals. In the 1976-78 period, researchers in the field were chiefly concerned with human applications, yet it was a simple step for companies such as Lilly, Merck, and Upjohn to comprehend the application to animal health and nutrition. Animal production has been the first industry to receive new production techniques from biotechnology, and the animals involved range from cattle to abalone. Total U.S. sales of products related to animal health were $1.9 billion in 1982, rising to $2.3 billion in 1984. Large mammals have received greatest attention, mostly because U.S. livestock-rearing returns $70 billion each year. Poultry is also receiving greater research attention. The growth of global meat consumption predicted to result from adoption of modern production techniques may enlarge the animal health market even more (Kenney, 1986, pp. 217-238).

Technological effects are being felt in beef and dairy cattle farming. The life cycle of the cow is becoming more rigorously controlled because new reproductive technologies now make possible increases in ova at ovulation from 8 to 20 eggs (superovulation). It is possible to cut embryos to produce identical twins, quadruplets, and occasional octuplets. These ova are artificially inseminated and then flushed from the cow after 6 days. They are sexed and implanted into surrogate mothers, with the dairy farmers choosing the female embryos and the cattle farmers opting for males. The surrogates have their cycles placed in phase with the donors, so the embryo will be accepted. Bovine reproduction is being

Table 5—The introduction of genetic engineering products

Product	Predicted completion of product[1] (circa 1981)	Product first reported
	Year	
Rennin	1985	1984
Casein	1985-89	NA
Animal growth hormone	1985	1983
Foot-and-mouth vaccine	1985	1981
Hog diarrhea vaccine	1985	1982
Blue tongue vaccine	NA	
Methanol bacteria	1985	NA
Bacterial/miscellaneous feeds	1985	1981
Amino acids	1981	1981
Antibiotics	1985	1983
Anabolic steroids	1985	1984
Pesticides	1985	1984
Pesticide-resistant plants	1985-89	1983
Cloned livestock	1985-90	1984
Gasohol-fermentation bacteria	1985	
Improved yeasts	1985-89	1983
Cellulose-digesting bacteria	1985	1983
Salinization osmoregulation	1985-89	NA
Nitrogen-fixation cereal enzyme	1985-90	1984
Cereal nitrogen-fixation synthesis	1990	NA

NA=Not available.
[1]Predicted years are furnished by the Chicago Group for Policy Research, Chicago, IL, 1981. Table compiled by Lappe, 1984, p. 56.

entirely transformed, with the calf genetically selected by human beings (Seidel, 1986, pp. 68-72).[17]

Calves are injected with new vaccines, developed both in public and in private facilities, to expedite growth to maturity. At the Plum Island Agricultural Research Facility at Greenport, Long Island, New York, a completely effective anthrax vaccine was produced using biotechnology (Byerly, 1986). A new vaccine has been developed by Molecular

[17]The actual number of embryo transplants in dairy cattle in the United States went from 20,000 in 1979 to 100,000 in 1986, still only a small percentage of calves born, and has remained constant since. According to Professor Seidel, approximately 12,000 embryos are exported annually.

Genetics, Inc., to prevent scours. Bovine interferon is being tested for use against shipping fever, an affliction that occurs when animals are shipped to feedlots. Shipping fever costs the cattle industry $250 million a year. The vaccines are shortening animal turnover time and permitting cattle to be raised under less sanitary conditions, possibly in confinement, and in greater densities. The possibility exists of farmer-administered diagnostic kits, which would lessen reliance on expensive veterinary services.

Feed also receives attention from the new technology. Feedstuffs are composed largely of carbohydrates and protein, the protein furnished chiefly by soybean meal. A new protein substance has been developed, known as single-cell protein (SCP), which is obtained by yeast grown on a methanol feedstock. Phillips Petroleum and other fuel producers hope to market this product, particularly when and if less developed nations become consumers of animal products. The product is not cost competitive on the world market, but may be profitable in countries where natural gas is burned off as a waste product. The possibility of synthetically producing the amino acids missing in the current protein in bovine feed mix with yeast or bacteria is near. Finally, the option of genetic alteration in maize to produce high lysine and tryptophane for cattle feed exists to provide an alternative to the current addition of amino acids as a feed supplement.

Another innovation approaching the market stage is the microbial production of bovine growth hormone or bovine somatotropin (bST). It increases lactation in dairy cows more than 10 percent, with no increase in feed consumption. That means more milk at less cost (Fallert and others, 1987, p. 1). Genentech has estimated the market value of bST at $500 million. The pork industry is not far behind beef and dairy industries in similar innovations. Growth hormone, interferon, and other vaccines are in preparation or have come on line. The pig is being redesigned to be less fatty. The reproductive technologies used with cattle, however, seem less applicable to swine and have not been developed. Though poultry has lagged in basic research, Amgen has cloned a gene that produces chicken growth hormone. The company is hopeful that the time for broiler turnover can be reduced by 15 percent, from 8 to 7 weeks. Other biotechnological applications, such as the cloning of salmon, are viable (Amgen, 1983; Hughes, 1986, pp. 67-107; Johnstone, 1983, p. 328; Smith, 1982, pp. 13-14).

Plant Biotechnology

While the animal food production systems possess great opportunities, the options in plant biotechnology show even greater promise. Since the seed is the carrier of essential genetic information, it is of primary importance to biotechnology research. Other areas include manipulation of soil micro-organisms, bacteria which live on plants, and the production of plant diagnostic kits to help identify diseases. The market for seeds and micro-organisms is virtually unlimited, while diagnostics will be restricted to areas such as turf grass and citrus or in markets where customers are not price conscious (DNA Plant Tech. Corp., 1983).

Among the first plant-related products to be marketed will be engineered bacteria, such as

the ice-minus type, to prevent crop frost damage. The market potential is enormous, given the toll frost takes on crops. Florida, for example, suffered $500 million in frost damage in December 1983. On a global scale, the amount would be in the billions of dollars. Nitrogen fixation through bacteria or through use of the nitrogen-fixation (NIF) genes will address a market of $10 billion in the United States alone (David, 1983, p. 755; Martin, 1986, pp. 112-116; Marx, 1982, pp. 62-67; Tangley, 1983, pp. 681-682). This market is undeveloped because of the complexities involved in manipulating the 17 NIF genes and the reliance on artificial fertilizer (Dundon, 1983, pp. 112-113).

The most likely direction is for biotechnology to genetically alter the plant or link its maturation with certain specified inputs, such as pesticides, herbicides, and fertilizers. The pattern of new seeds and pesticides is well established in the United States, and the economic necessity of purchasing both inputs provides justification for the adoption of new varieties (Kloppenburg and Kenney, 1984, pp. 3-18). In animals, transgenic farm mammals protected by patents and supporting legislation will be sold to breeders.

Although the capability to splice genes and put them into plants and animals using bacteria or viruses has been refined in the past few years, there are still significant limitations. Genes possess the capacity to rearrange themselves on the chromosome as a consequence of different stimuli and then to behave in a wholly different fashion (Doyle, 1985, p. 233). Thus, the possibility of the cloner or plant geneticist replacing the traditional plant breeder is unlikely at present, and a vast amount of basic research lies ahead to unravel the transcription processes of DNA before the exact function of genes can be predicted.

Protoplast fusion and plant tissue culture possess more immediate possibilities of application to plant breeding. Plant tissue culture makes possible the regeneration of exact replica plants from single plant cells, although the tissue culture process gives rise to unique or somoclonal variation. Cell fusion and tissue culture will provide breeders with new material and techniques for rapidly scanning plant cells for desired characteristics (Evans and others, 1938; Hughes, 1986, pp. 134-138).

Future discoveries in plant molecular biology will make possible the understanding of how herbicides and plant growth regulators function. The new knowledge will enable scientists to design better chemicals or perhaps design better plants that will respond to crop chemicals in a desired manner. It might be possible to design plants with better natural pest defenses. Research begins with alteration of DNA, and the reprogramming will confer the ability to determine the characteristics to which a particular plant responds. The implication is that one can produce engineered plants that will respond only to particular proprietary chemicals and healthy transgenic animals that can be raised safely in stressful environments, eat less feed, and possess less fat. The markets for such products could be in the billions of dollars.

Private Industry in Agricultural Biotechnology

With farmers spending $145 billion in 1992 for operating inputs, the market appears large. One product alone, the herbicide Roundup, made by Monsanto, approached $500 million in sales in 1982. Monsanto's contract with Genentech for development of Roundup (glyphosphate)-resistant seed could create a large niche in the future market. Beyond the current market exists the prospect of expanding world food demand (Budiansky, 1983, pp. 19-22; *Chemical Week*, 1983, p. 47).

Multinational corporations have purchased seed companies with biotechnology research capabilities because the seed is the primary vehicle, the source of distribution, and the source of profit (Kenney, 1986, pp. 3-18; Kenney and others, 1982; Kloppenburg, 1985; and Mooney, 1979). Each corporation chose a market sector where its competitive position appears strong (Journal of Commerce, Aug. 3, 1982, p. 22B; Storck, 1979, pp. 10-13). The aim of the multinational corporation is a protectable niche or area for successful competition.

The first significant product development project derived from an alliance between Monsanto and Genentech in 1979 to produce bST. To compete with Monsanto, other multinational corporations contracted with biotechnology companies to develop different processes for making bST. The result is likely to be a competitive market in bST if an effective, simple delivery system can be devised. The smaller feed companies, unable to develop and produce bST, may be displaced if their feed packages do not contain the growth hormone. The bST hormone may also act to consolidate the smaller feed additive producers (Kenney, 1986, pp. 224-225).

Food processors are hoping to expand their opportunities as a result of the biorevolution. Engineered microbes can convert wastes or low-value products into those of higher value. Whey, derived from cheese production, can be converted into marketable lactose. French researchers are trying to invent a process using microbes to transform inexpensive vegetable oils into products similar to expensive oils with a flavor like cocoa oil (Cantley and Sargent, 1981, pp. 323-334; Elkington, 1985, pp. 142-43).

General Foods, Ralston Purina, Campbell Soup, Nestle, Hershey, Frito-Lay, and other food-processing companies are developing in-house research capacities or funding university and biotechnology startup research. Participants in this aspect of research are looking for piecemeal rather than industry-wide effects because of the inability to identify commercially important functions. These companies have been motivated to invest in in-house genetic engineering research capabilities and in startup companies because of concerns that large chemical and pharmaceutical companies may become involved in food processing (*Food Engineering* 1983, p. 21; Pellon and Sinskey, p. 16). Although food processors and chemical and pharmaceutical companies possess different production processes and markets, all three industries are obtaining a common knowledge base through biotechnology and are expecting to benefit financially from that knowledge.

The final group of investors in biotechnology is large farm operations. Boswell Farms, a large California cotton grower, has funded Phytogen to produce new varieties of cotton. Brown and Williamson Tobacco Company has contracted with DNA Plant Technology to produce improved tobacco varieties (Amgen, Inc., *General Economic News*, 1983, p. 3; Miller, 1985, p. 26). Only the largest corporate farms can afford such expenditures for research. Other farmers depend on public research or purchase of the finished inputs.

Multinational corporations are becoming well positioned in agriculture through biotechnology because their marketing networks are already in place. New discoveries simply mean new lines. Where seed and chemicals can be linked in a package, separate marketing networks for seeds and chemicals can be combined, reducing overhead expenses. The dispersion of farmers and the need for large marketing networks pose barriers to entry for smaller firms. Farmers are the ideal market because innovations that promise increased profits are willingly accepted (Danbom, 1979, pp. 66, 70, 87-88).[18] In the past, farmers converted to hybrid corn even though the cost of additional inputs absorbed much of their additional profits. Farmers are likely to adopt new biotechnological products, such as transgenic cattle and pigs, even though other expenses may rise. Nitrogen-fixing seed, for example, may reduce fertilizer costs, but will likely cost more than conventional seed.

The hope of large profit margins derived from a proprietary molecule, protected through hybridization or the new patent laws, is still the driving mechanism behind the agricultural thrust of the multinational corporations. Most of the corporations view biotechnology as another tool to diversify away from bulk commodities (*Journal of Commerce*, Dec. 22, 1983, p. 22). These companies have invested heavily in building agricultural research staffs in-house.

The scarcity of skilled plant pathologists and molecular biologists in the 1980's has led multinational corporations to negotiate long-term research agreements with universities. These were negotiated in addition to the normal grants of various types (*Journal of Commerce*, Aug. 18, 1983, p. 22). Another corporate strategy is to sign contracts with agricultural biotechnology startup corporations. The growth of startup companies was limited because multinational corporations moved into plant agricultural applications. In veterinary applications, however, startup companies became more important because animal health products derived directly from human health research, such as the HGH-animal growth hormones, human monoclonal diagnostics, animal monoclonal diagnostics, and human and animal vaccines.

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[18]The author documents distrust of scientific agriculture among farmers during the period of industrialization. Farmers were willing to accept the Babcock test for butterfat content of milk and other innovations if the cost and the risks were small, while the opportunity for gain appeared good.

Biotechnology Startup Companies

There were only seven biotechnology startup companies devoted entirely to agriculture in 1985: Agrigenetics, Advanced Genetic Science, Calgene, Genetic Engineering Company, DNA Plant Technology, Molecular Genetics, and Sungene (Buttel and others, October 1985), and that number has remained stable. A few smaller agricultural biotechnology firms exist, but none have issued public stock offerings. Large biotechnology startup companies have research in agricultural applications, such as Genentech in bST, Cetus in scours vaccine, and Collaborative Research in rennin.

A distinguishing feature of agricultural biotechnology startup companies is the concentration on plant research. Plant biology requires special skill. The first startup dedicated to plants was the International Plant Research Institute (IPRI), founded by University of California, San Francisco, and professor Martin Apple in 1978. IPRI underwent financial reorganization by 1982. Other important companies began within 3 years of IPRI. With the exception of Agrigenetics (now part of Lubrizol), which owns 13 seed companies and possesses funds to finance research, the companies rely on contract funds. Molecular Genetics, Inc., performs both animal and plant biotechnology and has successfully marketed its scours vaccine. Some staff leaders of these startup companies have come from the land-grant institutions, which have experienced a significant loss of research intellect as a result (Kenney, p. 1986, 226; Kloppenburg, 1985, p. 349).

Universities outside of the land-grant system possess some plant molecular biologists. Nonetheless, the shortage remains sufficiently acute that a number of European and Third World scientists have been recruited by American firms. Some of these scientists maintain both managerial positions in private companies and faculty status at universities. These individuals belong to many of the most prestigious institutions (Kloppenburg, 1985, p. 350).

The range of relationships between universities and startup scientists is quite varied if envisioned as a continuum with consulting at one end and full ownership at the other. In between, a scientist might be a permanent advisor, under contract within the university setting, a joint appointee, a holder of stock options, or a partial owner. These relationships are likely to apply to multinational corporations as well. Consultants for one corporation alone numbered 24 in 1983, and came from universities throughout the Western World (Kloppenburg, 1985, p. 353). These new relationships within the public and private universities are creating conflict-of-interest problems for university administrators.

Scarcity of personnel is not the major obstacle for startup companies. The companies are affected by the seed-agricultural chemical industry as long as their survival relies exclusively on contract research. Large investments of multinational corporations and their marketing power may displace smaller companies, although the capacity to secure patents on a critical gene or process may provide a negotiating base for the startup (Comai and others, 1983, pp. 370-371). Startup companies that can find a niche in plant discovery or in

animal vaccines, protected by patents, have the best possibility of survival.

Once the number of accomplished scientists in the job market increases, the edge of scientific expertise that currently exists on the scientific advisory boards of the startups is likely to be eroded. Startup company advisors consist of distinguished scientists who can obtain preferential access to products and scientific expertise created in the board members' laboratories. The startups' laboratories are frequently convenient to major universities, and hence, are close to necessary professors (Kenney, 1986, p. 230).

Biotechnology in the Agricultural Research System

As the hybrid phenomenon in corn and other commodities altered the public research agenda a generation ago, biotechnology is again forcing adjustments. Public research is under pressure from the seed industry and other larger corporations to withdraw from investigations considered competitive with private product development. Traditional land-grant scientists are skilled in plant breeding but inexperienced in the new molecular biology. Among the few who are knowledgeable, a number have left the system for higher paying jobs with private companies. The changing technical base has made universities outside of the land-grant system important competitors in plant sciences. Various land-grant constituencies, like the small private seed companies and the farm bloc, have been weakened. Large, multinational agribusiness input companies have become more assertive. They are applying pressure on land-grant institutions to retreat from more traditional areas, such as the development of cultivated varieties on which the small seed companies depend for their existence (Kenney, 1986, p. 231).

At the Federal level, "the Agricultural Research Service is phasing out varietal development programs and is encouraging the State experiment stations to follow suit" (Kloppenburg, 1985, p. 359). Howard J. Brooks, national program leader for Horticultural and Sugar Crops of USDA's Agricultural Research Service (ARS), has stated that varietal releases have declined over the past 6 years. He believes that the cost of commercial seed is likely to rise and that the free exchange of plant materials, due to changes in patent laws, is being curtailed (Brooks).[19] Brooks appears to validate Kloppenburg's thesis that the emphasis now placed on biotechnology provides an additional reason for moving public breeders

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[19]From May 2, 1980, to February 2, 1988, 2,001 germplasm lines and varieties were released, an average of 284 per year. Over this period of nearly 8 years, 79.6 percent of all releases were germplasm lines, the remaining 20.4 percent were varieties. While I do not have data, I am fairly sure that all ARS plant releases prior to about 1978 were variety releases. About 1978, ARS made a major change in policy toward emphasis on developing and releasing germplasm lines and deemphasized development of improved varieties.

"Since May 1980, 75.6 percent of all ARS plant releases have been cooperative with State agricultural experiment stations or industry. Only 24.4 percent have been released unilaterally by ARS, and these are largely varieties of horticultural crops such as apples, pears, peaches, plums, apricots, oranges, tangerines, blueberries, strawberries, blackberries, pecans, walnuts, and tree fruit rootstock where ARS has assumed primary responsibility. In addition, ARS has variety development programs on vegetable and ornamental crops, all of which serve a national need" (Brooks, 1988).

away from the commodity form.

Criticism of the agricultural research system from external institutions has appeared sporadically throughout its history. The most recent phase began in 1972, when the National Academy of Sciences found the system to be parochial and overly involved in marginal research (Marshall, 1982, p. 33). Criticism reappeared in 1982 in separate reports by OTA and the Rockefeller Foundation. Both faulted the system for insufficient basic research. However, an OTA report for 1986 acknowledged that basic research had intensified within the public institutions, while the private sector has increasingly taken over the applied aspects. The same report estimated the private financial research investment to be about $3 billion or approximately equal to the public expenditure (U.S. Congress, 1986, pp. 18-19, 265).

A central role in land-grant research has historically been played by the plant breeders, who synthesized knowledge from other disciplines, such as entomology, plant pathology, and soil science, and integrated it successfully into the new seed (Kenney, 1986, p. 231). One example is Norman Borlaug at Texas A&M University, who developed a variety of dwarf wheat and systems for its propagation throughout the Third World. Genetic engineering initially undermined the breeder's position because the new techniques made plant design possible through gene-splicing. The claims of the molecular biologists placed breeders on the defensive (Kenney, 1986, p. 231). Neither plant breeder nor molecular biologist can replace the other. By opening their disciplines to one another, they not only benefit mutually, but also expand and successfully apply the knowledge base. Directors of graduate programs within land-grant institutions believe that integration of curricula must occur in genetic engineering, in in-vitro horticulture, and in whole plant manipulation (Kloppenburg, 1985, p. 360-61).

Public plant breeding has reached a turning point. After 1987, as the scientist-years devoted to research by the private sector equaled the scientist-years of public endeavor, there were more private than public breeders. The call for privatizing practical breeding is growing louder. Private breeders' arguments are being supported by emphasizing the importance of adding "release time" for the integration of genetics and other biotechniques into the land-grant curriculum. Graduate programs in plant breeding and agronomy are moving toward the incorporation of biotechnological expertise in training and, in the process, disengaging from varietal release. The shift is occurring slowly, as public agencies concentrate once again on basic research. The public sector will provide improved raw materials to private enterprise, which, in turn, will determine how these materials will be used and what form the product or the commodity takes in the market (Kloppenburg, 1985, p. 362).

Land-grant universities involved in important molecular biology work are limited to large institutions such as the University of Wisconsin, University of California at Davis and Berkeley, the University of Minnesota, and Cornell University. Wisconsin and UC Berkeley are rated among the top 10 universities in cellular and molecular biology, while the others

in the top 10 consist of large private universities and medical schools. Land-grant universities did not possess as much expertise in plant molecular biology as the private universities when multinational corporations began turning to agricultural biotechnology. Multinational corporations began to purchase research outside of the traditional agricultural system at Rockefeller University, Harvard Medical School, MIT-Whitehead Institute, and Washington University. Corporate funding has rendered these institutions competitors in research with land-grant universities nationally (Kenney, 1986, pp. 231-232). Pressure has mounted to include private institutions in the competitive grants process maintained in USDA-sponsored research.

Multinational corporations want the universities to concentrate on basic research in plant and animal biotechnology. The corporations also want private institutions to become eligible for USDA-administered monies available for agricultural research heretofore restricted to land-grant institutions and ARS laboratories. The bulk of USDA allocations to universities ($290 million through the Cooperative State Research Service for FY 1986) goes to agricultural research stations on a formula basis, guaranteeing that public research is decentralized. USDA's competitive grants system, administered along lines patterned after NIH and NSF procedures and thus open to a wider range of institutions, allocated $44.5 million in FY 1986. USDA's Agricultural Research Service spent an additional $501 million on research in its own laboratories in FY 1986. All these funds present an inviting reservoir for non-land-grant institutions seeking new research dollars (U.S. Congress, 1985, pp. 8-11; Kenney, 1986, p. 232). The total USDA commitment to biotechnology research rose from $17 million in 1985 to $162.6 million in 1991 (USDA Investments in Biotechnology, Nov. 1, 1991, p.2).

Competition for public funds found expression in the report *Science for Agriculture*, issued after a 2-day conference at the Winrock International Conference Center in 1982. Conference sponsors and participants included the Rockefeller Foundation, the White House Office of Science and Technology Policy, private industry, land-grant universities, and USDA. The Winrock report faulted the agricultural research system for parochialism and backwardness in basic science, but recommended that formula funds be continued to State experiment stations. However, the report suggested that all future real increases should go to the competitive grants program for use in basic research. Also, USDA and land-grant universities were urged to sponsor workshops and symposia to bring experts together from all relevant research settings to discuss the most current science areas, identify research needs, and explore collaborative arrangements to meet those needs. The report called for creation of mechanisms to strengthen linkages between basic and applied research performed in the public sector and the commercial sector of industry. Farmers and consumers were mentioned only as groups that divert USDA attention from basic research to political concerns (Kenney, 1986, pp. 233-234; Rockefeller Foundation, 1982, pp. 2, 12, 26).

The Winrock report sought the achievement of two objectives. One was the restructuring of agricultural research into a few "centers of excellence." The second objective was to bring

other schools into competition with the existing land-grant universities for USDA research funds. The traditional agricultural research system reacted negatively to the report. The smaller institutions were more upset than the larger ones. The prospect of competition with Harvard, MIT, and Stanford for funds was not appealing to many land-grant universities. Smaller States would be unwilling to part with Federal matching funds on the grounds of national well-being (Kenney, 1986, p. 234).

The new biotechnology provides an opportunity and an inducement to transform the agricultural research funding system. Techniques of biotechnology can and are being imported into the agricultural system to strengthen its research capabilities. The land-grant system has used the current fascination with biotechnology in seeking increased funding levels through private and public means. Administrators within the land-grant network, after observing the movement of substantial private funds into private universities, wished to obtain similar monies for their institutions. Some unique arrangements have been negotiated with private industry. The most important consists of long-term research, one-university/one-corporation contracts. Between 1974 and 1983, about $140 million was spent at 13 universities, medical schools, and independent research laboratories. The major corporate grants have gone to private institutions, with the exception of the University of California, Davis (UC Davis) and a 1986 contract between Sohio and the University of Illinois. The likely reasons for this choice are the closer ties between private universities and wealthy individuals, trustees, and corporation members, and the public nature of the land-grant system, which renders its proceedings more open to public scrutiny (Kenney, 1986, pp. 55, 57). Though fewer in number, contractual relationships with public institutions have raised new and unanswered questions in the areas of academic freedom and conflict of interest. "The real threat," argues Kloppenburg, "lies in the manner in which the university may be transformed by new links which private enterprise has forged with researchers who retain their university posts" (Kloppenburg, 1985, p. 348).

Connections to private industry are not limited to research contracts with molecular biologists and biochemists. The magnitude of the financial contracts is another factor that deserves some attention. Agrigenetics has funded projects at 12 land-grant institutions, each of which received between $500,000 and $2 million. For plant science departments, sums of this size are considerably larger than amounts received in the past. The $567,233, which two plant breeders at Cornell University received in 1982, was 10 times the size of any other private grant to the experiment station. The $2.3 million spent by Allied Chemical at the University of California, Davis, in 1981 was equal to all other grant and contract funds received by the California Agricultural Experiment Station that year. Similarly, Sohio granted $1-$2 million to the University of Illinois' Department of Agronomy (Kloppenburg, 1985, p. 352).

These grants contain specific restrictions as to the flow of information and the kind of research to be pursued. For example, half the members on the committee to decide how Illinois was to use its Sohio money were drawn from Sohio personnel. The flow of information is likely to be affected, and probably restricted. A new reluctance exists among

breeders to share germplasm (Kloppenburg, 1985, pp. 352-354).

Although industry representatives deny the existence of restrictions on the flow of information, concerns are being raised by both public and private institutions. The private independent seed companies are also concerned about such outcomes. Their livelihood depends on products that come solely from public research (Kloppenburg, 1985, pp. 355-356).

Public Funding for Land-Grant Institutions

State experiment stations were sensitive to allegations that public stations serve private commercial interests, and many experiment stations were unwilling to commit large sums of money to developing biotechnology. Experiment station directors began a concerted attempt in the 1980's to obtain new support for their basic biology programs. When traditional appropriation channels appeared to be blocked, a group of influential directors introduced a biotechnology initiative as a separate budget item beginning in 1981. The Experiment Station Committee on Organization and Policy (ESCOP), the National Association of State Universities and Land-Grant Colleges (NASULGC), and then USDA Assistant Secretary for Science and Education Orville Bentley endorsed the measure. Individuals from these groups convinced Congress to add an additional $20 million in competitive grants for biotechnology for fiscal year 1985. The amount remained relatively constant through 1990, when $18,775,000 was appropriated. Thereafter, funding for biotechnology research through the entire Department of Agriculture increased dramatically.

Funding of the biotechnology initiative through the competitive grants mechanism had strong backing from State experiment station directors because of the continuing need to sustain this avenue of research. Modest increases in formula funds accompanied increases in competitive grants to assuage anxieties over losses in funds by the smaller land-grant institutions. Experiment stations accepted directed grants as another potential source of assistance (Kerr, 1987, pp. 186-187).

USDA currently distributes research funds in three ways. First, funds are allocated to the Agricultural Research Service (ARS) for in-house research. ARS designates these funds among its 140 research facilities on the basis of research programs, without regard to geographic dispersion. ARS research deals with agricultural matters of regional, national, and international concern. The ARS budget for FY 1990 was $585 million. Second, funds are distributed through the Cooperative State Research Service (CSRS) for further distribution to States on a formula basis determined by State farm and rural population. This research is performed by State agricultural experiment stations, colleges of veterinary medicine, black land-grant colleges, and Tuskegee University, and is directed at problems of local, regional, national, and international concern. The CSRS budget for 1990 was $340,478,000 plus $45,108,000 for facilities. Third, funds are allocated through the Office of Grants and Program Systems (OGPS) to a wide variety of institutions on a competitive basis. OGPS received $17 million for distribution for 1984 (General Accounting Office,

Table 6—Biotechnology research funding through the U.S. Department of Agriculture

Agency	FY 1991	FY 1992	FY 1993
		Million dollars	
Agricultural Research Service	81.1	83.9	90.5
Cooperative State Research Service	76.0	90.4	68.5
Economic Research Service	0.2	0.2	0.2
Forest Service	4.3	4.9	8.5
Total	161.6	179.4	167.7

The USDA budget figures for FY 1993 do not include possible Congressional actions on facilities and special grants that may increase the final appropriation (Biotechnology for the 21st Century, 1993, pp. 115-17).

1985, p. 10). Although OGPS was consolidated into CSRS, the amount allocated for competitive research in 1990 was $42,521,000.

From these totals, a General Accounting Office (GAO) questionnaire determined that approximately $40.5 million was expended during the 1984-85 period on 778 biotechnology projects. That figure represented about 6.3 percent of total USDA funding for agricultural research. The five States with the largest number of projects for that period were California, New York, Maryland, Florida, and Texas. In addition, the five States receiving the greatest number of USDA biotechnology research dollars were Maryland, New York, California, Florida, and Illinois (General Accounting Office, 1985, pp. 10-11). According to the CSRS budget office, the total amount for 1990 was $46.4 million. For 1992, the amount was $90.4 million.

GAO found 495 biotechnology projects at agricultural experiment stations and colleges of veterinary medicine at a total funding level of $10.7 million in 1984. The average life for one of these projects is 82 months. In the 495 projects tracked by the GAO questionnaire, the types of techniques employed were also identified (table 7).

Table 7 shows the popularity of the recombinant DNA and the protoplast fusion techniques. In most of these genetic transfers involving plants, the agrobacter bacteria/plasmid vector system, first examined by Smith at USDA, was employed. Eighty-seven of the 495 projects tracked by GAO involve the deliberate release of genetically engineered organisms as part of the experimentation process. The altered organisms in these experiments include crops such as beans, rice, corn, wheat, grapes, potatoes, and lettuce. Also included are specific types of viruses, bacteria, and fungi, as well as forest, fruit, and ornamental trees, and florist-related plants. One project involves development of a larger variety of salmon. The objectives of the projects vary widely, such as weakening of disease-causing organisms that affect plants and animals, stimulation of growth, improvement of quality in specific foods, and development of more effective biocontrol agents. The States in which the

Table 7—Biotechnology research techniques used on 495 reported projects, 1984

Techniques	Instances technique was used	Projects using technique
	Number	*Percent*
Direct manipulation of genome:		
Recombinant DNA	267	54
Chemical synthesis of nucleic acids	95	19
Site-directed mutagenesis	91	18
Direct manipulation of cells:		
Microinjection	27	6
Transfection	79	16
Transformation	148	30
Embryo manipulation and transfer	66	13
Cell culture and protoplast fusion	233	47
Other	93	19

Source: General Accounting Office, 1985, pp. 12-13.

greatest number of the 87 projects are underway are North Carolina (13), California (10), Texas (8), and Florida (6), while the remainder are scattered among 23 other States (General Accounting Office, 1985, pp. 14-15).

Of all the issues raised by biotechnology, environmental release has caused the greatest concern so far. Both public and private universities and commercial firms are involved in environmental release projects. The release of altered bacteria, developed by Advanced Genetic Sciences, Inc., Oakland, CA, was delayed in testing for 5 years by litigation. The ice-minus bacterium, commercially known as Frostban, was tested late in April 1987, after meeting the court requirements of filing an environmental impact statement that involved greenhouse testing and other preliminary research. The bacterium is designed to prolong the growing season of strawberry plants by preventing formation of ice-crystals on the leaves. The released bacteria may attain more significance as a precedent-maker than as a commercial success. The product was projected to be marketed in 1992 but has yet to appear. Experts speculate that its cost may prove prohibitive for the ordinary farmer. Nevertheless, according to Richard Godown, president of the Industrial Biotechnology Association, the legal impediments to environmental release have been cleared away (Pollack, 1987, pp. 1, 12). It now appears likely that other environmental release projects will gain permission from the Environmental Protection Agency and USDA to proceed to the open field.

As the recombinant DNA techniques spread from medicine into other disciplines, Federal

agencies began to confront concerns that undesirable mutant organisms might adversely affect the environment. State experiment stations proposed, through the NASULGC Division of Agriculture in 1984, that a National Biological Impact Assessment Board of Federal, State, and private sector experts be created to develop guidelines for the release of such organisms. The proposal suggests that the existing experiment station system, with the ability to monitor new plant cultivars released over many decades and the more recent efforts in pesticide impact assessment, offered a reliable mechanism for assembling the data necessary to regulate biotechnology as it progresses beyond the laboratory stage. Nearly every experiment station has been engaged in an aspect of biotechnological investigation since the mid-1980's, and each is rapidly developing the special competence necessary to perform the proposed tasks (Kerr, 1987, p. 186).

A Biological Sciences Coordinating Committee was formed on the national level in 1986, consisting of Federal agencies concerned with biotechnology regulation and formulation of research guidelines. The Office of Agricultural Biotechnology within USDA was created to formulate guidelines in agricultural research and regulation. The guidelines were completed and distributed to agricultural experiment stations early in 1992.

The Land-Grant System in a State of Flux

Land-grant institutions have not formally established an explicit policy for dealing with the effects of biotechnology on their institutions. Given the diversity of these universities, perhaps no single policy is possible or even desirable. Yet, the new technology does reveal the continuation of historical tensions arising from the desire to remove some inequities, carry on the existing mission, and discover new clientele.

The older problem of equitable sharing of funds between the land-grant colleges and their 1890 (traditionally black) colleges continues, although some progress was made with the passage of the 1977 farm legislation (U.S. Congress, 1977, pp. 95-113), which provided permanent formula funding for these institutions for the first time in their history. Passage of special funding legislation of $50 million in 1982 was also helpful to the 17 institutions involved. Yet, no proposals for biotechnological investigations came in from the 1890 Institutions and Tuskegee University as of the summer of 1987 (Rexroad) or in 1990 (CSRS Grants Office, 1991). It has been suggested that new technologies, of which biotechnology is one, be placed initially at the 1890 Institutions as a means of bringing them into full partnership within the land-grant system. Thus far, this idea has not been translated into action. NASULGC issued a report in 1982 on biotechnology that provided little guidance (Kenney, 1986, p. 235).

Land-grant universities are repositioning themselves to serve a new constituency. Large chemical and pharmaceutical firms are replacing former clients, demanding different services, and centralizing the agricultural input industry. Multinational corporations have purchased seed companies breeding and release of new seed varieties (Kenney, 1986, p. 236). Most varietal release programs of public universities were discontinued by 1986.

Many small, independent companies have disappeared. The loss in competition may translate into higher seed costs for farmers over the long run, though a precise estimate of cost is difficult to calculate.[20]

Transformation of land-grant institutions is also complicated by shortage of expertise. Efforts are being undertaken to integrate breeding programs with genetic engineering methods within some schools. Frederick Buttel of Cornell University believes biotechnology will widen the existing gap between the institutions with major programs coupled with substantial State funding, and the less well-supported universities. Also, within the extension division of the land-grant universities, Buttel sees a loss of constituency, as large farmers go increasingly to private management consultants and agribusiness representatives for technical assistance, instead of to county agents (Buttel, 1987, p. 14).

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[20]Fluctuations are likely to occur in either direction until consolidation becomes complete. One finds references to a reduction in the price of hybrid wheat seed by Cargill, for example, on two occasions over the past 5 years. See "Hybrid Seed Prices Cut Again," Progressive Farmer.

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Progress in Biotechnology and Effects Upon Producers and Consumers

Biotechnology should have a large effect on productivity and is predicted to exacerbate longstanding problems of farm policy (Buttel, 1985, pp. 68, 71; Buttel, 1986, pp. 234-43). The overall effect of biotechnology is likely to be broad in agriculture, affecting not only farm families as consumers and producers, but the future plants, livestock, fuels, and foods that will be produced and consumed. The economic structure within the agricultural industry has already been altered, along with national research priorities, as multinational corporations position themselves to obtain a larger share of the agricultural market.

These trends may facilitate further consolidation of agriculture, depending on Government policy. The net effect of modern farm technologies has been an increase in farm size and productivity, which, in turn, has reduced the number of farms and farmers. Industrialized agriculture has moved farming from reliance on a few, easily accessible inputs, to a full dependence on technologies and products whose origins are remote from the farm. Biotechnology is another step along the way.

Increased specialization is likely to be another outcome of the adoption of biotechnology. Critics have argued that our agriculture has already become overspecialized and genetically uniform to a dangerous degree. Doyle points to the southern corn leaf blight and avian flu as illustrations. In the case of the avian flu, genetically uniform chickens all possessed the same vulnerability to one specific virus and either perished or had to be destroyed. Having fewer and more specialized farms increases vulnerability of the entire agricultural system (Doyle, 1985, pp. 130-135).

Dislocations, vulnerability of food supply, environmental stress, and possible disruption by exotic species clearly are risks. An illustration involving many of these interrelated factors is presented in the case of bovine growth hormone (somatotropin) or bST, a single application of biotechnology.

Bovine Somatotropin (bST)

Although bovine somatotropin (bST) is a naturally occurring compound, its practical use is a product of biotechnology. Minute quantities of this protein are manufactured by the cow's pituitary gland. Conventional methods of extraction, isolation, and concentration of the substance are costly and time-consuming. Until now, bST could be obtained only from slaughtered animals. Biotechnology has made possible the isolation of the gene responsible for manufacture of bST, the transference from an animal donor into E. coli bacteria, production in fermentation-type vats, and isolation and purification on a scale suitable for commercial use (Kalter, 1986, p. 204). Trials at Cornell University in the early 1980's showed that injected bST increased milk production in dairy cows as much as 40 percent above normal levels during the last two-thirds of lactation (Bauman, 1985, pp. 1352-1362;

Fallert and others, 1987, p. 37; Kalter, 1986, p. 204).[21]

Approval of bST by the Food and Drug Administration (FDA) occurred on November 5, 1993. At present, the FDA is allowing the sale of milk and meat from bST-treated cows in FDA-approved research herds for human consumption (Fallert and others, 1987, p. 7). Analyses have been undertaken of production costs, surveys designed to measure acceptability of the new product, estimates of feed, and studies of the projected effects on the price of milk, existing surpluses, existing trends, and price support mechanisms. An exhaustive and authoritative analysis was undertaken by Richard Fallert of USDA's Economic Research Service in 1987 and updated in June 1990. His data indicate that bST acceptance is likely to improve over the next few years, which will result in a decrease in the national dairy herd, a net decrease in the demand for feed, although individual cows will require more sustenance, a net benefit to consumers if price supports are allowed to adjust to balance production and use, a net decrease in land size required for pasture as more farmers leave dairying, further downward pressure upon the price of milk products for the dairy farmer, and decreases in the number of commercial dairy farmers (Blayney and Fallert, 1990, pp. 13-24; Fallert and others, 1987, pp. 7-9; Kalter, 1986, p. 203; Kenney and Fallert, 1987).

The arrival of bST in the dairy industry occurred after several decades of technological and management advances in milk production. Bulk milk handling, silo unloaders, and improved milking equipment changed the industry in the 1950's by saving farmers time and labor. Higher rates of concentrate feeding, greater knowledge of animal nutrition, and better quality feeds increased dairy cow output. Then came artificial insemination, progeny testing, and progress in disease control. The use of bST is but an extension of existing trends (Fallert and others, 1987, p. 4).

The average cow produced nearly 13,000 pounds of milk in 1985, more than twice the 5,842 pounds produced in 1955. For some well-managed herds, average output per cow exceeds 20,000 pounds. Such rapid increases in productivity have led the industry to concentrate production on fewer, larger farms. The number of farms with dairy cows fell from 2.8 million in 1955 to 272,000 in 1985, while the average herd size grew from 8 to 40 cows. Commercial dairy farms (175,000 farms with 5 or more cows in 1986) possess an average of 65 cows (Fallert and others, 1987, pp. 4-5).

Large farms with well-managed herds are likely to be the first beneficiaries of the new technology. Indirect effects may be reduced demand for corn-based feed and reduced herd size. Shortrun estimates project a 25-30 percent decline in the national herd to restore equilibrium market conditions within 3 years after adoption of bST (Kalter, 1986, pp. 213-214).

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[21]The 40-percent increase is the subject of some controversy; some investigators favor a lower figure, from 12.1 to 15.5 percent, depending on the region involved (see Fallert and others, 1987).

The financial realities for bST are the same as for previous technological innovations. Farms with low debt loads, good soil resources, and superior management are best situated to survive. Farm production, agribusiness, research, education, and public policy will probably undergo dramatic changes as a consequence (Kalter, 1986, p. 214). In the mid-1980's, USDA initiated a temporary buyout program to reduce the size of the national dairy herd in response to the mounting dairy surplus. Additional Federal attention may be required to address social concerns, such as development of alternative enterprises for less efficient farmers or retraining for more productive pursuits, initiation of a suitable support price during a period of transition, and policies that address the perception of hormone in milk.

A shift in regional patterns of dairy production is also possible, although the number of farms is predicted to decline in every section. The Lake States and Northeast regions may have the highest rates of exit because of their lower milk prices relative to other regions, higher capital costs, and average milk production levels per cow. The Pacific region may have a lower exit rate because of high levels of milk production per cow. The Corn Belt, Southern Plains, and Appalachia are also likely to experience moderate losses due to higher milk prices than other regions. The Federal milk order price differential and high fluid milk use are responsible for the stronger demand in these regions (Fallert and others, 1987, p. 58).

It will be necessary to expand product testing and extension education because the new technology is complicated. To sustain competition in dairy States characterized by moderate-sized producers, for example, public investment in research and in the teaching of technology transfer will probably have to be increased (Yonkers and others, 1986, p. 58). Likewise, reducing Government dairy price support for agriculture may accelerate the trend toward fewer, but larger farms, as moderate-sized farms are less able to cope with risks associated with free market agricultural policies than either small part-time or large commercial farms (Knutson, Richardson, and Phillips, 1987, pp. 74-75). With annual rates of return about twice those of smaller farms, regardless of region, the survival chances of the larger farms appear assured.

Projections for quick adoption of bST and the resulting increase in production were based on the presumption of FDA approval by early 1990 and acceptance, not only by dairy farmers, but also by the consuming public. A survey of dairy farmers in New York State, and similar studies in other regions, seems to indicate willingness to proceed with bST use (Kalter, 1986, p. 212). bST did not receive final FDA approval until November 5, 1993.

A petition was sent to the FDA requesting an environmental impact statement on bST by Jeremy Rifkin, head of the Foundation on Economic Trends. Rifkin charged that use of bST would damage the environment, cause unnecessary suffering to cows, and create disruption of the dairy economy. He was supported by the Wisconsin Family Farm Defense Fund, Wisconsin's Secretary of State Douglas LaFollette, and the Humane Society of the United States located in Washington, DC. Milk produced using bST on approved

herds was rejected by at least two dairy cooperatives in California and students at the University of Wisconsin-Madison protested bST test milk sold on campus in 1987 (*Dairymen's Digest*, 1987, p. 19; *The Milkweed*, 1987, pp. 1-5). Although industry has been active in promoting bST before the public, the persistence of protest suggests that the acceptance of bST may take considerable time.

Beyond the scope of this study lies the international market implications of bST. The sale of the bST hormone is likely in other milk-producing countries, making a glut predictable, and volatility within the world market will probably ensue. Each nation values its own domestic dairy market and, if present policies continue, will find reasons for obstructing imports. In a freer market system, bST may enhance the American competitive edge (Fallert and others, 1987, pp. 14-15). However, bST-treated dairy products could provide the rationale for exclusion in nations that do not use the hormone and whose citizens remember the adverse effects of DES, a synthetic hormone now outlawed in beef cattle. It caused cancer in adults and enlarged genitalia in newborn children.

Biotechnology and Rural Employment

The effect of biotechnology employment on the nonfarm rural economy and structure has been slight. Most biotech firms have located in urban areas on the west and east coasts. The South has only 10 firms out of over 200 nationally. The number of these companies has not increased over the past 3 years, leading to speculation that a decline is likely in the near term. If biotechnology firms follow the pattern of other high-technology producers, the next phase will be characterized by rapid growth of existing firms within the same geographical locations where innovation is occurring. The concentration is a result of corporate strategy emphasizing research and development, product design, and marketing, which requires the use of skills prevalent where the original research and development began. Firms prefer to subcontract with other firms and with suppliers located in close proximity. In biotechnology, proximity frequently implies nearness to new information, which is an advantage in an industry with a short production cycle. With the exception of locations near land-grant universities/experiment station facilities, rural areas are likely to be bypassed in terms of employment during the commercialization/agglomeration phase between research and merchandising when the products are finished and prepared for manufacture (Buttel, 1987, p. 12).

In the third (or dispersion) stage of the product life cycle, the characteristics of market and employment expansion, pursuit of economies of scale in production, and dispersion of production units closer to their markets will be evident. This last phase is likely to have the greatest effect on rural America. It will probably be reached within 10-15 years for pharmaceuticals, and later in bulk or commodity chemicals. The actual effect may depend on the manufacture of bioproducts in conjunction with microelectronics, such as biochips or protein components that will reduce the size and electrical requirements of computer hardware to the molecular level. Facilities to perform this function can be located in any region, with only a modest supply of technical and managerial workers. A shift to non-

metro areas appears easier than for previous producer-goods industries (Buttel, 1987, p. 12).

Agricultural and forestry material may become important feedstocks and a substitute for fossil fuel when new biotechnology production processes become generalized in bulk/commodity chemicals. This development could benefit rural America, although it is unclear whether the emergence of these new production processes will actually occur in rural areas. A.J.M. Roobeek, a Dutch researcher, anticipates a net labor displacement as genetically modified micro-organisms and robots are used in the production process as substitutes for skilled and semi-skilled production workers and conventional equipment in pharmaceutical and chemical plants (Buttel, 1987, pp. 12-13; Roobeek, 1985).

Rural America has two possibilities in its favor: the opportunity that biotechnology production facilities will locate outside of urban areas, and the future importance of starch and lignocellulose feedstocks in chemical and pharmaceutical production. The processing of large amounts of these agricultural commodities would create new jobs. Yet, there exists a major liability as well: employment within the chemical and pharmaceutical industries may be rendered obsolete by biotechnology (Buttel, 1987, p. 13).

Effects on Farm Structure and the Environment

Agriculture in the short run will produce the same commodities as it does currently, with continuing adjustment in response to shifts in regional comparative advantage and the fluctuations of world food trade. Biotechnology-related changes in farm structure will be shaped by the degree to which these new technologies increase productivity, are capital intensive, whether or not they require large fixed investment, and how they affect national and international markets. The effects will vary by commodity. Animal production, particularly dairying, followed by pork and beef cattle, will most likely be affected first and most dramatically. Several horticultural crops will be affected, probably to a lesser extent, and effects on field crops are expected to be slower. Rapid increases in dairy productivity are predicted in the second half of this decade, while field crops are expected to proceed along conventional lines (Buttel, 1987, pp. 13-14).

The immediate aim for research on crops by private industry appears to be a blending of chemicals and seed, or chemicals and seed embryos. Millions of individual plant embryos can be regenerated from the original embryonic tissue in the laboratory through somatic embryogenesis. The cultured embryos are then encapsulated in an organic gel and coated with a biodegradable polymer to make "artificial seed" (Kloppenburg, 1985, p. 366). Biotechnology startup companies are in the seed-encapsulating business, which appears to be a promising enterprise. Much private research energy is devoted to achieving herbicide resistance in a wide variety of crops. The intent is to tie resistant seed to special chemicals produced by the same supplier to obtain greater market control. As with bST, the short-term return is likely to be considerable (Doyle, 1985, pp. 214-220). For example, annual sales of Monsanto's herbicide, Roundup, in the 1980's were about $400 million. Sales and profits could be even greater if tied to seeds altered to be resistant to Roundup.

It is unlikely that concerns about the growing toxicity of the environment, based on contamination of ground water, human cancers, and impoverishment of the ecosystem linked to herbicides, will abate if chemical dependency is perpetuated through the new technology. Environmentalists hope that less herbicide will be applied in the future, yet herbicide-resistant seed makes the crop tolerant to larger amounts of chemicals. The farmer, until the present, has retained a substantial degree of control over the onfarm production process, and over the allocation of farm labor. The package approach to input linkage and marketing, which is likely to be facilitated by biotechnological advance, could begin to reduce the farmer's managerial role in plants (Kloppenburg, 1985, pp. 369-370; National Research Council, 1984, pp. 40-42), although this is less clear in the case of bST.

The Office of Technology Assessment (OTA) has estimated that most of the new biotechnologies will be divisible inputs, that is, usable in small quantities, but slightly more capital intensive than current inputs. OTA projects a continuation of the longstanding trends of concentration of agricultural production into fewer and larger farms. OTA, like other studies, stresses the effect of bST in dairy farming as traumatic, with dairy farms declining 30 percent or more within a decade of commercial introduction (Buttel, 1987, p. 14; U.S. Congress, OTA, 1986, pp. 40-42).

The Breadth of Biotechnology

Numerical representations, project listings, and cited examples do not adequately cover the scope and the possibilities of biotechnology at present. Some long- and short-range effects have been discussed, but not the diversity of projects and the most recent breakthroughs. Four additional areas of direct effect deserve attention: future plants, animals, foods, and fuels.

Future Plants

The chronology on the facing page provides some perspective on how biotechnology, despite its revolutionary character, is an outgrowth of the scientific exploration and commercial applications that preceded it.

The chronology indicates the ability of science to alter every major food crop, monocots as well as dicots, through direct gene manipulation. Although a variety of techniques have come into existence, one of the most commonly used is the Agrobacter insertion of the Ti plasmid studied first by Smith. It is used routinely in the transformation of nightshade plants such as tobacco, tomato, and petunia. Extension to other, more important crops is being made with species in other dicotyledonous families. Although data have been cited that Agrobacterium can be used in transfer to the monocots, clear evidence exists only for asparagus. Because the bacterium does not induce crown gall in monocots, such as rice, corn, and wheat, other methods of gene transfer have been developed for these crops (Goodman and others, 1987, p. 52; National Research Council, 1984, p. 21).

From Natural to Laboratory Gene Transfer in Plants

1840
Von Leibig studied nutritional requirements for plant growth.
1860
Charles Darwin published his theory of evolution (1859); Wallace arrived at the same conclusions in the United States. Impact of theory felt in the United States after Civil War.
Sach's nutrient solution defined.
Gregor Mendel active.
1880
Role of chromosomes in cell division understood.
Burbank potato developed. Burbank established experimental gardens in California.
1900
DeVries studied mutations in plants.
USDA plant germplasm collections started.
Mendel's laws of inheritance rediscovered.
Embryo culture begun.
Early work on heterosis in corn (maize) commenced.
The crown gall phenomenon, agrobacter bacterial transfer of DNA studied by Erwin Frink Smith at the Beltsville Station, MD.
1920
Muller and Stadler demonstrated induced mutations by x-rays.
First interspecific gene transfer in wheat made.
Manipulation of ploidy levels using colchicine succeeded.
First plant growth substances (auxins) discovered.
1940
Commercial hybrids in corn widely grown.
Genetic transformation shown to be cause of crown gall disease.
Hoagland's solution defined.
1950
Cytokinin discovered.
1960
Mustage and Skoog medium defined.
Protoplast technology originated.
Proliferative organogenesis demonstrated.
Totipotency of single plant cell demonstrated.
Anther culture led to production of haploid plants.
1970
Somatic embryogenesis from protoplasts demonstrated.
Restriction endonucleases discovered.
First recombinant DNA experiments conducted.
First protoplast fusions reported.
Plant meristem culture devised.
Transfer of plasmid DNA as cause of crown gall disease described.
1980
Mendelian inheritance of nonsexually transferred genes in plants demonstrated.
1986
Researchers at University of Nottingham, England, regenerated rice plants from single-cell protoplasts, removing a significant barrier to genetic engineering in the cereals.
1987
Researchers at Friedrick Meischer Institute in Basel, Switzerland, and the John Innes Institute (U.K.) moved genes of maize streak virus into corn cells via agrobacter bacteria, demonstrating that members of the grass family are amenable to genetic manipulation using the agro-infection technique.
1990
USDA's Plant Genome Research Program was created with a budget of $14.7 million for FY 1991, and it will locate important gene markers on chromosomes, determine gene structure, and facilitate gene transfer.

(Doyle, 1987; Goodman and others, 1987, p. 52).

Not only is the potential of biotechnology likely to be realized within this generation, but the extensive product applications derived from altered plants are also likely to be commercialized. The cloning of oil palms has been underway since 1977 and continues. The Weyerhauser Corporation has experimented with conifer embryos for a generation, and the test-tube production of plantlets has been reported for a number of commercially important species, such as redwood, white spruce, longleaf pine, western hemlock, and Douglas fir. The heavy investments by chemical companies in herbicide-resistant crops, microbial pesticides, and microbial inoculants should be successful in the short run. As Doyle has pointed out, pesticide/herbicide resistance has received far greater research investment than the nutritional content of plant foods (Doyle, 1985, p. 319; Elkington, 1985, pp. 114-116).[22]

One of the most promising areas of crop improvement is nitrogen fixation; however, complexities have slowed the pace. The "NIF" genes, 17 genes that confer nitrogen fixation in bacteria, have undergone extensive study and mapping at Sussex University, England. Given the complexities of moving so many genes, prospects for the introduction of self-fertilizing crops in the short term appear remote. Another avenue is to enhance the symbiotic relationship between leguminous plants and the *Rhizobium* bacteria, which fix atmospheric nitrogen. In this case, genetic manipulation of the bacterium is easier than manipulation of the plant. When inoculated into plants, improved strains of *Rhizobium* have produced increased vigor and growth (Elkington, 1985, pp. 119-120).

Fragrances and flavors derived from expensive imported plants have become a target for biotechnology. For example, natural shikonin (*Lithospermum eryghrorhizom*) costs about $4,500 per kilogram and requires 3-5 years before the roots may yield 2 percent of the drug. It is used for burns and wounds, and as a dye for silks and cosmetics. Tissue culture research using the most productive cells of the plant has brought about significant increases in yield, as high as 15 percent, resulting in reduced costs. The technologies now available are liable to perpetuate more broadly based advances in plants (Elkington, 1985, pp. 121-123).

One of the newest and most promising projects is the U.S. Department of Agriculture's Plant Genome Program. Begun on October 1, 1990 and funded at $14.7 million for FY 1991, the intent is to improve agronomic, horticultural, and forest species by mapping out an entire plant genome. It is a collaboration of four agencies within USDA--the Agricultural Research Service (ARS), the National Agricultural Library (NAL), Cooperative State Research Service (CSRS), and the Forest Service (FS). As the knowledge base is accumulated through ARS-funded competitive grants, it will be placed in a plant genome database developed at NAL for wide dissemination. The database will include plant genome information on four agriculture species--maize, soybean, wheat, and loblolly pine. The collection and evaluation of the database information is the responsibility of Frank

[22] Most material on future plants, animals, foods, and fuels comes from Elkington, 1985, pp. 138-171.

Green and Olin Anderson (wheat), Edward Coe (maize), Randy Shoemaker (soybeans), and David Neale (pine). Cooperators in the project are taking pains to ensure that all database-related activities are performed in a coordinated manner. The ultimate master goal is a generic master database design (Probe, 1991, pp. 1, 3, 5-6).

Animal Applications

In viewing the sweep of animal improvement and disease control by public science over the past 120 years, the knowledge base in genetics, immunization, and veterinary sciences has expanded to facilitate a revolution in productivity based on healthy, eugenically designed farm animals (Wiser, 1987, pp. 224-230). Future dairy breeds will be larger and more productive sources of milk products. The pig of the future will probably contain less fat and more protein, conforming with continuing U.S. dietary preferences. Biotechnology will supply the necessary growth hormone in both cases, which will be administered in the fashion of anabolic steroids, such as diethylstilbestrol (DES). The new bioproducts will probably be safer for the consumer and more effective in producing the desired results. The confinement production of pigs, beef, and chickens will probably continue, with the animals subject to the same trauma, medicated feeds, and consequent antibiotic resistance as before. Critics of confinement will find no new options generated by the new bioproducts for a change toward greater humaneness within the industry. FDA regulators will find no new factors to assist them in determining the risks of medicated feed to the public at large. Since animal products containing DES and other synthetic growth hormones are now banned in the European Community, biotechnological products are likely to experience the same negative pressures. Whether the intent is social well-being or economic exclusion, or both, these are actualities that public policy will have to address.

Production, growth, and marketing of animal protein will become more efficient. With exact methods of sexing animals and embryo transfers, commercial breeders will save substantially in labor and in costs. The dairy herd will be able to progress into the highest quality breed in one generation, not four or five. This is a benefit for American herds, but an even greater advantage for South American breeders as the technology is exported and adopted. Such a development is likely to have an immediate effect when viewed in light of the U.S. herd buyout and export program of top livestock conducted in 1986-87.

Other new ideas are being developed. For example, a protein has been identified that, when injected into sheep, will cause the fleece to shear with few side effects. This protein, called epidermal growth factor, is extracted from the salivary glands of male mice. It may also be extracted from cow's milk and then grown in fermenters using bacterial or yeast technology. Research in fish development and farming is yielding larger, faster growing trout and carp that can survive better in heavy-metal-polluted water that would normally kill the existing species. Environmentalists have argued that a better use for biotechnology would be to reduce acid rain, rather than to facilitate adjustments to it by fish and wildlife. The Chinese are reengineering carp along similar lines and trying to develop silkworm lines for use as model research species in place of *E. coli* and *Drosophila* in developmental

biology. Genetic engineering is liable to bring extensive advances to the entire silk industry. Now that the gene for the giant silk protein has been cloned, the possibility exists that future silk will come from fermentation vats (Elkington, 1985, pp. 134-137).

New Foods and Food Producers

The new fermentation applications of biotechnology are resulting in new foods and new food producers as well as sophisticated refinements throughout the existing production process. This development is not restricted to the United States, but is a worldwide trend. Scotland, a large producer of whiskey, is now being challenged by Japan. However, Scottish entrepreneurs are responding to the Japanese rivalry by creating a new, competitively priced soy sauce. Biotechnology will probably play an expanded role in refinement of conventional fermentation processes involving dairy products, beverages, cocoa, and development of new strains of bacteria and yeasts. Yet, there is a bias among the biogenetic companies against the food and drink markets because the profit margins are considerably less than in pharmaceuticals. Any new product will be viewed by licensing authorities as new and novel and, therefore, will be subject to the same costly approval procedures as pharmaceuticals.

Biotechnology can shorten certain time spans that will benefit the food industry. The new tests for *Salmonella*, for example, pinpoint food contaminants, frequently in less than 36 hours, which is an improvement of several days over the older methods. A commercially available enzyme can reduce the ripening period for cheesemaking by 2 months (about a third) for cheddar cheese. The savings are projected at more than $50 million annually for the industry, once the enzyme is further refined and becomes acceptable to cheesemakers. Toxicity testing of such enzymes, as required by Federal regulations, has caused concern within the industry. The process for regulatory clearance is still new. A possible test case has emerged about genetically engineered rennin in cheese produced by Genencor, a joint venture between Genentech and Corning Glass Works.

Genencor completed the world's first large-scale trials of cheeses made with rennin produced by genetically engineered bacteria in the 1980's. The product is comparable in flavor and texture with the naturally created cheese and possesses the advantage of production in unlimited quantities. Unlike natural rennin made from the stomachs of calves, the new product would be acceptable to vegetarians. Another U.S. biotechnology company, Collaborative Research, received the first British patent for recombinant rennin in 1984, which the company claimed to be the first patent on rennin as well as the first patent on an industrial enzyme.

Other biotechnology firms are seeking saleable bioproducts of cheesemaking. Whey, for example, has received considerable interest as a source of protein, a flavor-enhancer, binder in hamburgers, and substitute for egg whites in baking, although the cost has yet to become competitive. Costs in the health and diet markets, however, are not as critical. Another byproduct of whey is methane gas. Eight thousand tons of cheese will produce about

80,000 tons of whey waste from which 300 tons of protein can be extracted and a volume of methane gas equivalent to 600 tons of oil. In Wales, biotechnology is concentrating on novel uses of Welsh milk in yogurt and in production of a milk liqueur to rival Bailey's Irish Cream, which currently commands the British liqueur market.

In an experimental stage within the Champagne region of France, work is underway on a faster champagne production process. Yeasts are encapsulated in a gelatinous membrane so that the sediments can be removed more easily. If this is accomplished properly, many filtration steps and subsequent losses of liquid will be eliminated. Costs will be cut dramatically, but at no loss in the quality of the product. Brewing industries worldwide have embarked on biotechnology research as much to ensure survival as to find new profitable products. United Breweries of Denmark (composed of Carlsberg and Tuborg) launched Carlsberg Biotechnology in 1982 to develop new technologies and to commercialize enzymes and other products involved in the brewing process. New yeasts are being developed that are tailored to the barley and hops of different regions of the world.

The U.K. Brewing Research Foundation is one of a number of organizations developing diet beers. They are working with new yeast strains that break down dextrin compounds and produce a low-carbohydrate, low-calorie brew. Yeast fusion techniques or rare mating, the crossing of normal brewing strains with mutant strains that will not fuse in the normal way, have potential for the brewing industry. Many of these traditional fermentation industries are not only making products for themselves, but are diversifying into new areas.

Allied Breweries of the United Kingdom, for example, attempted to market a continuous fermentation process, originally developed for beer production, aimed at the fuel-alcohol market. In the United States, a number of new biostartup companies are funded by brewers like Adolph Coors, which is trying to develop new metal-cleaning products expected to be environmentally safer than the existing chlorinated products. As pharmaceutical firms have moved into agricultural products, some brewers are venturing into pharmaceuticals. Anheuser-Busch signed an agreement in 1983 with Interferon Sciences to develop yeasts for recombinant interferon production. Kirin, one of Japan's leading brewers, entered into a joint venture with Amgen to develop and market the hormone erythropoietin, while Suntory has the marketing rights in Japan for Schering-Plough's gamma interferon.

Dairying companies like Snow Brand and Meiji Milk are moving into medical biotechnology. Snow Brand is making the transition to medical biotechnology by way of health foods and foods with some medical effect. Snow Brand already sells milk products for people who cannot tolerate the milk ingredients phenylalanine and histidine. The company is developing products designed for heart disease and cancer patients, and is also moving into plant biotechnology. Specialty businesses, such as spice companies, are investing funds in biotechnology to improve production.

Japan dominates the world in the production of amino acids, which are used as additives in

animal and human foods. The best-selling amino acid is monosodium glutamate (MSG). Besides glutamic acid, other key amino acids are aspartic acid, methionine, and phenylalanine. Aspartic acid and phenylalanine are the two main components of the new sweetener, aspartame.

In the United States, Genex developed the bioprocess for producing these last two amino acids and derived much of its revenue from sales to G.D. Searle, which markets aspartame as Equal (a granulated sugar substitute), or NutraSweet (in diet versions of Coca-Cola, Pepsi-Cola, and Seven-Up). Genex also developed an even sweeter tasting amino acid, serine. Although no new sweeteners had been cleared for marketing in the United Kingdom since the banning of cyclamate in 1969, the British government cleared three in 1983: Searle's aspartame, which is 200 times sweeter than sugar; Hoechst's Acesulfame K, which is not as sweet as aspartame, but more stable; and Tate & Lyle's Talin, which is 3,000 times sweeter than sugar and derived from a rare African fruit. The gene for this sweetener, thaumatin, has also been cloned into *E. coli* and into yeast at the Unilever Research Laboratory in the Netherlands.

Another aspect of the application of biotechnology to sweetener production is that other natural fruit sugars are being used instead of cane sugar. This is most apparent in the soft drink industry. Altered enzymes are used to convert glucose into fructose or fruit sugar, a process developed commercially in the 1960's. Fructose is found now in Coca-Cola and Pepsi-Cola. The conversion process was done initially in a batch reactor, but a continuous system was developed in 1972 that facilitated the scaling-up of production. A big industrial plant can convert about 900 tons of corn starch into high-fructose syrup every day.

Substitution of the high-fructose corn syrup (HFCS) for cane sugar has produced some adverse effects. A link has been established between the new product and the inducement of diabetes in laboratory mice (Cohen and others, 1971, pp. 17-21; Lappe, 1984, pp. 251-252). The livelihood of millions of Third World people has been threatened by the substitution of HFCS for cane sugar. Income from sugar exported from the Caribbean declined from $686 million in 1981 to $250 million in 1985, a figure that suggests that the social fabric of the region was seriously affected. Relocation of 500,000 field hands, widespread neglect of sugar farms, and diversification to other crops have occurred (Doel and Junne, 1986, pp. 88-89). Farmers may be tempted to grow crops from which illegal drugs are produced to earn more money. Pressures on U.S. borders are liable to increase as illegal immigrants press forward in greater numbers to find work in areas familiar to them. Substitutions of this kind will probably continue, producing further disruptions at home and abroad.

Vitamins and food flavorings are another area of biotechnological interest. More productive microbial synthesis of vitamins such as B12 is possible, and blue-green algae may become a source of vitamin E. W.R. Grace has invested in Synergen to have the company screen large numbers of micro-organisms for possible flavoring and other food

additives (Elkington, 1985, p. 151).

Another area likely to have a significant effect is single-cell protein (SCP). SCP includes dried cells of micro-organisms such as bacteria, algae, molds, and yeasts. Interest in this simple technology has led to trials in the alkaline waters of Mexico's Lake Texcoco. Alkaline waters are a traditional source of *Spirulina*, which is still dried and eaten by people living near similar ponds in other parts of the world. An Israeli company, Koors Food, has become interested in this technology. The company's main interest is a green algae, grown in brine ponds, which produces glycerol, a vital raw material for chemicals, detergents, cosmetics, tobacco, pharmaceuticals, and explosives. SCP has also been produced by the action of bacteria, yeasts, and fungi growing on feedstocks such as molasses, methane, methanol, ethanol, cheese whey, cassava starch, and a range of agricultural and forestry wastes. The product has created hope that the food problems of the Third World can be solved through SCP technology. In the short term, this hope appears premature. SCP is highly capital intensive, involves large outlays for facilities, and will probably face stiff price competition from existing sources. The economics are liable to be better for nations that possess surplus methanol and have an agricultural deficit, such as the former Soviet Union and the Persian Gulf states. Israel's major competitors in the development and production of SCP are the former Soviet Union, ICI Corporation, and Phillips Petroleum. SCP may be marketed by Phillips for direct human consumption, although it was originally intended for the animal-feed industry. It will probably be used to fortify flour or rice in the Third World, rather than as a food by itself.

Food use of various fungi is being pursued by Ranks Hovis McDougall (RHM), Europe's fourth largest food manufacturer. Since the 1960's, this large bread producer has spent over $45 million on a fungus that can be knit into acceptable substitutes of fish, chicken, and meat. In 1984, RHM began to enlarge its production. Thousands of fungi have been studied since 1968, leading to discovery of a new micro-organism, *Fusarium graminearum.* The mold, which is related to mushrooms and truffles, is odorless and tasteless, and contains about 45 percent protein and 13 percent fat, a composition similar to that of grilled beef. The fat content is less than that in raw beef, and *Fusarium* is high in dietary fiber. The relatively slow-growing mold cells, known widely as mycoprotein, have the advantage of a nucleic acid content below the acceptable ceiling of 1 percent. Mycoprotein possesses an amino acid content close to that recommended by the Food and Agriculture Organization of the United Nations as "ideal." Even more unusual is the versatility of the fungus, which has the capacity to be constituted as soups, fortified drinks, biscuits, and convincing mock chicken, ham, and veal. Mycoprotein and its derivatives are an entirely new product of biotechnology and are considered by the FDA to be a new food. The key to the adaptability of the mold is the ability to control the length of fibers. Jack Edelmen, RHM's research director, believes that mycoprotein is an economical way of converting any surplus carbohydrate into foods of much higher nutritional and commercial value. In the United Kingdom, the feedstock might be based on wheat; in Ireland, the potato; and in tropical countries, cassava, rice, or sugar. RHM is scaling up production and is investing in animal and human trials to obtain FDA approval. The only obstacle remaining is public

willingness to accept the new product at mealtime.

New foods and drinks that will be available by the turn of the century or sooner may not even be currently imaginable. Consumers will probably not know that biotechnology is involved in their diet. While the manufacturer may stress the natural aspect of the product, it is unlikely that genetic engineering will be mentioned on the product label. Tomatoes, for example, may look and taste alike, but with the cloning of the ripening gene, they are apt to be different from those grown yesterday and today.

Future Fuel

According to the Volkswagen Corporation, automobile fuels by the year 2000 are likely to consist of gasoline, methanol from coal, diesel oil, and liquefied petroleum gas, with only a small percentage of ethanol derived from biomass. "Gasohol," used widely during the energy crisis of the 1970's in the United States, is a blend of 10 percent ethanol with 90 percent gasoline. The alcohol production process involves three steps: reduction of the material to water-soluble sugars, fermentation to produce alcohol, and distillation by boiling to separate the alcohol from the water. Considerable applied science and social science research went into alcohol development as an alternative source of energy. Brazil and other countries actually became committed to full-scale production, with mixed results. For a number of reasons, the energy crisis abated by the 1980's, and the avenue of alternative fuels was de-emphasized in the United States. Nevertheless, certain discoveries were made. Alcon Biotechnology, a joint venture between John Brown Engineers and Allied Breweries, developed a continuous-fermentation process that could be housed in a standard shipping container. The process appealed to and gained approval in countries such as the Philippines, which had been trying to produce more fuel alcohol to offset growing oil import bills. Although significant sales of the new process did not materialize, the process may revive if oil prices rise significantly.

Fermented fuel from biomass has made headway in a few parts of the world, and other processes, such as production from waste products, are being investigated by biotechnology companies. Biomechanics, for example, was one of the first companies to become involved in anaerobic waste treatment technology. Anaerobic digestion of wastes takes place in the absence of air and results in the conversion of organic matter, by bacterial action, into a useful mixture of methane and carbon dioxide. In this process, over 93 percent of the effluent is converted into gas, leaving 3 percent as sludge, which is more efficient than the comparable biomass conversion into alcohol. The first commercial bioenergy plant was built in Ashford, Kent, England, by RHM, and was followed by a second facility in Bordeaux, France. As part of a continuing development program, five mobile plants have been sited at industrial locations in the United Kingdom. They were used to treat effluents from dairy, cider, pectin, confectionery, yeast, brewing, distilling, and chemical plants. In Italy, the process was used to treat effluents from cheese and ham processing, and in Spain, in slaughterhouse operations. Savings on water charges for effluent treatment and energy savings derived from use of the methane show that a bioenergy plant can make a financial

profit not realized through aerobic treatment, as well as satisfy statutory requirements for disposal of waste.

In the United States, firms like BioTechnica have been examining methods in which landfill waste-disposal sites can be converted into "bioreactors" for methane production. Many landfills take in 5,000 tons of refuse every day. One percent of the national energy need could be satisfied by this type of process. The new concept envisions designing the landfill site from scratch as a giant bioreactor, with gas production as the basic objective. Although the overall energy contribution is likely to be small, the magnitude of the national requirement makes the technology important.

Another viable route for energy production appears to be in developing enzymes, like cellulase, which break down cellulose. An estimated billion tons of cellulose that could be converted into chemical energy goes to waste in the United States each year. The gene that codes for cellulase has been isolated by scientists at Cornell University and grown in large quantities by *E. coli.* Although still in the development stages, the finding shows how rDNA technology can eventually transform biofuel production.

The energy crisis of the 1970's produced many new ideas about energy generation, one example being photobiological generation, the production of hydrogen by whole micro-organisms. Before support for this approach was reduced by the Reagan administration in the 1980's, a number of photosynthetic bacteria, nonphotosynthetic bacteria, cyanobacteria, and green, red, and brown algae were discovered. These produced the enzyme hydrogenase, which is necessary to make hydrogen. Professor David Hall of King's College, London, believes that such a system could supply the world's current energy needs using 0.5 million square kilometers (0.1 percent of the earth's surface), an area about the size of France (Elkington, 1985, p. 151). If fossil fuel reserves become depleted, these energy alternatives may become future realities. Whether the farmer or rural areas will benefit by this possibility depends on the methods actually employed and their location.

The Competitive Position of the United States in Biotechnology

> The current issues before the Congress focus piecemeal on the problems related to capital formation,[23] patent protection,[24] drug pricing,[25] and research funding. These relate almost exclusively to the economics of biotechnology, not its ethics or future direction. Once again we are building more and faster cars without the highways to carry them. We cannot continue to rush forward with this new tool

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[23]See The Enterprise Capital Formation Act of 1991, S. 1932. 102d Cong., 1st Sess. (1991).

[24]See The Biotechnology Patent Protection Act of 1991, H.R. 1417. 102d Cong., 1st Sess. (1991).

[25]See The Orphan Drug Amendment, H.R. 4638. 101st Cong., 2d Sess. (1990) and S. 2576, 101st Cong., 2d Sess. (1990), H.S. Rep. No. 635. 101st Cong., 1st Sess. (1990).

without considering what is at the end of the road. (Senator Albert Gore, Jr., 1991, *Harvard Journal of Law and Technology*, p. 29.)

Then-Senator Gore articulated the prevailing view among lawmakers and the executive branch, but not industry, advocating regulation and sharing of benefits of biotechnology widely among people. In the 1980s, Orville G. Bentley, former Assistant Secretary of Science and Education for USDA, was more concerned with American competitiveness. "Fundamentally, we have to realize that what we do in science and in the development of new technology has a great deal to do with the competitive position of U.S. industry--especially our great American agricultural industry" (Bentley, 1987, p. 28).

This was also the view shared by then USDA Deputy Assistant Secretary of Economics Ewen M. Wilson. In testimony before the House Subcommittee on Livestock, Dairy, and Poultry on June 11, 1986, Wilson advocated bST: "The potential benefits of bGH [bST] are greater efficiency, lower costs of production, increased consumption, improved profitability for remaining dairy farmers, a greater ability to compete in the world dairy market, and also to compete with substitute dairy products. Other countries also are conducting research on bGH. We cannot, nor should we, stop technological development from taking place" (U.S. Congress, House of Representatives, 1986, pp. 6-7). Public information released by the manufacturer of bST, the Monsanto Corporation, states clearly that, "bST will keep American dairymen competitive with growing dairy imports and will in the longrun reduce cost to society" (Monsanto, 1987). The National Research Council's Committee on a National Strategy for Biotechnology in Agriculture released a report in 1987 that calls for the subsidizing of research at the level of $500 million each year, with a greater opportunity to involve private universities (National Research Council, 1987, pp. 1-11).

The need to keep the United States competitive is also advanced by land-grant college deans and by private universities to justify requests for funds or permission to perform experiments that may not be deemed absolutely safe. The argument can be reduced to a simple phrase: "if we do not do this, we as a Nation will lose out." Competition, however, must be evaluated in the light of the nature of biotechnology itself and its likely use by other countries.

Biotechnologies compete frequently among themselves. Single-cell protein and protein from soybean products are likely to be competitive as both animal and human protein supplements. The new sweeteners will also be in competition. This kind of competition is likely to continue throughout the entire processing and marketing process, resulting in greater efficiencies as less expensive inputs are substituted for more traditional ones. An informed manager is usually anxious to continue to cut his production costs.

Although there are common foods and food products widely grown and consumed throughout the world, many are unique to specific local conditions. If the new applications are to have maximum social benefit, biotechnology will have to serve a diverse clientele

and be put to different uses. In the Far East, the Japanese are heavily invested in using biotechnology to revitalize their fisheries. An altered wheat variety that could tolerate the Russian winter would have a large effect upon the grain-exporting nations. Biotechnology may lead to microbial inoculants or crop strains that enable crops to absorb phosphate from high-aluminum soils. South America could then become self-sufficient in agriculture and possibly a new exporter in exotic crops. Advances in the livestock biotechnologies will continue to decrease animal disease, perhaps enabling Africa to develop a meatpacking industry. The hope is that each country will use the new technology to its people's best advantage, suiting it to individual food preferences and greater opportunities for larger numbers.

Biotechnology can make the United States more competitive, but it also helps our competitors. However, given our high level of national commitment and expertise, it is not likely that our Nation will become second to any other in this new technology. Other variables can be equally as important as technological edge. These include the tenacity with which nations maintain domestic markets for homegrown food and fiber, and consumer fears about new products. Richard Fallert points out that the introduction of bST is likely to have little effect on the present protected international market. In a freer market, however, he attaches greater importance to the hormone. What the United States, the leading advanced Nation, chooses to do will be studied and emulated by other nations. Our policy choices can influence whether the benefits of biotechnology will be equitably distributed. The United States can generate greater insecurity, or conversely, greater interdependence among nations. The competition argument, by itself, will not lead to a greater appreciation of the complexities involved in unraveling the new relationship between biotechnology and international trade.

Production of major American crop, animal, and dairy products will probably expand dramatically as a result of the new technology. Yields in wheat are expected to expand by 25 percent by 2005. Corn and soybean yields are predicted to grow at a rate of 1.2 percent each year to the year 2000. These increases will result in large expenditures for storage, and a global glut is possible in dairy, as other producing nations adopt bST. Biotechnology will be surplus-producing and price-depressing, for middle-sized and large farms, and an ideal technology for large-scale agriculture, major food processors, and large-volume traders. It is ideal for saving money in food processing, clones to fit monoculture-style production, and securing raw material specificity, whether for genes involved in string beans to withstand flash freezing or blanching, or to maximize protein levels in wheat for making bread or barley for brewing. Biotechnology is also ideal for weaning agriculture away from its dependence on chemical herbicides, pesticides, and growth regulators, some of which are known causes of disease and death. Research is being conducted in this direction, yet the emphasis is on crops that can genetically withstand the damaging effects of herbicides (Doyle, 1987, pp. 14-17). Future judgments about the new technology will take into account its success or failure in achieving a safe, healthful, and expanding food supply; a prosperous agriculture for producers; an agriculture less vulnerable to natural disaster; and an international arena with diminished world tensions.

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Toward Regulation of Biotechnology in Agriculture

Regulation is an evolving process, usually the result of perceived dangers or of catastrophes that call the existing rules into question and are then changed in the face of new realities. Regulations are sometimes the result of social activists who successfully galvanize public opinion or the judicial system into action. In the case of biotechnology, both causes have led to debates and regulatory activity in agriculture. A decade before regulation of biotechnology, the question arose as to controlling recombinant DNA research in the interest of public health. Today, not only the research, but also product development and distribution are at issue.

Discussions about the risks to human beings of recombinant DNA in viruses and bacteria began in the early 1970's by Paul Berg of Stanford University and other scientists. Molecular biology had progressed from studies of *E. coli* bacteria to work with animal cells in tissue culture and animal viruses. In particular, there was great interest in tumor viruses that afflicted either natural hosts or could be manipulated to produce tumors in species not normally afflicted. Concerns were raised that it would be possible to insert genetic material from a tumor virus (SV40) into common human gut bacteria (*E. coli*) and induce human cancers, although no simple methods had been found. Certain experiments were postponed voluntarily. A small gathering of scientists convened in January 1973 at Asilomar, CA, to discuss hazards involved with tumor viruses (Kenney, 1986, p. 23).

Before the Cohen-Boyer breakthrough, the opportunity to insert genes into viruses and bacteria had been restricted to a few highly sophisticated laboratories. Afterward, genetic transfer could be performed by substantially larger numbers of technicians. The announcement of the Boyer experiment was made in June 1973 at the Gordon Conference on Nucleic Acids attended by 130 molecular biologists (Watson and Tooze, 1981, pp. 1-3).

As a result of the announcement, a spontaneous discussion took place over the risks that might ensue. Discussions led chairpersons Maxine Singer, of the National Institutes of Health (NIH), and Dieter Soll, of Yale University, to write to the President of the National Academy of Sciences on July 17 requesting the creation of a committee to examine the consequences of recombinant DNA techniques (Singer and Soll, *Letter*, in Watson and Tooze, 1981, pp. 5-6). A second copy of the letter was sent to the periodical *Science* to notify the public of the scientists' concerns; it was published in August 1973. The warning was clearly laid out by the letter's second paragraph: "Certain such hybrid molecules may prove hazardous to laboratory workers and to the public. Although no hazard has yet been established, prudence suggests that the potential hazard be seriously considered."

Although not all the biologists favored sending out the second letter to *Science* (48 to 42 in favor), the two published statements became a primary link in a chain of events that has culminated in the current regulatory activity. The popular press seemed to ignore the warning, and news articles were published extolling the achievements of the new technology. Nevertheless, research scientists were determined to be heard. Berg and a few

other scientists asked the National Academy of Sciences for guidance, and Berg agreed to chair the Committee on Recombinant DNA established by the Academy. As chairman, he sent a statement of views to *Science* and to the British weekly journal *Nature*, precipitating adverse national headlines in the United States. The Berg statement recommended that a voluntary moratorium be placed upon certain kinds of experiments and, in the interim, an NIH advisory committee be established to offer oversight, develop appropriate procedures, and devise guidelines for "investigators working with potentially hazardous recombinant DNA molecules" (*Science*, 1974, p. 303; Watson and Tooze, 1981, pp. 3, 11). In October 1973, NIH appointed a DNA Molecule Advisory Committee to create the requested guidelines (Doyle, 1985, p. 244).

The Berg letters stimulated an immediate reaction from scientists working within universities in relevant biological areas. Dr. Waclaw Szybalski of the University of Wisconsin first suggested the means of biological containment for experiments outlined by Berg. Sydney Brenner at Cambridge, England, and the Berg group began to plan an international conference, a second Asilomar Conference, to confront the safety question. In Britain, the moratorium letter had the most immediate effect. The government intervened directly, possibly because of a fatal accident with smallpox virus at the London School of Hygiene and Tropical Medicine in 1973 (Auerbach, 1974; *Letters* in Watson and Tooze, 1981, pp. 4, 12, 15-16).

At the second Asilomar Conference in February 1975, 140 scientists met to discuss perceived biohazards. The conference produced a working consensus among the majority of participants as to what was acceptable, issued a report to the National Academy of Sciences, and published an article of findings in *Science*. The conference publicized advances in molecular biology and raised fears of potential epidemics caused by escaped organisms (Berg and others, 1975, pp. 991-997; Kenney, 1986, pp. 23-24; Rogers, 1975, pp. 36-42).

A day after the 1975 Asilomar Conference ended, the NIH Recombinant DNA Advisory Committee (RAC) met for the first time, but did not issue its guidelines for the next 16 months. The final product was the result of considerable infighting between those who wanted loose restraints and the middle-of-the-roaders (Krimsky, 1982). In the same year, Senator Edward Kennedy's Subcommittee on Health held a special session on genetic engineering that raised questions as to the role of Government in overseeing potentially dangerous research. By the end of 1975, the debate had become a discussion topic in the public press, such as in the *New York Times*, the *Boston Globe*, and the *Washington Post*. A new phase began in 1976 as the debate within the scientific community became increasingly politicized (Kenney, 1986, p. 24; Watson and Tooze, 1981, pp. 137, 143-153, 157-174).

Perhaps the most dramatic debate occurred in Cambridge, MA, in 1976, when the city council asked Harvard University to justify its decision to build a P-3 containment facility, which is considered relatively secure and includes airlocks and other special features. After

a bitter debate, the council asked Harvard and Massachusetts Institute of Technology administrators to refrain from any P-3 type experiments until a civilian review board could compose recommendations for council consideration. In January 1977, the council voted to permit P-3 experiments, subject to certain restrictions, in addition to those prescribed in the NIH guidelines, which had already been issued at the beginning of the hearings. These guidelines, which became a model for research in the more developed nations and for USDA in drafting its own regulations, were a set of rules for conducting biotechnological research and were binding on publicly sponsored research only. An indirect result of the debate fell on the scientific community. If localities could regulate laboratory research on the basis of protecting the public health and safety, the independence of scientists to pursue their own interests would become limited (Kenney, 1986, pp. 24-25; Watson and Tooze, 1981, pp. 91-93, 103).

Other State and local governments established rDNA committees, which exacerbated anxieties within the scientific community over control of personal research. A series of local laws on the one hand, and the absence of national legal uniformity on the other, implied that researchers at some institutions would possess an advantage over others in areas where strict regulations were enforced. Such a situation would tilt the competition for research funds in favor of the least regulated institutions. While scientists raised the issue of hazards, they also experienced anxieties about their own work becoming handicapped by regulations (Kenney, 1986, p. 25; Watson and Tooze, 1981, pp. 93-94, 132-134).

NIH's 1976 guidelines, since their inception, did not possess the strength of Federal regulation. They were mandatory only for recipients of Federal funding and could be ignored by private researchers. Nor was the production of large amounts of bioproducts covered. The Senate Subcommittee on Health, after a series of oversight hearings on the guidelines, determined that regulatory legislation was necessary to extend mandatory safety procedures to all research. The Pharmaceutical Manufacturers Association, environmental groups, and other interested parties joined the debate. Senator Edward Kennedy and Congressman Paul Rogers introduced legislation a year later (S. 1217 and H.R. 7897) to render the guidelines mandatory and appoint advisory groups selected from the general public. Opposition among biologists coalesced in 1978 to resist legal control, and the final decision in Congress was to do nothing. The factors involved were not only the lobbying by scientists and by university administrators organized as "Friends of DNA," but also the increasing realization of the valuable products that could come from rDNA, and the fact that no hazards had yet materialized (Kenney, 1986, pp. 25-26; Watson and Tooze, 1981, pp. 139-142, 178-185).

Commercial opportunities that could be derived from the new techniques quickened the tempo of research. The NIH guidelines were broken when researchers inserted a rat insulin gene into bacteria, in the haste to produce human hormones from bacteria. At the University of California, San Francisco, microbiologist David Martin noted the internal stress arising within his department as a result of private commercial interest in human

insulin. Some researchers thought there should be no commercialization. The debate over regulation became bitter by 1978, as environmental groups and other activists sought tighter controls over rDNA research, and scientists and industry resisted. Eli Lilly and Genentech, then involved in a joint venture to produce genetically engineered insulin, took issue with an NIH rule limiting the size of laboratory batches of genetically produced substances to 10 liters, which is a volume too small for commercial production. The Pharmaceutical Manufacturer Association subsequently requested the Department of Health, Education, and Welfare, of which NIH was a subordinate part, to propose new guidelines that would be voluntary for industry. In 1979, the pharmaceutical industry also stopped an FDA proposal to make the sale of any genetically engineered drugs contingent upon mandatory compliance with NIH guidelines (Doyle, 1985, p. 245; Kenney, 1986, p. 26).

Revisions in the guidelines began in 1978 as it became clear that many of the regulations were too restrictive. While the public was given a greater voice in regulatory bodies, actual containment requirements for many experiments were relaxed. The American Pharmaceutical Association lobbied successfully for a voluntary registration system for industry rDNA research and research not funded by NIH. Also, RAC membership was increased from 16 to 25 members, with about a third to be public members. Institutional Biosafety Committees (IBC's) were to be established at each institution to ensure enforcement of the guidelines instead of direct enforcement by NIH. These committees were required to have at least two members and not less than 20 percent of the membership from outside of the institution. The public participation requirements resulted from lobbying by interest groups. Yet, as public concern diminished, the guidelines were correspondingly loosened. This occurred twice in 1980, once in 1981, and once in 1983. The exemptions of other host-vector systems, which were of scientific or industrial interest, were made less stringent. The guidelines were revised to permit closed sessions by the RAC to protect proprietary information presented by corporate laboratories. Another major change came in 1981 when the distinction between large-scale and small-scale experiments was dropped, satisfying a request by Eli Lilly (Kenney, 1986, p. 6; Watson and Tooze, 1981, pp 263-304,).

After 1978, the NIH guidelines came under attack from numerous scientists, many of whom were now employees of companies or were on retainer. The concerns that local governments would introduce regulations led to the decision to retain some Federal regulation, although in reality, the 1983 revision made nearly all rDNA laboratory experiments exempt from the guidelines. By 1979, the giant pharmaceutical and chemical companies had entered into the legislative process, having recognized the financial importance of the new techniques. Congress continued to hold hearings, realizing that lawmakers must take a new role in facilitating the establishment of the biotechnology industry. Doubts over safety soon gave way to optimism that large financial returns would accrue from the new technology. Congressional hearings and RAC meetings were held in 1980 in an atmosphere of intense entrepreneurial activity characterized by the growth of the small biotechnology startup companies and increased interest of multinational corporations (Kenney, 1986, p. 27).

The most significant relaxation of guidelines related to the environmental release of altered bacteria. Such releases had originally been prohibited. By 1978, waivers of this prohibition were provided, and by 1982, review and approval procedures were substituted for the waiver. The guidelines were revised and amended to allow for environmental release of genetically altered crops, livestock, and microbes. However, the NIH field-test approvals, even those approved for federally funded research, complied with the National Environmental Policy Act, a fact which became apparent from later lawsuits (Doyle, 1985, p. 246).

The legacy of the rDNA debates included a number of city and town ordinances, a continuing oversight in rDNA experiments by the RAC and Institutional Biosafety Committees, and increased public awareness of the importance of science. The debate did little to delay the development of biotechnology. Genetic engineering became an industrial tool in less than a decade. The debate may even have sped development by attracting the attention of venture capitalists to the commercial value of the new techniques (Kenney, 1986, p. 27).

The Challenge of the Foundation on Economic Trends

Most scientists were satisfied with the outcome of relaxed guidelines, yet some remained concerned and continued to raise the issue of risk in public and in private. To such scientists, regulatory agencies seemed to take a passive interest in the new biotechnological research, although the FDA had tried unsuccessfully to compel compliance of genetically altered drugs for sale with existing NIH requirements. Administrators probably felt that some regulation might be necessary, but made no requests for new legislation, believing that existing statutes were adequate. Although many new concerns had arisen since the late 1970's, the same regulatory posture continued to be maintained. Nevertheless, some actions were taken. Temporary guidelines were issued by USDA and EPA in research and in product development. Scientists were reprimanded for violating these guidelines, and risk was more rigorously assessed.

A small group of activists called the Foundation on Economic Trends, headed by Jeremy Rifkin, was the catalyst for this change in attitude. The Foundation on Economic Trends succeeded, in May 1984, in winning an injunction from a Federal court to prevent field spraying of the ice-minus or anti-frost bacteria in California. Later protests by Rifkin resulted in the fining of the commercial manufacturer for conducting unauthorized tests. In 1986, citing the National Environmental Policy Act, Rifkin was able to stop construction of an Army testing laboratory at Dugway Proving Grounds in Utah until an environmental impact statement was filed. He sued the combined Armed Services to compel a similar assessment of their other 129 contract labs. Until 1988, he caused postponement of the sale of a genetically altered vaccine against swine pseudo-rabies (Van Biema, 1988, p. 16). State and Federal regulatory agencies were influenced by the lawsuit and became active. Rifkin's challenge and the regulators' response became a precedent-setting event in agricultural biotechnology. Although observers viewed the commercialization of bST as

pivotal in the development of biotechnology in the 1980's, Rifkin's intervention in the research of Steven Lindow had even greater implications (*The Milkweed, 1987*, p. 5).

The Lindow Experiments with Ice-Minus Bacteria

The Lindow test of ice-minus bacteria (*Pseudomonas syringae*) was one of three experiments approved by NIH. One involved altered corn plants (August 1981) at Stanford University, and another entailed field testing of modified tomatoes (April 1983) at Cornell University. Steven Lindow's proposed microbial field testing of ice-minus at the University of California, Berkeley, was the first of the three in readiness. He applied for approval to NIH/RAC in 1982 and was given permission. A test date of September 1983 was set. On September 14, 1983, Rifkin's foundation, the Environmental Taskforce, Environmental Action, and Michael W. Fox of the National Humane Society filed suit against NIH for approving the project. A number of charges were brought, the most notable, in the judgment of Judge John Sirica, being the failure of NIH to conduct an adequate assessment of the potential environmental risks of the field test. The fact that the approving NIH committee contained no ecologists, plant pathologists, botanists, or population geneticists weighed heavily in the court's decision to postpone the test. Lindow and the University of California attempted to go forward with testing a second time in May 1984, but were enjoined from doing so by Judge Sirica, who responded favorably to a request for a restraining order by Rifkin and his co-plaintiffs (Doyle, 1985, pp. 248-249). The Sirica decision created intense activity among many Federal agencies to determine the regulatory responsibility in this new area (Witt, 1985, p. 125).

Although no new Federal legislation had been passed to regulate the new technology and the NIH guidelines had been relaxed and applied only to federally funded research, Congress continued to hold hearings throughout 1983 and into 1984. Representative Albert Gore, then chairman of the House Science and Technology Subcommittee on Investigations and Oversight, held hearings in 1983 on the release of genetically altered organisms into the environment. The subcommittee's report called for creation of a Federal interagency task force to review release proposals, assess risks, and develop release guidelines. In the interim, it wanted prohibition of releases by EPA, NIH, USDA, or any other Federal agency. Specifically, the report asked NIH to cease its practice of evaluating and approving proposals for deliberate release from commercial biotechnology companies, which were under no obligation to comply, and that the EPA regulatory role be expanded (Doyle, 1985, pp. 248).

After these developments, the White House became involved. Christopher DeMuth of the Office of Management and Budget (OMB), with help from the Departments of State and Commerce, began to challenge EPA's assertion of authority. DeMuth believed that regulation hampered innovation. Commerce Secretary Malcolm Baldridge, who was Chairman of the Cabinet Council on Economic Affairs, assumed control over the issue, which had previously been with the Cabinet Council on Natural Resources and the Environment, chaired by EPA Administrator William Ruckelshaus (Doyle, 1985, pp. 249-250).

Views from private industry ranged from concerns that regulation would threaten the American lead in biotechnology to acceptance of regulation of the new bioproducts under the existing statutes. The White House and private industry moved in the direction of a "super-RAC" concept, which was a larger review panel of biotechnology experts to provide advice to appropriate Federal agencies. By October 1984, the White House, 15 Federal agencies, including State, Commerce, Health and Human Services, EPA, FDA, USDA, and the National Academy of Sciences, and at least 4 congressional committees were examining biotechnology regulation and related environmental effects (Doyle, 1985, pp. 151-152).

Risk Assessment and Common Sense

Before discussing developments since 1984, it is useful to examine the models proposed and accepted for assessing risk by regulatory agencies. In every risk assessment, there are two variables: the magnitude of the potential hazard and the probability of the occurrence. Perceptions of risk vary, depending on the person making the determination. For example, a researcher whose experiment contains a risk of 1 chance in 100 might consider himself foolish not to proceed. On the other hand, a Government agency might regard the risk as too high if it is aware of several hundred researchers about to release organisms in a short period that have the same probability. A collective industry view might be similar, since a single dramatic mishap could damage the public trust for all participants (Regal, pp. 1-34). The risk event can determine the fate of the industry.

The magnitude of risk is potentially large for some bioengineered life forms. Although micro-organisms, for example, can be genetically programmed to self-destruct and can die out naturally, they can never be recalled from the environment, once released. The probability of occurrence has to be greatly reduced, as P.J. Regal and other scientists have argued, to 1 chance in 10,000 to ensure safety. The essential risk has been broken down into four general areas: the release of a novel organism with unpredictable and irreversible effects; the creation of a new microbial agent, that is infectious to humans or animals, or one that broadens the conventional host range of pathogens; the generation of bioeffluents, which place additional stress on the quality of land and water; and the production of engineered organisms that might have adverse secondary effects of an unanticipated nature (Krimsky and Fraenkel, 1985, p. 610). Estimates of possible damage are difficult because no accidents have yet been recorded during the research phase. One frequently used and controversial model has been the effect of introduced species that actually become established in nature. Seventy-one out of the 854 artificially introduced life forms caused the extinction of resident species through habitat alteration, predation, or competition, although this effect by itself cannot measure the full magnitude of the resultant damage. The gypsy moth larvae are an example of a dominant exotic species, which, while not causing species extinction, have destroyed about 10 percent of hardwood trees in the eastern United States. While extinction forms a convenient criterion for tabulation, it is

only one possible ill effect (Regal, pp. 10-23).[26] Since historical precedents for the new technology are limited, a model that best approximates the consequences of such manipulations is necessary to arrive at the most realistic assessment.

A number of models have been advanced by scientists and industry leaders, each containing basic assumptions about the ecological consequences of released recombinant organisms. The introduced-species concept has also been questioned as to approximation with an organism containing one or a few altered genes. A brief consideration of models will provide insight from which to judge the present approaches to protect the consumer and the environment.

First is the early biotechnology model, which assumes that genetic manipulation is merely a projection of older selection and breeding techniques and concludes that the results will be safe. The limitation of this model is the fact that all forms of manipulation by humans are not equivalent. Domestic species are bred for particular features. During the breeding process, many of their wild traits may be lost, and many undesirable traits may persist. Proponents of this model argue that the same risks will be true for biotechnologically created species. Although gene splicing performed through breeding may not be minuscule compared with what is now being tried with recombinant techniques, traditional breeding has never taken genes from human interferon, for example, and placed them into corn, or taken cattle genes and placed them into tomatoes. While not the ordinary intent of agricultural biotechnology, the introduction of highly unusual traits into wild species, directly or indirectly, constitutes a new and unknown gamble with nature. The model lacks both exactness and generality.

Another frequently advanced model, the "Ordinary Sexual Species Model," assumes that recombination by genetic engineering is similar to ordinary sexual recombination in the many ordinary bisexual species throughout nature. This is only superficially true. In ordinary recombinations, genes from remotely related creatures are not mixed as they may be with new gene-splicing techniques. However, the number of genes separated and joined in new combinations is vastly larger than in single gene insertion. Although humans and cowpeas have genetic sequences that are more similar than expected by chance, humans and grasses do not interbreed, and such engineered combinations of genes would be unusual in comparison with ordinary sexual recombinations. The "Unintended Super-Species Model" allows for the likelihood that many recombinant organisms will have novel genetic options. This implies completely new survival modes and advantages at once. For example, plant species belonging to groups that require medium amounts of moisture may be made drought resistant for the first time in their phylogenetic history. Such a shift in habits would expose the population to new natural selection pressures leading in time to more general genetic reorganization. In either case, ecological release can result in increases in numbers or shifts in habits. Nor are recombinant techniques, as is

[26] I am indebted to P.J. Regal for the model frameworks presented.

often implied, comparable to wide hybridization in plant breeding. Recombinant techniques do not involve the giving up of one set of chromosomes for another. The recombinant organism has foreign genes added to a stable genome, whereas in wide hybridization, the organism has two sets of non-coadapted chromosomes that originate from long-separated gene pools. Recombinant organisms could rapidly evolve into ecologically disruptive "super species," particularly if bacteria or insects are involved. A crude game theory metaphor is helpful in making a general point. In a chess game, a player may or may not gain an advantage by obtaining new pieces, depending on the point of play. If a rook or knight is added during the end game, however, a decisive advantage over the other player would result. The importance of the wide taxonomic difference between host and donor species in making the recombinant organisms is that the player organism can escape its phylogenetic legacy and gain qualitatively unprecedented move potentials (that is: acquire a rook). Alternatively, the transferred genetic material can just as likely be nonadaptive. Only substantial research on natural populations and the evolutionary process, and on genetically engineered organisms, can give society the perspective it needs to assess such risks.

The "Biotically Regulated Species Model" assumes that the engineered species, like native counterparts, will be subject to control by local competitors, predators, parasites, and pathogens. Should the altered population begin to increase, a compensatory increase in population of predators, parasites, and pathogens would return the rogue population to a presumed equilibrium. The question here is simply the accuracy of the assumption.

In reality, other physical (abiotic) factors, such as temperature and rainfall, play as large a role in the prevention of population growth. Damaging outbreaks of native pest species are not uncommon, despite predators and parasites. If genetic modification reduces the role of one or more restricting factors, the competitors might or might not bring the population into equilibrium. Population explosion is not a false issue. Damage does not result only from exceptional numbers. Changes in habits, such as when exotic gray squirrels began eating bark and killing trees in Britain, can be important.

In the "Untuned Engine Model," a popular argument for perceiving recombined organisms as safe is the notion that genomes and nature have been optimized over a long evolutionary history. As a corollary, any alteration will have a harmful rather than beneficial effect on any population left untended in nature. The organism is compared with a high-performance machine: additional tinkering will only untune it and make its survival more difficult in the environment. Although this approach has a strong common sense appeal, the most recent evidence suggests that organisms are only adequately adapted for survival, but not optimally or perfectly adapted. Biomechanical analysis and comparative studies show that there is usually room for improvement. The human eye, for example, is a remarkable biological organ, but it is considerably flawed as an optical device. The conclusion, then, is the average exotic introduction is quite unlikely to become established in nature, yet the possibility is real and cannot be completely dismissed. Genetically altered cats, dogs, pigs, burros, horses, water buffalo, bees, and goats have become established in new

environments, and have sometimes caused expensive damage.

Another commonly argued model, the "Pregnant Pole-Vaulter," is based on the belief that the engineered species will be so burdened by novel combinations of metabolic functions that it will not be able to survive in nature without human assistance. There are living organisms, however, that bear many burdens in nature and still survive. No categorical statement can be made that a feature, which is costly to the organism, will reduce fitness. Any judgment of survivability for organisms with new metabolic functions would have to be made on a case-by-case basis. If the benefit-to-cost ratio is favorable for the organism, then the burden is not considered too great.

A model that claims safety in genetic manipulation is the "Hopeless Monster" case, which bases its central premise on the mutations caused by radiation damage to DNA sequences. Mutations are more likely to harm than to benefit the organism. The addition of functional genetic material from one species into another in reality is not equivalent to the random disruption of a DNA sequence. Organisms that are vigorous in nature are not likely to become crippled. Random genetic mutation could be more harmful than beneficial, but not infinitely more likely to be harmful. Safety is promised through a variety of built-in leashes, deliberate crippling devices, based on limited laboratory models. Yet, it is uncertain how long such crippling genes would be maintained in populations under natural selection.

The "Bankrupt Venture" model argues safety based on the belief that over the millennia, all combinations of traits have been tried, and unfit forms have been eliminated by natural selection. Genetic engineering is thus unlikely to create anything new, and the forces of natural selection will eliminate an altered organism. When the theoretical permutations and combinations of different kinds of gametes are considered, it becomes apparent that all the possibilities have not and never will be realized. Theoretically, one human being alone can produce, through spermatogenesis, more combinations than the total number of atoms in the known universe. This model also ignores the known causes and patterns of extinction, the time scale involved, and biogeography.

The "Baroque Pest Model" argues that because pests and pathogens sometimes show a variety of complicated traits in their life cycles, a great number of rather specific genes would have to be added to a benign organism to transform it into a pathogen. This argument presupposes starting out from pure cytoplasm. Traits allowing for the vigor of the pathogen may have already been present in its benign ancestor. The step from benign parasite to pathogenicity may involve a simple shift to a new host and minimal modifications. Avian influenza viruses, for example, are known to become suddenly virulent and also to infect and kill mammals such as seals.

This brief excursion into theoretical modeling is necessary to arrive at the present "Exotic Species Model" (1986), which is accepted by ecologists (but disputed by molecular biologists) as the most relevant biotechnology research and regulation model (Regal). This

model assumes that most species introductions fail. Most surviving introductions are relatively harmless. A small fraction of intentional/accidental introductions have been disasters, such as the gypsy moth, fire ant, chestnut blight, and "killer" bees. It becomes necessary to study and evaluate genetically engineered species on a case-by-case basis to try to prevent any major disaster. The overall risk, however, is statistically so low that there is no need to call a generic moratorium on all research and development. Scientists may be unable to predict the results of genetically engineered species in abstract terms, but on a case-by-case basis, when details are available, ecologists working with other molecular biologists should be able to give advice that can considerably improve the predictions.

It is important to keep the "Exotic Species Model" in mind when reviewing the policies of USDA and other relevant agencies both in regulation and in research. USDA and other regulatory agencies, while taking applications on a case-by-case basis, may adopt ultimate guidelines based on a framework advanced by Dr. James Tiedje and others on the Scientific Committee on Problems of the Environment and the Committee on Genetic Experimentation (SCOPE/COGENE). Widely accepted by the scientific community, the framework became a point of departure by ecologists working to create guidelines for the environmental release of materials in agriculture. It stated that the "phenotype of a transgenic organism, not the process used to produce it," should be the focus of regulatory oversight (Tiedje, p. 297). The Tiedje report emphasized that survival and reproduction of the introduced organism, its interactions with other organisms, and the effects of the introduced organism on the ecosystem all be considered. It encouraged use of small-scale field tests, "when justified by laboratory and/or greenhouse studies, under conditions that minimize dispersal and under appropriate regulatory oversight."

The USDA Role in Regulation: Jurisdiction and Structure

An Agriculture Recombinant DNA Research Committee (ARRC) was formed in USDA in 1976, to coordinate research policies among the various USDA agencies and between USDA, the National Institutes of Health, and the National Science Foundation. USDA leaders recognized that a uniform set of guidelines was necessary in research, regardless of the source of funding. They endorsed and adopted the NIH guidelines for research in recombinant DNA and established an internal policy requiring compliance with these guidelines as a condition for receiving research funds (U.S. Department of Agriculture, *Memorandum*, 1979).

Since 1976, USDA has developed a multi-level regulation and review process that reflects the complexities of the USDA/land-grant research system. Philosophically, USDA viewed agricultural and forestry products developed through biotechnology as similar to conventional products. Thus, the existing regulatory framework, with the addition of new advisory committees and NIH guidelines, was deemed sufficient for the regulation of new research and resultant products. The existing mandate covers plant and animal quarantine laws, veterinary biologics imported into the United States or shipped interstate, and products related to meat inspection. USDA cooperated with other Federal agencies in

determining the regulatory jurisdiction of genetically engineered organisms that fell within the purview of more than one agency. A "Memorandum of Understanding" between USDA and EPA, dated October 3, 1984, defined the general principles of cooperation, coordination, and communication to be used by the two agencies. A June 8, 1982, memo between USDA and FDA (47 FR 26458) related to jurisdictional questions involving animal biologic products (*Federal Register*, 1984, p. 50898).

The White House Cabinet Council on Natural Resources and the Environment established an interagency working group in August 1984 to study and coordinate the Government's regulatory policy for new bioproducts. The working group recommended a two-tiered review mechanism (fig. 1).

Within each of the five agencies, a scientific advisory committee would provide detailed review of applications or issues submitted to them. The NIH/RAC would continue to serve as scientific advisor for biomedical research, while the USDA, FDA, and EPA would address mainly commercial applications. According to this arrangement, each agency would send to its advisory committee a summary of each application relating to recombinant RNA, recombinant DNA, or cell fusion for funding or administrative review. Upon completion of the review, the advisory committee would submit its report to the agency/applicant that initiated the process. It also would send a copy to the parent board, the Biotechnology Science Board, for review and comment (*Federal Register*, 1984, p. 50898).

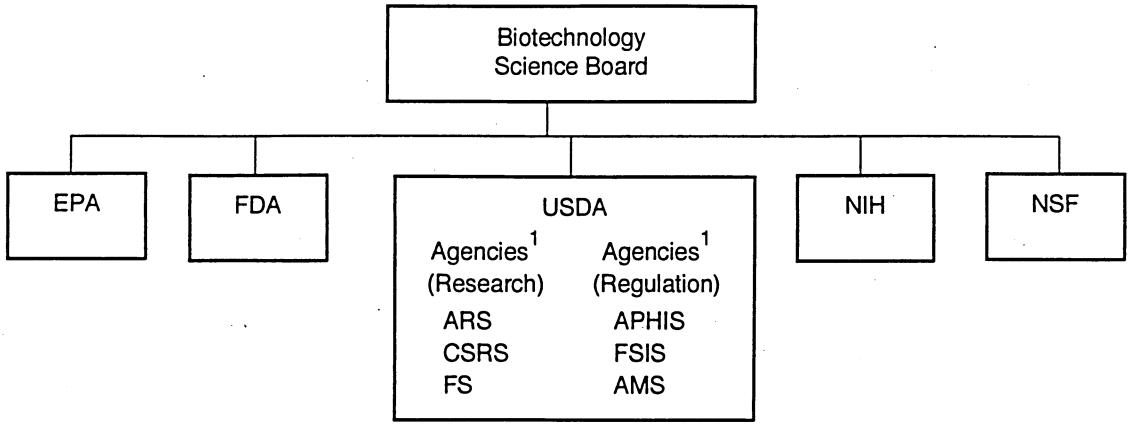
USDA accepted the premise that the science base necessary to evaluate risks had to come from agencies and individuals both inside and outside of USDA. Agency staff must be supplemented therefore by an "independent scientific review mechanism," the two-tiered advisory structure of scientists selected by each of the five Federal agencies described above.

Although this proposal was eventually rejected in 1985, a body with similar functions to those suggested for the Biotechnology Science Board was formed. The Biotechnology Science Coordinating Committee (BSCC) was created by the Federal Coordinating Council for Science, Engineering, and Technology in the White House (FCCSET). The various Federal agencies sent delegates to serve on the BSCC. At one time EPA, FDA, and USDA sent two each. For USDA, the delegates were the Assistant Secretary for Science and Education and the Assistant Secretary for Marketing and Inspection Services. In 1990, the BSCC was dissolved and its science functions redistributed to the Biotechnology Research Subcommittee and functions of the FCCSET Committee on Life Sciences and Health Regulation Issues were transferred to the Federal Coordinating Council.

USDA is involved heavily in biotechnology research and regulatory activities, but the internal structure for regulation and oversight is just beginning to function. Supervision of Federal research in biotechnology has been delegated to the Assistant Secretary for Science and Education, while the regulatory functions in biotechnology have been delegated to

Figure 1

Proposed structure of the review mechanism



[1] APHIS is the Animal and Plant Health Inspection Service; FSIS, the Food Safety and Inspection Service; AMS, the Agricultural Marketing Service; ARS, the Agricultural Research Service; CRSR, the Cooperative State Research Service; and FS, the Forest Service.

Source: *Federal Register*, 1984.

Assistant Secretary for Marketing and Inspection (*Federal Register*, 1985, p. 29367). The Biotechnology Environmental Coordination Staff (BECS) has been created to coordinate biotechnology regulatory activities within APHIS. This staff is also responsible for assuring that those biotechnology regulatory activities are conducted in accordance with Federal and USDA regulations. Recently, BECS has been replaced by the Biotechnology, Biologics, and Environmental Protection Staff.

The regulations of APHIS and FSIS have the greatest effect on biotechnological products. Two laws, the Federal Plant Pest Act and the Plant Quarantine Act, authorize APHIS to regulate the importation and interstate movement of organisms and pests, which USDA interprets as pertinent to cover the environmental release of certain genetically engineered organisms and products. APHIS proposed and implemented a permit system for environmental release. According to the Assistant Secretary for Marketing and Inspection Services, Kenneth Gilles, the agency will scrutinize the process by which engineered organisms will be produced and the product itself (Gilles, 1987, p. 5).

Besides plants, plant products, and plant pests, APHIS regulates all veterinary biologics imported into this country and shipped between as well as within States. Emphasis is upon product safety, purity, potency, and efficacy. These regulations cover chemically synthesized antigens, products derived from rDNA methods, monoclonal products, and master seeds. APHIS also exercises control over importation and interstate movement of disease organisms and vectors (Gilles, 1987, p. 6). USDA's FSIS is responsible for assuring consumers that meat and poultry products in interstate commerce and from abroad

are wholesome, unadulterated, and properly labeled and packaged. FSIS notifies APHIS when disease, discovered at slaughter, might affect animal health. APHIS informs FSIS of diseases that might affect animals coming to slaughter. FSIS will be responsible for ensuring that novel food animals, that is the chimeras and transgenics resulting from genetic manipulation, meet Federal inspection laws for wholesomeness and that package labels accurately identify the product and its contents. The basic criterion to be used is the safety of genetically created animal products for human consumption.

Although responsibility for biotechnology resides with the two assistant secretaries in USDA, a third structure, the review mechanism, has been developed. The Committee on Biotechnology in Agriculture (CBA) functions to assist the research and regulatory agencies in making difficult decisions. Co-chaired by the assistant secretaries for Science and Education, and Marketing and Inspection Services, the CBA functions both as a policy body and a bridge between research and regulatory agencies within USDA (Gilles, 1987, p. 7).

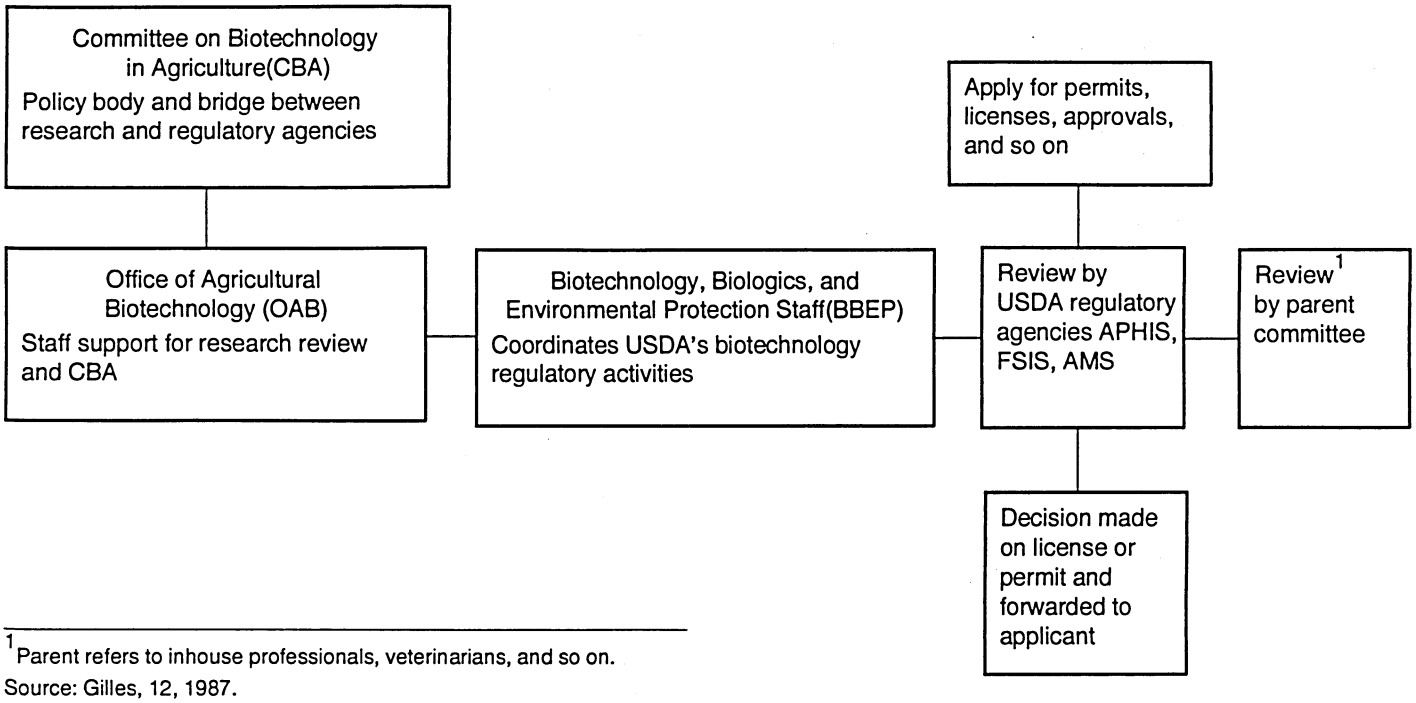
To support the CBA, a second body, the Office of Agricultural Biotechnology (OAB) has come into existence. It coordinates USDA's policies and procedures on all facets of biotechnology research and provides staff support to the CBA (Fig. 2).

The Evaluation Process in Public Agricultural Research

The process of evaluating research proposals involving biotechnology is as complicated as that which regulates the introduction of products of bioengineering. The Food Security Act of 1985 empowered the Secretary of Agriculture to establish appropriate controls with respect to the development and use of biotechnology in agriculture. The previously described structure for regulation represents an outgrowth of that mandate. Agricultural research is not only an in-house function of USDA, but is also connected with work performed at every State agricultural experiment station and veterinary facility in the United States. In order to develop comprehensive research control, USDA had to involve the land-grant colleges and universities in the early stages. Since 1982, the Committee on Biotechnology within the land-grant college national organization (NASULGC) has been functioning and working closely with the Assistant Secretary for Science and Education and others in formulating a national program.

In November 1986, the NASULGC National Biological Impact Assessment Program (NBIAP) was published and accepted. The program recognized and endorsed the use of the NIH guidelines and the system of Institutional Biosafety Committees (IBC's) currently in existence as a model for public agricultural research. Also, the projected use of the numerous field and laboratory testing locations of the State experiment facilities and extension systems across the Nation received formal acceptance (Bentley, 1987, p. 7; U.S. Department of Agriculture, Division of Agriculture, 1986, p. 7).

Figure 2
USDA regulatory review mechanisms



[1] Parent refers to inhouse professionals, veterinarians, and so on.
Source: Gilles, 12, 1987.

The program proposed the formation of an Agricultural Biotechnology Recombinant DNA Advisory Committee (ABRAC) mechanism to advise USDA on public and environmental safety (see fig. 3 for the structural relationships). This committee is publicly chartered, open to public review, and reports to the Assistant Secretary for Science and Education. ABRAC is intended to review the membership of the locally designated IBC's, but has not done so at present. The responsibility of review and approval of local research will fall upon these IBC's working in cooperation with the principal investigator and a biological safety officer.

Membership in the local IBC requires at least eight members with expertise in rDNA and related technologies. Two or more members are unaffiliated with the research entity and represent the interest of the local community. One or more members represent the technical laboratory staff, and the biological safety officer of the institution must be included. IBC meetings are open to the public, but privacy and protection of proprietary interests are respected (*Federal Register*, 1986, pp. 23389-23390).

The IBC's must review research projects for compliance with NIH guidelines, and then approve and register them. The review must include assessment of containment levels and facilities of the research entity. The principal investigators have to be notified of the results and must follow the recommendations of the committee. As a member of the IBC, the biological safety officer is authorized to make on-site inspections to ensure compliance,

devise emergency plans for accidents, and provide technical advice to the principal investigator and IBC (*Federal Register*, 1986, p. 23391).

The principal investigator is obligated to comply with the committee recommendations through appropriate approvals by the IBC, to determine if the guidelines apply, and to inform the IBC and Office of Agricultural Biotechnology within 30 days of any accidental consequences of research. Furthermore, the principal investigator must abide by the APHIS requirements regarding plant and animal health protection, permits, and so on, and, in the case of certain kinds of experiments, to report directly to the Assistant Secretary for Science and Education (*Federal Register*, 1986, p. 23390). The system's local biosafety committee places the greatest responsibility for maintaining public safety on the investigator. The administrative leadership in Washington, DC, is sufficiently removed from the local research center so that it can play the role of outside reviewer.

An Office of Agricultural Biotechnology (OAB) exists as an administrative office, which reports to the Assistant Secretary for Science and Education. The OAB assists the Assistant Secretary with policies pertaining to laboratory and field research, experimentation on biotechnological products prior to their commercialization, and all matters of oversight of biotechnology in agriculture. In addition, the Assistant Secretary has specific functions which include: (1) establishing and maintaining the Agricultural Biotechnology Research DNA Advisory Committee, (2) delegating requirements as necessary to implement NIH guidelines, (3) establishing and maintaining the National Biological Impact Assessment Program (NBIAP), (4) providing administrative support for the Committee on Biotechnology in Agriculture and acting as co-chairman of the CBA, and (5) reviewing proposals to determine compliance with NIH guidelines and adequacy of safeguards (*Federal Register*, 1986, p. 23391). OAB collects and coordinates knowledge and ties together the other parts of the overall regulatory structure. The ABRAC scrutinizes research projects, reviews environmental assessments of the projects, suggests changes in protocols and research guidelines, and offers advice to other Federal and State agencies on related projects (*Federal Register*, 1986, p. 23391). OAB, NBIAP, and OICD developed a published pamphlet in 1989 to guide researchers in the international exchange of agricultural biotechnology (USDA, *Guidance for U.S. Researchers*).

ABRAC membership is conjoined with NBIAP and organized as follows: (1) members and the chair are appointed by the Secretary, and (2) the committee consists of 15 members with expertise in rDNA research in plants, animals, and microbes; ecology/epidemiology/ environmental science; agricultural production practices; biological containment; biological field release, applicable laws and regulations; standards of professional conduct and practice; public attitudes; public health; and occupational health and ethics. Representatives from other relevant agencies may participate as nonvoting members and offer technical assistance (*Federal Register*, 1986, p. 23391).

NBIAP is becoming established under the Assistant Secretary for Science and Education by the Secretary of Agriculture to provide advice on laboratory and field biotechnology

research. The program's two objectives are to provide scientific evaluation of proposed research projects to ensure for safety, and to draw on existing agricultural science sources for research monitoring of genetically engineered organisms to assess their on-site performance in controlled-release experiments.

NBIAP is consulted by the Assistant Secretary and/or ABRAC to assess and evaluate projects in diverse agriculture-related areas. As indicated in figure 3, this body constitutes a peer review mechanism. NBIAP selects and maintains rosters of experts, designates safe research sites, and gathers and sustains knowledge on tests, effects upon the ecosystem, and so on. Developing guidelines is also a function of this body (*Federal Register*, 1986, p. 23392).

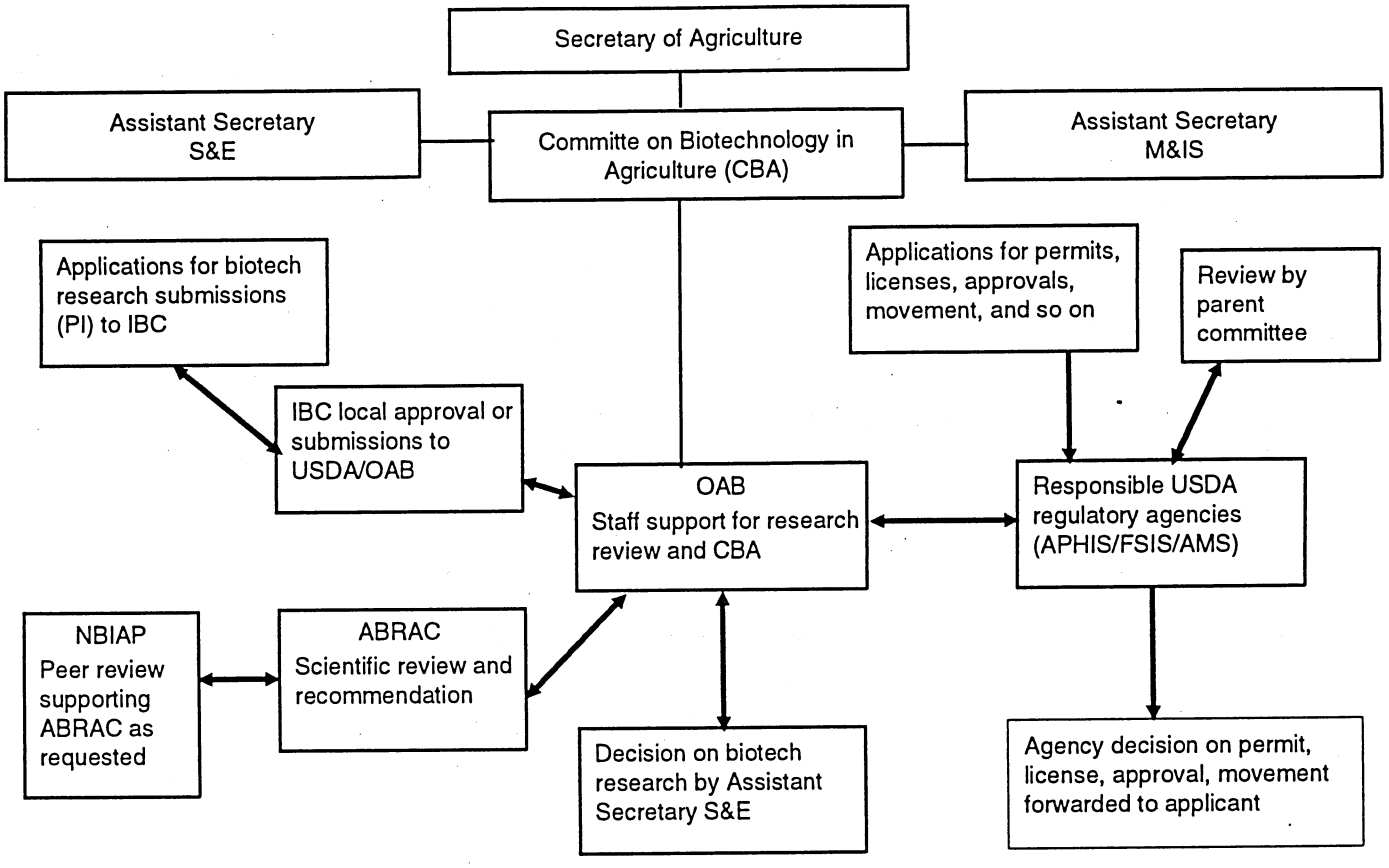
APHIS published its "final rule" on genetically engineered organisms and products in the *Federal Register* on June 16, 1987. The purpose of the regulations is to control the movement and the release into the environment of experimental, genetically engineered organisms and products which are plant pests. The regulations establish procedures for obtaining permits for environmental release of a regulated article and for obtaining a limited permit to import or move a regulated article (*Federal Register*, 1986, p. 23392). APHIS derives its authority from the Federal Plant Pest Act, the Plant Quarantine Act, and the Federal Seed Act. Both APHIS and EPA are paying attention to micro-organisms and plants (APHIS only), which are used in the environment, are pathogenic, contain genetic material from pathogens, and are intergeneric or new. Although some overlap in jurisdiction appears unavoidable for the two agencies and also with FDA, many of the turf battles appear headed toward solution. A joint jurisdiction has been accepted by the agencies involved, with one agency assuming the lead. Table 8 illustrates the nature of the arrangement.

According to Terry Medley, Director of Biotechnology and Environmental Coordination Staff of APHIS, 46 interstate permits had been issued by January 1988, 12 of them for environmental release. States involved in the testing receive advanced notification and review. Exchanges of information are guaranteed, and an option exists for petitioning for review (Medley, 1988). Many States, specifically California, Florida, and Arizona, have special quarantine laws likely to affect engineered organisms. As a consequence of the Lindow experiment, California has developed a special review process that involves notification of county officials at the place of application, a period to receive comment from citizens, and final decision to proceed, which rests with the California Department of Food and Agriculture (Jones, Tobi, 1988).

The increase in demand for reviews and permits and the experience in granting them has led APHIS to propose changes in procedures to simplify the process. As of April 30, 1993, a notification and petition process has been added as options to the existing framework for the movement and release of certain genetically engineered plants (*Biotechnology Notes*, April/May 1993, p. 1).

Figure 3

Flow chart for biotechnology applications: Research and review*



Terms:

ABRAC	Agricultural Biotechnology Recombinant DNA Advisory Committee
AMS	Agricultural Marketing Service
APHIS	Animal and Plant Health Inspection Service
CBA	Committee on Biotechnology in Agriculture
FSIS	Food Safety and Inspection Service
IBC	Institutional Biosafety Committee
M&IS	Marketing and Inspection Service
NBIAP	National Biological Impact Assessment Program
PI	Principal Investigator
OAB	Office of Agricultural Biotechnology
S&E	Science and Education

(Courtesy, Daniel Jones, OAB, 1987.

*This structure can be changed by Departmental reorganization. The CBA has been inactive for several years. A subcommittee, The Biotechnology Council, has met approximately monthly since.

Table 8--Examples of joint regulatory jurisdiction

Regulated item	Regulatory groups (lead group underlined)
Transfer of gene from *Bacillus thuringiensis* to tobacco to cause insect resistance	EPA, APHIS
Transfer from *B. thuringiensis* to soybeans to cause insect resistance	EPA, APHIS, FDA[1]
Genetically engineered *B. thuringiensis* to enhance selectivity and performance for control of Lepidoptera species in cotton	EPA, APHIS, FDA[1]
Pseudomonas syringae with ice nucleation gene deleted to suppress the growth of ice-nucleating bacteria on vegetables	EPA, APHIS, FDA[1]
Genetically engineered *P. syringae* to aid in snowmaking for ski resorts	EPA, APHIS
Genetically engineered *Rhizobium* to cause nitrogen fixation in corn	EPA, APHIS, FDA[1]
Genetically engineered herbicide resistance to corn (genetic source: rodent)	APHIS, FDA[1]
Genetically engineered herbicide resistance to sunflower (genetic source: manmade)	APHIS, FDA[1]
Improved variety of kudzu via genetic engineering	APHIS
Genetically engineered nonplant parasitic nematode for improved insect control in corn	APHIS, FDA[1]
Genetically engineered phage (virus) to lower the freezing temperature of citrus	EPA, APHIS, FDA[1]
Nonpathogenic, genetically engineered micro-organism to extract gold from ore	EPA

[1]If the item is used for feed or used in livestock or poultry, it would be regulated by FSIS. Also, occasionally there will be no lead agency (Butts, 1987, pp. 16-19).

Current Activities of ABRAC

For the past 3 years, ABRAC has advised the Assistant Secretary for Science and Education on biotechnology research. The NIH guidelines were intended for biomedical research and contained no provisions for governance of environmentally released organisms. The most significant accomplishment of the committee has been its counsel in the completion of USDA guidelines for research of genetically modified organisms outside of contained facilities. *Agricultural Biotechnology: Introduction to Field Testing* was printed in November 1989. It contained material for agricultural researchers on confinement procedures for outdoor testing, roles and responsibilities of the principal investigator and the IBC's, USDA review procedures, regulatory requirements, confinement of altered organisms, and professional and social obligations connected with the research. ABRAC completed its work on the guidelines at its December 5, 1991, meeting. They were published in April 1993.

ABRAC has also reviewed two specific research proposals involving outdoor testing of engineered organisms. The first concerned the living organism that causes *brucellosis* in cattle, and the second related to transgenic fish in managed research ponds. These reviews enable ABRAC to test the provisions of the outdoor guidelines in actual practice.

EPA and the Regulation of Agricultural Biotechnology

EPA derives authority to regulate pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and other chemicals under the Toxic Substances Control Act (TSCA). The regulations are administered by a corresponding Office of Pesticide Programs and Office of Toxic Substances. EPA views micro-organisms as chemical substances. This perspective is based in part on the historical precedents established by the Federal agencies in registering bacteria. In 1948, *Bacillus poplilae* was the first to be registered and, in 1961, *Bacillus thuringiensis* was registered. Over the intervening years, a number of protocols and regulations governing bacteria have been declared by the EPA (Westin, 1988).

EPA must be notified before an environmental release can occur. Under TSCA, notification may be made by a premanufacturing notice, significant new-use rule, or under section 8(a) of the act. The Office of Pesticide Programs issued an interim policy on October 17, 1984, for small-scale field testing (Butts, 1987, p. 160).

A coordinated framework for the regulation of biotechnology had been developed by 1986. EPA established a two-level mechanism for evaluation of proposed small-scale field tests for possible risk to human health or environmental safety and to determine whether experimental use permits should be required before the test could be initiated. The first level applies to all genetically engineered or nonindigenous microbial pesticides not otherwise covered by level two. The second level applies to three categories of microbial agents: (1) those formed by deliberately combining genetic material from organisms of

different genera, (2) those genetically engineered microbial pesticides derived from source organisms that are pathogens, and (3) those that are nonindigenous pathogenic microbial pesticides (Butts, 1987, p. 16).

The revised policy does not apply to studies conducted under enclosed, contained conditions, or to the environmental release of an indigenous, nonpathogenic micro-organism until it is used on more than 10 acres of land or more than 1 acre of water. Large-scale field testing requires an experimental use permit. Commercial use requires registration (Butts, p. 17).

According to Ron Evans, Chemical Control Specialist, Office of Toxic Substances, a complete listing of EPA regulations was to be issued in 1990. The amended regulations were issued in the Spring of 1993. Regulators within EPA and FDA will be asking the same question of bioproducts as conventional chemicals: "Is it new?" If it is intragenetic, then it is not considered new, and traditional criteria will be applied. New organisms with mobile genetic elements require risk evaluation and fall under an intergeneric category (Melone). Risk factors include the following considerations: survivability and replication, new niches, host range, competitiveness, human health effects, and environmental fate (Westin, 1988).

FDA and the Regulation of Agricultural Biotechnology

Under the Food, Drug, and Cosmetic Act, FDA possesses authority to regulate food products that result from the use of biotechnology. FDA can require pre-clearance of food additives, including sweeteners derived from biotechnology. During the Eisenhower years, the Food Additives Amendment was added to existing law. Until 1958, additives were presumed safe unless proved otherwise. After 1958, additives had to be proved safe before they could be marketed. The Food Additives Amendment also introduced a new category of substances that were exempted from the act and not subject to pre-market clearance. These substances came to be known as GRAS or "generally recognized as safe," and eventually constituted the GRAS list of accepted substances (Doyle, 1985, p. 147).

The first GRAS list was compiled in the early 1960's. It became accepted practice to add other substances, such as cyclamates, unless specifically challenged by FDA. In 1969, the cyclamate danger became public knowledge, which prompted President Richard Nixon to call for a complete review of all GRAS substances. As a result of that review, FDA decided that new varieties of food crops should be included as a category to be scrutinized (Doyle, 1985, p. 148).

In 1970, FDA proposed that "foods that have had a significant alteration of composition by breeding or (genetic) selection" be included for review and regulation under the new GRAS process. This was the first attempt by FDA to regulate raw agricultural crops. Reaction was swift, after the proposed regulations appeared in the *Federal Register*. Food

industry representatives, seed industry lobbyists, land-grant college officials, and USDA complained that they had not been consulted and that the regulations were too broad. From 1971 until 1974, opponents tried to prevent the proposal from becoming a reality (Doyle, 1985, p. 148).

Alan T. Spiher, the administrator conducting the GRAS review in the early 1970's, attempted to extend FDA authority to nutritional content and natural toxicity of commodities altered by natural means. A regulation to do this was promulgated in 1971, but has never been enforced (Doyle, 1985, p. 153).

Biotechnology seemed to provide a good opportunity for FDA to reassess its plant-breeding regulation. Acting Commissioner Mark Novitch told the National Food Policy Conference in March 1984 that FDA would be examining microbiological safety, nutritional quality, the formation of new, unexpected compounds, and unpredicted substances in genetically altered foods (Doyle, 1985, pp. 153-54). However, Special Assistant to the Commissioner, Henry I. Miller, constantly maintained that "FDA proposes no new procedures or requirements for regulated industry or individuals." Miller stressed the importance of the "physico-chemical nature, its purity and potency" of the product, rather than the methods used in its creation. Although he expressed concerns as to novel toxicities and the occurrence of mutation in the coding sequence of a gene during fermentation, these considerations predated the arrival of altered products (Miller, 1987).

FDA may regulate food crop plants that have been altered, such as corn. Concern has recently arisen over the human consumption of *Bacillus thuringiensis* toxin residues resulting from the insertion of its genetic coding into food crop plants, and over whether the tolerance-setting process of FDA and EPA is adequate (Butts, 1987, p. 16). The novel toxicity criteria may apply in this case.

On the other hand, the new mycoprotein pending approval by the FDA answers affirmatively the question, "is it new?" Therefore, the GRAS rule cannot be applied. Mycoprotein must be subjected to the testing prescribed for a new food. The variety of products and applications continues to need a case-by-case approach.

Testing the Rules: The Strobel Case

In June 1987, Gary Strobel, a plant pathologist at Montana State University, injected 14 elm trees with a genetically altered strain of *Pseudomonas syringae*, which in laboratory experiments had protected the trees from a fungus known to cause Dutch elm disease. Strobel announced in August that he had performed the field test without notifying and receiving approval from EPA or from the university's Institutional Biosafety Committee. EPA warned Strobel that he could perform no additional field trials without a co-sponsor for a year, and had to obtain IBC approval before applying for permission from EPA. The following month, the Montana State IBC reprimanded Strobel, who cut down and burned the 14 elms. The scientist described his behavior as "civil disobedience" over

confusing regulations. During the ensuing investigation of his work, it was revealed that Strobel had conducted outdoor tests of genetically altered *Rhizobium meliloti* in Montana, South Dakota, Nebraska, and California in 1984 without proper approval (Meyer, 1987, pp. 1, 6).

Opinion ranged from sympathetic disapproval to outrage. The incident created sentiment in favor of new legislation to regulate biotechnology from people such as Representative George Brown of California to the American Phytopathological Society and the National Academy of Sciences. Biologist Fred Betz, an EPA official, reflected that perhaps the pendulum had swung too far in one direction. He favored a high degree of compliance by researchers, but added that if scientists continued to indulge in civil disobedience, "I personally don't think there's much that can be done" (Meyer, 1987, p. 7).

In the absence of information, the effect of Strobel's released bacteria in four States is impossible to gauge. The danger of deliberate disregard for regulations, adequate or otherwise, cannot be prevented. Or in the words of Erwin Chargaff, a pioneer in rDNA research, "what one cretin can do, a genius cannot undo." The Strobel case calls for a response measured by the scope of danger the scientist has created for others. The difficulty in determining the extent of his negligence is the lack of existing data. There is no good way of determining the risk we routinely assume under the present guidelines system. On the positive side, Strobel's actions were taken in public view, and the appropriate agencies are involved in responding to them.

On the other hand, there are no regulations, guidelines, or criminal sanctions for a group of individuals, commonly known as "hackers" who operate outside of the law. With rudimentary knowledge and equipment, they are capable of the genetic manipulations once restricted to sophisticated university laboratories. Society is vulnerable to their experiments and altered products. The regulatory agency directors are aware of this danger, but have developed no means of coping with it.

Conclusions

USDA, EPA, and FDA are creating a comprehensive monitoring and evaluation process with penalties for noncompliance as well as protection of proprietary data. The program appears to be accumulating data by which to judge the efficacy and safety of experiments as well as the information contained in individual research proposals. The quality of the databases as well as the implementation generally should determine the outcome of the overall effort. Responsibility for successful regulation will fall on the principal investigator and the local IBC, which supervises the scientist's research. USDA, in overseeing the research and product development process, is seeking to protect the public, facilitate development of the industry, and protect the environment.

Some of USDA's administrative mechanisms for the review of biotechnology are patterned after those of NIH. These mechanisms include science-based biotechnology

research guidelines, a staff of full-time employees to handle day-to-day activities (OAB), and a Federal advisory committee of experts to review proposals and establish approval conditions for release experiments (ABRAC). USDA has established review mechanisms unique to the special needs of agriculture. These include expanded research guidelines that apply to agricultural situations, a national infrastructure to identify outdoor test sites, and expert reviewers for evaluating proposals, as well as post-release monitoring of test site environments (NBIAP). Such a structure should enable the scientific community to provide adequate guidance to individual investigators in evaluating planned introductions of bioengineered organisms into managed ecosystems (Jones, Daniel, 1988, p. 3).

These regulations have been created in an atmosphere of contradictory pressures from scientists, environmentalists, and private industry. The greater the diligence and rigor of the process, the greater the likelihood of success, and the greater the prospect of informed judgment preventing unforeseen disaster. Interest groups have been involved from the beginning of the regulatory process. However, it is speculative whether they will have a significant input into a national agenda for the new technology. Modification of the existing structural arrangements and NIH guidelines is likely to occur in the short term, as regulators seek to keep pace with this rapidly expanding knowledge base and industrial applications. In providing a scientific basis for field testing, ABRAC has worked to enhance safety in research. But, historically, even the most effective regulations have had difficulty keeping pace with the progress of an evolving industry. The new guidelines face challenges from administrators in OGC and OPM who will likely make further modifications.

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