INDUSTRY STUDIES 2000

Bio Technology

ABSTRACT

The rapidly emerging biotechnology industry is a critical element of national power. Advances in biotechnology are resulting in novel biomedical and pharmaceutical products and processes that are relieving human suffering, improving health, and increasing the quality of life for the world's citizens. Biotechnology is transforming agriculture, improving the productivity, quality, safety, affordability, and environmental compatibility of food and fiber production around the world. The application of biotechnology to fields as diverse as bioremediation, forensics, artificial intelligence, and nanotechnology is similarly providing widespread benefits to humans and exciting new economic opportunities for entrepreneurs. As the preeminent global leader in this new industry, the United States is well positioned to maintain its competitive advantage in the future. Even so, there remain many challenges to this dominance, including a variety of ethical concerns and a growing public unease about genetically altered food.

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Agricultural Research Center, Beltsville, MD

Armed Forces Institute of Pathology, Rockville, MD

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Gene Logic, Incorporated, Gaithersburg, MD

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INTRODUCTION: WHAT IS BIOTECHNOLOGY?

Defining biotechnology is a little like defining the meaning of life—it depends on whom you ask. Some have defined biotechnology broadly as "the manipulation of living organisms or their components to perform practical tasks or provide useful products." Examples that fit such a definition include selective breeding to improve the performance of crops or livestock and the process of fermentation to make cheese, beer, and wine—a technique that is at least 8,000 years old. This definition, however, does not capture the essence of modern biotechnology. The basis for modern biotechnology is not the manipulation of whole organisms, but the manipulation of the very building blocks of life itself, particularly the deoxyribonucleic acid (DNA) molecule.

The fundamental material of life, DNA contains sequences of nucleotides, each consisting of a sugar molecule, a phosphate group, and a base. There are four different chemical bases in DNA—adenine, guanine, cytosine, and thiamine—and thus four different nucleotides. DNA nucleotides are arranged sequentially in two complementary strands twisted together in a spiral double helix structure. The simple, but elegant, circumstance that adenine always pairs with thiamine and guanine always

matches up with cytosine accomplishes the linkage between strands. Thus, when reproducing cells divide and the strands of the double helix separate, each strand functions as a precise blueprint for a new complementary strand. Like the cell itself, the DNA molecule is duplicated.

The nucleotides are arrayed along the DNA molecule in an almost infinite variety of sequences. The varying lengths of these sequences spell out specific genes. Generally, a gene is the portion of a DNA molecule that contains the instructions to manufacture a specific protein. Because proteins are the biological molecules that govern virtually every one of a cell's activities, including regulating metabolism, catalyzing chemical reactions, combating infections, and manufacturing new cells and tissues, life as it is now known could not exist without proteins.

TOOLS AND APPLICATIONS OF BIOTECHNOLOGY

To the layperson, the toolbox of the biotechnologist may seem more like a sorcerer's grab bag of magic. Nevertheless, the tools at the scientist's disposal, such as gene transfer, cloning, and monoclonal antibodies, have developed to the point that even high school students, properly supervised, can employ them.

Gene Transfer. The transfer of a DNA sequence—constituting a gene of interest—into a cell where it does not normally exist modifies the host cell. Gene transfer is typically accomplished by snipping the DNA sequence from the donor organism, using restriction enzymes, and then recombining that sequence into the DNA or ribonucleic acid (RNA) of a special virus called a bacteriophage, or phage. Serving as vectors, phages carry and inject the recombinant DNA into bacteria. The cellular machinery of those bacteria then make multiple copies of the recombinant DNA—containing the gene of interest—during the normal process of cellular division. Because complementary bases of the donor and host DNA will pair up, it is possible to recombine DNA from entirely different species and, by extension, to transfer a gene expressing a desirable trait into an organism that does not normally have that trait.

Cloning. The process of creating, from a single organism, multiple new individuals of the same genetic composition as the original is called cloning. Simple cell division is a form of cloning, as is the growth of a new plant from a cutting; the descendent cells all have the same DNA as the original. In modern biotechnology, cloning is accomplished by transplanting the nucleus of a parent organism into an egg cell whose original nucleus has been removed. The resultant organism is then genetically identical to the parent from which the transplanted nucleus was derived.

Monoclonal Antibodies. Certain white blood cells produce infection-fighting proteins called antibodies. Specific antibodies target specific disease agents. Monoclonal antibodies are all descended from one cell. Biotechnologists produce these in quantity by fusing certain white blood cells with cancer cells. The resultant hybridoma cell makes multiple copies of the antibody specific to the parent white blood cell, and these antibody copies can then locate and attach themselves to specific chemicals or disease agents of interest.

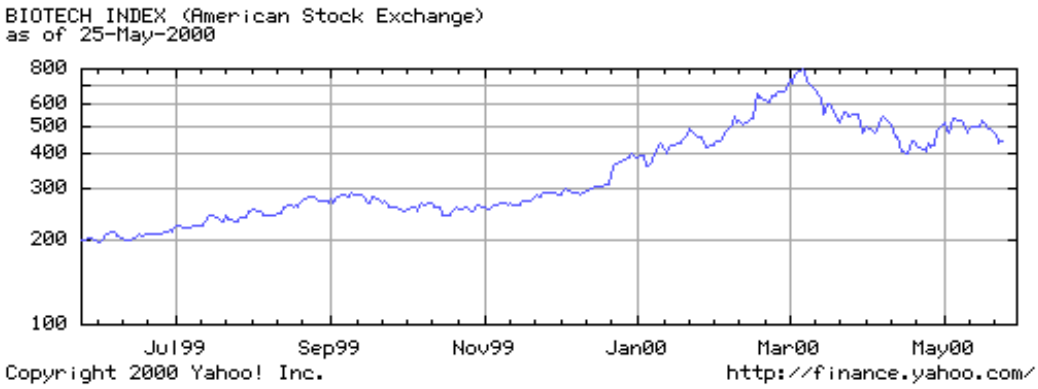
INDUSTRY OVERVIEW, STATUS, AND PROSPECTS

The birth of the modern biotechnology industry dates from 1973 when Stanley Cohen and Herbert Boyer discovered the recombinant DNA process that makes it possible to manipulate DNA

sequences readily. Since then, the biotechnology industry has grown rapidly. Today, there are nearly 1,300 biotechnology companies in the United States, providing employment to approximately 153,000 people. Most of these biotechnology firms are relatively small, with two-thirds employing fewer than 135 people. Europe, the United States' closest biotechnology competitor, has roughly the same number of biotechnology firms (approximately 1,200), but these are even smaller, employing only about 4,000 people.

Only one-fourth of U.S. biotechnology companies are publicly held. Market capitalization for the industry was approximately $150 billion in 1999, up substantially from $97 billion in 1998. Swings in the U.S. stock market have reduced biotechnology stock values significantly in the second quarter of 2000, however, with a drop of nearly 50 percent between early March and late April alone (Figure 1). Even so, the biotechnology stock index is still up over 100 percent since June of 1999.

Figure 1: Biotechnology Industry Average Stock Performance



Principal Sectors

Health Care. Biotechnology is contributing substantially to the phenomenal advancement of health care. As patents for traditional drugs expire, the pharmaceutical industry is increasingly turning to bioengineered products. Gene therapy and localized tissue repair could lead to routine treatments for genetic diseases. Embryonic stem cell research also holds great promise for treating genetic diseases. Groundbreaking discoveries in genomics could result in additional revolutionary medical therapies.

The biotechnology pharmaceutical industry is unique in the business landscape, partly because it is an extremely long-term business. New products take 7–12 years to move from development to the marketplace. Thus, a new biotechnology company that is fortunate enough to have a marketable product may need 8 or more years to build a reliable revenue stream. Compounding this problem, the price tag to bring a drug in the late stages of the approval process to market today is about $200 million—a cost that is projected to grow to $500 million in the next 10 years. These costs accelerate at the later stages of the drug development and approval process because of the expensive human

testing and drug-specific manufacturing preparation that the Food and Drug Administration (FDA) mandates. These requirements place tremendous financial stress on small biotechnology companies.

Meanwhile, a survival struggle of a different kind is occurring in the mainstream pharmaceutical companies (a.k.a. "big pharma"). Patents on 75 major U.S. drugs, representing annual sales of $50 billion, will expire by 2005, and the big companies have only meager offerings to fill the void. The value of expiring patents was $6 billion in 1999, will rise to $13 billion by 2001, and is projected to be $16 billion by 2005. At the same time, big pharma's internally developed pipeline of new drugs is expected to generate only 5–6 percent annual sales increases during this period, less than half the rate of historical growth.

Big pharma's long-term survival will depend on bringing bioengineered products into its pipelines. The big pharma companies have two choices: continue to act alone or pursue a more open business model that relies upon collaboration. Either way, the mainstream companies will need to expand their research and development (R&D) in support of new product development. The net effect of these factors is a continuation of merger and acquisition activity.

The pharmaceutical industry will need a continuing supply of investment funds, through federal grants and/or venture capital sources, to fund (R&D) of new biotechnology products. New medical biotechnology applications will also require health insurance companies to reassess their reimbursement practices. For example, it may be more cost-effective to provide coverage for genetic treatment of Alzheimer's than to pay for long-term nursing care. Although demographic factors, changes in health care delivery systems, integration of service providers, and competition will all affect the future of the nation's health care system, the largest single influential factor is likely to be advances in biotechnology.

Agriculture. Biotechnology is transforming agriculture not only by genetically modifying animals and crops for improved performance, quality, nutritional value, environmental compatibility, and safety, but also by engineering organisms to produce valuable hormones and drugs to promote human health efficiently. The first applications of biotechnology to agriculture, now widely adopted, involved engineering plant varieties to require fewer pesticides. More recently, agricultural biotechnology has focused on improving food quality, nutritional benefits, and food safety—exemplified by the development of vitamin A–enhanced rice for Asian farmers.

While public agencies such as the U.S. Department of Agriculture (USDA) and land grant universities have traditionally funded agricultural research, the private sector is now funding most of the research in this area. A handful of seed companies, pharmaceutical companies, and "life science" companies are carrying out much of the current agricultural biotechnology research. To date, the greatest impacts have been on corn, soybean, and cotton plants; in 1999, approximately 40 percent of U.S. acreage in these crops was planted with genetically modified varieties. Despite widespread adoption by U.S. farmers, there is increasing pressure from environmental groups to cease production of genetically modified food organisms.

Environment. The most significant applications of biotechnology to the environment have involved bioremediation, the use of naturally occurring organisms (e.g., bacteria, yeast, fungi, and plants) to convert noxious or hazardous substances in soil or water into nontoxic compounds. Many municipalities are now using microorganisms to remove pollutants from sewage systems and to clean up abandoned industrial sites. Bioremediation in the treatment of solid wastes is also reducing the need for landfills. Various companies are even marketing combinations of microbes in dry, dormant states for "do-it-yourself" bioremediation.

Biofiltration systems can control plant emission odors and clean up oil spills. New anaerobic, on-site systems are allowing cost-effective remediation of areas difficult to reach (e.g., under buildings).

The use of biotechnology to avoid pollution is of increasing importance. Closed loop in-plant

processing involves the use of bioreactors to treat hazardous products, such as methylene chloride, so that they never enter the atmosphere, soil, or groundwater.

Forensics. The science that deals with the application of medical knowledge to legal questions is forensics. With a broad range of well established applications in both civil and criminal cases, forensic science makes it possible to monitor the compliance of various countries with international agreements, such as the Nuclear Non-Proliferation Treaty and the Chemical Weapons Convention. The expanding applications of DNA technologies to forensic science have generated excitement, both in the criminal justice community and in the popular media. Much of this interest has resulted from well publicized cases where DNA technology has been used to convict or exonerate individuals accused of crimes.

Emerging Technologies, Applications, and Opportunities

Within a surprisingly short period of time, the ability of scientists to isolate and transfer genes has spurred enormous amounts of scientific research. The announcement of new discoveries is becoming routine, and genetically engineered products and applications are beginning to appear in our society. The prospect of genetically modified food on our tables and pigs' hearts in our bodies either has already become a reality or is generating some serious ethical debate. The most sensational example has been the unprecedented worldwide debate over the implications of cloning that followed the breakthrough in sheep nuclear transfer at the Roslin Institute in Edinburgh, Scotland.

Bioinformatics. The convergence of two revolutionary technologies, biotechnology and information technology has given birth to a new discipline called bioinformatics. This marriage between biology and computing has enabled easier, faster, and more cost-effective capture, management, analysis, and dissemination of biological data.

Bioinformatics will be at the core of biology in the 21st century. Its tools will comprise a spectrum from the DNA chip, capable of measuring and monitoring the activity of thousands of genes at one time, to the graphical representation of molecular data. In fields ranging from structural biology to genomics, easy access to data and analytical tools are already fundamentally changing the way in which scientists conduct research and approach problems. Today, scientists using desktop computers can connect to the Internet, use a bioinformatics tool to find DNA sequences, and answer both basic and complex biological questions. Ultimately, DNA chips will be indispensable for screening the population for both inherited and acquired diseases, such as breast cancer and acquired immunodeficiency syndrome (AIDS).

Computer-aided bioinformatics will stimulate future developments in the biomedical and pharmaceutical industries. Bioinformatics will make it possible to sort and analyze efficiently and effectively vast amounts of new biological data—including data from the Human Genome Project—and apply the findings to new health care products and processes.

Other computer technologies will contribute to developments in the biomedical and pharmaceutical fields. For example, modeling and simulation, with an emphasis on visualization techniques, can create tissue simulation technology and the manufacture of tissue-equivalent phantoms for densitometry, calibration, and research. Automated workstations, enabled by robotics, will not only save time and increase the accuracy of processing, but also will provide a complete audit trail in support of quality control and testing of new pharmaceutical products. A new supercomputer that IBM is building will "model the way a human protein folds into a particular shape that gives it unique biological properties."

Bioremediation. Although bioremediation historically has been ineffective in the presence of metals and chlorine, new technologies can now remove complex hydrocarbons from sites that also contain inorganic compounds. In addition, scientists are examining the potential for gene transfer between bacteria to help degrade organic contaminants in the presence of metals and are investigating the transfer of genetic resistance to heavy metals into bacteria.

Among the other emerging technologies is a procedure that combines traditional remediation methods (air-sparging and soil vapor extraction) with bioremediation to reduce chlorinated solvent contamination. Researchers have also developed a genetically engineered microbe that can absorb large amounts of radioactive material, which may have potential value in cleaning up radioactively contaminated sites. The Microbial Genome Program of the Department of Energy is likely to increase our understanding of the reasons that certain bacteria are resistant to radiation. Techniques of phytoremediation, the use of living plants to absorb wastes, also show substantial promise. For example, hybrid poplars have been used successfully to remove chlorinated solvents from waste sites.

Nanotechnology. The ability to manipulate individual atoms and molecules—nanotechnology—could revolutionize the 21st century in the same way that the transistor and the Internet ushered in the Information Age. The central thesis of nanotechnology is that it is possible to build almost any chemically stable structure that can be specified, even at the size of single atoms. Advances in nanotechnology could conceivably lead to breakthroughs such as molecular computers that can store the contents of the Library of Congress in a device the size of a sugar cube and new materials that are 10 times stronger than steel with a fraction of the weight.

Nanotechnology can exploit the significant similarities between DNA and computers to advance artificial intelligence. Using what is essentially a four-letter alphabet, DNA stores the information that living organisms manipulate in almost exactly the same way that computers operate on strings of *1*s and *0*s. The resulting nanocomputers may enable in vivo augmentation of human intelligence.

Nanomedicine—the monitoring, repair, construction, and control of human biological systems at the molecular level—shows great promise. Future medical applications could include microscopic nanomedical devices that travel through the circulatory system, repairing living cells and delivering medicines. Equally exciting, advancements in both molecular biology and nanofabrication technology offer the potential to engineer functional hybrid organic/inorganic nanomechanical systems, to create organic molecular motors utilizing chemical energy sources.

Biomedical/Pharmaceutical Commerce. Pharmaceutical companies will likely realize new drug opportunities through expanded applications of emerging technologies such as high throughput screening, signal transduction, combinatorial chemistry, and genomics. These technologies will enable researchers to screen potential pharmaceutical compounds rapidly and identify those with the greatest potential therapeutic benefits. They will also facilitate development of new medicines based on gene therapy (i.e., the process of manipulating a patient's genetic system to correct inherited genetic disorders). Finally, advances in structural rational drug design, a technique by which researchers develop new medical compounds based on improved understanding of the structures of proteins, including their key functional receptor sites, are likely to benefit the biomedical field greatly.

Agriculture. There are substantial future opportunities to bioengineer plants for nonfood purposes, such as medical treatments through "neutraceuticals" (i.e., plant-based therapeutic products) or the detection of biological weapons on the battlefield through plant sensors. Further developments in agricultural biotechnology may mirror those in medical biotechnology. For example, research on the genomics of plants, animals, and their pests will likely lead to new technologies and practices that will further enhance agricultural productivity and, as with medical biotechnology, will present challenges for researchers regarding proprietary methods and knowledge.

Public encouragement and support for the application and adoption of biotechnology by resource-poor farmers in the United States and overseas will be important, particularly in zones of high biotic stress where advances in biotechnology could help address the water, pest, and productivity constraints of those environments. The challenge is to overcome public concerns about biotechnology crops in domestic and export markets. It is also necessary to maintain a world trading and regulatory environment that encourages continued expansion of agricultural productivity; reduced use of agricultural chemicals; and assurance of abundant, high-quality, safe, and affordable food.

Research and Development. Genetic research is greatly expanding the knowledge of human anatomy, physiology, and biochemistry. Spurring the research is a conviction of its practical value, a certainty that human benefits will follow in the wake of discovery. Research in genetic sequencing will help to reveal the biochemical underpinnings of human senses and memory, better understand factors that affect human development and aging, and more precisely comprehend the similarities and differences among humans—ultimately making it possible literally to unlock the secrets of life.

Biotechnology is one of the most research-intensive industries in the world. Although the private sector largely funds this research—it is estimated that R&D investment by the U.S. biotechnology industry was $9.9 billion in 1999—public funding is also increasing. The fiscal year (FY) 2000 and FY 2001 federal R&D budgets for biotechnology show dramatic increases, especially for the National Institutes of Health.

CURRENT AND EMERGING ISSUES

Public Perceptions and Concerns

Genetically Modified Organisms and Food Labeling. Currently, federal regulations do not require specific labeling of genetically modified foods. Based on research to date, U.S. regulatory agencies have concluded that genetically engineered crops, farm animals, and their products present no more risk to the consumer or to the environment than do traditional agricultural products. Critics of this federal position contend that only a thorough knowledge of both product development and composition can ensure safety. Fueling this debate are fears of potential unknown or untested side effects. Religious or dietary considerations have also engendered opposition to genetically modified organisms (GMOs). For example, individuals who are following a strict vegetarian or nonpork diet, but have an incomplete knowledge of product components, could potentially violate their dietary laws and practices by unwittingly consuming food that contains genes from swine.

Nonetheless, substantial problems could arise from a labeling program that requires the separation of biotechnology products from traditional products at all stages (i.e., from the laboratory to the field to the grocery store). Soybeans, for example, are used in a variety of foods such as tofu, baked goods, vegetable oils, and animal feeds. The inherent complexity of separating genetically modified soybeans, which presently account for 50 percent of total U.S. soybean production, would be likely to increase the cost of the final product significantly.

Food labeling policies of the FDA have thus far focused more on the safety of the product than on the method of production. By a 78 percent majority, consumers have supported FDA's policy of mandating food labeling only when there is a substantial change in a food's composition, nutritional value, or allergenicity. The FDA requires a special review of genetically engineered foods if any of the following apply:

- **The gene transfer produces unexpected genetic effects.**
- **The levels of toxicants in the food are significantly higher than those in comparable "traditional" foods.**
- **Nutrients in the genetically modified food differ from those in traditional varieties.**
- **The introduced genetic material is associated with allergies.**
- **The new food differs significantly in composition from that of comparable varieties.**
- **The food contains genes that could reduce the effectiveness of useful medicines.**
- **Plants developed for pharmaceuticals or polymers will also be used for food.**
- **Plants used for animal feed have changes in nutrients or toxicants.**

Environmental Concerns. Some observers are worried that agricultural biotechnology could lead to the evolution of pesticide-resistant insect strains that could contaminate organically grown crops through wind-borne pollen. Genetically modified farm animals and crops could interbreed with natural strains, weakening the latter by transferring genes less fit for survival in the wild. There is also concern that cross-pollination of wild plants with genetically modified crops could result in "superweeds," mass sterility of native plants from genetically modified species containing a "terminator" gene, inadvertent incorporation of allergenic genes in modified crops, or pesticide toxins in the residues of genetically modified crops that would depress soil microbial activity.

The application of biotechnology to environmental bioremediation shows substantial promise, but contains some risk. Thus, the Environmental Protection Agency (EPA) strongly controls these applications. For example, because different contaminated sites have different soil characteristics, the EPA requires surveys to determine the proper mix of nutrients and microorganisms for a specific site. In general, there has been public and government reluctance to use genetically engineered microorganisms for restoring contaminated sites because of environmental concerns similar to those expressed for genetically modified crops.

Animal Testing. As the pace of biomedical research and discovery accelerates, so do the ethical debates over the use of animals in advancing biotechnology. In the United States, the principal guidance on the use of animals in research is the Animal Welfare Act of 1966.

Animals have played an important role in medical breakthroughs, benefiting not only people, but also other animals. Among the advances directly attributable to animal research are the development of vaccines for rabies, smallpox, and polio; the development of anticoagulants; the discovery of the Rh factor; and the understanding of DNA. These advances notwithstanding, it is incumbent on the medical and scientific communities to seek alternatives to animal models in biomedical research wherever possible. This is not just an ethical issue; it is also a question of cost-effectiveness. Housing and caring for laboratory animals is inherently expensive, as is compliance with the handling and reporting requirements of the Animal Welfare Act and other regulations. High-quality modeling and simulation tools are greatly reducing the need to use live animals for research.

Ethical Issues

Privacy. Advances in genetics and their applications present new and complex ethical and policy issues both for individuals and for society. Perhaps the most critical social issues relate to genetic privacy—the right of individuals to decide for themselves what genetic information others may know about them and what genetic information they may want to know about themselves. Genetic profiles carry vast amounts of highly personal information. It is one of the few areas stemming from genetic research where potential misuse threatens to penetrate many sectors of life, including employment, law enforcement, insurance, finance, and education. As Arthur Caplan, Director of the Center for Bioethics at the University of Pennsylvania Health System noted, the very same genetic information that could help an individual achieve a better quality of life may also destroy it if the knowledge is used inappropriately. Thus, many argue that without genetic privacy, discrimination based solely on one's genetic makeup could become commonplace.

Informed Consent. Both law and ethics require that the medical applications of biotechnology begin with an informed consent process. The physician must advise the patient about options for the treatment of a specific diagnosis, presenting the risks and benefits of the medical procedures, including all forms of gene therapy, so that the patient can make a rational decision concerning the treatment.

Recently, the Clinton Administration announced two initiatives to protect patients in gene therapy research projects. First, even before their projects commence, researchers must submit to the FDA the methodologies that they will use to monitor safety. Second, representatives of the National Institutes of Health (NIH) and the FDA must meet jointly with gene therapy researchers on a quarterly basis to review safety reports. The FDA also plans to initiate a new rule that would allow its representatives to disclose information about the safety of gene therapy treatment. Both regulations are likely to promote patient safety and greater attention to informed consent.

Gene Patenting. The science of cellular biology has come a long way, from distinguishing the various components of the cell to determining the complete basic chemical genetic construct of cells. This year, 2000, the mapping of the human genome will be essentially complete. This incredible accomplishment has fostered a vigorous debate concerning the efforts of certain commercial gene-mapping enterprises to patent human genetic sequence information.

Patents convey legal protection—for a limited time—of the commercial benefits associated with a discovery, such as the specific composition and medical uses of human genes or proteins. A genetic patent seeker must meet three requirements:

1. The discovery must be novel. In gene patenting, novelty requires determination of a previously unknown gene or protein sequence.
2. The discovery must be useful. It is not enough just to find a new gene or protein sequence; the patent seeker must specify its uses (e.g., whether it is useful as a drug, a target, or a diagnostic marker).
3. The application must contain detailed instructions on the use of this new material (i.e., the patent seeker must demonstrate that the described "invention" actually works).

A patent gives information-based research companies exclusive rights to market the data that they uncover. These data then become vital for new discoveries and for the development of products by other companies. Such information has been instrumental in the discovery of numerous compounds for the drug industry. Patenting this information also protects U.S. company interests. "Unless a patent on a process (or a patent on the final product) [is] obtained, the final product could be produced overseas and imported into the U.S. without infringing a patent on the materials used in the

process."

Patenting a process used to uncover genetic information or to produce a certain product can prohibit competitors from using the same process to work on a totally unrelated biotechnical area. In addition, it can prolong the time to market for competing products. Because of the patent holder's exclusive rights to data and processes, a rival company cannot begin to develop a comparative product until after the patent life of the process or product that the company wishes to copy has expired. The patent process also can drive up the costs of new product development. Having to pay for access to basic, but critical, data will cause a company to pass on the cost to the consumer. Another drawback of the patent process is that private companies profit from public funding. Many of the original techniques and procedures used to garner the data that companies are offering for a price were first developed under government grants.

In March 2000, President Bill Clinton and British Prime Minister Tony Blair issued a joint statement urging that information on the human genome sequence be shared publicly for the good of science. Despite the strongly negative stock market reaction, the joint statement essentially reiterated existing U.S. and British policy that the basic chemical sequence of the genome is not patentable, but the functions of the 30,000–120,000 genes that can be extracted from that sequence are patentable. The U.S. Patent and Trademark Office is currently tightening its rules regarding how much must be known about a gene's functions before it can be patented. The concern is that if the rules are too loose, the "ownership" of genes may slip into the private sector before their function is properly understood.

Cloning. Public interest in cloning continues to be strong. The successful cloning of mammals first made major news on February 23, 1997 with the birth of Dolly, a cloned sheep. Since then, there have been reports of cloned pigs, cloned cows, multiple clones of mice, and cloned monkeys. Furthermore, Dolly has given birth to a healthy lamb, named Bonny. This rapid advance in the cloning of mammals has led to debate over the potential for human cloning.

Human cloning remains highly controversial. In 1998 and 1999, members of the U.S. Congress submitted several bills to restrict or ban the cloning of humans. One scientist publicly stated in 1998 that he could begin to clone a human being within 90 days. He has since raised more than $15 million and purchased land in Japan to begin human cloning experiments. The Public Health Service Act and the Food, Drug, and Cosmetic Act, administered by the FDA, regulate the clinical research in all cloning technology. The current FDA policy will not permit such human cloning experiments until there are answers to "major unresolved safety questions."

Embryonic Stem Cell Research. Although there are many kinds of stem cells in the human body, embryonic stem cells are the most fundamental and extraordinary. They are found in the early-stage embryo, known as the blastocyst, when the embryo consists of approximately 140 cells. Unlike the more differentiated adult stem cells or other cell types, embryonic stem cells are pluripotent, retaining the ability to develop into nearly any cell or tissue type. Because of their versatility, embryonic stem cells offer great medical promise in the treatment of injuries, (e.g., spinal cord injuries) and diseases (e.g., Parkinson's disease, Alzheimer's disease, heart disease, diabetes), as well as in the development of transplant organs.

Although scientists had long recognized the potential value of embryonic stem cells, isolating and cultivating these cells involved extraordinary technical challenges and proved elusive for many years. In late 1998, Geron Corporation announced that it and scientists from two universities had succeeded in establishing human embryonic stem cell culture lines by means of two different methods. Using one approach, scientists at the University of Wisconsin isolated embryonic stem cells using "leftover" 1-week-old embryos produced by in vitro fertilization at a fertility clinic. Using the other approach, scientists at Johns Hopkins University in Baltimore retrieved stem cells from the developing reproductive cells of 5- to 9-week-old aborted fetuses. Their achievement has been hailed as one of the biggest breakthroughs in modern medicine.

Organ Transplants. The shortage of human organs and the struggle to prevent a patient's immune system from rejecting the transplanted organ severely constrain the clinical usefulness of organ transplantation. Xenotransplantation, the use of animal organs for clinical transplantation into humans, can potentially alleviate both of these problems. There have been transplants to humans from pigs for years, but there is significant opposition to the expansion of this practice to include the use of animal organs being genetically grown and harvested for human transplantation. Opponents cite barriers such as physiological unsuitability, potential animal retroviruses, and a host of ethical concerns in condemning this new endeavor. Recognizing the risks, the FDA in December 1999 circulated draft guidance for public comment. One section of the document states that "xenotransplantation recipients should never donate whole blood, …source plasma…or any other body parts for use in humans."

Gene Therapy. "Genetic research has advanced in dramatic fashion in the last decade." It is now possible to attempt therapeutic genetic modification in humans. Gene therapy (i.e., the alteration of the genetic makeup of some of a patient's cells by supplying healthy copies of missing or flawed genes) holds promise in the treatment of many human diseases, including those for which treatment is currently ineffective or nonexistent. Without a doubt, gene therapy has the potential to serve as an alternative to pharmaceutical intervention in disease treatment or control. Practitioners may be able to correct disease manifestations by altering the genetic material of somatic cells, either by the vector transfer of DNA directly through blood or tissues or by the infusion of cells that have been modified by gene therapy in the laboratory. The rationale and strategies for the genetic treatment of particular diseases are varied, providing optimism and hope for its use. Clearly, gene research and therapy pose numerous overarching moral, ethical, and theological concerns that will influence and help determine the appropriate avenues for researchers and scientists to follow. In addition, government regulation and policy will continue to play an integral role in shaping the future of this innovative technology.

Trade Issues

The United States is competing for global biotechnology leadership with its trading partners. This competition influenced the negotiations concerning an international biosafety protocol and increased tensions in the trade relationships between the United States and the European Union (EU), Canada, Japan, and others.

The level of acceptance for U.S. biotechnology–based products varies throughout the world, but is generally polarized between non-European and European consumers. Typical of non-Europeans, as many as 90 percent of Australians support medical and environmental applications, and approximately 67 percent support food and nutritional applications. Similarly, more than 90 percent of Japanese consumers in a survey believed that biotechnology would provide benefits to them in the next 5 years.[9]

The level of acceptance in Europe is lower, with interest in purchasing GMOs ranging from 70 percent in Portugal to 30 percent in Germany. Several EU countries continue to block the entry of GMO products because of concerns for the environment and for consumer safety. Austria and Luxembourg, for example, have essentially refused to permit genetically modified corn into their countries. In October 1998, the EU's Scientific Committee on Plants refused to approve a GMO high-starch potato that had been developed by a Dutch firm. Taking a slightly less stringent stance, Britain wants mandatory monitoring of the effects of any GMO product that has received approval for marketing to ensure that the product is safe for health and the environment.

The EU now requires the labeling of all products that contain GMOs. The United States claims that there is no scientific basis to presuppose that GMOs are any more risky or substantially different

from other products, however, believing that trade decisions should be based on sound scientific investigation.

The distaste of EU consumers for GMOs, environmental concerns, agricultural market reactions, and a lack of investment capital for developing new products tend to increase trade tensions between the United States and the EU. Some EU consumer opposition to GMOs arises from a significant lack of trust in the institutions of food safety regulations. The poor handling by government officials of the "mad cow disease" crisis, caused by consumption of beef infected with bovine spongiform encephalopathy (BSE), has fomented grave concerns about the truthfulness of government assurances that GMO food is safe. These concerns have essentially eliminated trade of GMOs between the United States and the EU.

Canada has joined Argentina, Australia, Chile, and Uruguay in supporting the U.S. negotiating position concerning a biosafety protocol. The United States strongly opposes the requirement for advance permission from the importing country before shipping GMO soybeans and corn.

Good support for biotechnology products exists in Japan. In 1996, Japan began importing GMOs, and it currently imports six crop categories from the United States: soybeans, rapeseed, potatoes, tomatoes, cotton, and corn.

Agricultural Biotechnology in Developing Countries

Biotechnology could help improve the health and economic status of developing nations, thus contributing to a more stable and secure world. Expanded overseas adoption of agricultural biotechnology would help offset European opposition to GMOs and would provide greater international support for U.S. positions relating to trade in genetically modified crops and farm animals (e.g., in the World Trade Organization, the Biosafety Convention, and the Codex Alimentarius). An increased market for biotechnology products would disproportionately benefit U.S. companies because of the dominant U.S. position in this emerging industry.

It is important for the United States to develop and support policies that ensure equitable access to the benefits of biotechnology for all nations. Private medical and agricultural firms may be reluctant to market biotechnology products and applications in developing nations, because it is unlikely that they can charge prices in these markets sufficient to recoup their R&D costs.‘ ‘ ‘ Creative public–private partnerships, such as the Global Alliance for Vaccines and Immunization (GAVI), could overcome this impediment. The GAVI combines public and private funds in an effort to find vaccines for the most common communicable diseases of developing countries. In agriculture, where applications are more local, it might be more effective to encourage partnerships in which U.S. firms grant royalty-free licenses to foreign public research entities for the use of proprietary research methods and germ plasm in markets that they are not directly targeting. Without such efforts, it will be impossible to address the health, poverty, and hunger problems in developing nations adequately, potentially resulting in an antitechnology backlash in those same countries.‘ ‘

Regulatory Issues

The biotechnology industry often presents difficult regulatory issues. The death of Jesse Gelsinger, who died while undergoing experimental gene therapy in Pennsylvania, revealed serious and

widespread lapses by researchers in gene therapy. In response, the FDA halted gene therapy research at a number of leading research institutions and strengthened the rules for monitoring the safety of such research. Additionally, the Clinton Administration has requested the authority to impose large fines on violators.

The increased knowledge of human genetic structure alters a variety of regulatory issues. The patenting of gene sequences by private firms led to a public outcry, resulting in a proposed tightening of relevant guidelines. Similarly, concerns about medical privacy and discrimination led the federal government, in a precedent-setting move, to ban its own agencies from using genetic information in employment decisions. Nevertheless, the issue of genetic privacy remains unsettled both in law and in medical ethics.

In agriculture, the federal government has tightened its oversight of foods produced with genetically altered ingredients. The new rules will require firms to notify the FDA of the intent to market food with genetically altered ingredients, develop tests to detect such ingredients, and establish a labeling process.

The EPA regulates environmental biotechnology. Its authority comes from the Resource Recovery and Conservation Act for waste storage, treatment, and disposal, and the Comprehensive Environmental Response Compensation and Recovery Act (commonly called the Superfund) for site cleanup. Consequently, the EPA has a major impact on selection and application of technologies for both upstream processing and site remediation strategies.

Biowarfare and Bioterrorism

The U.S. National Security Strategy highlights the need to contain the spread of biological weapons and to enhance domestic preparedness for a biological weapons attack. No fewer than 17 nations, including Iraq, Iran, North Korea, Cuba, Russia, and China, as well as several international terrorist organizations, have known or suspected bioweapons programs.[,]

The potential use of biological agents significantly increases the complexity of defense strategies because of the unique characteristics of bioweapons. Combating biowarfare and bioterrorism requires an appreciation of the way in which biological agents work and the challenges of disseminating them. The rapid advances in biotechnology mean that increasingly insidious bioweapons are becoming increasingly accessible to even minor actors.

Possible bioweapons include living organisms, both microorganisms (e.g., bacteria, rickettsiae, fungi, viruses) and macroorganisms (e.g., harmful insects); chemical products of living organisms, including biological toxins; artificially manufactured substances that mimic the action of biological substances; and GMOs. Biological agents may be targeted directly against humans, through injection or topical application; deployed against agricultural crops, livestock, poultry, and fish; applied as a contaminant of food, animal feed, or drinking water; disseminated as an aerosol; or introduced through a natural vector, such as an insect or infected plant material.[,] The motivation behind the use of bioweapons may be to commit selective or mass murder; to incapacitate enemies; to achieve political goals; to undermine social stability or create mass panic; or to pursue economic objectives through destabilization, blackmail, extortion, or market disruptions.[,]

Biological agents have several advantages as weapons. They are compact, highly effective, and relatively easy and inexpensive to obtain or produce (Table 1). In addition, the technology to produce bioweapons is "dual-use," meaning that it could also be put to legitimate purposes, such as in the manufacture of vaccines, which would provide cover to bioterrorists. Finally, biological agents are

silent, invisible, microscopic, and odorless. Thus, their introduction produces no fanfare, and they can strike without warning. Because of rapid reproduction times, pathogens can spread rapidly, but may go undetected or undiagnosed for days, slowing response times by authorities. Once they have detected an agent's presence, authorities may believe that a disease outbreak is "natural," further slowing their response.

Table 1. Cost and Effectiveness of Weapons of Mass Destruction

Type of Weapon	Cost/Km^2	LD-50/120 Km^2*
Conventional Explosives	$2,000	1,000,000 tons
Nuclear	$ 800	1 megaton
Chemical (Sarin)	$ 600	158 tons
Biological (anthrax)	$ 1	6.5 kilograms

*Amount of weapon required to kill 50 percent of the population in a 120-km^2 area.

Source: Defense Intelligence Agency. 2000. The Worldwide Agricultural Biological Warfare Threat. Unclassified briefing, Biological Warfare Assessments Division, Office for Counterproliferation Support.

Ideally, bioweapons are highly infectious, communicable, and lethal; capable of efficient dispersal; easily produced in large quantities; stable in storage; and resistant to environmental degradation. Furthermore, there are no vaccines or effective treatments for these ideal bioweapons. Biological agents are not ideal weapons, however, particularly in a battle. First, they are difficult to disperse. It is best to disseminate them as an aerosol cloud, but microscopic pathogenic agents lose virulence or die rapidly on release because of exposure to ultraviolet radiation and desiccation. It is also difficult to control the dispersal path of the agents. Additional disadvantages include the need to protect handlers from accidental contamination; the problems of maintaining quality control and containment during the manufacture and harvest of agents; the poor survival, in storage, of agents; and the challenge of maintaining bioweapons in a delivery state.

Biotechnology could be a two-edged sword in relation to bioweapons. Unfriendly interests could exploit the potential for creating new life forms artificially. New knowledge about the gene sequences of living organisms could lead to genetically engineered pathogens, toxins, or synthetic "superbugs" that could be used as bioweapons.[9] Enemies could develop and deploy a "cocktail" made up of multiple biological agents or a combination of chemical and biological agents, which would

severely impede efforts to identify the cause of illness and to provide effective treatment. Genetic engineering could produce vaccine-resistant pathogens. For example, Russian scientists recently reported the development of a genetically engineered anthrax strain that is resistant to the current anthrax vaccine. There is even some concern that genetically engineered crops could serve as vectors for toxins or disease agents that target human populations—plants would simultaneously function as toxin/pathogen bioreactors and delivery devices.

Conversely, advanced biotechnology techniques could help counter biowarfare and bioterrorism. For example, DNA "fingerprinting" of potential pathogens could facilitate diagnostic tests to identify pathogens and their precise origins—even for soldiers on the battlefield. Genetically engineered vaccines could provide protection against specific biological agents. Transgenesis and other genetic engineering technologies, particularly in agriculture, could improve genetic resistance to specific pathogens or confer broad-scale resistance to diseases or pests.

Education and Training

The biotechnology industry is expected to explode in size and importance in the 21st century, causing a huge demand for biotechnology workers. In Silicon Valley, the Private Industry Council in Sunnyvale predicts a 50 percent increase in biotechnological jobs over the next 3 years, making the biotechnology industry today comparable to the semiconductor industry of the early 1970s. A senior vice president at Genentech predicts that the top three biotechnology labor needs will be scientists in research, pharmacological, and process sciences; manufacturing engineers; and clinical scientists—people with medical backgrounds who can design and manage clinical trials. To meet these needs and remain competitive in the world marketplace, the United States will need workers who are educated in these fields.

According to the National Research Council (NRC), the level of science, mathematics, engineering, and technology education of most U.S. citizens is inadequate for full participation in this increasingly technological world. The NRC assessment is consistent with the results of the Third International Mathematics and Science Study where U.S. twelfth graders' performance was among the lowest of the participating countries. Underachievement at the secondary school level has led to declining enrollments in science, mathematics, and engineering programs at the undergraduate college level, creating a shortage of adequately trained high-technology workers.

To remedy this situation, the NRC recommends that secondary school students be required to demonstrate achievement in science, mathematics, and engineering in order to gain admission to colleges. Further, the NRC recommends that colleges require all entering students to enroll in some type of technically oriented course, regardless of their planned major. It would likely take at least a decade to establish a standards-based curriculum for K–12, which would be a necessary precursor to implementing these recommendations throughout the nation. Success in fixing educational deficiencies in our current science and mathematics curricula is key to the U.S. retaining its dominance in biotechnology in the 21st century.

CONCLUSIONS

The United States is the undisputed world leader in biotechnology, years ahead of its nearest rival. The biotechnology industry serves national interests in several ways. It promotes and strengthens the

pure scientific and applied research necessary for developments in related commercial areas. Advances in biotechnology R&D should lead to new applications, products, and processes that will improve human health and welfare, enhance environmental quality, strengthen U.S. economic prosperity, and further increase the competitive advantage in biotechnology presently held by the United States.

Biotechnology is fundamentally changing the way we live our lives. There are tremendous opportunities—along with some significant risks—to the United States and the world. It will soon be possible to change humans on a molecular scale, presenting the potential to cure diseases and live longer lives. Cloning, bioengineered foods, genetic patenting, and advanced knowledge of inherited diseases will threaten long-cherished beliefs about how we interact with nature, who we are as a society, and what we are as human beings. There will be serious challenges in the areas of biowarfare and bioterrorism.

The United States needs to prepare now to meet these fantastic opportunities and challenges. As a society, we must thoroughly debate the ethical issues. We must carefully review government regulations to ensure the safety of food and medical care. We must strongly oppose the use of biotechnology in warfare and terrorism. These steps will contribute to the peace and prosperity of the United States.

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