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Biotechnology for the 21st Century

**A Report by the
FCCSET Committee
on Life Sciences
and Health**

**February 1992
FY 1993**

Biotech

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EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

MEMBERS OF CONGRESS:

I am pleased to forward with this letter the report entitled "Biotechnology for the 21st Century," prepared by the Committee on Life Sciences and Health (CLSH) of the Federal Coordinating Council for Science, Engineering, and Technology (FCCSET), to supplement the President's Fiscal Year 1993 Budget.

This Presidential Initiative recognizes the critical role of biotechnology in our nation's future technological strength, economic growth, and the health and quality of life of its people. This country has been the world leader in biological research for the past thirty years which has provided the foundation for the current U.S. pre-eminence in biotechnology research. This leadership, however, is clearly being challenged as the field changes and expands rapidly.

The strategic framework outlined in this report is a coordinated, interagency effort intended to develop and implement a national Biotechnology Research Program to assure the nation of a vigorous base of science and engineering for future development of this critical technology. If aggressively exploited, this effort will maintain the momentum of U.S. leadership in health-directed biotechnology research and will expand research in critical areas where applications of biotechnology research promise significant breakthroughs including agriculture, energy, and environment.

The Biotechnology Research Program is an integral component of the President's overall approach to challenges in science, technology, and education. Improvements in the scientific and engineering research base in biotechnology will have far-reaching effects and will lead to enhancements in manufacturing, agriculture and aquaculture, mineral processing, and the production of chemicals and fuels.

The coordination and integration of the interagency research and development strategy for this Initiative was led very ably by Dr. James Mason, Chairman of the Committee on Life Sciences and Health, and by Dr. David Galas, Chairman of the Biotechnology Research Subcommittee, as well as their interagency committee members, associates, and staff. They are all to be commended on the excellent work that is manifest in both the Initiative and the report.


D. Allan Bromley
Director



BIOTECHNOLOGY FOR THE 21st CENTURY

The FY 1993 U.S. Biotechnology Research Initiative

A Report from the Committee on Life Sciences and Health

Federal Coordinating Council for Science, Engineering, and Technology



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John Turner, DOI/FWS

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D.A. Henderson, OSTP

Rachel E. Levinson, OSTP

Nancy Milton, OMB

Winnie Stachelberg, OMB

EXECUTIVE SECRETARIES

D. Jay Grimes, DOE

Kathy L. Hudson, DHHS

Additional Participants

Claire Broome, CDC

Tim Condon, ADAMHA

Charles Dickens, OSTP

Robert Frederick, EPA

Maryanna Henkart, NSF

Barbara Lujan

Seth Pauker, FDA

Nelson Wivel, NIH



The Biotechnology Research Subcommittee gratefully acknowledges the following individuals for their contributions to this document:

Stanley Abramowitz
B. S. Anthony
Houston Baker
Nat Barr
James Beall
Richard Broadwell
David Bubbenheim
Leon Cammen
Brad Carpenter
James Cassatt
Marvin Cassman
Tom Cebula
Jan Cervený
Richard Chadwick
Y. T. Chien
Charles Coulter
Sara Dillich
Gregory Dilworth
Machi Dilworth
Daniel Drell
George Duda
Jackie DuPont
Hank Eden
Murray Eden
Jesse Edwards
Eric Eisenstadt
Jerry Elwood
Shirley Fisk
Marvin Frazier
Gary Gilliland
Margaret Gordon
Churchill Grimes
Thora Halstead
Philip Harriman
Ben Haynes
Frederick Heinekin
Kiki Hellman
Caroline Holloway
John Hunt
Daniel Jones
Elke Jordan

Eric Juengst
Marvin Kalt
Peter Katona
Chuck Kostner
Becky Lawson
Ellen Liberman
David MacKenzie
John McLelland
James McVey
Jerry Miksche
Evelyn O'Connor Miller
Richard Moorner
Robert Newburgh
David Newman
John Norvell
Richard Parry
John Payne
Robert Rabson
Louise Ramm
Terry Rausch
Paul Richardson
John Riley
Joann Roskoski
Pete Salisbury
Phil Sayre
Paul Scott
Gerald Selzer
Linda Schilling
Murray Schulman
David Smith
R. Oneal Smitherman
Martha Steinbock
Philip Taylor
Judith Vaitukaitis
Susan Vargo
Ruxton Villet
Don Wiley
Debbie Wilson
John Wooley
Bernard Zahuranec



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EXECUTIVE SUMMARY

The goal and strategic objectives of the Biotechnology Research Initiative are shown in Figure 1. Several over-arching priorities have been adopted to ensure and extend U.S. leadership in biotechnology.

Priorities

- Maintain momentum and capitalize on strengths in general scientific and technological foundations and health-related research that have led to current U.S. leadership in biotechnology.
- Fill gaps in support for research in critical areas beyond health where applications of biotechnology now promise breakthroughs, particularly in manufacturing/bioprocessing and the environment.
- Enhance programs designed to capitalize on a broad range of organisms that have not, thus far, served as subjects of biotechnology research.
- Strengthen research and infrastructure programs directed toward analysis of the structure and function of biological macromolecules such as DNA and proteins.
- Expand interdisciplinary research and the infrastructure for research at the interfaces of biology with chemistry, physics, mathematics, computer science, materials science, and engineering for the benefit of all areas of biotechnology.
- Increase training programs at all levels to provide the essential human resources for future biotechnology research and development.

These priorities have guided the development of an investment strategy for biotechnology research that will both advance the mission of each individual Federal agency and contribute to a coordinated national biotechnology research effort.

The scientific revolution that has vastly increased our understanding of the living world now offers us continuing opportunities to use this knowledge to improve public health, to enhance the quality of life, and to contribute to economic growth. The science and engineering research that makes possible these practical applications, broadly termed biotechnology research, is the subject of this report. The President has selected biotechnology research as a budget initiative for FY 1993 in recognition of its technological importance.

The U.S. Federal investment in biological research of the past thirty years laid the foundation for a strong biotechnology enterprise in which the U.S. is currently preeminent. Because the field is moving rapidly, historical leadership does not ensure continued superiority.

As a result, the Bush Administration has worked to increase investment in this potentially high-payoff area. The President has, through the FCCSET, put in place the mechanism to make a sustained investment in areas such as biotechnology, which have the potential to improve America's productivity. The President's budget proposal of \$4.03 billion represents a 18% increase in Federal investment in biotechnology in the last two years. This increased investment is being combined with the efforts of Biotechnology Working Group of the Council on Competitiveness to remove unnecessary or outdated regulatory barriers in order to maximize the benefits that exciting developments in biotechnology can provide to American society.

Biotechnology research is now supported by 12 different Federal agencies because of its broad applicability to the missions and goals of these diverse agencies. The Biotechnology Research Initiative is the result of an intensive, interagency, cooperative effort to categorize, analyze, and coordinate the broad spectrum of Federal research programs.



The President's budget requests \$4.0 billion for biotechnology research. This represents an increase of \$271 million or 7% over FY 1992. These resources will be distributed across a number of agencies for investment in areas of biotechnology research offering exceptional promise.

This report discusses the integrated research strategy and budgets for Federally-funded biotechnology research. The strategic framework and priorities discussed in this report will guide a continuing effort to

ensure the nation a solid base of science and engineering for future development of this critical technology. The development and application of biotechnology to new products and processes is the role of the private sector. The 1993 budget provides for increased Federal investments in areas of applied biotechnology research, to assist the development of generic precompetitive areas of biotechnology that have potential for large benefits to the economy.

FIGURE 1

Biotechnology Research Framework

GOAL

- Sustain and extend U.S. leadership in biotechnology research for the 21st Century to enhance the quality of life for Americans and the growth of the U.S. economy.

STRATEGIC OBJECTIVES

- Extend the scientific and technical foundations for the future development of biotechnology
- Ensure the development of the human resource foundations for the future development of biotechnology
- Accelerate the transfer of biotechnology research discoveries to commercial applications
- Realize the benefits of biotechnology to the health and well-being of the population and the protection and restoration of the environment

IMPLEMENTATION STRATEGIES

- Enhance the support of research in the biological sciences related to biotechnology, with particular attention to interdisciplinary areas at the boundaries between biology and other disciplines
- Ensure the development of the essential infrastructure for biotechnology research
- Enhance education and training programs to ensure the human resources needed for the development of a vigorous biotechnology research enterprise
- Promote rapid translation of basic research into practical use by developing cooperative activities among government agencies, industry, and academia
- Support the development of focused programs in the applications of biotechnology to the concerns of each agency's mission and establish appropriate interagency programs

Biotechnology is a set of powerful tools based on biological knowledge.* Mastery of these tools will ultimately touch every facet of American life from the food we eat and the water we drink to the energy that fuels our machines and the materials from which they are constructed. Biotechnology offers novel approaches to conquering disease, easing world hunger, and reducing environmental pollution. It also promises to continue to impact our nation's economic growth and industrial leadership. However, if we are to realize the full economic and social benefits of biotechnology, a vigorous and broadly based science and engineering research enterprise is essential.

The impact of biotechnology on the nation's economy is growing explosively as increasingly diverse industries capitalize on the fruits of biotechnology research. In 1991, sales of biotechnology products approached \$4 billion and sales are expected to increase to over \$50 billion during the next 10 years.² Nationwide, hundreds of companies, representing industrial sectors from agriculture to energy and manufacturing are using biotechnology to develop products and processes. The vitality of these industries is influenced by many factors including capital availability, regulatory constraints, and market forces, but "an issue central to the competitive position of U.S. efforts in biotechnology is a sufficient and stable level of funding for areas of science crucial to the field."³

The impact of biotechnology on society and the economy in the coming decade could be profound, and grow dramatically in the next century, if projected technical advances are realized. A strong research program is needed to exploit these emerging opportunities and further, to enhance our nation's technical capability to meet increasing challenges from foreign competition. In recognition of biotechnology's technological importance, Biotechnology Research has been selected as a Presidential Initiative for FY 1993.

BIOTECHNOLOGY PAST AND PRESENT: ORIGINS AND IMPACTS

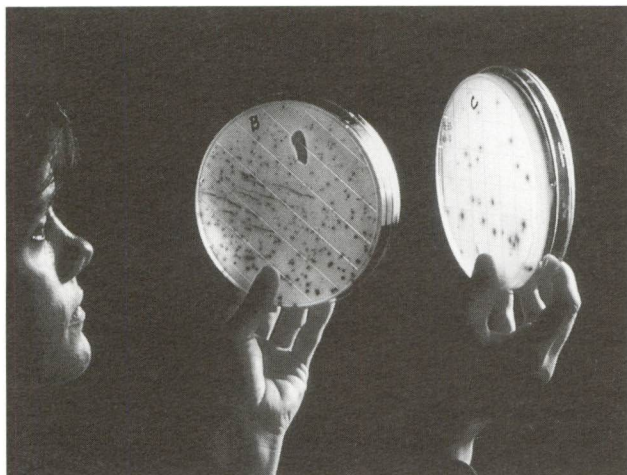
Scientific knowledge of the living world has been growing exponentially for the past forty years. Key developments from which modern biotechnology has emerged are based upon our expanding understanding of the structure and function of living cells, how they retain and transmit genetic information, and how they respond to chemical and physical signals. These developments include DNA cloning and sequencing technologies, DNA synthesis and amplification methods, monoclonal antibody technologies, and macromolecular structural analysis. These advances are the result of fundamental research supported largely by U.S. federal agencies, most notably the National Institutes of Health (NIH). Clearly, a strong foundation has been laid, placing the United States at the forefront of biological and biotechnology research.

*Biotechnology is broadly defined to include any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals, or to develop microorganisms for specific use.¹ The development of materials that mimic molecular structures or functions of living systems is included. This report is limited to **research** directed toward biotechnology, and further, to "new biotechnology," i.e., involving recombinant DNA, DNA transfer techniques, macromolecular structure, cell fusion, bioprocessing, etc.

¹ U.S. Congress, Office of Technology Assessment, *Commercial Biotechnology: An International Analysis*, OTA-BA-218 (Washington, DC: U.S. Government Printing Office, January, 1984), page 3.

² Burrill, G.S. and K.B. Lee, Jr., *Biotech '92: Promise to Reality*, (San Francisco, CA: Ernest & Young, 1991), page 31.

³ U.S. Congress, Office of Technology Assessment, *Biotechnology in a Global Economy*, OTA-BA-494 (Washington, D.C.: U.S. Government Printing Office, October, 1991), page 21.



Foundations of biotechnology include studies of bacterial viruses which are represented here as clear spots on petri dishes otherwise coated with a cloudy film of living bacteria. Modified viruses are now used as vectors for transferring segments of DNA (genes) from one organism to another.

The key to maintaining our competitive position in the world biotechnology marketplace continues to be strong support for basic research and research training.

*Council on Competitiveness
Report on National
Biotechnology Policy (1991)*

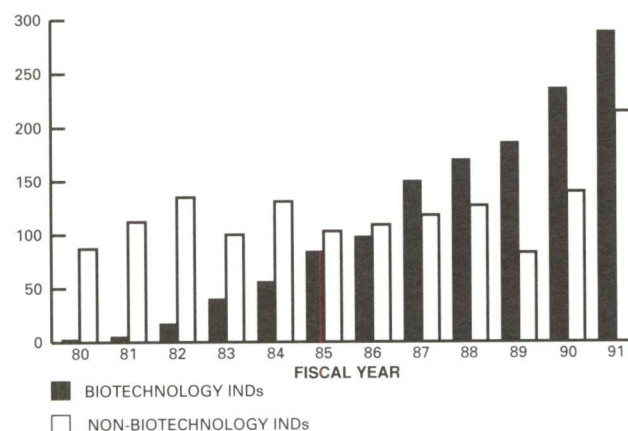
Biotechnology has thus far had its greatest impact in the area of human health through the development of new pharmaceuticals, diagnostics, and other medical products. During the past two years, a record number of new biotechnology-produced pharmaceuticals have been introduced - from vaccines for hepatitis to the powerful anti-anemia drug, erythropoietin (Figure 3). Progress in the science underlying these advances will ensure that biotechnology's impact on health will continue to expand during the next decade. Prospects include new drugs, diagnostics, and vaccines as well as gene therapy. In the future we can expect specific cancer vaccines as powerful weapons against this deadly group of diseases, as

well as cures for many inherited diseases based on the use of genetically engineered human cells. Equally important, biotechnology is likely to lead to significant reductions in health care costs, particularly through advances in prevention, early diagnosis, and treatment.

The impact of biotechnology could soon be felt in many areas besides health. The next decade should see unprecedented applications of biotechnology to agriculture and aquaculture, to the restoration and protection of the environment, to the production of chemicals and fuels, and to many other areas. New biological technologies have the potential to make major contributions and even to transform these fields. For example, biotechnology can be used to produce fuels and chemicals from renewable resources and with lessened adverse effects on human health and the environment.

Commercial biotechnology emerged in the mid-1970's with the founding of the first modern biotechnology companies. The 1980's witnessed an explosion of activity that was marked by a period during which more than 100 new U.S. companies were founded yearly to develop biotechnology products.

FIGURE 3
Biotechnology Growth as measured in Biologic Applications to the FDA for Investigational New Drugs (INDs)





Cost Savings Associated with Improved *Haemophilus influenzae* Type B (HIB) Vaccine



\$ 359.3 million: Savings with improved Hib vaccine for every cohort of children vaccinated (i.e., over their lifetime)



\$ 177.6 million: Savings using former Hib vaccine

Cost savings associated with improved *Haemophilus influenzae* Type B (HIB) Vaccine. The improved vaccine was created using techniques of genetic engineering.

A remarkable number of Federal agencies, recognizing biotechnology's potential for widespread fundamental breakthroughs, have initiated or expanded biotechnology research efforts in support of their respective missions:

Department of Agriculture (USDA)
Department of Commerce (DOC)
Department of Defense (DOD)
Department of Energy (DOE)
Department of Health and Human Services (DHHS)
Department of the Interior (DOI)
Department of Justice (DOJ)
Department of Veterans Affairs (DVA)
Agency for International Development (AID)
Environmental Protection Agency (EPA)
National Aeronautics and Space Administration (NASA)
National Science Foundation (NSF)

These 12 Federal agencies support a variety of biotechnology research programs. Many of these programs are new, reflecting the growing recognition of

the wide spectrum of applications. Coordination of agency research programs can increase the effectiveness of the total Federal effort. Development of short-term applications for immediate needs is important, but the Biotechnology Research Initiative also takes a long-term view to ensure the strength of U.S. biotechnology in the 21st century.

The United States has begun to exploit the promise of biotechnology, but our position of international leadership is challenged. Several countries have declared biotechnology research as a high priority for the 21st century. A critical role for the Federal government, academia and industry in meeting this challenge is to ensure an uninterrupted flow of new ideas and new techniques to U.S. industry.

PURPOSES OF THIS REPORT

This report outlines the Federal role in biotechnology research and describes the foundation for a coordinated national initiative that will, over the coming years, maximize the effectiveness of the Federal investment in biotechnology research. Specifically, this report:

- (1) Defines the baseline of programmatic activity and Federal funding in biotechnology research,
- (2) Highlights ongoing agency programs and new initiatives,
- (3) Outlines national strategic objectives for biotechnology research,
- (4) Presents the first interagency Federal biotechnology research budget, and
- (5) Suggests directions for future efforts.



STRATEGIC FRAMEWORK FOR BIOTECHNOLOGY RESEARCH

GOAL

Sustain and extend U.S. leadership in biotechnology research for the 21st century to enhance the quality of life for Americans and the growth of the U.S. economy

The goal and strategic objectives (Figure 1) of the Biotechnology Initiative represent an integrated strategy to maintain the strength of the science and engineering research base for biotechnology; enhance cooperation among government, academia, and industry; extend U.S. technological leadership; and speed the pace of development of new and important products and processes.

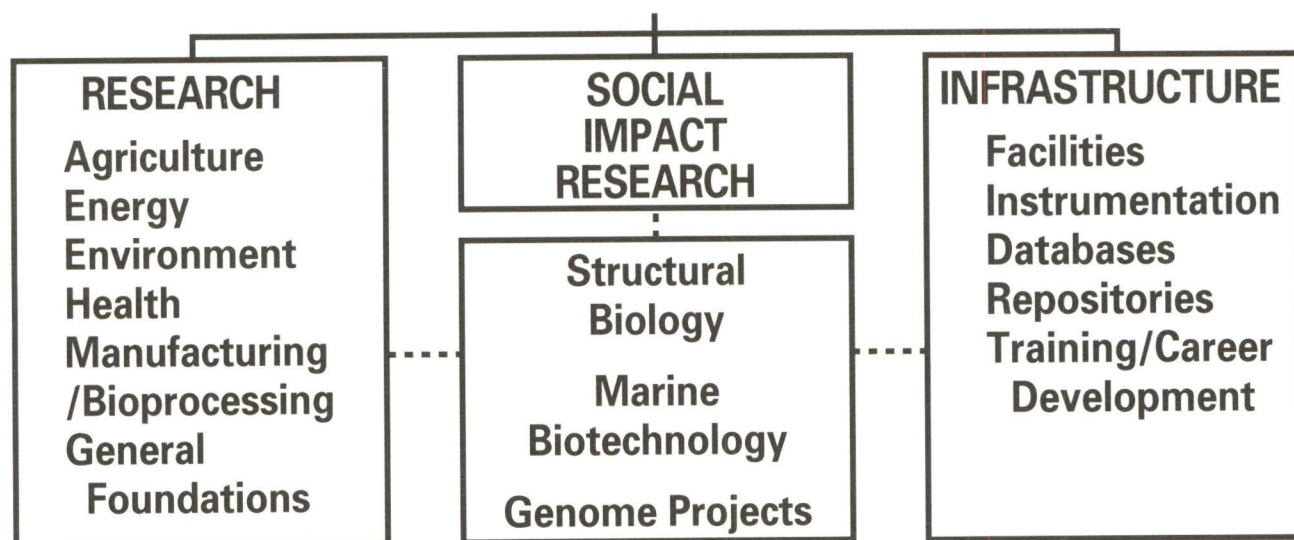
CURRENT FEDERAL PROGRAMS

In developing this Initiative, a concerted effort was made to obtain a detailed and consistent accounting of current Federal commitments in biotechnology research. Although approximate budget numbers have been previously compiled for Federal activities in biotechnology, and although data on specific categories of biotechnology research have been collected by individual agencies,⁴ no comprehensive description of biotechnology research across the Federal government has previously been available.

This Initiative provides a uniform and comprehensive classification system for all Federal biotechnology research programs (Figures 5 and 6). This Initiative consists of six research areas: agriculture, energy, environment, health, manufacturing/bioprocessing, and general foundations research. The Ini-

FIGURE 5

U.S. BIOTECHNOLOGY RESEARCH INITIATIVE



⁴U.S. Congress, Office of Technology Assessment, *Biotechnology in a Global Economy*, OTA-BA-494 (Washington, DC: U.S. Government Printing Office, October, 1991); U.S. Congress, Office of Technology Assessment, *New Developments in Biotechnology*, OTA-BA-360 (Washington, DC: U.S. Government Printing Office, July, 1988); President's FY 1992 budget

FIGURE 6
Components of the Initiative

RESEARCH

Agriculture

Biotechnology research applicable to food, feed, fiber, ornamentals, and forestry production

Energy

Biotechnology research applicable to the production of energy and fuels

Manufacturing/Bioprocessing

Biotechnology research applicable to the chemical industry, materials, manufacturing processes; development of pharmaceutical production/manufacturing processes; mineral processing; and scale-up

Environment

Biotechnology research applicable to restoration, maintenance, and remediation of the environment and ecosystems analysis

Health

Biotechnology research directed towards improving, restoring, and preserving human health

General foundations

General scientific and technical foundations research broadly applicable to agriculture, energy, manufacturing, environment, and health

SOCIAL IMPACT RESEARCH

Research on the social, ethical, economic, and legal issues associated with biotechnology research, development, adoption, or utilization

INFRASTRUCTURE

Facilities

Acquisition, construction, renovation, or maintenance of facilities dedicated to biotechnology research.

Training/Career Development

Programs dedicated to training or career development in biotechnology such as pre and postdoctoral fellowships and training grants

Instrumentation

Acquisition and maintenance of major specialized instruments for use in biotechnology research

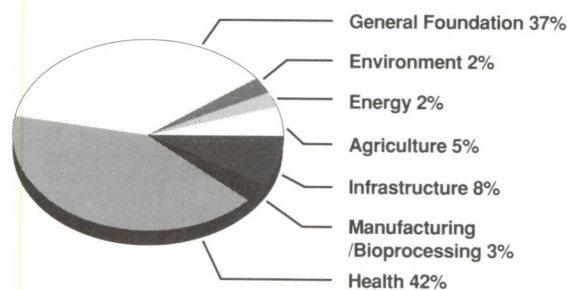
Repositories

Shared repositories of biotechnology research resources such as DNA clone libraries, germplasm centers, and stock centers

Data Bases/Reference Standards

Acquisition and management of data bases, information resources, and reference standards relevant to biotechnology research

FIGURE 7
Current Federal Investment in Biotechnology Research



FY 1991 = \$3,379.4M
FY 1992 = \$3,759.3M
(Social Impact Equals Less Than 1%)

tiative also includes two supporting components: research on the social impact of biotechnology and support for the infrastructure of biotechnology (training, facilities, and various research resources). Finally, the Initiative includes three research areas that merit special attention: marine biotechnology, structural biology, and genome research⁵.

The FY 1991 and FY 1992 biotechnology research budgets of 12 Federal agencies are shown in Figure 7. Four or more agencies currently support research programs in every area of biotechnology research. For example, nine agencies have ongoing programs in environmental biotechnology and eight agencies

⁵Support for these three areas is included in the budgets for the six primary research areas and the two supporting components. For example, support for research on the genomes of agriculturally important species is included under **Agriculture**.



have ongoing programs in manufacturing/bioprocessing. These programs were developed in response to individual agency missions and, although they are largely complementary rather than duplicative, enhanced interagency coordination and cooperation are needed.

The largest components of the total investment in biotechnology research are general foundations and health. Together, investment in these two areas constitutes nearly 80% of the total Federal investment in biotechnology research (Figure 7). This large fraction reflects the fact that biotechnology was spawned primarily by U.S. support of life sciences research, particularly NIH support of human health research.

The present investment in biotechnology research directly supporting applications to the environment, manufacturing / bioprocessing, energy, and to a lesser extent, agriculture, is relatively small. The collective fraction of the federal investment in these areas is only about 12% of the total. In fact, two of these areas, environment and manufacturing/bioprocessing, together represent less than 5% of the total Federal investment in biotechnology research, and support for biotechnology research using marine organisms is probably 1% or less. The Initiative will make Federal investments more commensurate with the expanding opportunities in these areas.

The vitality of the biotechnology research enterprise demands the maintenance of a strong infrastructure: facilities, instrumentation, research resources and a supply of trained personnel. The level of Federal investment in the infrastructure for biotechnology research is about 8% of the total.

New opportunities offered by scientific and technological advances often raise new sets of social, ethical, legal, and economic concerns. While few of the issues raised by biotechnology are new, some deserve heightened attention because of the scale and

pace of change. Research on the social, ethical, legal, and economic issues associated with biotechnology is a relatively small, but important, component of the overall biotechnology research program budget. Most of this investment is directed towards research on the ethical, legal, and social issues associated with the human genome project and is cooperatively supported by the National Institutes of Health and the Department of Energy. As in the scientific research areas, health represents the focus of a large fraction of the overall investment in social impact research. The smaller investment in research on the impacts of the applications of biotechnology to agriculture, the environment, and energy should increase with the expanding applications of biotechnology in these areas.

PLANNING AND PROGRAM PRIORITIES

Analysis of the FY 1991 and FY 1992 Federal investment in biotechnology research highlighted areas of strength, and identified significant research opportunities. The priorities below address areas of critical need that fall within the mandates of multiple Federal agencies and that will influence multiple areas of application. These priorities address essential research areas and infrastructure for which increased emphasis will significantly enhance the scientific base of the national biotechnology effort and whose neglect would impede further development of biotechnology. It is essential that these priorities be implemented together if the objectives of the Biotechnology Research Initiative are to be achieved.

PRIORITY

Maintain strong support for broadly applicable general foundations research to sustain the momentum of progress in all areas of biotechnology.



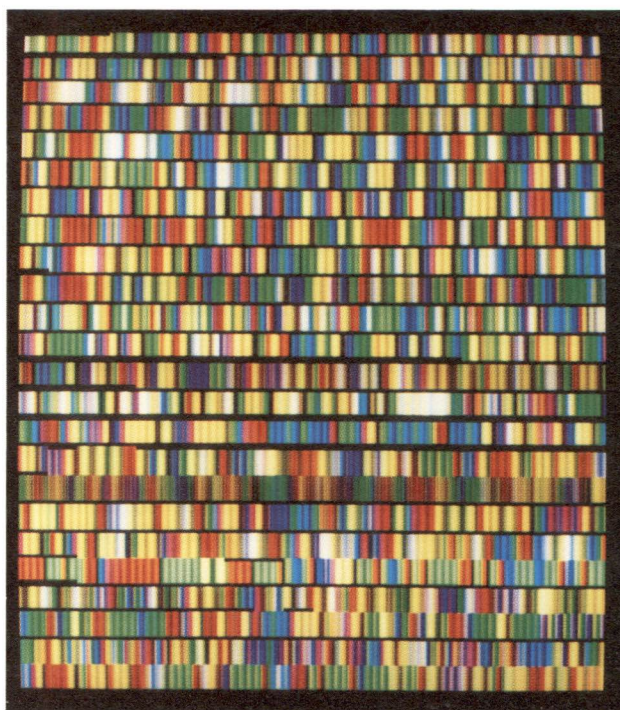
A constant flow of fundamental biological knowledge and creative approaches to its practical application are requirements for the progress of biotechnology. General foundations research is broadly applicable to many areas of biotechnology. Biotechnology has grown out of an attempt to understand the molecular basis of life and modern research in cell and molecular biology continue to contribute to biotechnology. Examples of general foundations research include techniques for manipulating DNA, for introducing new genetic material into cells, for growing specific cell types, for studying the structure and function of macromolecules, and for storing and analyzing data from genome studies.

PRIORITY

Maintain strong support for health-related biotechnology research to capitalize on the opportunity for applications to human health.

Biotechnology research provides powerful tools for the advancement of health care technologies; an understanding of the molecular basis of disease represents the ultimate answer to the fundamental question of what causes disease, and by implication, the specific targets for early diagnosis and effective intervention. The health-related research initiatives are intended to pursue these opportunities.

The fruits of earlier basic research on recombinant DNA have been well documented. The first generation of drugs included genetically engineered proteins such as insulin and white blood cell stimulating factors. Soon transgenic animals may be used as factories to make significant quantities of important proteins at a lower cost than current methods of production. The possibility now exists to use these techniques to make biomaterials such as synthetic collagen to preserve liver cells in a matrix, and thus create alternatives to the use of whole organ transplants for liver failure.



Computer representation of DNA sequence information from an automatic DNA sequencing machine. Each column contains information from a different DNA molecule with each subunit, or nucleotide, indicated by a different color. Automated DNA sequencing is far faster and more efficient than manual methods.

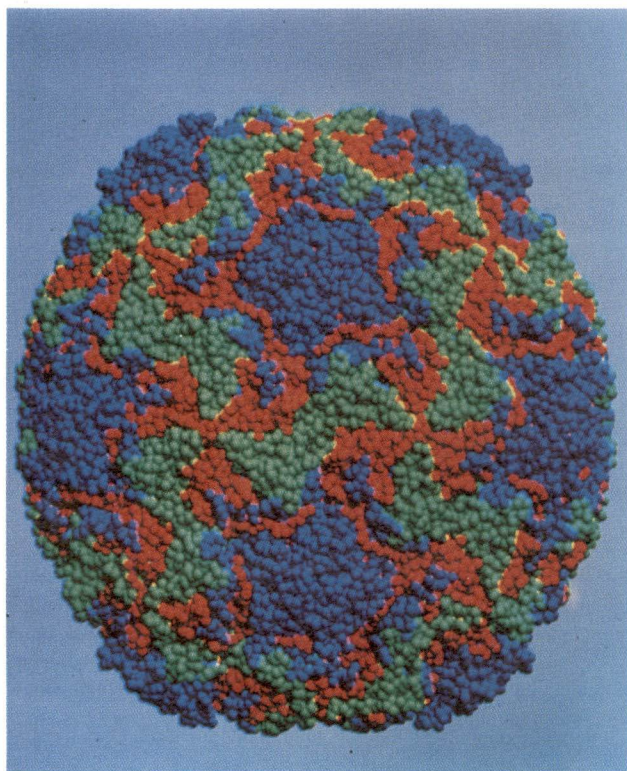
Somatic cell gene therapy, one of the most recent results of biotechnology research, offers tremendous potential for the prevention, treatment, and cure of a wide range of diseases. The early focus of these techniques is on the treatment of inherited blood diseases, and pulmonary and cardiovascular disorders. Other exciting prospects involve using gene transfer techniques to augment drug delivery systems by inserting the gene for a therapeutic protein into cells taken from a skin biopsy and returning the protein-producing cells to the patient.

It is apparent that applications of biotechnology to health will continue to be commercially important. Sustaining the commercialization of innovative



health-related products will require that the government agencies responsible for their review have the necessary science base to evaluate product safety, efficacy, and quality.

Whatever the advances to date, much more is promised in new and improved screening methods for a diversity of diseases, safer and more effective vaccines, gene therapy, and new highly specific pharmaceuticals. The Biotechnology Research Initiative maintains strong support for health-related biotechnology research to capitalize on opportunities to improve human health.



A three-dimensional reconstruction of the human cold virus. Understanding of the structural and chemical details of the viral surface will make it possible to design highly specific drugs to interfere with the virus' ability to infect cells.

PRIORITY

Significantly increase the Federal investment in biotechnology research related to the environment and coordinate the effort closely among Federal agencies.

As the environmental effects of modern industrial society become increasingly evident, the need for environmental restoration and protection becomes more urgent. Among the tools available for these purposes, biotechnology holds perhaps the greatest promise. Environmental biotechnology has a direct and fundamental role in bioremediation, bio-restoration, waste treatment, environmental diagnostics and analysis, the preservation of biodiversity, and the development of environmental risk assessment technologies. Examples of recent developments in this field include the engineering of microorganisms that degrade specific toxic organic chemicals and others that emit visible light signals when they encounter specific chemicals in the environment. The processing or treatment of wastes using engineered microorganisms or engineered biocatalysts also shows great promise, but the field is only in its infancy. This Initiative significantly increases support of biotechnology research related to the environment and emphasizes enhanced coordination of agency programs.

PRIORITY

Significantly increase the Federal investment in biotechnology research related to manufacturing/bioprocessing and closely coordinate Federal agency efforts.

Industry is just beginning to apply biotechnology to a wide spectrum of manufacturing processes, such as the manufacture of specialty chemicals. Nonethe-



less, biotechnology research in bioprocessing/manufacturing is likely to have major applications to the manufacture of pharmaceuticals, food products, chemical feedstocks, fuels, and a variety of novel products such as biomolecular materials and bio-sensors. Modern bioprocessing technology is able to achieve economically efficient manufacture of many desirable end products by using renewable resources and biocatalysis that minimizes energy consumption and reduces waste products. Biological processes require lower temperatures and pressures than traditional chemical processes and are inherently more energetically efficient. Applications of biotechnology to energy production and use are closely related to bioprocessing and are likely to be an important part of our economic future by promoting production of fuels from renewable resources and enhancing recovery of fossil fuels. In addition to direct future economic benefit, the applications of biotechnology in manufacturing and bioprocessing are expected to have significant payoffs in lower environmental costs for these activities. The Biotechnology Research Initiative significantly increases support for, and coordination of, manufacturing/bioprocessing research to exploit this rich source of technological innovation.

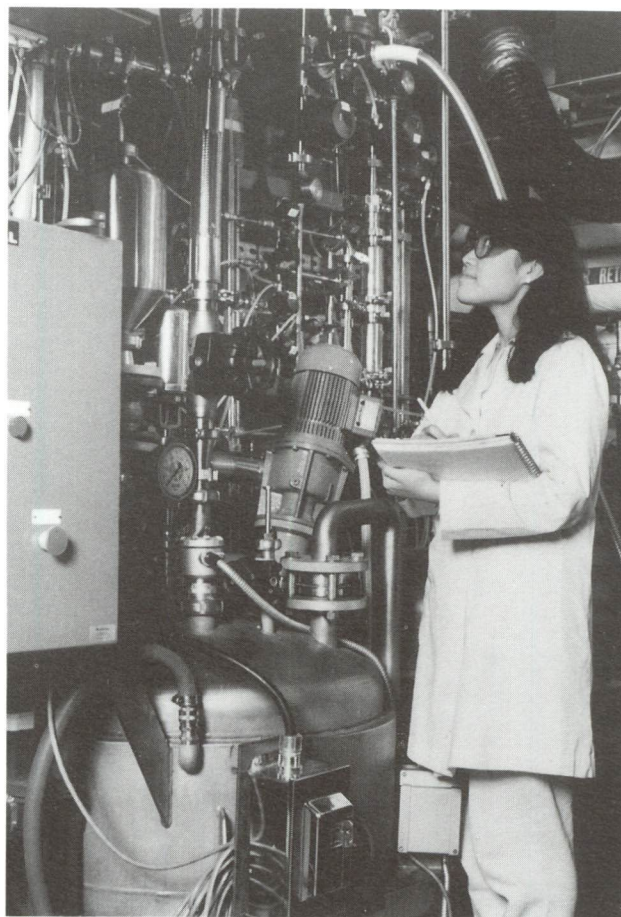
PRIORITY

Enhance existing programs and establish new programs as needed to facilitate the study and utilization of organisms not currently under investigation in the laboratory.

Biotechnology in this century has arisen largely from research in molecular genetics and biochemistry using a few common laboratory organisms: the bacterium *Escherichia coli*, the yeast *Saccharomyces*, the fruit fly *Drosophila*, the round worm, certain crop plants, and laboratory rodents. However, organisms not now used in laboratory research offer great potential for many areas of application. Research on the molecular genetics, biochemistry, regulation of

gene expression, cell interactions, and development of a wider array of organisms is essential to the future growth of biotechnology.

Many examples illustrate how biotechnology research on different types of organisms can be productive. The discovery that taxol, a natural product of the Pacific Yew tree, has important anticancer activity clearly illustrates the value of a better understanding of plant metabolic pathways, methods of regulating plant growth, and techniques for large-scale plant cell cultures. The succulent Virginia oyster offers a second example. This species is rapidly succumbing to disease and disappearing from the waters of the Chesapeake Bay. With its departure goes an important sector of the regional economy. If



A student monitors a large reactor used in bioprocessing research.



more were known about the molecular genetics of this shellfish and its natural defense mechanisms, it should be possible to develop effective techniques to protect these animals from pathogens.

The exploration of the biosphere for interesting and useful organisms and biochemical processes has just begun. Many currently unknown or unstudied species of microorganisms will prove valuable for their production of useful molecules, such as enzymes. New approaches to environmental restoration and bioprocessing of fossil fuels will also emerge from this area of research. Fundamental knowledge of microbial ecology will facilitate new approaches to environmental and energy problems and improve the assessment of environmental effects of genetically altered organisms.

Although microbes are important, they are certainly not the only organisms of potential value for biotechnology. For example, most plants and invertebrates are exclusively or predominantly marine, yet many marine organisms are yet to be identified and characterized. Fundamental research on the molecular biology of plants of all kinds is progressing, although studies of plant cell biology still lag well behind studies of animal systems. To capitalize on our competitive position in world agriculture the United States must have a broad and strong research program in plant biotechnology, with significant components devoted to both crop and non crop species.

The importance to biotechnology of the rich diversity of the biosphere cannot be overestimated. Programs should be developed to provide for characterization and maintenance of a wide variety of naturally occurring organisms as research resources. Examples of immediate needs include germplasm collections for plant species, culture collections for diverse microorganisms, and stock centers for marine organisms.

PRIORITY

Increase emphasis on research and infrastructure dedicated to the investigation of the structure and function of macromolecules, such as proteins and DNA.

Just as machines are built to carry out specific functions, so biological structures have been shaped by evolution to meet the needs of life. The ability to precisely modify the function of biological molecules therefore requires detailed knowledge of, and the ability to manipulate, these structures. The basic science, instrumentation, facilities, and techniques fundamental to resolving and understanding molecular structure and functions are collectively known as "structural biology." Significant new advances in this area include the engineering of biological catalysts, enzymes, to alter their reactions, engineering of peptides to serve as signals to the immune system for vaccine production, new techniques for crystallization of proteins (including crystallization of proteins under conditions of zero gravity in space), and powerful new methods for using x-rays to determine molecular structure.

Computer mathematical methods are important components of structural biology research, both for the analysis of structural data and for the theoretical prediction of function. For example, progress on the problem of predicting the three-dimensional folding pattern of a protein from physical and chemical principles would dramatically enhance the prospects for "molecular design."

The field of structural biology is currently in the early stages of rapid expansion, both in technical capabilities and in the amount of data being acquired about macromolecular structure. Continued expansion will depend increasingly on highly specialized



facilities that need to be shared on a national basis to be economically practical (synchrotron x-ray sources and neutron sources, for example). This has already been recognized by Europe and Japan, which are currently developing major new synchrotron radiation facilities. The development of national facilities, laboratory instrumentation, and specialized training in the interdisciplinary field of structural biology are major components of the Biotechnology Research Initiative.

PRIORITY

Strengthen and expand interdisciplinary research, and the infrastructure for such research.

Much of the most promising research in biotechnology involves problems at the interfaces of traditional disciplines. Often this calls for collaborative research between scientists and engineers with diverse skills. The future vitality of American biotechnology depends in large part on the scientific interfaces between biology and other disciplines, including chemistry, physics, mathematics, computer science, and engineering.

Several different interdisciplinary areas will receive special attention. The coupling of engineering, systems design, modeling, and computational studies with biology, chemistry, and physics in all areas of biotechnology are especially important. Examples include the effective collaboration among bioprocess and systems engineers, cell and molecular biologists, protein chemists, and mathematical modelers necessary for the design of advanced bioreactors. Likewise, microbial physiologists, ecologists, biohydrogeologists, chemists, and environmental and chemical engineers must work together to make progress in bioremediation research. For the longer term, the interface between mathematics and molecular biology is very rich in potential rewards. The analysis of DNA and protein sequence information can lead to an understanding of chemical and biological function and the theoretical understanding of com-

plex biological systems. It is from this kind of forward-looking fundamental research that much of the biotechnology of the 21st century will emerge.

Infrastructure needs for interdisciplinary research include databases and reference standards to assess quality and to assure comparability of results from different laboratories. The Biotechnology Research Initiative strengthens and expands interdisciplinary research and the infrastructure for such research to ensure the vitality of American biotechnology.

PRIORITY

Increase training programs at all levels to provide the essential human resources for biotechnology development.

Scientific opportunities in biotechnology cannot be realized if trained personnel are not available. Today, too few technical and scientific personnel are being trained in the scientific disciplines associated with biotechnology. For example, training is critically needed in protein, glycoprotein, and carbohydrate chemistry; in theoretical and computational biology; and particularly in general microbiology. The disappearance of general microbiology departments from many American universities has not been compensated by the development of a modern equivalent. As a result, the study of the diverse bacterial and other microbial populations is being hampered by a lack of adequately trained researchers.

In addition to strong discipline-based training in the fundamental sciences critical to biotechnology, there is an increasing need for training at the interfaces of biotechnology-related disciplines. Training programs are needed to enhance our expertise at the interfaces between engineering and cell and molecular biology; between mathematics, biology, and computer science; and between chemistry, biology, and physics. Similarly, clinical researchers are needed who have been trained to translate biotechnology



discoveries from the laboratory bench to the bedside. Efforts are needed, as well, to attract and retain students in biotechnology-related science and engineering through the pre- and post-doctoral levels, and to retrain individuals with experience in other disciplines for careers in biotechnology.

This Initiative emphasizes several areas: multidisciplinary training related to the areas mentioned above, broad training in molecular microbiology, and training in selected areas of biochemistry. Increased emphasis will also be given to training for mid-level technicians and technologists who are critical for biotechnology research and commercial development. The human resources represented by women, minorities, and the disabled must also be tapped effectively in all these training efforts.

Finally, efforts are needed to enhance public literacy concerning biotechnology. Public misperceptions of biotechnology, and of science generally, may impede future translation of research into practical applications. Research on the social and economic impact of biotechnology will play an increasingly important role both in formulating future policy and in enhancing public confidence in biotechnology.

FY 1993 COORDINATED BUDGET

The President's Budget requests \$4.03 billion for biotechnology research (Table 1). This represents an increase of \$271 million or 7% over 1992 levels (Table 2). These resources will be contributed by 12 Federal agencies with biotechnology research programs in a number of areas (Table 3).

Agriculture

Agricultural biotechnology research is applicable to food, feed, fiber, and forestry production. While USDA has the primary responsibility within the Federal government, seven other agencies support agricultural biotechnology research. Traditional biotech-

nologies have been practiced in agriculture since the beginning of civilization through plant and animal breeding. Currently, the knowledge base for the application of modern biotechnology to plants, animals, and microbes of agricultural significance is smaller than that for human health. Yet there is now the opportunity to obtain essential information for the application of the new techniques of biotechnology to agriculture. Techniques now exist to produce higher quality food and fiber, crops and animals with greater tolerance to stresses, and new approaches to waste management. The budget includes \$208 million for agricultural biotechnology research, an increase of 9% over 1992 levels. In addition to USDA's significant contributions, NSF's fundamental plant biotechnology research will increase by 25%. Programs in NIH, FDA, and AID will also be enhanced.

Energy

The nation's decreasing petroleum reserves, coupled with increasing consumption, has made this country increasingly dependent on imported oil. The National Energy Strategy promotes the development of alternative energy resources. A rational long-term energy plan includes the increased use of biological systems to maximize the efficient and economic use of both renewable and fossil fuels while also decreasing the environmental impacts of energy production and use. Biotechnology offers one key to the success of this plan. In recognition of the vast potential in this area, the FY 1993 budget includes \$107 million in funding, a 33% increase over last year's level.

Environment

The environmental effects of modern industrial society require tools for environmental restoration and protection. Among the tools available, biotechnology holds great promise. Examples of recent developments include the engineering of microorganisms



that degrade specific toxic chemicals and others that emit visible light signals when they encounter specific chemicals in the environment. The processing or treatment of wastes using biotechnology also shows great promise. The budget includes \$83.3 million for environment-related biotechnology research—a 21% increase over 1992 levels (Table 3). Five agencies—DOE, EPA, DOD, NSF, and USDA—contribute resources to this area (Table 1). Support for research focused on bioremediation and protection of the environment, including applications to diagnose and analyze environmental problems, are significantly expanded under the 1993 Initiative. Among the programs targeted for enhanced support are DOE and EPA programs to investigate the use of a range of microorganisms and enzymes for bioremediation and NSF's interdisciplinary research program.

Health

Biotechnology provides powerful tools with which to develop new approaches to the prevention, diagnosis, and treatment of human disease. While the first generation of biotechnology products included genetically engineered proteins such as insulin and white blood cell stimulators, the future may well see the use of transgenic animals as factories to produce large quantities of these and other important proteins. An understanding of the molecular basis of disease represents the ultimate answer to the fundamental question of what causes disease, and by implication, provides the specific mechanisms for disease intervention. To maintain the current strong support for health-related biotechnology research and to capitalize on the potential applications for human health, the budget proposes \$1.68 billion in this area. These resources will support exciting new investigations into the development of gene therapy, molecular medicine, and vaccines.

Manufacturing/Bioprocessing

Industry is just beginning to apply biotechnology to a wide spectrum of manufacturing processes. Bio-

technology research is likely to have important applications to the manufacture of pharmaceuticals, food products, chemical feedstocks, fuels, and a variety of novel products such as biomolecular materials. Modern bioprocessing is able to achieve economically efficient manufacture of many desirable products by using renewable resources and biocatalysts that minimize energy consumption and reduce waste products. In recognition of the opportunities in this emerging field, the budget proposes \$124 million in manufacturing/bioprocessing research, 25% over 1992 levels.

The FY 1993 budget will support manufacturing/bioprocessing research programs in 8 Federal agencies. NSF's varied manufacturing and bioprocessing research programs will be strengthened. NSF's programs to explore the boundaries between fundamental biology, biochemistry and engineering and its program to investigate the molecular properties of biological materials will be accelerated. Enhanced DOE efforts include research into production of fuels from biomass and alternative feedstocks for chemical processes. DOD will strengthen programs to develop a variety of biomaterials and biosensors. An important effort at the NIH will investigate the structure, function, and design of molecules and processes for use in health care.

General Foundations and Infrastructure

The budget includes \$1.5 billion to support general scientific and technological foundations research, an increase of \$82 million or 6% over 1992 levels. NSF, DOE, NIH, and DOD programs will be enhanced. DOE will develop its planned x-ray synchrotron facilities critical for research on the structure of biological macromolecules. Ongoing structural biology efforts at NIH, NSF, and DOD are also expanded through the Initiative. These research programs and facilities for structural biology provide a solid foundation for future biotechnology research.



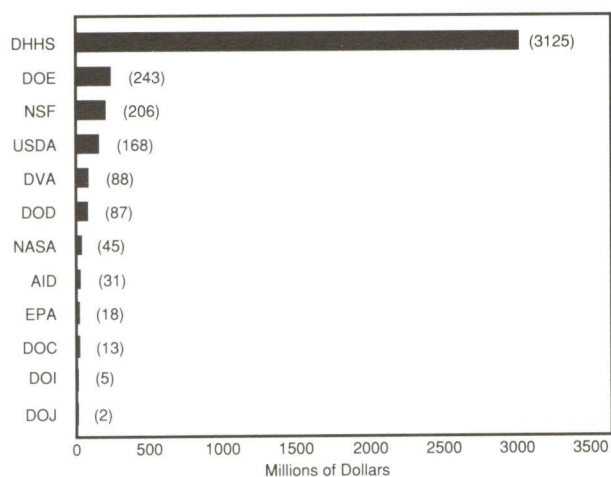
THE FUTURE

During this first year of the Biotechnology Research Initiative, a Strategic Framework was established, a system for classifying biotechnology research was developed, program and budget information from 12 Federal agencies collected and analyzed, and a coordinated FY 1993 budget was developed. This is the first stage of a process that will be developed and further refined. The communication that has been established as a result of developing the Initiative

has already led to mutual understanding of agency goals, responsibilities, and constraints, and to ideas for new cooperative activities.

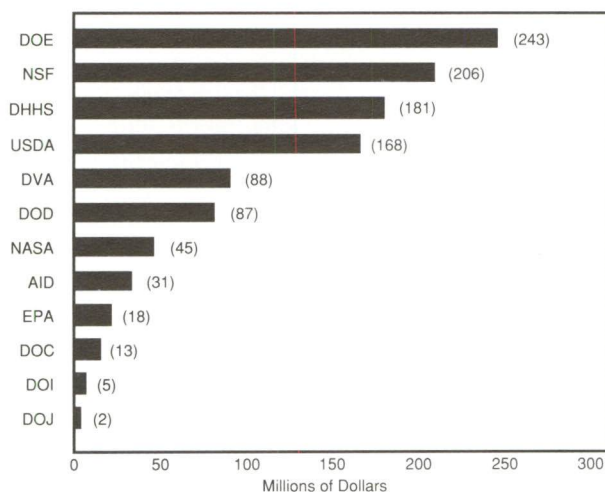
Building upon this foundation, detailed reviews of individual programs are now being carried out to identify special needs for research, infrastructure, and interagency collaboration. Technology transfer efforts will also be analyzed and possible incentives identified to enhance a more rapid transfer of fundamental research discoveries into practical use.

FIGURE 11
The President's FY 1993 budget for Biotechnology Research by Agency.



FY 1993= \$4,030 M

FIGURE 12
The President's FY 1993 budget for Biotechnology Research by Agency, not including the NIH.



FY 1993= \$1,087 M

TABLE 1
FY 1993 Biotechnology Research Budget
(\$ Million)

Agency	Agricul.	Energy	Environ.	General	Health	Manufac.	Social	Infrastr.	Total
AID	12.7	0	0	0	18.0	0	0	0	30.7
DHHS	30.8	2.3	0.5	1354.7	1502.7	17.7	5.2	211.1	3125.0
NIH	12.4	2.3	0.5	1354.7	1346.6	17.7	5.2	204.5	2943.9
FDA	18.4	0	0	0	17.8	0	0	0	36.2
CDC	0	0	0	0	27.1	0	0	6.6	33.7
ADAMHA	0	0	0	0	111.2	0	0	0	111.2
DOC	3.0	0	0.6	2.4	1.8	3.5	0.1	1.6	13.0
DOD	0	0	11.5	26.5	30.2	18.4	0	0	86.6
DOE	2.1	91.1	18.5	69.5	14.0	13.2	1.9	32.4	242.7
DOI	0	0	4.3	0	0	0.7	0	0	5.0
DOJ	0	0	0	1.4	0	0	0	0.9	2.3
DVA	0	0	0	0	88.4	0	0	0	88.4
EPA	0	0	18.3	0	0	0	0	0	18.3
NASA	4.4	0	0.6	4.9	5.3	3.7	0	25.8	44.7
NSF	35.0	8.8	20.5	35.4	19.5	43.0	1.3	42.5	206.0
USDA	119.5	4.7	8.5	4.9	0.5	23.6	0.7	5.3	167.7
TOTAL	207.5	106.9	83.3	1499.7	1680.4	123.8	9.2	319.6	4030.4

TABLE 2
FY 1991 - 1993 Biotechnology Research Budget
(\$ Million - % Increase)

Agency	FY 1991	FY 1992	FY 1993
AID	19.0	21.5 ¹ (13%)	30.7 (43%)
DHHS	2662.7	2963.0 (11%)	3125.0 (5%)
DOC	12.7	13.0 (2%)	13.0 (0%)
DOD	79.6	81.0 (2%)	86.6 (7%)
DOE	152.7	181.9 (19%)	242.7 (33%)
DOI	5.9	5.2 (-12%)	5.0 (-4%)
DOJ	1.8	2.2 (22%)	2.3 (5%)
DVA	80.6	85.6 (6%)	88.4 (3%)
EPA	14.3	15.9 (11%)	18.3 (15%)
NASA	26.5	36.6 (38%)	44.7 (22%)
NSF	162.0	174.0 (7%)	206.0 (18%)
USDA	161.6	179.4 (11%)	167.7 ²
TOTAL	3379.4	3759.3 (11%)	4030.4 (7%)

¹Number is from the FY 1992 Presidential budget; no appropriation for 1992 has yet been passed

²Number does not include possible Congressional actions on facilities and special grants which may increase the final appropriation for FY 1993



TABLE 3
FY 1991 - 1993 Biotechnology Research Budget by Area
(\$ Million - % Increase)

	FY 1991	FY 1992	FY 1993
Agriculture	174.2	190.5 (9%)	207.5 (9%)
Energy	65.5	80.4 (23%)	106.9 (33%)
Environment	62.3	68.6 (10%)	83.3 (21%)
General Foundations	1259.5	1417.5 (13%)	1499.7 (6%)
Health	1421.3	1593.8 (12%)	1680.4 (5%)
Manufacturing/Bioprocessing	88.9	98.8 (11%)	123.8 (25%)
Social Impact Research	6.5	9.0 (38%)	9.2 (2%)
Infrastructure	301.2	300.7 (-.2%)	319.6 (6%)
Research Facility	35.0	37.2 (6%)	30.4 (-18%)
Training/Career Development	139.3	145.0 (4%)	161.4 (11%)
Instrumentation	80.2	66.5 (-17%)	74.0 (11%)
Repositories	16.5	18.0 (9%)	19.1 (6%)
Data Bases	30.2	34.0 (13%)	34.7 (2%)
TOTAL	3379.4	3759 (11%)	4030.4 (7%)



APPENDIX A

BIOTECHNOLOGY RESEARCH AREAS

	RESEARCH AREAS	PAGE
1.	AGRICULTURE	20
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AGRICULTURE

Traditional biotechnologies have been practiced in agriculture since the beginning of civilization through plant and animal breeding, and food processing. As yet, however the knowledge base for application of modern biotechnology to plants, animals, and microbes of agricultural importance is far more limited than that for human health. The application of biotechnology will benefit agriculture in areas such as:

- New and improved agricultural products resulting in higher quality food and fiber,
- Improved crops and animals with greater tolerance to stress,
- New uses for agricultural commodities,
- Better management of agroecosystems including maintenance of soil productivity and water management,
- Better diagnostics to help ensure food safety, and
- Better microbial pest-control agents.

Specific examples of biotechnology applied to agriculture include molecular characterization of genes influencing field performance of crop plants, livestock, trees, and aquaculture species; and development of recombinant veterinary drugs and biologics, microbial pest control agents, and diagnostics for food safety.

MAJOR AGRICULTURAL RESEARCH AREAS

Using the new tools of biotechnology, researchers have produced virus-resistant varieties of cucumbers, tomatoes, and potatoes, and new and improved varieties of flowers.



Plant systems:

The ability of plant breeders to produce crop plants and forest trees with specific desirable traits is greatly enhanced by an understanding of the function of plant genes. Researchers are now beginning to work out detailed genetic maps for some plant species. When genes can be identified and isolated as DNA sequences, they can be transferred into plants by recombinant DNA techniques, employed as probes to find similar genes in other plant species, and used to study how expression of genes in plants is regulated.



Research on molecular genetics techniques. A tobacco plant has been genetically altered by insertion of the gene for the firefly light-emitting protein. This gene has been engineered to serve as a visible marker of gene expression. When the gene is active the plant lights up.



Modern biotechnology provides entirely new mechanisms for the development of new crops, enhancement of the quality and value of existing crops, and development of environmentally sound biocontrol and pest management strategies. More input-efficient plants and improved plants that tolerate environmental extremes are feasible goals of modern plant biotechnology.

Complementary DNA probes for the diagnosis of diseases such as bovine viral diarrhea, bluetongue, infectious bovine rhinotracheitis, and pseudorabies are already a reality.

Animal systems:

The new biotechnologies of gene cloning, gene transfer, *in vitro* culturing, and sexing of embryos have been developed and are being refined for practical use in animals. Transgenic embryos or offspring have been produced from rabbits, chickens, fish, sheep, swine, and cattle. Genes can be targeted for expression in specific tissues, but more efficient methods and a better understanding of the genes to be transferred are needed. Further research is needed to gain an understanding of the genes influencing animal growth; environmental adaption; meat, milk, and egg composition; and disease resistance.

New technologies such as those that use recombinant DNA and monoclonal antibodies now enable us to detect, identify, and control many animal diseases. Diseases can be controlled by several methods, including vaccination, enhancement of the immune response, early diagnosis, therapy, and disease vector control. Research is especially needed on the genetics of the immune system in different animal species, the genes controlling virulence traits of pathogens and parasites, and the use of monoclonal antibodies and nucleic acid probes for use in disease treatment and diagnostic procedures.

TRANSGENIC FISH

Biotechnology has been used to transfer genes for growth hormone into carp and catfish to produce large, fast growing strains and to study the genetic basis of cold-hardiness.

Aquaculture:

Aquaculture in the U.S. produces over 600 million pounds of edible protein annually, and is growing at nearly 10% per year. In a period of expanding demand for fishery products, aquaculture will provide a major source of food because of the efficiency of aquatic species in converting feed to protein. The finite limit of the harvest from natural fisheries and the expanding international demand for aquatic products indicate that aquacultural production could make a significant contribution to foreign trade and the reduction of seafood imports.

Aquatic animals are particularly well suited for research in biotechnology. Experimentation is facilitated by the availability of large numbers of eggs and sperm, external fertilization, and ease of *in vitro* rearing of embryos. Applications of biotechnology in aquaculture require greater understanding of gene structure and expression in aquatic organisms. The development of methods for gene transfer, and large-scale cryopreservation of gametes and embryos can be expected to lead to production applications in a number of species.

Food Science:

The use of biotechnology techniques, such as recombinant DNA technology for enzyme and protein engineering, plant and animal cell tissue culture, and biosensor applications, will increase efficiency of production of foods and food ingredients, reduce production costs, enhance nutritional value, improve processing characteristics, and provide safer and more convenient food products.



Food Safety:

There is a pressing need to provide consumers with greater margins of safety from possible chemical or microbiological contamination. Fortunately, biotechnology offers attractive, affordable approaches to meet this need. Food biotechnology research can provide rapid diagnostic tools such as DNA probes, polymerase chain reaction-based tests, and biosensors utilizing enzyme-, cell-, or antibody-based detection systems that will more effectively ensure the safety of raw ingredients and finished products.

Biotechnology can be used to identify and trace the sources of microorganisms or other contaminants in foods quickly and inexpensively .

THE FEDERAL INVESTMENT

Seven Federal agencies of the government support agriculture related biotechnology research. While the U.S. Department of Agriculture has primary responsibility for support of research in agriculture, other agencies contribute to agricultural biotechnology research in pursuing their own missions:

AID collaborates with developing countries to support research and development that will improve agricultural productivity. Biotechnology plays an important role in AID's efforts.

DOC-NOAA supports research on organisms from the oceans. This contributes to biotechnology research underlying aquaculture.

DOE supports research on plant science, plant/microbe interactions, and nitrogen fixation from the point of view of plants as converters of solar energy and as renewable sources of energy.

DHHS supports research on food safety through the FDA and supports basic research on components of plants and animals as models for health-related research.

NASA supports research on plants and animals related to the development of life support for space travel, and research that capitalizes on the space environment to understand basic plant mechanisms.

NSF supports fundamental research in plant genetics and cellular and molecular biology. It also supports fundamental research on animal systems applicable to agriculture and aquaculture.

The total Federal investment in agricultural biotechnology represents a very small fraction, about 5%, of the total U.S. investment in biotechnology research. Support for the plant sciences accounts for approximately half of these expenditures. This investment is reflected in a rapid increase in the number of permits issued for small-scale field testing of engineered plants within the last year. These plants include disease-free clones of fruit and vegetable crops, fast-growing trees for reforestation, and insect-resistant and herbicide-tolerant cultivars. Investments in genome mapping and sequencing of economically important species and the continued collection and characterization of germplasm are essential to continuing progress in the applications of biotechnology to the plant sciences.

Much fundamental research on animal systems has been conducted in the context of health research and therefore has focused on organisms that are considered models for the human, chiefly laboratory rodents and primates. Much less has been invested in studies related to the health of agriculturally important animals such as livestock and on the fish and shellfish of interest for aquaculture.

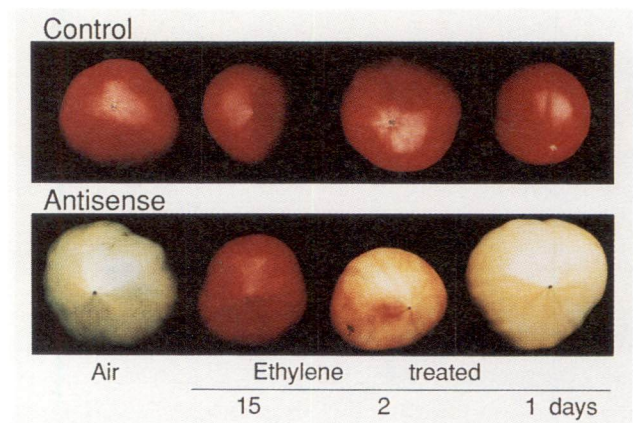
Despite a long history of reliance on fish as an important source of food, the science of aquaculture is relatively young. Tremendous potential exists to use

modern biotechnology to improve aquaculture. A number of basic studies of fish molecular biology are under way to increase our understanding of how fish respond to their environment at the molecular level and to develop ways to use this knowledge to increase the efficiency of fish production. The current U.S. investment in biotechnology research for aquaculture is approximately 3% of the total expenditure for agricultural biotechnology research.

OPPORTUNITIES IN PLANT SYSTEMS

Biotechnology provides new opportunities to study the molecular bases of a wide variety of genetically regulated processes in growth, development, metabolism, pest defense, and responses to environmental stress. The collection, storage, and characterization of germplasm, and development of innovative tools and techniques will enhance the potential of this new technology to help resolve many of the national and global agricultural and forestry problems. In addition, advances in biotechnology have opened up new ways to address fundamental plant science problems. Many fundamental questions in plant growth and development remain unanswered. To capitalize on these opportunities, fundamental knowledge tools, and techniques such as the following are needed:

- Genome maps for species of agricultural importance, e.g., crops and trees. Structure, function, and regulation of genes for agriculturally important traits such as growth, stress resistance, and food and fiber quality, and methods for genetic transformation of agriculturally important species.
- Improved techniques of germplasm collection, characterization, and maintenance, including seed, pollen, and tissue cultures by cryopreservation, and enhanced DNA profiling techniques for characterizing germplasm variation.
- Mechanisms regulating growth, development, and reproductive physiology of agriculturally important plant species.



An "antisense" gene has been inserted into a tomato plant to block the function of a gene required for the production of the organic molecule, ethylene. Ethylene is the normal signal for ripening in tomatoes. Tomatoes that cannot make ethylene do not ripen until they are exposed to external ethylene. Thus, the ripening of tomatoes, and probably many other fruits can be precisely controlled.

- Mechanisms of plant responses to stresses such as salinity, drought, flooding, extreme temperatures, and ultraviolet radiation, etc.
- Mechanisms of natural plant resistance and defense that can be used to protect agricultural species from pests, pathogens, parasites, and predators.
- Biological control agents to manage pests, pathogens, parasites, and predators such as biologically based alternatives for the control of major insect pests and preventive measures against disease such as viral cross protection.
- New diagnostic tools using DNA probes, monoclonal antibodies, and other biotechnologies for detecting pests, pathogens, and parasites.
- Knowledge of root-colonizing microorganisms to reduce requirements for chemical fertilizers.



OPPORTUNITIES IN ANIMAL SYSTEMS AND AQUACULTURE

The new biotechnologies of gene transfer, cloning, *in vitro* culturing, and sexing of embryos have been developed and are being refined for practical use in animals. New technologies such as those that use recombinant DNA and monoclonal antibodies now afford an opportunity to understand, detect, identify, and control many animal diseases. To capitalize on these opportunities the Initiative will address the following areas:

- Genome maps for species of agricultural importance such as poultry, livestock, and aquatics. Structure, function and regulation of genes for agriculturally important traits such as growth, stress and disease resistance, and food quality. Methods for genetic transformation of agriculturally important species;
- Mechanisms regulating growth, development, nutrition, and reproductive physiology of agriculturally important animal species;
- Biochemistry and physiology of animal growth hormones to facilitate the successful application of genetic engineering for increased animal production;
- Mechanisms of natural host organism resistance and defense that can be used to protect agricultural species from pests, pathogens, parasites, and predators;
- New diagnostic tools using DNA probes, monoclonal antibodies, and other biotechnologies for detecting pests, pathogens, and parasites;
- Biological preventive measures against disease such as recombinant vaccines for poultry, livestock, and aquatic species; and
- Faster-growing, more feed-efficient, disease-resistant and more attractive varieties of aquatic plants and animals for use by the aquaculture industry.

OPPORTUNITIES IN FOOD SCIENCE AND FOOD SAFETY

Biotechnology offers significant opportunities in the production of food ingredients, new foods, and the development of analytical tools. To derive optimum benefit from these technologies, additional research is needed to define the biochemical mechanisms associated with the production of new ingredients, foods, and process byproducts.

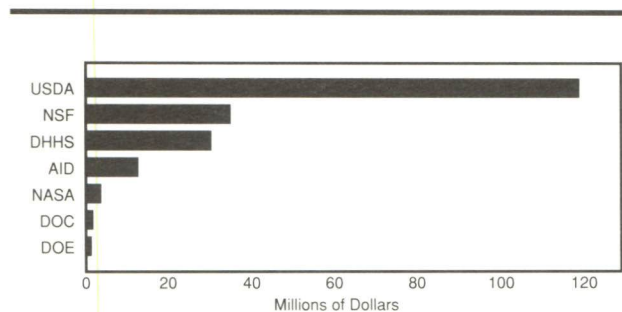
Food safety is of paramount importance to producers, processors, distributors, and consumers. In response to this need, biotechnology research offers advances in food safety, particularly in the development of new detection methodologies for pathogenic microorganisms, chemical contaminants, and natural toxins in food. To realize the benefits of biotechnology, we must address the needs for fundamental knowledge techniques, and tools in the following areas:

- Effects of various food processing conditions on the composition of foods with special attention to changes in levels of significant nutrients or possible toxicants; and
- Biotechnology-based methods including biosensors for rapid detection of microbial and chemical contaminants of foods using monoclonal antibodies and/or nucleic acid-based techniques, including DNA probes, polymerase chain reaction, and restriction fragment length polymorphisms.

The past investment and the President's FY 1993 budget for biotechnology research in agriculture are shown in Figure 15 and Table 4.



FIGURE 15
The President's FY 1993 budget for biotechnology research in Agriculture.



FY 1993= \$207.5 M

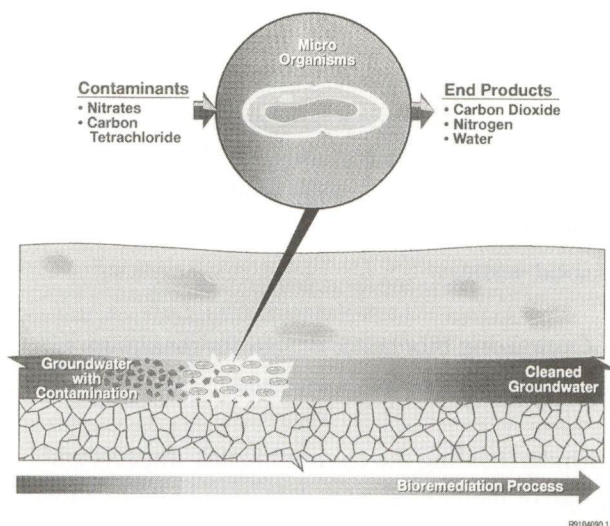
TABLE 4
Federal Investment in
Agriculture Biotechnology
(\$ Million)

	FY 1991	FY 1992	FY 1993
USDA	106.4	114.5	119.5
NSF	25.6	28.7	35.0
DHHS	25.6	28.9	30.8
AID	7.6	9.4	12.7
NASA	4.3	4.2	4.4
DOC	3.0	3.0	3.0
DOE	1.7	1.8	2.1
TOTAL	174.2	190.5	207.5

Bioremediation:

Bioremediation is the biotransformation of pollutants, toxic substances, and metals at the site in which they are found (*in situ*). Seven agencies have research programs relevant to bioremediation. Projects range from understanding microbial communities to engineering *in situ* systems. The primary goal of much of the research in bioremediation is the isolation, identification, and biochemical characterization of microorganisms capable of carrying out specific chemical transformations.

The research supported by each agency is specific to its mission. For example, the Department of Agriculture supports research on bioremediation of sites contaminated by pesticide and herbicide runoff, while DOE research focuses on remediation of sites contaminated with organic-radionuclide complexes. Although there are similarities between various bioremediation approaches, the broad range of potential applications ne-



Schematic illustrating bioremediation of contaminated ground water using microorganisms. Natural or genetically engineered bacteria can be used to destroy organic contaminants and potentially to immobilize metals and radionuclides. Nutrients can be supplied through an injection system to the contaminated water to stimulate the bacteria. Monitoring wells are used to evaluate the extent of remediation.

cessitates a wide diversity of microbial and biochemical research and a coordination of effort.

Biore Restoration research:

This research develops techniques to stabilize, improve, or restore the biological integrity of threatened or endangered species and ecosystems. The goal of this research is to modify desired species in order to restore their populations and to develop biotechnologies which will restore the overall biological structure and function of degraded ecosystems. Current biore restoration research is focused on:

- Development of methods to increase the reproductive potential of species for gene pool protection and recovery of endangered and threatened species.
- Genetic improvement or adaptation of a few selected species (e.g., loblolly pine, halophytes) to enhance their survival and growth in stressed, changing, or man-made environments (e.g., an environment established to mitigate the toxicity of mine spoils).
- The development of new biotechnologies for use in maintaining the integrity of complex ecosystems.



Acid mine drainage results from the oxidation of iron sulfide minerals exposed by mining activities. Stream health is jeopardized by the smothering action of deposits, such as the iron visible here, and by acidic conditions.



Wetlands constructed on active and abandoned mined sites can be used to treat acid mine drainage. The metals in the drainage are precipitated and/or filtered by the wetland and microorganisms.

Environmental risk technologies research:

Environmental applications of biotechnology evolve through research and development, from conceptual design within the laboratory, to proof of concept in field tests, and ultimately to full scale use.

Throughout this developmental process, assessments of the biotechnology product are necessary to identify and mitigate any negative effects on the environment. Risk assessment technologies are needed to establish criteria and testing methods that can be used to evaluate the environmental impact of biotechnology products and their uses.

Existing research programs are, for the most part, directed toward characterizing organisms under natural circumstances. This requires a description of population dynamics, organism interactions, and the effects of changing environmental conditions. The research also includes the development of testing procedures to identify legitimate environmental concerns before widespread use (e.g., testing for effects of biological pest control agents on nontarget species).

The goal of risk assessment research is to develop acceptable tests and a scientific understanding of the important environmental parameters that will lead to sound evaluations of biotechnology products: those

that can ensure appropriate oversight without interfering with the safe introduction of new products into commerce.

THE FEDERAL INVESTMENT

Given the potential of biotechnology for addressing needs related to the environment, it is notable that the total FY 1992 Federal investment in this area is only \$69 million. The Federal investment in environmental biotechnology research by agency is shown in Figure 22 and Table 6.

Of the total \$69 M investment, the funding level for bioremediation research and treatment biosystems research is approximately \$42 million dollars for FY 1992. This is distributed among 9 different agencies and departments. Each agency focuses on its specific mission with little overlap of specific research goals. The basic research needed for developing sampling techniques to isolate indigenous organisms that will perform biotransformation processes, understanding metabolic pathways to identify toxic metabolites that may result from incomplete transformations, designing *in situ* systems, and understanding the microbial ecology of bioremediation systems will require a long-term, coordinated effort.

All agencies plan to continue their current programs in environmental biotechnology for FY 1993. Increases are provided for programs in three agencies:

- EPA will initiate an effort in environmental diagnostics, carrying out field evaluations of many of the new molecular techniques for measuring microbial community structure and function, and then to use those parameters to measure ecosystem status.
- DOE will initiate an environmental biotechnology effort focused on the application of molecular biological methods to energy-related environmental research.



- NSF has identified environmental biotechnology as one of its biotechnology thrusts for FY 1993 and will support interdisciplinary groups, centers, and individual investigators for fundamental research in this area.

MAJOR OPPORTUNITIES AND KNOWLEDGE GAPS

Environmental Analysis/Natural Resources:

The use of molecular techniques to characterize microbial community structure and function is a new and promising area of research that may lead to new ways of analyzing ecosystems and monitoring changes. The development of molecular probes to measure the responses of organisms to environmental cues has great potential but needs further development. Molecular methods provide powerful tools for the study of biodiversity, particularly at the genetic, population, and species levels, but the use of these tools in environmental applications has only begun.

The field has developed to the point where it is possible to isolate and identify microbes never before accessible and to determine how organisms function in their environments. Molecular probes provide sensitive assays to investigate the response of organisms to their environments. Biotechnology expands considerably the potential for more rapid and sensitive measures of biodiversity. Molecular methods are allowing investigation of species interrelationships on a scale not previously attainable. Further support is required for:

- Basic research on the use of molecular techniques to characterize microbial community structure and function in natural and stressed ecosystems.
- Application of biotechnology to the measurement of biodiversity and maintenance of threatened species and communities.

Treatment Biosystems:

The science and engineering bases for the field of environmental treatment biosystems are, as yet, poorly developed. The emphases of current research are to isolate and identify microbes that can degrade or transform wastes; to understand, optimize, and control their metabolic pathways for the degradation of targeted compounds; and to translate these into biotreatment systems applications. Biotechnology can enhance these efforts and provide new approaches to particularly perplexing waste remediation problems.

A better fundamental understanding of microbiological ecology will permit the design of improved microbial reactors for waste treatment. The development of bioremediation methodology and treatment biosystems requires a total systems approach. Multidisciplinary studies and training programs involving microbiologists, ecologists, physical scientists, and engineers are needed.

Bioremediation:

The magnitude and severity of polluted sites argues strongly for concerted efforts to find new, efficient, and cost-effective methods to clean them up. Biotechnology can play a key role in adding to the list of environmentally compatible techniques to reduce the pollution burden on our environment.

The major emphasis across the agencies is on the identification and understanding of microbial systems. DOE's Deep Microbiology Program exemplifies an attempt to apply that understanding to the development of specific applications. To implement specific bioremediation applications, further research is needed on sampling and selection techniques to isolate flora with useful metabolic pathways, phenotypic identification and genetic dissection of traits that allow the bacteria to persist, and the engineering of reactors.

Biorestoration:

The feasibility of using biotechnology for the biorestoration of altered ecosystems and to protect the gene pools of threatened and endangered species needs to be explored. Given the number of threatened and endangered species and the extent of degraded or stressed populations and environments, it is important to pursue biorestoration as a solution to many environmental problems. Interdisciplinary research involving molecular biologists and geneticists, ecologists, environmental engineers, and chemists is needed to promote progress in this area.

Environmental Risk Assessment Technologies:

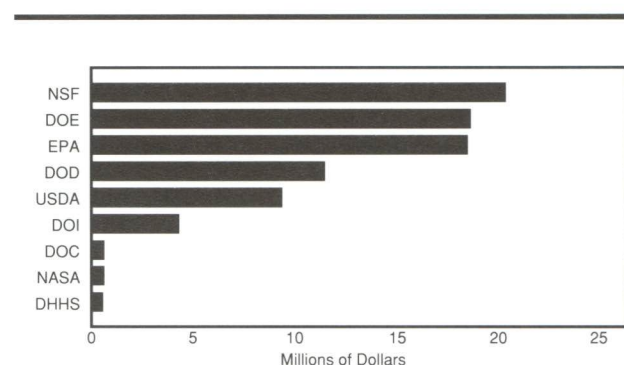
Research efforts in this area will be enhanced to keep pace with the needs of a burgeoning industry. Research on potentially toxic secondary metabolites that may result from the biotransformation processes employed in bioremediation is particularly urgent.

Environmental biotechnology research has received little attention considering the potential it offers for significant breakthroughs in understanding and contributing to a healthier world. Biotechnology must be fostered as a key component of environmental research programs across Federal agencies. Progress in environmental biotechnology research depends upon increasing our fundamental knowledge of microbial ecology, structure and function of microbial communities, and other environmentally relevant biological processes.

Past investments and the President's FY 1993 budget for biotechnology research on the environment are shown in Figure 22 and Table 6.

FIGURE 22

The President's FY 1993 budget for biotechnology research on the environment.



FY 1993= \$83.3 M

TABLE 6
Federal Investment in
Environmental Biotechnology
(\$ Million)

	FY 1991	FY 1992	FY 1993
NSF	12.6	13.7	20.5
DOE	11.3	12.5	18.5
EPA	14.3	15.9	18.3
DOD	9.6	12.3	11.5
USDA	7.8	8.2	8.5
DOI	4.9	4.4	4.3
DOC	0.9	0.6	0.6
NASA	0.6	0.6	0.6
DHHS	0.3	0.4	0.5
TOTAL	62.3	68.6	83.3

HEALTH

The contributions of biotechnology to health are extremely diverse, ranging from the elegant techniques of molecular biology used to diagnose disease to the development of more rational approaches for designing new therapeutic agents. As a result of the demonstrated applications of biotechnology, molecular mechanisms of disease can now be elucidated, diagnostic methods improved, therapeutic modalities increased, and safer, more effective vaccines developed.

HEALTH BIOTECHNOLOGY RESEARCH AREAS

Molecular medicine:

An understanding of the molecular basis of disease represents the ultimate answer to the fundamental question of disease causation, and by implication, the ultimate specific target for disease prevention and treatment. Application of recombinant DNA methodology, monoclonal antibodies, the production of transgenic animals, gene amplification using the polymerase chain reaction, and the new methods for protein production and purification can all now be used to improve the prevention, diagnosis, and treatment of disease.

Applications of biotechnology to molecular medicine include: *gene manipulation to construct vectors for targeted gene delivery, characterization of molecules such as hormone receptors, studies of mechanisms of cellular communication, and development of diagnostics such as molecular probes for diseases.*

Therapeutics:

Recombinant DNA technologies make possible new classes of agents used as drugs; in particular there are proteins such as cytokines, growth



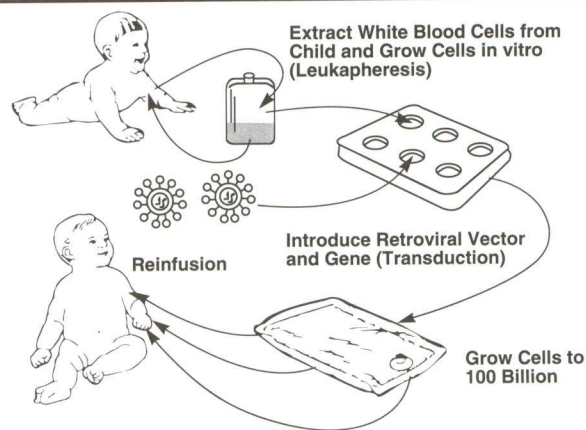
factors, and thrombolytic agents. Equally important is the development of monoclonal antibodies which can be targeted to tumor cells or infectious organisms. There are also rapid and exciting advances in the creation of chimeric toxin molecules which can be directed to kill specific cell populations, such as cancer cells, while sparing normal cells.

Gene therapy is now a reality with five human trials already under way and more to follow in the near future. While the immediate focus is on diseases caused by a defect in a single gene. The techniques of gene transfer can also be used to augment drug delivery systems and target gene delivery using cells such as skin or liver cells.

Drug discovery is being enhanced by the use of molecular modeling and the development of cell receptor based agents. With the discovery that the genes associated with cancer are also present in non-humans, there has been considerable effort and real promise in using laboratory organisms such as yeast to screen various types of anticancer drugs.

The use of biosensors such as silicon sensors to measure metabolites, enzymes, and other cellular products in small biological samples is increasing. Some

First Human Gene Therapy Experiment September 14, 1990



Human gene therapy experiment.



types of sensors can generate an electronic signal in response to minute quantities of sugars. This property suggests applications for drug delivery involving insulin, for example.

New techniques for constructing artificial organs are emerging. For example, efforts are under way to improve methods of culturing human liver cells and placing them in a matrix that could serve as an "artificial liver." Similarly, there are important advances in developing "artificial blood" and "artificial platelets."

Vaccines:

Traditionally, vaccines have been used to prevent infectious diseases, but rapid advances in recombinant DNA research, monoclonal antibody production, gene transfer, and gene therapy, coupled with new approaches to immunotherapy, offer hope for the development of new types of vaccines that are effective against many diseases and vaccines that are effective against cancer cells. New vaccines may also be developed for contraception and for the treatment and prevention of autoimmune diseases and allergic and inflammatory disorders.

New information on the antigenic determinants of infectious agents has made it possible to clone and express these antigens in large quantities and in an especially pure form.

THE FEDERAL INVESTMENT

The Federal investment in health biotechnology research is shown in Table 7. The total FY 1992 investment is approximately \$1.6 billion dollars, most of which is provided by the National Institutes of Health. It should be noted that NIH's long-term investment in biotechnology research has been a major factor in the Nation's current position of leadership in biotechnology, and particularly in health-related biotechnology.

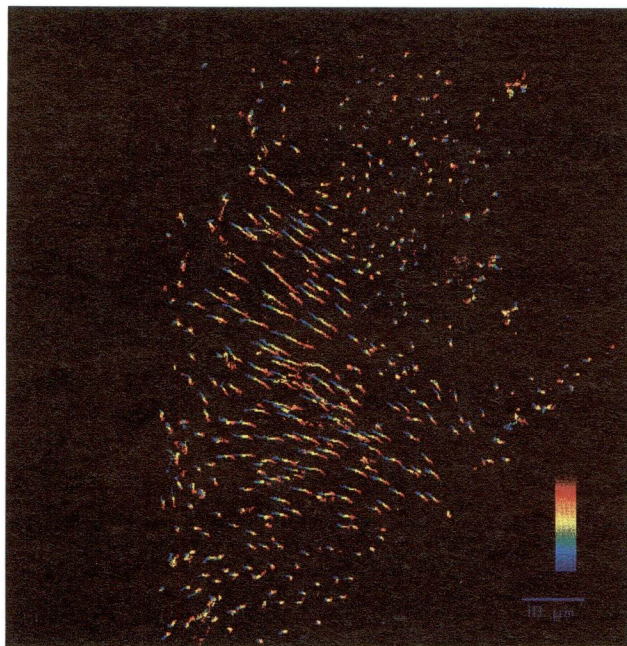
The investment in health-related biotechnology research continues to offer rewards not only in the alleviation of human suffering, but also in savings in total health care costs.

MAJOR AREAS OF OPPORTUNITY

Molecular Medicine:

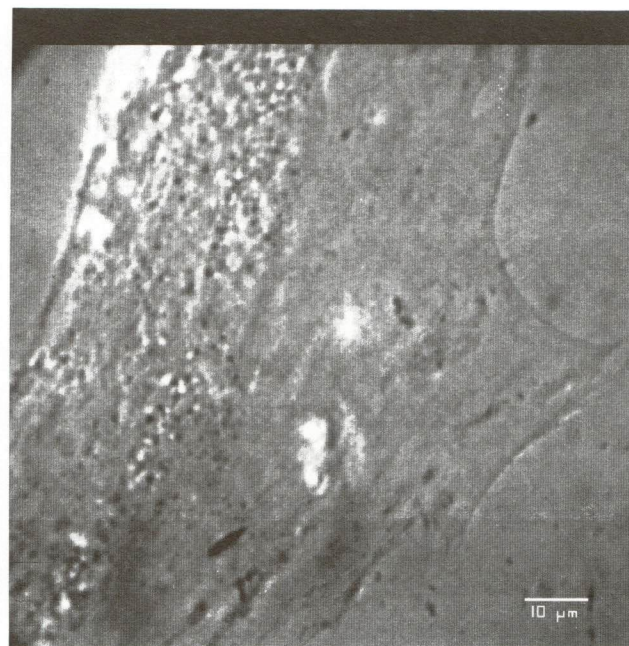
An understanding of the molecular events occurring in the development of disease offers the best prospects for developing preventive and therapeutic interventions. A major advance has been the recent description of the series of genetic events leading to the development of colon cancer. This research will lead to methods for early diagnosis and intervention for colon cancer, the second leading cause of cancer deaths in this country. There is mounting evidence that two major classes of genes involved in cancer, tumor suppressor genes and proto-oncogenes, interact with a major cell cycle regulator. A principal goal of cancer research is to understand how the products of these genes interact with the cell cycle regulator and how growth factor signalling pathways function.

There is increasing evidence that genes play a significant role in the development of cardiovascular diseases. This is evident in cases of familial hypercholesterolemia, in which the gene for the low density lipoprotein receptor is missing or defective. As a result, patients have greatly elevated levels of serum cholesterol and suffer heart attacks by the age of five or six. Because of extensive research on this condition over the past decade, gene therapy for this disorder appears imminent. There has also been recent success in identifying the gene responsible for hypertrophic cardiomyopathy, a marked enlargement of the heart which can be fatal. These findings give encouragement that other genetic factors in heart diseases will soon be identified.



This figure demonstrates the defect in a cell from an individual with familial hypercholesterolemia.

A fluorescent label was attached to low density lipoprotein (LDL) particles which then bound to receptors for LDL on the cell surface. High resolution fluorescence microscopy was used to track the movement of individual LDL receptors. Their trajectories were analyzed statistically, and the colored image (shown in a) was reconstructed by a computer. The



colored streaks illustrate the location of LDL receptors over a 4 minute interval. Normal cells would cluster and internalize the LDL particles in the process of normal cholesterol metabolism. The genetic defect in this cell makes it unable to internalize LDL and cholesterol metabolism is abnormal.

Part b is a phase contrast image illustrating the shape of the cell.

One of the most important areas of research is directed toward understanding the regulation of the immune system. This research is fundamental to solving problems in transplantation and in understanding host defense mechanisms. When this basic information is available, it should be possible to address the problems involved in organ transplantation and in the treatment of autoimmune diseases, such as rheumatoid arthritis, and possibly diabetes.

Because of rapid developments in neurosciences, the decade of the 1990's has been designated as the "Decade of the Brain." Increased understanding of the molecular basis for a number of neurological diseases will permit molecular approaches to determine the mechanisms of convulsive disorders such as epilepsy. With biotechnology, it is now possible to at-

tempt the development of biopolymers as conduits for nerve growth which could encourage nerve regeneration after injury. There has also been some early success in producing genetically modified cells for brain implantation, such as the use of a patient's own fibroblasts to produce a neurotransmitter or neurotrophic substance required to ameliorate the patient's disease.

Research in the area of bioelectronics and bionetworks will benefit from the development of biosensors, including the use of biological models for designing visual and audio sensing devices, the development of sensors, transducers, or electronic devices utilizing biological molecules, and establishing biologically based interfaces between living neurons and silicon-based circuitry.



Two other important areas of molecular medicine focus on biomaterials and diagnostics. The former involves the development of methods to evaluate the safety and efficacy of biomaterial-based medical devices, concentrating on their degradation and performance characteristics. The latter involves the development of diagnostic methods for the detection of infectious agents, particularly in blood and related products, and for the detection of cancer and other diseases.

Another important area of research involves naturally occurring infectious diseases which have the potential to affect military operations. Work performed in laboratories and among troop populations is directed toward prevention, diagnosis, and treatment of viral, bacterial, and parasitic diseases. The biotechnological component of this research is aimed at elucidating modes of action and transmission of diseases, diagnostic techniques, and vaccine design and development.

Another major area of emphasis is a program that focuses on chemical and biological warfare defense and has elements of both molecular medicine and therapeutics. Research in the field includes developing methods for molecular recognition of biomolecules, discovering specific enzymes capable of degrading chemical and biological agents, and finding biological transduction pathways that can be used to signal binding of a particular substrate by a macromolecule.

The goal of the human genome program is to map and sequence the human genome. In the course of this program, important contributions are being made toward locating disease genes and DNA repair genes. In addition, information is being generated about genetic damage from radiation and energy related chemicals. Considerable information is accruing on the organization of genetic information in chromosomes and the control of gene expression which will improve our ability to predict the occurrence of diseases such as leukemia.



With the aid of new techniques, geneticists determined that this baby had inherited only one of his parents' genes for thalassemia and will be unaffected by this blood disorder.

Several closely related programs are examining the biochemical and metabolic aspects of nutrition in humans. The effects of trace elements are being analyzed as well as the relationship of diet to immunological function, aging, and cancer. Studies are also being conducted on the biochemistry of mycotoxins, substances that are sometimes present in cereal grains, dairy products, and meats.

Therapeutics:

In the field of therapeutics, some of the most dramatic changes concern gene therapy. This was initially envisioned as a treatment for single gene deficiencies but many of the techniques show promise for treatment of cancer or infectious diseases such as AIDS. Recently a new technology has been developed that utilizes triplex DNA. Triplex DNA is created by adding an extra strand of nucleotides to the double-stranded DNA molecule and can be generated at specific sites on genes to interrupt gene function. Researchers are now exploring the possibilities of treating diseases with this technology.

Cystic fibrosis (CF) is a lethal genetic disease. Ninety-five percent of CF deaths occur from progressive airway disease, making the lung an impor-



tant target for therapy. The recent cloning of the gene responsible for CF has made the approach to definitive therapy a possibility. Introduction of normal copies of the CF gene into defective human airway cells can correct the major abnormalities associated with CF. This development greatly extends the prospects for gene therapy.

In the area of drug design, the development of chimeric toxin molecules for treatment of cancers and viral infections is progressing rapidly. New therapies are being designed to overcome multidrug resistance in cancer cells and infectious organisms such as the malarial parasite. Adoptive immunotherapy is another new approach to treatment wherein lymphokines are inserted into tumor-infiltrating lymphocytes or cancer cells to enhance the immune response to cancer. New classes of drugs are being analyzed which are inhibitors of viral proteins or which use RNA enzymes, ribozymes, as possible antiviral agents.

With the development of numerous drugs produced by recombinant DNA and hybridoma technology, it is important to develop appropriate models to assess the clinical safety and efficacy of these therapeutic products. Laboratory assays are necessary in the control testing of the products, as well as animal, cellular, and in vitro model systems.

Vaccines:

Advances in molecular biology now provide unique opportunities to produce safe and efficacious vaccines by recombinant DNA technology. Vaccine development has targeted diseases for which current vaccines have proven ineffective because of genetic changes in prevalent circulating strains. New research is directed toward developing new kinds of improved vaccines (polysaccharide-protein conjugates, anti-idiotypes, and immunogenic proteins) for preventing bacterial infections. Another high priority is the development of genetically engineered vaccines against HIV, the respiratory syncytial virus, Hepatitis A and C, and other viruses.

At present researchers are on the threshold of developing several new types of vaccines that would involve the design and synthesis of synthetic lipopeptides, fusion proteins, or immunologically potent virus-like particles. Another approach involves inserting genetic information into carrier organisms to produce a vaccine that protects simultaneously against many diseases.

The Federal investment in health-related biotechnology is a continued commitment to research that is translated into techniques and products of enormous value in health care. Many advances are still in the formative stages but hold great promise. The following are areas of exceptional promise which will be pursued through the Biotechnology Research Initiative:

- Gene transfer technology is on the threshold of widespread clinical application, but many basic genetic questions, such as the control of gene expression and the identification of regulatory factors responsible for tissue-specific expression of genes, require resolution in order to apply such technology on a large scale.
- The science base for the regulatory review of state-of-the-art, innovative products requires further development. This is essential to assure that products can be properly evaluated for safety, efficacy, and quality;
- Research is needed on drug delivery, particularly for therapeutic proteins, since drug development by itself is of limited value unless the drug can be delivered in an active form to the appropriate site within the body;
- Generation of genetically altered, bioactive proteins, with an emphasis on design and construction of new chimeras of biological response modifiers and monoclonal antibodies, which will have increased activity, specificity, and safety;

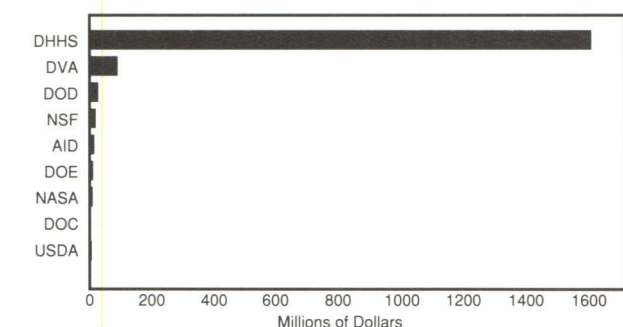


- Research on creation of different types of vaccines such as new recombinants, oral multicomponent vaccines, and vaccines which utilize the synthesis of lipopeptides or fusion proteins and on technologies. These technologies are critical to the development of the Children's Vaccine Initiative;
- Development of new transgenic systems to provide powerful tools for analyzing single parameters in multifactorial disease states, and function as an important means for toxicological assessment; and

- Training of clinical researchers who can take a primary role in translating basic research findings in biotechnology into treatments. The shortage of trained personnel is a significant impediment to advances in this area.

Past investments and the President's FY 1993 budget for biotechnology research on health is shown in Figure 26 and Table 7.

FIGURE 26
The President's FY 1993 budget for biotechnology research on health.



FY 1993= \$1,680 M

TABLE 7
Federal Investment in
Health Related Biotechnology
(\$ Million)

	FY 1991	FY 1992	FY 1993
DHHS			
NIH	1143.4	1293.5	1346.6
FDA	13.5	17.1	17.8
CDC	22.6	27.1	27.1
ADAMHA	79.0	94.0	111.2
DVA	80.6	85.6	88.4
DOD	35.0	26.2	30.2
NSF	17.3	18.6	19.5
AID	11.4	12.1	18.0
DOE	12.3	12.7	14.0
NASA	4.5	4.6	5.3
DOC	1.2	1.8	1.8
USDA	0.5	0.5	0.5
TOTAL	1421.3	1593.8	1680.4

MANUFACTURING AND BIOPROCESSING

Biotechnology research in manufacturing and bioprocessing is directed toward development of biological systems for making useful products such as biomaterials and chemicals, or for manufacturing processes. Bioprocessing offers the possibility of efficient manufacture of products using renewable resources, requiring minimum amounts of energy, and producing minimum wastes.

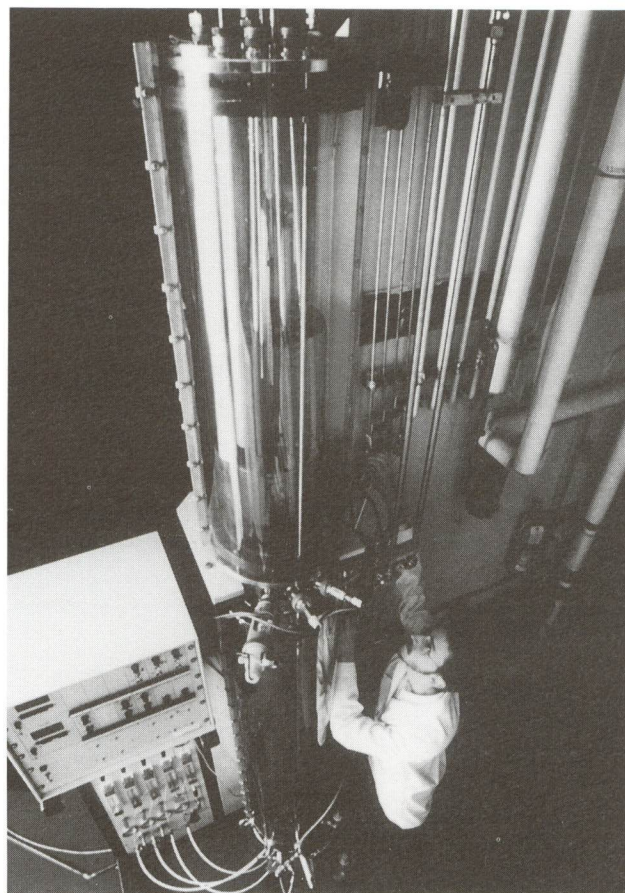
The term, bioprocessing, refers to the entire sequence of events in producing a substance (e.g. a chemical) using biological conversion processes. The sequence begins with the initial formation of a product by intact cells or by an enzymatic reaction (upstream processing), and continues through the separation and purification of the final product (downstream processing). Optimization of a bioprocess for commercial use requires monitoring and control of the bioprocessing system while it is in operation, coordination of upstream and downstream processing steps, and analysis of the overall costs of the process. Each of these components of bioprocessing is a subject of current research.

Research in bioprocessing is highly interdisciplinary, requiring contributions from cell and molecular biology, chemistry, physics, engineering, materials science, and computer science.

MANUFACTURING AND BIOPROCESSING RESEARCH AREAS

Bioreactor Design:

The design of an appropriate chamber, or bioreactor, in which the environment can be controlled so that a bioprocess can be carried out efficiently requires a basic understanding of molecular, genetic, metabolic and cellular functions involved in the growth of cells and the expression of cellular products.



A commercial bioreactor used in producing pharmaceuticals.

Metabolic Engineering:

Metabolic engineering involves the fundamental understanding and manipulation by use of recombinant DNA technology of the enzymatic, transport, and regulatory functions inside a cell to precisely alter metabolic pathways. Examples include increasing yields of ethanol, acetone, and butanol from anaerobic microorganisms, production of ascorbic acid (Vitamin C) from an industrial microorganism that has previously made only precursors of this compound, and improving yields of a variety of amino acids from microorganisms.



Biocatalysis:

Biocatalysis is the development of specialized enzymes and catalytic antibodies for particular uses. This necessitates detailed understanding of how enzymes and catalytic antibodies work on a molecular level. Studies involving x-ray, neutron, and synchrotron diffraction and nuclear magnetic resonance spectroscopy to elucidate atomic structure; dynamic studies to determine rates of reactions; thermodynamic studies to understand realizable yields; conformational energetics of enzymes and modeling studies to understand interactions of enzymes and catalytic antibodies with their substrates are all required for these efforts.

Separation and Purification Technology:

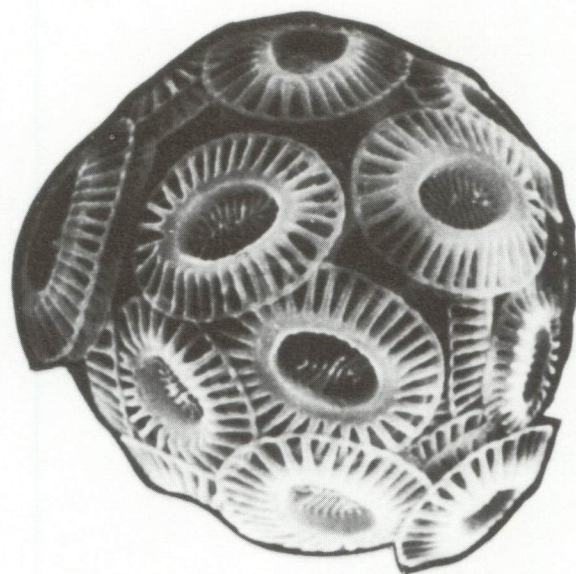
The development and modeling of techniques for separating and purifying products of biological origin (downstream processing), e.g., new materials for industrial scale chromatographic separations, and bioleaching of minerals are also areas of strong current interest. Economic utilization of biomass-based chemical feedstocks will require extensive process in this area.

Process Design:

Integration of upstream and downstream processing, modeling of bioprocesses, and the design and use of thermodynamic properties, thermophysical properties, and mathematical algorithms for process optimization, need to come together for effective process design.

Process Monitoring and Control:

The design of new and advanced methodologies for monitoring and controlling bioprocesses is essential to this component of bioprocessing. Recent developments in these methodologies include capillary elec-



This coccolithophorid, *Emeliana huxleyi*, is an example of a marine microorganism that surrounds itself with exquisitely fashioned coccoliths which are perfectly formed wheel-like structures approximately 2 micrometers in diameter. Understanding the formation of these structures could lead to new biotechnological processes for synthesis of precisely designed microstructures for use in electronics and miniature machines.

trophoresis for rapid analytical techniques and the design of biosensing devices and control networks.

Biomolecular Materials:

Substances, natural or man-made, with desirable and sometimes novel materials properties (e.g., chemical, electronic, mechanical, optical, structural), can be produced by processes which utilize or mimic biological phenomena. Examples include the biosynthesis of fibers of silk, wool and cellulose, adhesives for use in aqueous environments, and bioceramics (e.g., abalone shell).



Biocompatible Materials:

Biotechnology can assist in the design and fabrication of materials with an emphasis on their ability to be used in biological environments. Biocompatible materials such as soluble receptors, implants, prosthetic devices, etc. for clinical uses are engineered so that acute and chronic problems of biocompatibility and/or toxicity will be eliminated or minimized.

Tissue Engineering:

The development of biological substitutes to restore, maintain, or improve tissue functions requires the development and application of principles and methods of engineering and life sciences toward understanding structure-function relationships in normal and pathological mammalian tissues. Examples include living tissue equivalents of skin, blood vessels, bone, cartilage, bone marrow, nerve, liver cells, and pancreatic cells.

Such tissue can be grown on a matrix which can ultimately be integrated into the living system, acting as a hybrid artificial organ.

Biosensors:

Sensing devices are now being developed that use a biocomponent for rapid, sensitive and specific measurements of variables such as temperature, pH, conductivity, etc., or of chemicals. These devices can be used as analytical tools in bioreactors, in the natural environment (e.g., soil, groundwater, seawater), or even in living tissue.

Bioelectronics and Bionetworks:

This novel area is highly interdisciplinary and includes biologically-based interfaces between living neurons and silicon-based circuitry, simulation of neural networks for parallel computations and elucidation of brain function, and neural models for control and manipulation of robotic devices. Research

on devising biomolecules for use in electronic circuits is also proceeding.

THE FEDERAL INVESTMENT

Manufacturing/Bioprocessing is an area in which biotechnology offers vast potential rewards. The total Federal investment of \$99 million in FY 1992 is small in proportion to its potential. The distribution of the Federal investment among the agencies is illustrated in Table 8. It is a priority of the Biotechnology Research Initiative to significantly enhance research in this area.

MAJOR OPPORTUNITIES AND NEEDS

High-value-added, low-volume products, for which precision, specificity, and predictability are necessary, justify the expansion of bioprocessing technology. Examples include chiral compounds, pesticides, sweeteners, flavoring agents, fragrances, pharmaceuticals, products for separation technologies, and high-order structural materials.

Biological systems are commonly able to achieve economically efficient manufacture and processing of an end product, often using renewable resources and mild reaction conditions, and addressing environmental concerns by synthesizing products using minimum amounts of energy while producing negligible amounts of toxic waste materials. These techniques can provide the most efficient methodologies, and often the only methodology, for the production of bulk and specialty chemicals, pharmaceuticals, and materials. Expansion of these technologies is required for the United States to retain a competitive position in the production of chemicals, materials, and sensors using advanced biotechnology techniques.



The expansion of the knowledge base will help in the development of high-volume products and will lead, over time, to a shift from a petroleum feedstock-dominated economy to a biomass feedstock-dominated economy.

Plant Cell Derived Products:

Taxol is a compound in limited supply that has been shown to be a very effective anti-cancer agent.

Three yew trees, which take 200 years to mature, are needed to obtain enough material to treat one patient. Plant cell culturing is a possible alternative method for synthesizing this material and other therapeutic agents, as well as pesticides, flavors and fragrances, and a variety of plant-derived compounds.

Insect Cell Derived Products:

Insect viruses are currently being tested as a possible means of controlling insect populations. These viruses can be obtained from insect cell cultures.

These types of cultures can also be used for directed protein synthesis, and have been used to make gp-120, which is a protein being tested as a possible vaccine for AIDS.

Research Needs:

- Understanding at a molecular level of the relationships among enzyme structure, function, and energetics, so that proteins can be designed for particular end uses.
- Modeling techniques for drug and biomaterial design, and for understanding the interaction of proteins with their environment and the biomaterial/host surface environment.
- Modeling techniques to design separation technologies for particular purifications based on the molecular structure and dynamics of the biomolecule or chemical product to be purified.
- Understanding of why thermophilic enzymes are stable, in order to produce enzymes that would work at higher temperatures, thereby offering the promise of increased yields and faster reactions.
- Better techniques for tissue engineering and cell culture to produce biomaterials and replacement tissues of living systems.
- Understanding of the surface interactions between biosensors and the biological fluid or solvent they are in contact with, in order to produce stable biosensors which will reliably work in bioreactors, separation columns, and living tissue.

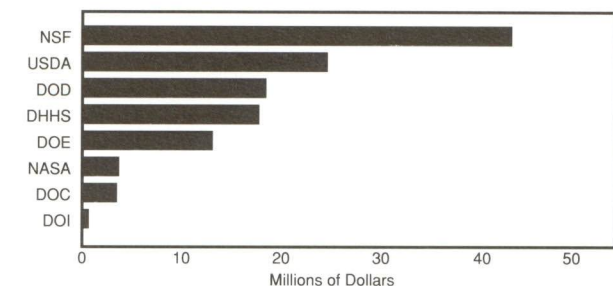
Infrastructure Needs:

Bioprocessing is an interdisciplinary research area involving engineering, chemistry, biology, physics and materials science. Federal programs must encourage the formation of interdisciplinary efforts involving academic, industrial and government laboratories and the training of scientists and engineers in this interdisciplinary area. Shared resources of capital-intensive instrumentation such as x-ray crystallography, NMR, neutron sources, super computer capabilities, synchrotron light sources, mass spectrometers, etc. are also critical needs.

Past support and the President's FY 1993 budget for biotechnology research in manufacturing/bioprocessing are shown in Figure 29 and Table 8.



FIGURE 29
The President's FY 1993 budget for biotechnology research in
Manufacturing and Bioprocessing.



FY 1993= \$123.8 M

TABLE 8
Federal Investment in
Manufacturing/Bioprocessing Biotechnology
(\$ Million)

	FY 1991	FY 1992	FY 1993
NSF	29.5	32.3	43.0
USDA	17.6	18.8	23.6
DOD	12.7	17.4	18.4
DHHS	16.7	17.0	17.7
DOE	5.3	6.4	13.2
NASA	2.6	2.6	3.7
DOC	3.5	3.5	3.5
DOI	1.0	0.8	0.7
TOTAL	88.9	98.8	123.8



While there is no sharp dividing line between research that will contribute to one specific area and research that will find broader applications, general foundations research is biotechnology research that is broadly applicable to the other research areas: Agriculture, Energy, Environment, Manufacturing/ Bioprocessing, and Health.

GENERAL FOUNDATIONS RESEARCH AREAS

The broad and fundamental nature of this important category of biotechnology research is illustrated by the following examples of research topics being pursued by Federal agencies.

Molecular genetics techniques: This area includes all aspects of research on recombinant DNA and DNA analysis. Examples include research on techniques for the introduction of genetic material into living cells, such as those of standard laboratory organisms as well as algae, invertebrates, crop plants, and fish; development of “reporter genes” for detecting and measuring gene expression; techniques for increasing the stability of foreign genes cloned into cells; genetic techniques used to substitute particular amino acids at defined locations in proteins; novel cloning techniques; and more rapid and sensitive techniques for DNA profiling (DNA fingerprinting).

Cellular techniques: Development of techniques for growing specific cell types under specific conditions, for manipulating cells, and for detecting and measuring the condition and responses of cells to specific signals and to more general chemical and environmental changes. Examples include techniques for cell fusion, techniques for culture of differentiated plant and animal cells, and techniques for measurement of specific intracellular molecules.

Biochemical and biophysical techniques: This area encompasses research leading to the development of techniques for the identification, synthesis, purification, characterization, and manipulation of nucleic acids,

GENERAL FOUNDATIONS RESEARCH

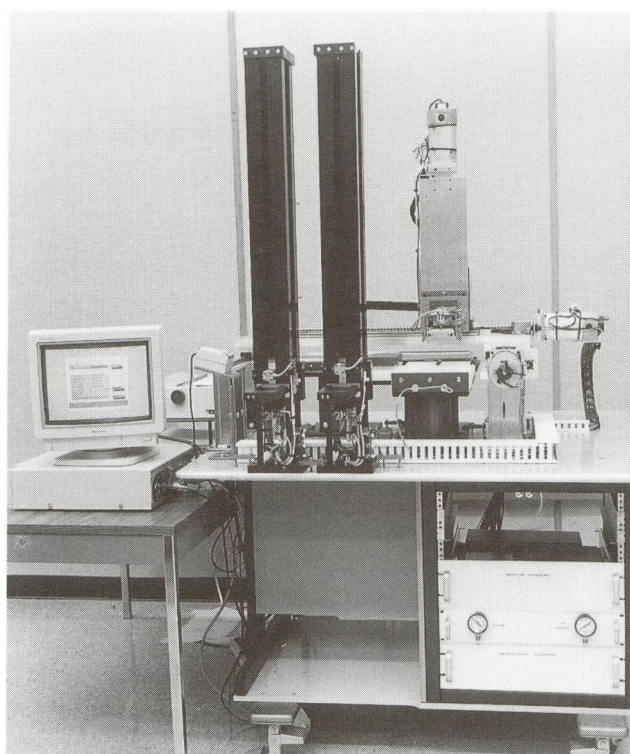


Cell fusion techniques used in research to develop disease-resistant elm trees. The clearer cell is from a disease resistant Pioneer elm; the green cell is from the disease susceptible American elm.

proteins, and other biological molecules. Examples include improved spectroscopic techniques, x-ray crystallography, new modes of microscopy for studies of structure and function of macromolecules, new separation and measurement techniques, new techniques for studying biochemical reactions, and methods for study of DNA damage and repair.

Instrumentation development: New instruments provide new techniques that play a key role in biotechnology research. Examples are instruments for study of macromolecular structure, cell imaging and tomography, and sequencing of DNA and proteins.

Informatics research and development: In biotechnology research, special problems are posed by the need for electronic storage and analysis of large volumes of data generated by research and by clinical and field trials. Increasingly, information of this sort is stored in large, highly structured databases to which an entire research community has access. The need to retrieve, analyze, or modify the contents poses informatics problems that are related to the types of information stored and to the structure of the particular database. Informatics is a particularly important component of the genome programs.



Automated instrumentation for genome research.

Theoretical and computational biology: This area focuses on mathematical and computer model technology and its use in providing a basis for the theoretical aspects of biology. These models can help to formulate, confirm, or reject hypotheses; reveal contradictions or incompleteness in data; and suggest the existence of new phenomena and new experimental approaches.

Nontraditional organisms for biotechnology: Development of organisms other than those now used in the laboratory as systems for gene transfer and for cell and tissue culture has potential applications throughout biotechnology. Examples include development of the baculovirus insect cell culture system for expression of recombinant proteins, fundamental studies of growth factors of invertebrates and fish, regulation of the cell division and growth cycle in algae, and studies of marine viruses.



A state-of-the-art computer software tool kit developed for biotechnology research. Potential applications include research in agriculture, energy, pharmaceuticals, and chemical engineering.

THE FEDERAL INVESTMENT

The Federal investment in General Foundations Research is shown in Figure 34 and Table 9. By far the largest contribution to the total is from DHHS, primarily NIH. The NIH investment represents a substantial fraction of the fundamental research in genetics and cell and molecular biology, which has provided the knowledge base from which modern biotechnology has grown. DOE, NSF, and DOD also make significant contributions to this area.

MAJOR OPPORTUNITIES AND KNOWLEDGE GAPS

Examples of potential payoffs from research on "non-traditional" organisms:

- ***New models for medical research and testing.***
- ***Disease-resistant shrimp, oysters, fish.***
- ***New flavors, scents, adhesives, fibers.***
- ***New processes for mining minerals.***
- ***Better waste management methods.***



- Use of nontraditional organisms in biotechnology. A wide range of organisms, microbes as well as various higher plants and animals, carry out diverse metabolic activities or have other special properties that promise a wealth of potential applications. Of fundamental importance are development of techniques for gene transfer, cell culture, and studies of the regulation of gene expression in selected nontraditional organisms.
- Theoretical and computational studies, particularly models of complex biological systems from molecules to organisms and bioreactors. Inadequate research in this area could represent a significant impediment to future progress in biotechnology.
- Development of techniques and instrumentation for visualization and measurement of intracellular metabolic states, signal transduction events, and secretory activity such as fluorescent probes and new modes of microscopy .
- Research on carbohydrate chemistry and glycoproteins related to protein processing in systems useful for biotechnology.
- Enhancing the state of the art in spectroscopic and imaging methods such as nuclear magnetic resonance and electron spin resonance.
- Research in techniques and instrumentation for the large scale study of DNA structure and sequences for DNA profiling (DNA fingerprinting).

DNA profiling is not yet widely used in forensics. Its use will, however expand as it promises to provide consistently reliable identification of criminals.

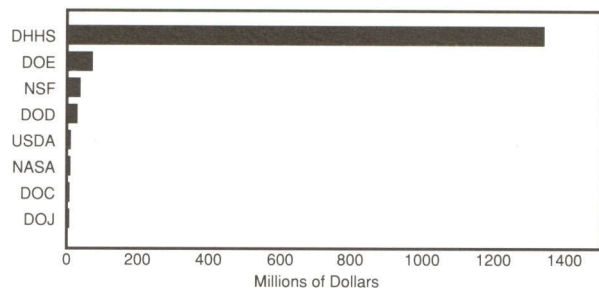
DNA profiling also has many potential uses beyond law enforcement including in identification of casualties of war or natural disasters, in identification of lost children, in establishment of human parentage and pedigrees for agricultural species, in characterization of genetic diversity in wildlife populations, and in establishing ownership of range stock. Rigorous research has been done to establish the techniques and databases required and to establish clearly the confidence limits associated with specific techniques. Development of instrumentation for large-scale, automated DNA analysis adapted for DNA profiling and training of personnel to carry out DNA profiling procedures reliably will also be required. (See section on Infrastructure.)



A research chemist observes an electrophoretic gel in research to develop standards for DNA profiling.



FIGURE 34
The President's FY 1993 budget for General Foundations Research.



FY 1993= \$1,499.7 M

TABLE 9
Federal Investment in
General Foundations Biotechnology
(\$ Million)

	FY 1991	FY 1992	FY 1993
DHHS	1143.8	1284.3	1354.7
DOE	54.3	63.2	69.5
NSF	29.1	32.7	35.4
DOD	22.3	25.1	26.5
USDA	4.6	4.8	4.9
NASA	1.8	3.7	4.9
DOC	2.4	2.4	2.4
DOJ	1.2	1.3	1.4
TOTAL	1259.5	1417.5	1499.7



GENOME PROJECTS

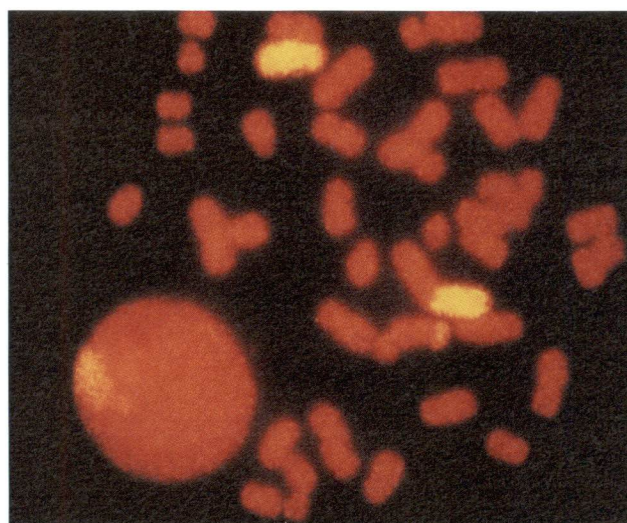
Genome projects represent a new kind of biological research that will play an increasingly important part in the development of biotechnology. The genome is the full program of instructions that directs the development of a complete organism from a single cell, ensures the constant maintenance and repair of its parts, and orchestrates its growth and metabolism. The human genome project is the first and most important of them.

A project on a small weed used as a model plant, *Arabidopsis thaliana*, is jointly sponsored by NSF, DOE, and USDA. USDA has initiated a plant genome project and is planning an animal genome project. The object of these projects is to obtain genome maps for several species of agricultural importance (for example, corn, soybean, cow, and swine). Genetic maps created for the major crop plants can be employed to locate and identify genes and ultimately to confer desirable traits (e.g., more protein, better taste, drought resistance, production of specific substances, salt tolerance, and modified climate tolerance). The impact of these projects on agriculture will be very significant, since they will enable the more facile and specific genetic modification of these organisms.

THE HUMAN GENOME PARADIGM

The Human Genome Project (HGP) is the first of the genome projects. It is technically and scientifically very ambitious and will serve as a paradigm for all future genome projects. The U.S. Human Genome Project, supported by the U.S. Department of Energy and the National Institutes of Health, was formally initiated as a national program in 1990. It is an effort directed to the mapping and sequencing of the DNA of all 24 human chromosomes, the biological repositories containing the instructions for the production of human cells. The HGP is a focused and technology-dependent basic research effort that breaks new ground for biological research in several ways. This is the larg-

est coordinated effort in biology ever directed at a single goal, and the first major interdisciplinary project in the life sciences. Its immediate objective is a delineation of the maps of chromosomes - genetic, physical, and DNA sequence. The HGP will create an encyclopedia giving biologists and physicians direct computer access to the information encoded in our chromosomes. When we succeed in deciphering the human genome, and along the way, our understanding of fundamental biological systems will be profoundly enriched, leading to major changes in the practice of biological science and clinical medicine. Accomplishing this daunting task will require further technological advances, instrumentation, and chemistries that will permit us to analyze the fundamental molecules of life, DNA and proteins. Development of the sophisticated new computational hardware and software is needed to interpret the vast information encoded in the human genome. As part of the HGP, the genomes of bacteria, yeast, the roundworm, the fruit fly, and the mouse will also be mapped for comparative purposes and to help with the interpretation of the information.



Detection of a translocation involving human chromosome 4 after fluorescence *in situ* hybridization (FISH) with a whole chromosome probe for chromosome 4.



BENEFITS OF THE HGP

The benefits that will come from the complete sequence map of the human genome fall into four categories:

- The development of the requisite technologies necessary to accomplish the HGP will revolutionize many aspects of biology, agriculture, and medicine.
- The practice of all biological sciences and the design of new experimental systems will be fundamentally altered by the information provided by computer access to genome maps.
- Use of genetic and sequence maps in the diagnosis and treatment of human disease will radically change the practice of clinical medicine in the 21st century.
- The information generated by the HGP and the new technologies that emerge from this endeavor, will be catalytic to the expanding biotechnology industry.

The HGP will require the development of more powerful technologies for DNA handling, mapping, sequencing, and analysis. There is potential for significant advances in the physical and genetic mapping techniques. Success in sequencing the entire human genome will require at least a 100-fold increase in the speed as well as a 10-fold decrease in cost for DNA sequencing. There are also challenging computational problems associated with the HGP.

In general, the key to successful technology development is a multidisciplinary approach, with the application of powerful tools from many different areas - applied mathematics, applied physics, chemistry, engineering, and computer science - focused on biological problems. Interactive research environments, where many different disciplines can be focused on

the development of a wide spectrum of needed techniques, will be a real key to the success of the HGP.

It has been estimated that the research leading to the recent identification of the gene for cystic fibrosis cost approximately \$150 million. If the genetic and sequence maps of the human genome had been known, it would have been possible to identify this particular gene for perhaps \$200,000. This potential savings in resources would also have been accompanied by a significant reduction in the time required to find the gene.

The medical impact of the HGP will be profound. Some of the changes in the practice of medicine we anticipate would occur without the HGP, but more slowly and at a greater cost. Of the 3,000 or so human disorders known to be associated with a single gene, such as cystic fibrosis, fewer than 10% are currently understood at the genetic level. This picture can be expected to change rapidly in the next few years.

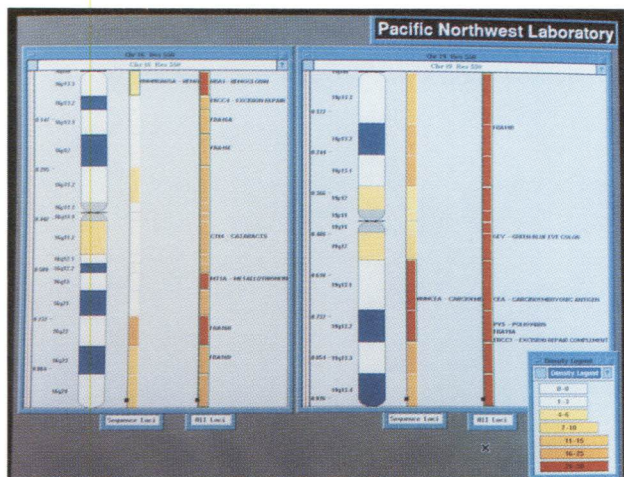
The development of automated instruments for examining genetic variation, raises the possibility of identifying the variant forms of genes that cause disease or predispose individuals to disease. The ability to recognize particular DNA sequences by molecular complementarity between probe and target DNA has spawned a field known as DNA diagnostics. This technology will increasingly impact the diagnosis of disease in which single-gene defects have been identified, the detection of dominant or recessive oncogenes that may predispose an individual to cancer, and the identification of infectious agents such as the AIDS virus.

Perhaps the most important area of DNA diagnostics will be the identification of genes that predispose individuals to disease so that preventive measures can be taken. The human genetic map will permit the identification of specific predisposing genes, and DNA diagnostics will facilitate their analysis in many different individuals. Approaches to circum-



venting the health limitations imposed by disease-predisposing genes might include new approaches to molecular pharmacology, manipulations of the immune system (immunotherapy), appropriate avoidance, or manipulation of environmental factors such as smoking, exposure to certain chemicals or ionizing radiation. In the future, genetic engineering will be used to replace defective genes in certain tissues or cell populations in the human body.

In the future, the diagnosis of disease-predisposing genes will alter the basic approach of medicine. Of the approximately 100,000 human genes, some are known and mapped, even sequenced, but perhaps 99% of them are still to be discovered. In future medical practice, a patient's genetic make-up will be characterized to produce an accurate profile of an individual's medical state thereby allowing patient and doctor to prevent potential problems. For each defective gene, therapeutic regimens will be available that will circumvent the genetic limitations. Thus, medicine will move from a dominantly reactive philosophy (cure sick patients) to a preventive philosophy (keep people healthy).



Computer generated maps of human chromosomes 16 and 19. The color density maps adjacent to each chromosome shows the relative amount of mapping (all loci) and of sequencing (sequence loci) that has been so far accomplished. Information is from the GenBank sequence and Genome Data Bases.

Although few of the ethical, legal, and social issues raised by these future possibilities are new to medical practice, many of the issues have never been adequately addressed. The HGP is devoting significant resources to investigating and attempting to anticipate these problems and to developing potential solutions. Today, the HGP is the largest source of support in the United States for ethical, legal, and social studies of biological importance.

The benefits of the HGP to biotechnology will be enormous due to the dual products of the effort: the information available from the sequence and genetic maps and the development of new techniques and instrumentation for genome analysis. Knowledge of the 100,000 human genes will provide a vast repertoire which can be employed by the pharmaceutical industry to attack fundamental aspects of human disease. Recent examples are the spectacular clinical successes of erythropoietin (EPO), a hormone which promotes the development of red blood cells, in treating chronic anemia, and granulocyte colony stimulating factor (G-CSF), a hormone which promotes the development of white blood cells, in cancer chemotherapy. In the future, we can look forward to hundreds, if not thousands, of additional proteins that will facilitate the development of new therapeutic approaches to a variety of diseases.

The HGP will spawn the development of new technologies and instrumentation. These will obviously create opportunities for companies that now produce biological instrumentation (e.g., chemical and biological robots for routine tasks such as cloning, mapping, or sequencing). Opportunities will also arise for companies to offer commercially services such as genetic mapping, DNA sequencing, cloning, and gene transfer to cells or organisms.

There will be striking industrial opportunities in biocomputing. New software will be needed for the image analysis associated with a wide variety of analytic and preparative instruments (DNA sequencers, chemical and biological robots, DNA mappers, mass



spectrometers, X-ray spectrometers, etc.). New database technologies will be required to store and distribute genomic information. The combinatorial problems of biology will require the development of new algorithms, new hardware, and, increasingly, the use of parallel computers.

The United States is currently the undisputed world leader in biotechnology. The potential benefits of genome science are clearly being recognized internationally, and human genome projects have been initiated in a number of other countries including Japan. The U.S. HGP is an important component of the Biotechnology Research Initiative that will help to ensure that we retain our superiority in biotechnology.

FEDERAL INVESTMENT

The HGP is presently funded at \$164 million, with \$105 million at NIH and \$59 million at DOE (FY

1992). The two components of the program are closely coordinated between the two agencies by several means, including a joint advisory group and joint working groups. NIH and DOE are also jointly funding the Genome Data Base at Johns Hopkins University, which is the current repository for worldwide genome mapping data. In the future, other genome projects will contribute substantially to the Biotechnology Research Initiative as they take advantage of the knowledge and technology gained from the HGP and begin to bear the fruit of new knowledge of the molecular genetic makeup of important organisms.



The ocean is a source of many economically important materials, including food, pharmaceuticals, minerals, and energy. As national and worldwide economic growth continues, demand for the world's natural resources will increase. Requirements for disposing of the waste products of civilization in environmentally sound ways will be more stringent and more costly. These demands and requirements may force more reliance on the ocean, and its resources must therefore be sustained.

Potential payoffs of marine biotechnology include:

- ***optimization of resources represented by cultured marine organisms: finfish, shellfish, plants, and microorganisms,***
 - ***new chemicals, biopolymers, and other materials,***
 - ***novel pharmaceuticals from marine organisms, and***
 - ***nonpolluting energy sources from metabolically novel organisms such as animals and microbes from hydrothermal vents.***
-

Key to the understanding of the ocean's biology and its potential to contribute to economic growth and human welfare is the application of modern methods of biological and biochemical analysis, including the tools of molecular biology, to specific areas of research and development. Modern methods have not, thus far, been widely exploited by marine scientists. The paucity of fundamental information about marine organisms is a major impediment to rapid advances in marine biotechnology.

The enormous diversity and uniqueness of marine organisms make them a vital resource. The majority of plant and invertebrate animal phyla on Earth are either exclusively or predominantly marine. This is particularly true of ancient groups of organisms which have evolved biochemical and physiological mechanisms to survive in environments short on surfaces to colonize and in a solution shared by millions of other organisms. As a result, many have sophisticated biochemical signaling and chemical warfare devices. They often exhibit processes and produce substances with no terrestrial counterparts. Many of these marine organisms are so poorly understood that they have yet to be fully described and named. The open ocean is home to a vast array of photosynthetic plants, bacteria, and other microorganisms whose poorly understood metabolic activity is vital to the Earth's well-being and can be exploited for useful purposes.

MAJOR MARINE BIOTECHNOLOGY RESEARCH AREAS

Molecular Genetics of Animals, Algae, and Microorganisms:

This area is key to the development of marine biotechnology, as it establishes the field's basic foundations. To capitalize on the biotechnological potential of marine organisms requires the ability to manipulate them genetically, physiologically, and biochemically. Basic studies of regulation at the genetic, biochemical, and physiological levels will yield not only powerful tools for exploiting organisms, but also lead to the development of diagnostic techniques to study marine organisms in their natural environments, thus helping interpret the complex interactions among physical, chemical, and biological ocean processes.



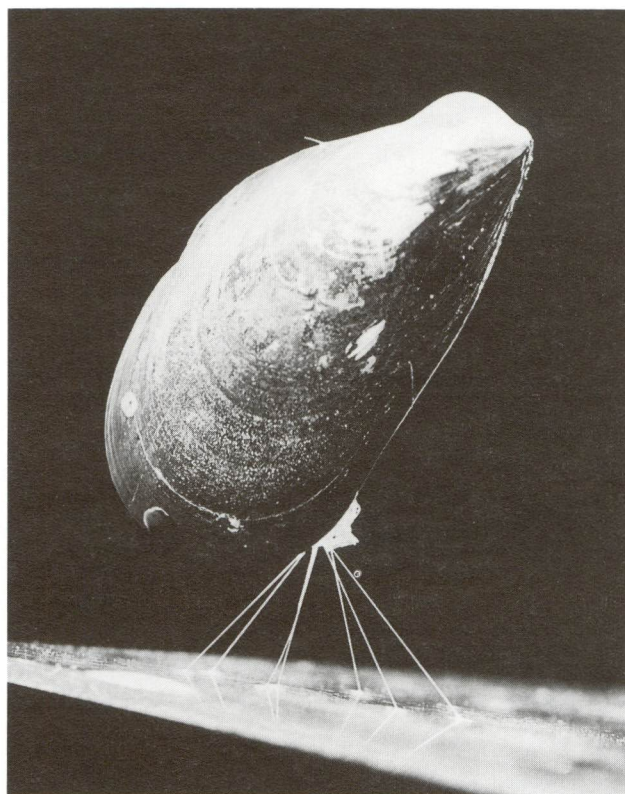
Recent topics in marine biotechnology research include:

- *marine viruses that display species-specific infectivity for marine organisms (these viruses will provide powerful new tools for marine biotechnology),*
 - *toxins produced by seafood-borne pathogenic microorganisms,*
 - *mechanisms by which pathogens enter, associate with, and become concentrated in shellfish.*
-

Biomolecular Materials and Biosensors:

In addition to a wide range of unique bioactive materials described below under "Primary and Secondary Metabolism," marine organisms are the source of a wide range of proteins and other polymeric materials useful or potentially useful as commercial products. Marine organisms have evolved elaborate sensory organelles, and some of these appear to be suitable for biosensor development. For example, the antennules of the blue crab have been used as a source of chemoreceptive nerve fibers that have been incorporated into biosensors for measurement of amino acids.

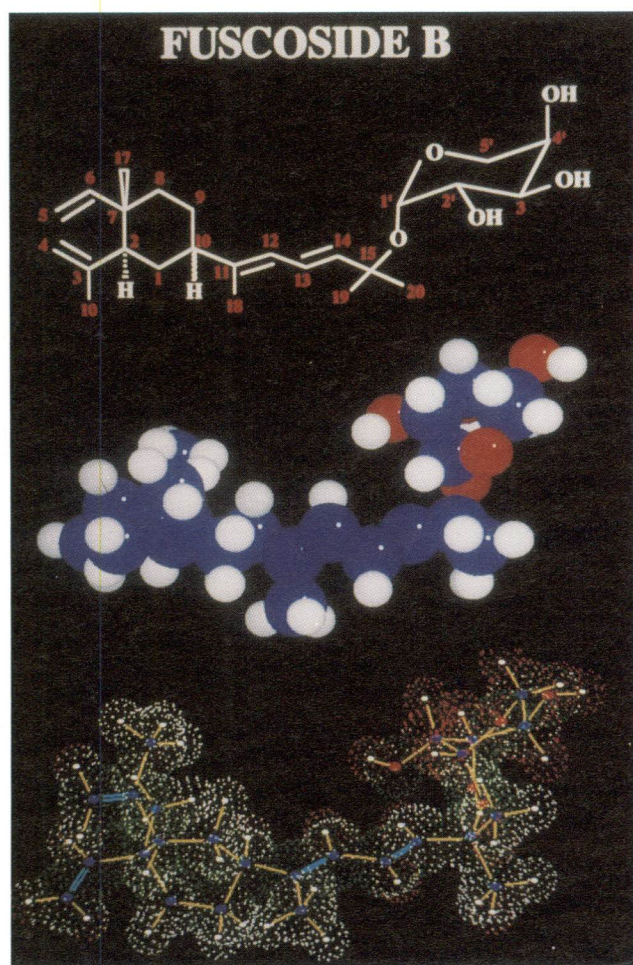
The market in the United States for agars, alginic acids, and carrageenans from marine algae is in the hundreds of millions of dollars. The market for chitosan was predicted to climb to \$2 billion over the next few years, in a range of products (Inside R&D, Oct. 4, 1989), e.g., chitosan-treated wheat seeds produce disease-resistant plants and 10 percent higher yields, and chitosan can be used to produce wound-healing gauze.



The marine mussel, *Mytilus edulis*, is shown suspended in water by threads attached with adhesive to a glass plate. Biotechnology research on adhesives produced by marine organisms should produce adhesives that can be used for many applications such as repair of teeth and undersea structures.

Primary and Secondary Metabolism:

Fundamental studies are being conducted on the primary and secondary metabolism of plants, animals, and microorganisms with a view to elucidating biosynthetic pathways, biochemical processes, and chemistry of novel metabolites in order to provide the basis for new pharmaceutical compounds, medical research materials, enzymes, and other chemical products. Of particular interest is understanding the biochemical relationships between marine invertebrates and the wide variety of microorganisms associated with them symbiotically or commensally. Research includes chemistry of novel lipids and other unique small molecules, study of enzymes respon-



Fucoside B, a natural anti-inflammatory agent has been isolated from marine organisms.

sible for unusual biosyntheses, and identification and isolation of bioactive secondary metabolites.

Biofilms and Biocorrosion:

Biofouling and biocorrosion are major contributors to commercial and U.S. Naval operating costs in marine environments. The occurrence of natural anti-biofouling processes is well established and merits intensive investigation at a molecular level in order to develop knowledge that will yield rational approaches to new methods for controlling or preventing destructive processes. These approaches require an understanding of the attachment mechanisms of organisms that form biofilms.

Bioprocessing and Bioremediation:

The marine environment is a potential source of novel biological pathways for processing and degrading a wide variety of natural and man-made substances. On-site biological degradation by naturally occurring organisms or consortia of organisms or by bioreactors based on such organisms may offer feasible approaches to the disposal and/or cleanup of hazardous materials. There is little basic information about the biological processes governing the maintenance and stability of marine consortia (for example algal mats) that appear to have prodigious biodegradative and bioprocessing capabilities. This category includes research focused on developing a descriptive and mechanistic understanding of how biodegradative and bioprocessing activities are distributed, regulated, and maintained.

Bioprocessing and bioremediation research is providing new methods for treating hazardous wastes, e.g., estuarine bacteria have been adapted for use in bioreactors to detoxify brines from industrial processing.

Aquaculture:

Aquaculture is the growth of aquatic organisms in a controlled environment. Such environments may be bioreactors, open lagoons or open/closed raceways. The aim of such culture is to be able to produce items of economic import such as pharmaceutical agents, food/feed additives, isotopically enriched chemicals, polymers, lipids with petroleum potential, and foodstuffs. Current research, not addressed under molecular genetics above, focuses on selective breeding, nutrition, physiology, endocrinology, disease, development and passage of drug resistance through bacterial plasmids, and engineering, including biochemical engineering for use of microorganisms or cells of higher organisms in bioreactors or photo-bioreactors to produce useful biochemicals.



Economically viable aquaculture requires that the entire life cycle of a species be completed in captivity, yet many species of potential importance do not reproduce in captivity. Thus, fundamental research in physiology and endocrinology is directed primarily to understanding reproduction of such organisms and developing methods for its control.

The U. S. trade deficit in seafood was \$2.4 billion in 1990; increasing U.S. capability in aquaculture of food species could address this significant problem.

THE FEDERAL INVESTMENT

The Federal investment in research supporting marine biotechnology will be approximately \$44 million in fiscal year 1992. Table 11 shows the approximate investment by agency and research area for the eight agencies or departments that invest in marine

biotechnology research. Much of the research requires or benefits from collaboration across traditional disciplinary lines. It ranges from development of generic techniques in molecular biology to solving specific problems of disease in aquaculture. Much of it involves cooperation among government, academia, and industry or between governmental agencies. Approximately 90 percent of the investment is used to sponsor academic research through grants and contracts and thus is focused on developing human resources through training and education of graduate students and postdoctoral associates.

AREAS OF OPPORTUNITY AND DIRECTIONS FOR THE FUTURE

There is growing recognition in the United States and abroad that the great diversity of living marine resources offers opportunities for meeting societal needs for goods and services in ways compatible with environmental protection, and that current re-

TABLE 10
FY 1992 Investment in Research in Support of Marine Biotechnology
(\$ Million)

	EPA	NIH	NOAA	NSF	USDA	ONR	FWS	FDA	DOE	Total
Mol. genetics	0.3	1.8	1.2	0.7	2.0	2.0	0.2	3.1		11.3
Biomaterials			0.2							0.2
Metabolism	0.1	8.0	1.0	2.5		2.0			0.2	13.8
Biofilms	0.1		0.2			1.0				1.3
Bioprocessing	0.2		0.4	1.2		2.0			0.2	4.0
Environment				3.5						3.5
Aquaculture		2.1	2.9	0.1	4.1		0.1	0.3	0.2	9.8
TOTAL	0.7	11.9	5.9	8.0	6.1	7.0	0.3	3.4	0.6	43.9



search efforts do not adequately address these opportunities. In Japan, the government is part of a major new initiative in marine biotechnology and provides an estimated \$180 million annually in funding. Prior to the development of the Biotechnology Research Initiative, there was no coordinated U.S. effort in marine biotechnology.

Over the past few years, some of the Scandinavian countries, Japan, China, and others have invested heavily in R&D supporting aquaculture. As a result, major aquacultural facilities are in commercial operation. Their production is having a significant impact on U. S. markets.

It is clear that Federal efforts in research laying the basis for further development of marine biotechnology must be intensified, to take advantage of largely untapped resources and to prepare skilled technicians and scientists for international competition in developing bioindustries in the 21st century. Just as important, application of biotechnological techniques is essential to elucidating oceanic processes affecting or controlling global processes. In addition to a wide range of research in molecular genetics, much of the needed research calls for interdisciplinary approaches—studies crossing the boundaries of biology, microbiology, and chemistry, and at the points of intersection among biochemical engineering, materials science, chemistry, and biology. The research opportunities and needs in this field are broad, but greater efforts in the following areas are critical:

MOLECULAR GENETICS OF MARINE ORGANISMS. To exploit the biotechnological potential of marine organisms, the molecular genetics of marine species must be understood. High priorities are:

- Understanding mechanisms controlling gene expression and developing techniques for introducing foreign DNA or amplifying native DNA.

- Exploring marine viruses and how they can be utilized in genetic engineering.
- Developing reliable molecular assays for human pathogens in seafood and recreational waters; developing molecular assays for and prophylactic measures to control bacterial, viral, fungal, and protozoan diseases of aquacultural species.

BIODEGRADATIVE PROCESSES. To broaden the options for bioremediation, we must increase our efforts to identify and characterize marine microorganisms and microbial consortia that degrade, detoxify or metabolize pollutants and industrial wastes and to determine the physicochemical requirements for their maintenance, growth and regulation. Highest priorities are:

- Identification, isolation, and determination of the function of enzymes responsible for useful degradative processes,
- Development of biological methods for processing wastes in seafood production and for recovery of by-products such as enzymes and amino acids.

PRIMARY AND SECONDARY METABOLISM.

Fundamental studies are needed of the cellular and molecular processes relating to the production and function of marine natural products. Among high priorities are:

- Elucidating biosynthetic pathways leading to important metabolites of marine organisms; isolation, function, and properties of associated enzymes, e.g., pathways by which algae produce polysaccharides; properties of derivatizing enzymes; mechanisms of and controls on production of exopolymers by algae; physical and chemical properties of polymers.
- Defining physical and biochemical relationships between marine invertebrates and microorgan-



isms, including dinoflagellates, associated with them, especially in regard to production of bioactive or toxic metabolites

OCEANIC PROCESSES.

- Applying techniques of biotechnology to defining the role of marine plankton (viral, bacterial, plant, and animal) in global carbon and nutrient cycling.
- Understanding the processes that promote and support biofilm formation, so that biofouling can be prevented and desirable attachment in aquacultural systems enhanced.

INFRASTRUCTURE, EDUCATION, AND TRAINING NEEDS:

- Groups and centers to promote interdisciplinary research, especially including biochemical engineering, in support of marine biotechnology.

- Research fellowships and traineeships (graduate student to senior investigator) in marine molecular biology. High-priority areas include marine microbiology in support of biotechnology and marine pharmacology/bioorganic chemistry.

No area of marine biotechnology has yet been completely explored or exploited, and the breadth of research opportunities represented by these areas cannot be addressed adequately with current levels of investment. The Biotechnology Research Initiative is laying the foundations for the development of an integrated, expanded research effort.



Structural biology is the determination of biological structures at nanometer resolution by physical methods, and the analysis of structures in terms of their biological functions.

An understanding of the relationships between macromolecular structure and function, together with the ability to predict and design structures with desired function will be a major factor in realizing the full potential of biotechnology.

Structural biology is a highly interdisciplinary field. It is a blend of molecular biology, biophysics, chemistry, advanced computing and computer graphics, and solid-state electronics. It is a field where experiment and theory increasingly interplay in the development of new understanding. Structural biology is in an exciting period. Spectacular advances have been made in x-ray diffraction and nuclear magnetic resonance spectroscopy (NMR), two techniques for determining structure. The coming together of diverse developments makes structural biology ready for an explosive increase in the determination and understanding of biological structures at high resolution.

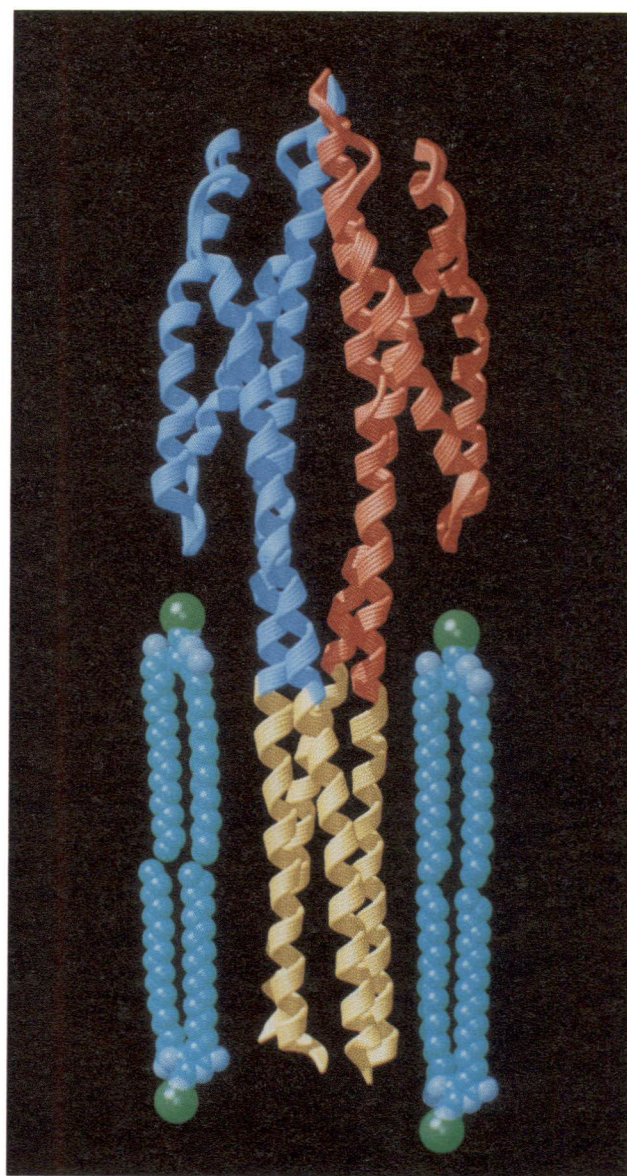
MAJOR STRUCTURAL BIOLOGY RESEARCH AREAS

Determination of structures:

This includes research to determine biological structure at nanometer resolution and the subsequent analysis of the structure in terms of its biological function. Examples are the determination of the structure of enzymes, viruses, and immunoproteins.

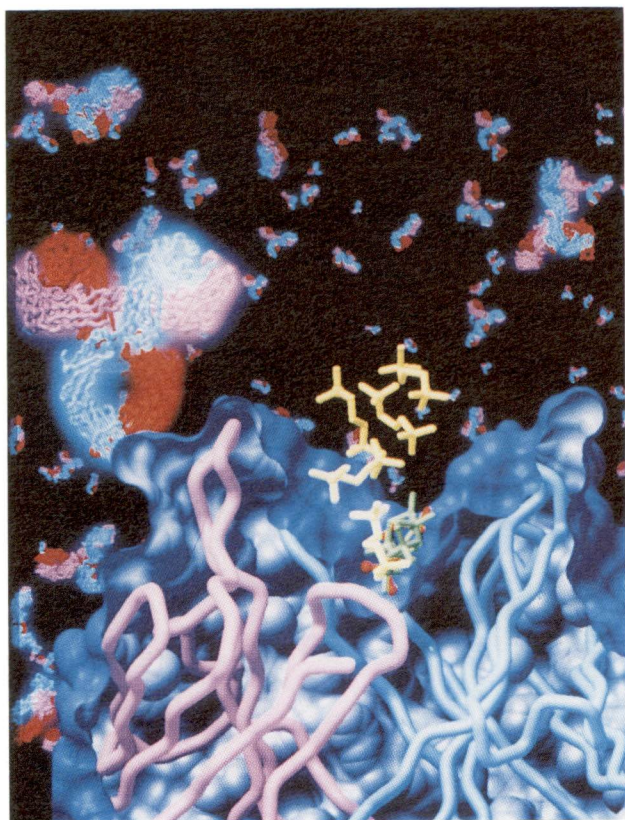
Analysis of structure/function relations:

Research in this area includes the analysis of known high-resolution structures in terms of their biological



A three-dimensional model of a bacterial receptor for the amino acid, aspartate. Transmembrane receptors are proteins cells use to receive information (in this case the presence of the nutrient, aspartate) and transmit a biochemical signal into the cell so that the cell can respond to its environment. The model was developed from data obtained by x-ray crystallography.

function. The analysis of high-resolution structures of mutated forms of proteins to determine mechanisms of enzyme catalysis or protein folding are examples.



Computer image of an antibody that catalyzes the cleavage of chemical bonds in choline esters and carbohydrates. Catalytic antibodies, which can be produced against a wide range of organic molecules, hold great promise for the development of a range of new production processes.

Methods development:

Research on the development of new, and improvement of existing, methods of determining and analyzing biological structures at high resolution are included in this area. The development of improved methods of structure determination using multidimensional NMR spectra and multiple-wavelength anomalous dispersion analysis of crystal structures are examples.

Instrumentation development:

The development of new and improved instruments for the determination and analysis of biological

structures constitutes this area. The development of fast, large-area radiation detectors and high-field NMR instruments are examples.

Provision of Facilities:

The construction and operation of specialized facilities required for the determination and analysis of high-resolution biological structures are included in this area. The provision of beamlines at synchrotrons and neutron sources is an example.

ESTIMATED FEDERAL INVESTMENT

Support for structural biology research is included in the budgets for the research areas from agriculture to manufacturing/bioprocessing and in the infrastructure category.

It is estimated that the Federal investment in Structural Biology is about \$300 million in FY 1992, with over two-thirds of this investment from the NIH. About half of these funds support the analysis of structure/function relationships.

AREAS OF OPPORTUNITY AND GAPS

Technological Opportunities:

- Time-Resolved X-Ray Diffraction
- Neutron Structural Biology
- X-Ray Absorption Spectroscopy
- Multidimensional NMR and Solid-State NMR
- Improved High-Resolution Imaging and Microscopies
- Computational Biology

Research Opportunities :

- Protein Engineering and Design
- Cellular Recognition
- Receptor-Based Drug Design
- Gene Structure



While some areas of opportunity are being developed at a reasonable pace, additional activity is vitally needed in others. The following represent three key gaps that must be given the highest priority.

- **Beamlines and Infrastructure at Synchrotrons and Neutron Sources:** The major gap in structural biology is that of additional beamlines, equipment, and research support staff for structural biology user facilities where synchrotrons and neutron sources are needed. These user facilities are increasingly important in the determination of biological structure, and the demand for access to these facilities has grown rapidly. Existing synchrotrons and neutron sources are oversubscribed.
- **Training:** Training in structural biology is a second area that is limiting the further growth of biotechnology. Scientific opportunities will not be realized if trained personnel are not available. The development of advanced instrumentation for this field is interdisciplinary, drawing on fields such as electrical engineering, computer science, and applied physics, as well as biology, chemistry, and biochemistry. A larger number of technical and scientific personnel must be trained to adequately develop and support the utilization of the new technologies.
- **Modern Laboratory Instrumentation:** In recent years, support for equipment in academic laboratories, particularly midrange instrumentation, needed for structural biology and related research, has not kept pace with the new generation of instruments for structural biology, for example, area detector diffractometer systems and 600-MHz NMR spectrometers. Many of these instruments

(NMR and mass spectrometers, and x-ray diffractometers for example) are essential research equipment for studies of structural biology. The driving factor for future instrumentation expenditures will be the need to acquire new generations of equipment that meet the rapidly changing technological requirements for frontier research on structural biology. Most research in structural biology and other areas of biotechnology is carried out in individual laboratories and funded by project-oriented support. The national effort in biotechnology requires that these laboratories have access to the most modern equipment.

The Role of Interagency Cooperation:

Structural biology in the U.S. is, and must remain, a cooperative national enterprise. The NIH, NSF, and private philanthropies provide most of the support for structural biology research in this country, although DOE has an essential and growing programmatic interest in the field. In addition, DOE has one critical role that is largely unshared with other agencies: to operate, equip, staff, and upgrade the capital-intensive, centralized user facilities where some of the most exciting structural biology research has been done and to construct new facilities for the next generation of breakthroughs. Furthermore, because of heavy reliance of individual investigators on specialized large facilities, it is an area where collaboration and joint planning among agencies is particularly crucial. In this regard, it is important to note that DOE, NIH, and NSF have, in the last few years, engaged in joint planning. These joint planning efforts have set the stage for development of the structural biology component of the Biotechnology Research Initiative.



Social Impact Research is aimed at understanding the social, cultural, ethical, economic, and legal implications of biotechnology research and its applications.

Scientific progress does not proceed in a social vacuum. In myriad ways, science and technology affect society and culture beyond providing new products. While biotechnology offers many promises of significant new developments and products in areas ranging from new pharmaceuticals and agricultural improvements to the anticipated benefits for human health, it is important to recognize that the social impact of new technologies can be widespread and unexpected.

The social issues associated with biotechnology research and its applications include education and communication, personal and cultural beliefs and values, the ethics of reproductive choices and practices, professional behavior, research practices, privacy and confidentiality, civil liberties, patenting and intellectual property, technology transfer, the economic impacts of regulatory processes on industry, and international competitiveness. It is the overarching purpose of social impact research to learn from the past and to apply these lessons to the future.

THE FEDERAL INVESTMENT

Social impact research, as a part of Federal scientific research programs, is relatively new and the current Federal investment in this area is modest.

The largest portion of support is associated with the Human Genome Project (HGP), jointly sponsored by the Department of Energy and the National Institutes of Health. The HGP has as its goal the production of detailed genetic and physical maps of the human chromosomes, as well as, eventually, the determination of the complete sequence of the 100,000 genes making up the human genome. Because of the unprecedented amount of detailed genetic information to be generated by the HGP, ethical, legal, and social implications are anticipated. Activities addressing

SOCIAL IMPACT RESEARCH

Social and Cultural Impact:

EDUCATION & COMMUNICATION

- Public Understanding of Biotechnology
- Expert Advice and Public Choice

SPECIFIC ISSUES

- Impacts on Family and other Social Institutions
- Impacts on Cultural and Personal Beliefs and Values
- Cross-Cultural Impacts

Ethical Impact:

- Impact on Reproductive Choices and Practices
- Professional Ethics
- Research Ethics
- Privacy and Confidentiality
- Equity

Legal Impact:

- Civil Liberties Implications
- Forensics and Criminal Law
- Intellectual Property Protection
- Regulatory Law

Economic Impact:

- Technology Transfer
- International Trade
- Global Competitiveness

these implications include development of educational curricula, teacher training, printed materials, workshops, and support for educational public television. Other activities include: studies on issues of privacy and confidentiality of genetic information; the impact of genetic information on individuals, on counseling, on reproductive decisions, and on medical practice; the past history of the uses and misuses of genetic information; and commercialization of ge-



netic technologies. While programs addressing the ethical, legal, and social implications of the HGP have similar overall goals and are closely coordinated, the DOE program focuses on privacy and confidentiality of genetic information, while the NIH program focuses on medical and health implications. The DOE investment in these activities is \$1.8 million, while the NIH is providing \$5.2 million in FY 1992.

The National Science Foundation is providing \$1.2 million in FY 1992 for social impact research related to the development, regulation, adoption, and utilization of biotechnology. Examples include: ethical analysis of policy issues and the responsibilities of university and industry researchers, impacts of patent law and other institutional arrangements on biotechnology advances, the process of innovation and invention, public opinion and acceptance, societal risk analysis and management, and the structure of the biotechnology industry.

The U.S. Department of Agriculture has two social impact research efforts. The Cooperative State Research Service (CSRS) supports research to understand the social and economic impacts of agricultural biotechnology research. This encompasses evaluation of the impacts of biotechnology products on rural communities, domestic markets, and international trade. Additional projects have investigated intellectual property protection and the international trade consequences of biotechnology regulation and trade barriers. Modest attention has been given to ethical considerations in agricultural biotechnology research and the effects of new technologies on the American farm family. CSRS is supporting its social impact research activities with \$500,000 in FY 1992.

The Economic Research Service of the USDA supports a program on the economic analysis of technology in agriculture. This program has three aims.

The first is a comparison of how risks associated with biotechnology are incorporated into market decisions. The second aim is an analysis of economic issues involving incentives and funding for agricultural research and development. The third aim is an assessment of key biotechnologies and possible future trends. USDA supported this program with \$200,000 in FY 1992.

The Department of Commerce is also currently supporting a social impact research effort in the area of biotechnology. Its marine biotechnology and aquaculture policy and economics program is focused on determining the adequacy of the current regulatory framework, studying Federal, state, and local government regulatory roles, areas of conflict in coastal management relating to aquaculture, economics of ocean disposal of wastes and hazardous materials, pollution abatement and environmental improvements, and the bureaucratic and regulatory climate for aquaculture. The DOC supported this program with \$100,000 in FY 1992.

The total Federal investment in Social Impact Research in FY 1992 is \$9.0 million.

AREAS OF OPPORTUNITY AND RESEARCH NEEDS

Social and Cultural impact in the area of Expert Advice and Public Choice:

Maintaining democratic control over an increasingly technological future requires that individuals and institutions make informed choices.¹ For this to occur, individuals must be able to understand, interpret, and evaluate relevant technological information. Society must, for example, be able to evaluate the risks of new drugs versus established surgical procedures, or the risks of new pest-resistant plants versus pesti-

¹National Research Council, *Improving Risk Communication*. National Academy Press, 1989, pg. 14-16.

cides. This requires more knowledge of how people use statistical information and how they might be assisted in using it more effectively.² In addition, enhanced and novel efforts towards public education are urgently needed.

Economic Impact : Research is urgently needed in two areas.

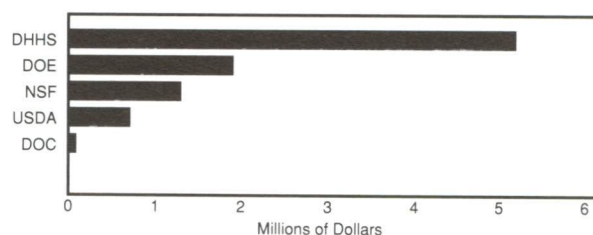
1. Factors influencing international competitiveness and the overall returns from research and development. This topic focuses on whether the U.S. or its foreign competitors will benefit from American technological innovations. It is concerned with the kinds of regulation and control of biotechnology development required in the face of international competition.
2. The impact of the regulatory environment and the potential liability to the Federal Government, firms, and individuals. This topic focuses on problems of potential liability related to biotechnology research and products.

In an increasingly complex and interdependent world, the relationship of U.S. biotechnology industries to those of potential foreign competitors and the regulatory environment surrounding technology transfer are urgent concerns. The importance of these issues is highlighted by a recent survey³ indicating that biotechnology firms consider the regulatory environment the main obstacle to their growth.

Despite the fact that the economic aspects of biotechnology may be the most important factors affecting the growth of the biotechnology industry, there is little economic research being conducted on biotechnology. It is important to extend support for research on the economics of biotechnology

The President's FY 1993 budget for research on the social impact of biotechnology is shown below.

FIGURE 41
The President's FY 1993 budget for Social Impact Research.



FY 1993= \$9.2 M

TABLE 11
Federal Investment in the
Social Impact of Biotechnology Research
(\$ Million)

	FY 1991	FY 1992	FY 1993
DHHS	3.3	5.2	5.2
DOE	1.4	1.8	1.9
NSF	0.9	1.2	1.3
USDA	0.8	0.7	0.7
DOC	0.1	0.1	0.1
TOTAL	6.5	9.0	9.2

²Office of Science and Technology Policy. *U.S. Technology Policy*. Sept. 26, 1990, pg. 4.

³The Scientist, July 8, 1991, pg. 5, 17, 25.

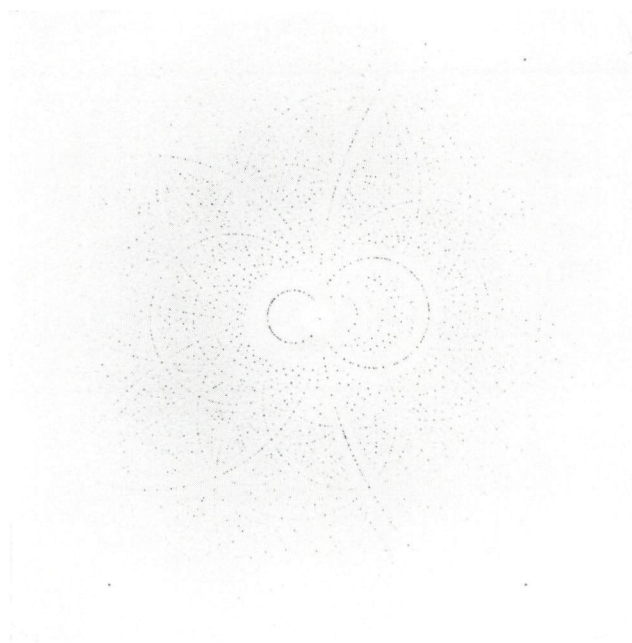
INFRASTRUCTURE

Infrastructure refers to activities that support the conduct of biotechnology research. Only programs having biotechnology as the principal focus are included in this report.

INFRASTRUCTURE AREAS

Facilities:

This includes support for construction, renovation, and maintenance of facilities dedicated to biotechnology. Examples include facilities for cancer research, agricultural research, the space program, biological field stations, marine laboratories, structural biology facilities, and computer facilities used for biotechnology research.



Laue diffraction pattern of a crystal of the enzyme, isocitrate dehydrogenase obtained using a new synchrotron facility. The use of synchrotrons for x-ray diffraction studies of protein structure permits diffraction patterns to be obtained with very short exposure times and permits the resolution of rapid changes in protein structure. Synchrotron facilities are critical for structural biology research.



Training/Career Development:

These programs are dedicated to training or career development in biotechnology, and they include pre- and postdoctoral fellowships and training grants specifically identified for support of individuals receiving training in biotechnology. Training in biotechnology is primarily at the graduate and postdoctoral levels. Training programs include general and targeted biomedical research (e.g., cancer, AIDS), cell and molecular biology, plant biology, biophysics, structural biology, genetics, biotechnology-related engineering, math, physical sciences, material sciences, and pharmacology.

Instrumentation:

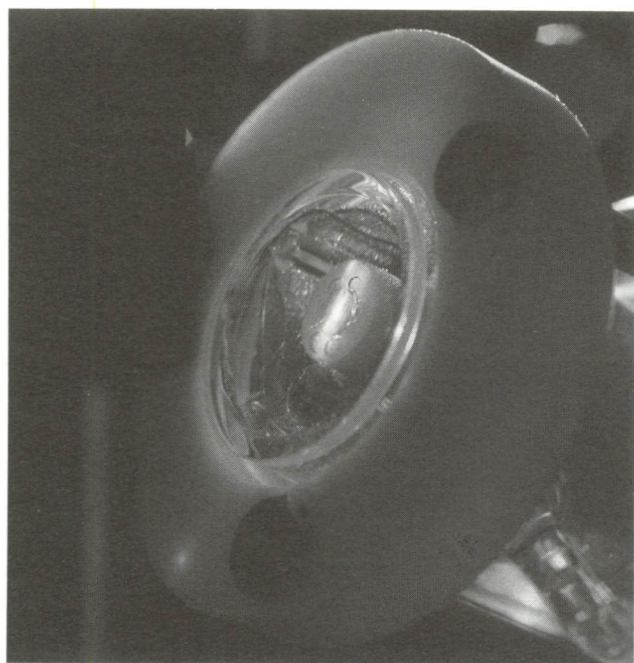
This area represents support for the acquisition and maintenance of major, specialized instruments (\$200,000 and above) for use in biotechnology research. (Instrumentation research and development is included in the general foundations research category.) Such instruments include supercomputers, commercial space hardware, NMR spectrometer, protein and nucleic acid sequencers, computer systems for computational biology, x-ray spectrometers and dedicated computers, microscopes, scanning fluorimeters, neutron sources, and synchrotrons.

Repositories:

These are repositories of shared resources for biotechnology research. Examples include banks of monoclonal antibodies, nucleic acid probes, cell lines, living organisms, DNA clone libraries, germplasm repositories, and stock centers.

Data Bases/Reference Standards:

This refers to support for development, management, and cataloging of databases, information resources, and reference standards relevant to biotechnology research. (Informatics research is included in the general foundations research category.) Examples include data



Surface Enhanced Raman Spectroscopy. A laser beam illuminates a silver surface upon which a protein is adsorbed. Surface Enhanced Raman Spectroscopy allows the direct observation of the vibrational modes of the protein. This information is useful in understanding protein dynamics.

bases containing scientific/technical data on genetics, proteins, DNA sequences and profiles, bioenergetics, germ plasm, genomic maps, etc. Also included are compilations of Federal and state regulations on biosafety, and reference standards for quality assurance of biotechnology-based measurements.

THE FEDERAL INVESTMENT:

Support for Infrastructure accounts for about 8% of the total Federal investment in biotechnology research.

Facilities support appears in the budgets of only a few agencies that support biotechnology research, and it represents only a small fraction of the budgets of those agencies. The Federal investment in facilities was \$35 million for FY 1991 and about \$37 million in FY 1992.

For FY 1993, several agencies propose to increase support for infrastructure related to structural biology research. Support for facilities for space research and for biomedical are also proposed.

Increases in **training** related to biotechnology are also on the agendas of several units of the NIH, as well as other agencies.

Instrumentation increases are requested by several agencies for upgrade of structural biology instrumentation and by NASA for instrumentation for space flight research.

Increases for **repositories** are requested by a few agencies for expansion of living stock centers and acquisition of new genes/probes identified with human diseases.

Increases are requested for **data bases and reference standards** to establish and distribute data on results of field tests using genetically modified plants, animals, and microbes; germ plasm repository contents; sequence and genetics-related information; a forensic DNA indexing system; and collection and organization of human genome information.

Areas of Opportunity

Facilities: Funding for facilities is low across all agencies, and deterioration of existing facilities and lack of funds for new facilities for biotechnology threaten to be major factors limiting progress in the future. However, specialized needs must continue to be supported to the extent possible:

- Upgrading and construction of synchrotron facilities for structural biology research:



- Access to containment facilities for recombinant DNA research at the P-3 and P-4 levels. This need is especially acute in some areas of the country and for academic institutions with relatively small, but nonetheless important, commitments to biotechnology research.
- Construction, repair, and replacement of plant growth chambers and greenhouses.
- Construction, renovation, and maintenance of animal facilities to meet animal care guidelines and regulations emanating from the Animal Welfare Act.

Training/Career Development: This is the infrastructure area promising the greatest overall impact on biotechnology. Programs are needed to enhance public literacy concerning biotechnology, as well as to attract and retain students in biotechnology-related science and engineering through pre and postdoctoral levels, and to retrain individuals with experience in other disciplines for careers in biotechnology. Particular needs include:

- Training at the interfaces of biotechnology-related disciplines
- Training in theoretical and computational biology
- Training that includes nontraditional organisms for biotechnology
- Training in carbohydrate and glycoprotein chemistry
- Training of midlevel technical personnel.

Several agencies have programs to promote general scientific literacy, as well as efforts to recruit and train independent investigators for the future. Relatively little attention has been given, however, to the large number of workers that will be required at the midtechnical level to transfer research results to applications. Specialized vocational training for biotechnologists is probably not the answer, however. The solution may lie, rather, in encouraging colleges

and universities to reinstate laboratories as integral parts of basic science courses.

Instrumentation: Funding for the acquisition of state-of-the-art equipment for biotechnology research must be available. Two related issues faced by academic institutions must also be addressed:

- Difficulties in obtaining funds for equipment maintenance.
- Problems in taking advantage of Federal instrumentation grants which require matching funds.



A student analyzes materials extracted from marine organisms using high pressure liquid chromatography. The availability of state of the art instrumentation is critical for training in biotechnology.



Databases and Reference Standards: Quality assessment and comparability of results across different laboratories will be a rapid growth area and major tool for dissemination of information for technology transfer. An expanding investment in databases must be a part of budget planning not only for genome projects but in all other areas of biotechnology.

Databases: Needs are growing as information increases in all areas of biotechnology, particularly genome projects. Examples include *Drosophila*, *C. elegans*, yeast, and *Arabidopsis* data bases, as well as human, mouse, and crop plant genome information.

Reference standards for quality assurance of biotechnology based measurements: Reference standards ensure accuracy and reliability in biotechnology research and commercialization, and allow critical measurements to be compatible among different laboratories. Reliable production of high-quality data reduces the need for duplication of data. The availability of reference standards for assigning measured values to proteins, glycoproteins, and DNA fragments are currently inadequate. Standards for measurement in quality assurance would have a major impact in a broad range of research areas from genome projects to manufacturing.

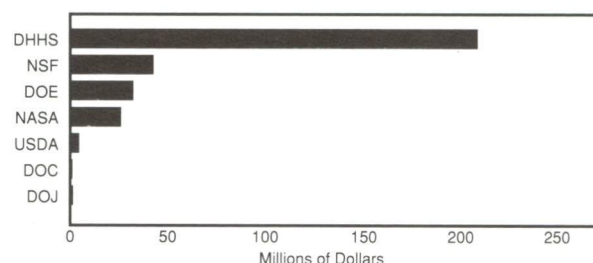
Repositories:

- Collection, characterization, and maintenance of germ plasm;
- Genetic stock centers for marine organisms and other non-traditional organisms. The wide range of organisms in addition to those traditionally used in laboratory research represents a resource for biotechnology which must be developed if the United States is to maintain its strong leadership in biotechnology; and

- Repositories for recombinant DNA reagents generated in genome projects, as well as for specialized purposes such as gene probes for specific genetic diseases.

Past investments and the President's 1993 budget for the infrastructure of biotechnology research are shown below.

FIGURE 45
The President's FY 1993 budget for the Infrastructure of biotechnology research.



FY 1993= \$319.6 M

TABLE 12
Federal Investment in
Biotechnology Research Infrastructure
(\$ Million)

	FY 1991	FY 1992	FY 1993
DHHS	212.6	193.4	211.1
NSF	40.8	39.0	42.5
DOE	12.6	16.9	32.4
NASA	12.7	20.9	25.8
USDA	20.3	28.0	5.3
DOC	1.6	1.6	1.6
DOJ	0.6	0.9	0.9
TOTAL	301.2	300.7	319.6



APPENDIX A

AGENCY CONTRIBUTIONS

AGENCY	PAGE
USDA	74
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DOI	95
DOJ	97
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NASA	105
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AGENCY OVERVIEW

The U.S. Department of Agriculture (USDA) supports a large agricultural research system based in the Department and in cooperating state universities. Four USDA agencies fund and conduct biotechnology research: the Agricultural Research Service (ARS), the Cooperative State Research Service (CSRS), the Forest Service (FS), and the Economic Research Service (ERS). Collectively, they fund research, ranging from fundamental studies of basic life processes to applied research that focuses directly on creating new products or solving agricultural problems. The total USDA commitment to biotechnology research has risen approximately tenfold between 1985 and 1992.

The new tools of biotechnology are enabling USDA-funded scientists to better understand the basic physiology of agriculturally important organisms and how these organisms interact with the environment. This knowledge is crucial to the development of strategies to enhance an organism's ability to flourish in a sustainable agricultural system with reduced fertilizers, herbicides, insecticides, and drugs. Another prime component of USDA-funded biotechnology research is the Plant Genome Research Program, which has as its goal the identification and mapping of genes of agronomic importance.



USDA biochemists check Petri dishes in which pesti- cide-degrading bacteria are grown.

In recent years, a great deal of USDA-funded, bio- technology research has focused on making U.S. ag- riculture more compatible with the environment. For example, ARS scientists in Pullman, Washington, have transferred a gene for insect resistance to pota- toes. If this is successful in the field, new varieties of potato will be developed that will be able to grow with reduced amounts of agricultural chemicals. Similarly, scientists at the University of Wisconsin have field tested a recombinant *Rhizobium* which shows great potential in helping legumes improve ni- trogen fixation, thus reducing the need for nitrogen fertilizers.

In the animal area, a major thrust of USDA-funded research has been to improve feed efficiency and growth rate in livestock. If the same or greater amounts of high-quality meat and milk can be de- rived from a smaller number of animals, agricultural efficiency will be improved and the impact of animal wastes on the environment can be reduced. USDA- funded research is also tackling the improvement of natural resistance to disease in animals and develop- ment of new vaccines which would allow producers to use fewer antibiotics and other drugs.

ONGOING PROGRAMS AND NEW INITIATIVES

USDA-funded biotechnology research is explicitly focused on agricultural problems and environmental issues associated with agriculture. This investment is beginning to lay the basis for new and improved strategies for supplying nutrients to crops, new and improved crops that resist pests and diseases, more productive and environmentally sound methods of livestock production, and improved processing tech- nologies which protect the environment while en- hancing the quality and safety of food available to consumers.



Use of biotechnology in developing leaner meat. The cut of meat with a thinner layer of fat came from an animal whose growth had been supplemented with somatotropin.

USDA BIOTECHNOLOGY RESEARCH PROGRAMS

Plant Systems

Animal Systems

Animal and Plant Genome Program

Biological Control Agency

Environmentally Compatible Pest Control

Value Added Products

Woody Plant Biotechnology

Biogeochemical Dynamics

Energy

Environment

Social Impact Research

Technology Transfer

Training\Career Development

USDA PRIORITIES FOR AGRICULTURAL BIOTECHNOLOGY RESEARCH¹.

- **Genome Mapping and Genetic Enhancement**
Genetic engineering can improve the productive efficiency of plants and animals, strengthen their resistance to common pests, and increase their tolerance to chemical and physical stress. New knowledge about the molecular and cellular processes of animal and plant inheritance is the key to developing new products and to enhancing the safety and nutrition of food.
- **Safe and Effective Pest Management**
Pest management strategies are needed that address genetic modifications and population changes in pest organisms while minimizing adverse effects on the environment.
- **Animal Health and Welfare**
New knowledge of molecular biology and the genetics of the animal immune system offers the potential for major improvements in disease resistance and acquired immunity.
- **Crops as a Biomass Source for Energy Production**
The development of a biomass-based energy industry using feedstocks from energy crops and byproducts of the food and fiber industry can contribute significantly to rural economic viability, as well as to reducing America's dependence on imported oil.
- **New Processing Technologies for Added Value**
Value-added products can increase demand for agricultural commodities and enhance the competitiveness of the U.S. food and fiber system.

1. Joint Council on Food and Agricultural Sciences,

Fiscal Year 1993 Priorities for Research, Extension, and Higher Education: A Report to the Secretary of Agriculture, Executive



biological materials must be developed and applied to add value; enhance quality, convenience, utility, and safety; and meet market demand.

- **Safety and Stability of Consumer Foods**

Emerging technologies offer opportunities to substantially improve food quality, safety, processing, and preservation techniques while also enhancing the global competitiveness of U.S. food products.

- **Waste Management and Use**

Industrial and municipal waste converted into environmentally compatible production inputs provides an agricultural solution to the nation's waste management problems.

DEPARTMENT OF COMMERCE



AGENCY OVERVIEW

The mission of the Department of Commerce (DOC) is to promote American economic security by helping business become more competitive. Competing successfully in the coming decades will mean offering the best possible products and services at the lowest costs. The DOC conducts basic and applied research to speed up the commercialization of biotechnology, provides analyses of foreign developments, and works closely with business and industry to open U.S. trade opportunities abroad and to remove domestic legal and regulatory barriers. Biotechnology research and economic analysis is conducted at the National Institute of Standards and Technology (NIST), the National Oceanic and Atmospheric Administration (NOAA), and the International Trade Administration (ITA).

NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY

Biotechnology Research Mission

Since its inception as the National Bureau of Standards in 1901, NIST has had the unique mission of providing American science and industry with a basis for accurate measurement. NIST's role in biotechnology is to develop the generic measurements, models, data, and standards needed by U.S. industry to accelerate the commercialization of bioproducts and thus ensure a significant share of the world biotechnology-related market. As with all NIST programs, a major emphasis of the biotechnology program is to provide advisory and research services to industry, other government agencies, and the scientific community.

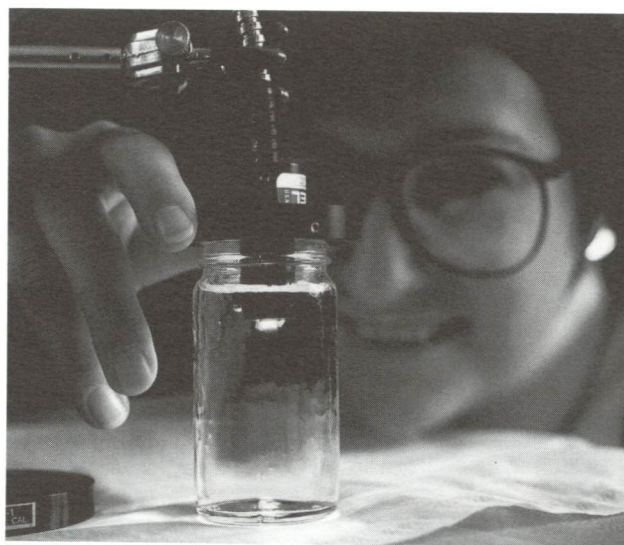
Ongoing Programs

NIST is building an interdisciplinary program to address the critical areas of biotechnology including bioprocess engineering necessary for efficient manufacture of pharmaceuticals, bulk, and specialty chemicals, and alternative fuels via biochemical pathways. The primary research efforts at NIST are focused on:

- process measurements, product separations/purifications, and engineering design properties for commercial-scale processing;
- measurements involved in protein engineering, with emphasis on molecular structure and function, protein crystallography, protein folding, protein-protein interactions, and computational chemistry and modeling; and
- suitable measurement methods and standards for analyzing the composition of complex biochemical solutions in all phases of biochemical production.

An important part of the NIST biotechnology effort is the Center for Advanced Research in Biotechnology (CARB), a joint venture with the University of Maryland and Montgomery County, Maryland. CARB combines interdisciplinary, biotechnology-related resources from academia, industry, and government to conduct research in structural and physical biochemistry and molecular biology.

In addition to its biotechnology research program, for the past twelve years NIST has been building a



Research at the NIST includes development of new types of sensors to measure biologically important substances such as glucose.



repository of biological specimens which are used to provide historical data and measurement quality assurance for environmental and biotechnology-related research. Specimens stored in the repository, the National Biomonitoring Specimen Bank (NBSB), include human livers; samples from the marine environment, including sediment, oysters, mussels, and fish tissue; marine mammal tissues; and human diet. The NBSB currently has an inventory of approximately 2500 specimens.

NATIONAL OCEANIC AND ATMOSPHERIC ADMINISTRATION

Biotechnology Research Mission

NOAA is responsible for managing marine fisheries and executes this responsibility, and part of the research in support of it, through the National Marine

Fisheries Service. Since 1972, NOAA has been the steward of the National Sea Grant College Program. This program has a broad mandate that includes conducting research, education, and advisory service in support of aquaculture and other types of marine biotechnology. Fundamental and strategic research in this field is advancing science and technology; spurring commercial development; and training students for industrial, academic, and governmental careers.

Ongoing Programs

All of NOAA's activities in biotechnology are in support of marine biotechnology. Most are conducted in academic institutions under the auspices of the National Sea Grant College Program. The National Marine Fisheries Service conducts research related to biotechnology in its laboratories and applies molecular techniques to identification of fishing stocks. In addition, it grants Saltonstall-Kennedy funds for some research in support of biotechnology through a program to strengthen the U.S. fishing industry. The National Undersea Research Program supports facilities for research and sponsors extramural research. NOAA is building a program in marine biotechnology focused largely on developing the scientific understanding and techniques necessary for:

- manipulating the genetic characteristics of aquatic animals, plants, and microorganisms that could be exploited for production of food, feed, and chemical products;
- controlling disease in aquacultural species and for detecting environmental human pathogens and biotoxins that contaminate seafood;
- defining effective systems for production of fish and shell fish;
- exploiting the biochemical processes of marine organisms through bioreaction, photo-bioreaction, bioprocessing, and bioremediation;



Biotechnology is applied to fisheries research. The harvest of an experimental crop of hybrid striped bass.



- controlling or preventing biofouling and biocorrosion; and
- defining secondary metabolism in marine organisms and associated cellular and molecular processes relating to bioactivity and production of biochemicals as a basis for new approaches to production of fine chemicals, polymers and other chemical products.

The National Undersea Research Program supports five centers for the study of processes in the world's oceans and lakes. Its facilities enable researchers to collect data, make observations, and conduct experiments not possible within the limitations of traditional laboratory and ship-based research.

NOAA also recognizes the importance of technology transfer. One of the components of its National Sea Grant College Program is the Marine Advisory Service. This program of formal and informal education is conducted through an interactive network of advisory specialists and regional agents who transfer information to the marine community, including aquaculturists and seafood processors. Researchers are encouraged to collaborate with industry and some acquire matching funds from this source. Collaboration of this kind provides a mechanism for exchange of information and for mutual intellectual stimulation between academe and industry.

INTERNATIONAL TRADE ADMINISTRATION

Biotechnology Research Mission

The biotechnology activities within the ITA are conducted by the Basic Industries program within the Office of the Assistant Secretary for Trade Development. The biotechnology mission of Basic Industries is to analyze and monitor foreign developments

in biotechnology, expand U.S. trade opportunities in biotechnology products and services, and foster efforts to enhance U.S. competitive strengths.

Ongoing Programs

The Basic Industries biotechnology efforts are focused on the following activities:

- Industry Analysis-Monitoring and assessing technical and commercial developments in biotechnology both domestically and internationally, and developing economic statistics on industrial biotechnology for the annual U.S. Industrial Outlook.
- Trade Promotion-Sponsoring trade missions and seminars to introduce U.S. companies to foreign markets; facilitating trade opportunities for U.S. firms; developing foreign marketing analyses and assisting state government agencies with trade facilitation and missions.
- Policy Issues-Developing U.S. Government policies in trade, regulations, intellectual property rights, research, databases, and other areas that advance the U.S. competitive position in biotechnology.

THE U.S. DEPARTMENT OF DEFENSE

AGENCY OVERVIEW

The Department of Defense strategic vision for defense technology takes a twenty-year view and relies on three streams of technology:

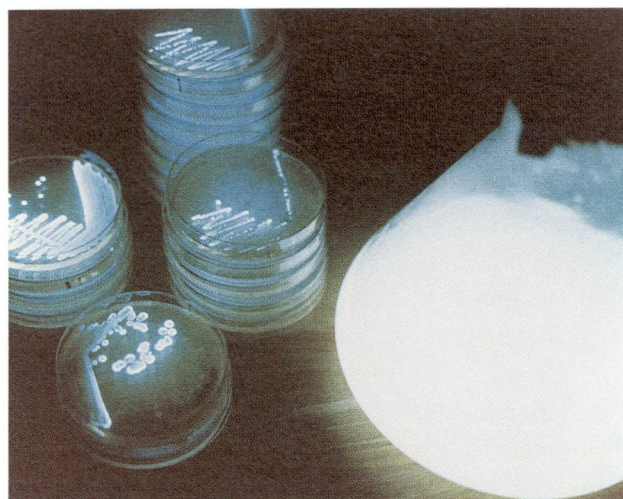
- (1) Putting in place evolutionary improvements in weapons systems, their subsystems, and support systems.
- (2) Generating innovative, highly leveraged breakthrough technology and inserting this technology efficiently into our military capability.
- (3) Seeking technology trump cards to sustain long-term dominance in the technological arms race.

One of the primary tools used in implementing this technology strategy is the Defense Critical Technologies Plan, which is updated each year. The current plan identifies biotechnology as one of twenty-one critical technologies considered essential for maintaining the qualitative superiority of U.S. weapon systems. Moreover, five of the other twenty-one critical technologies have significant biotechnology components: passive sensors, signature control, high energy density materials, composite materials, and superconductivity.

ONGOING PROGRAMS

The Army, Air Force, and Navy have active research programs in biotechnology that complement one another in content and focus. All three services have new and expanding programs in environmental control of hazardous waste. The Air Force has the oldest program with an emphasis on detoxification. The Army and the Navy programs focus on basic principles of detection and remediation of land-based and ocean-based wastes, respectively.

Each of the three Services likewise has a materials



The common laboratory microbe, *E. coli* has been made to glow in the dark by transplanting genes for bioluminescence from the marine bacterium, *Vibrio fischeri*. This technique developed with support from the Office of Naval Research recently has been used to engineer bacteria found in the soil to glow in the presence of certain pollutants.

program; these are closely coordinated to avoid duplication and to enhance rapid promulgation of promising developments. The Army has the lead in both medical and chemical/biological warfare defense (CBWD) research. The Navy supports research on biosensors other than those employed in environmental assessment or CBWD, with an emphasis on detection of physical or chemical factors for purposes of threat assessment, especially in wet environments.

Sensors Sensor technology plays a critical role in a wide range of DOD activities. Several of the most highly developed application areas are CBWD, threat detection at sea (e.g., antisubmarine warfare) and on land (e.g., explosive sniffers), drug interdiction, contaminant assessment, and identification of organisms responsible for biodeterioration (corrosion and fouling). Biological sensors exhibit extremely high selectivity and sensitivity, often exceeding levels obtainable using conventional technology. DOD sensor research is aimed at discovering the basic principles used by living systems and exploiting



them to design new sensors.

Environment The basic goal of the DOD environmental biotechnology research is to discover and apply Nature's strategies for coping with undesirable chemicals or organisms. Selected applications include decontamination of chemical warfare agents, biodegradation of hazardous waste products (especially fuel and explosives), waste reduction in painting and paint stripping, development of environmentally sound approaches for prevention of biodeterioration of surfaces exposed to marine environments, and development of biodegradable materials.

Materials Biological systems offer many examples of structural materials exhibiting properties superior to those available using conventional materials technology. Moreover, materials produced with biotechnology can be inexpensive, they need not use strategic critical materials, and their structures can be manipulated at the molecular level without the need for developing new manufacturing processes.

The ultimate goal of the DOD biotechnology materials programs is to develop generic materials with a range of properties that can be selected for specific applications. A second objective is production of fine chemical intermediates that cannot be produced economically in quantity at the desired purity by conventional chemistry. The DOD research programs aim at the following classes of materials: fibers, coatings, adhesives, plastics, elastomers, lubricants, composites, and electro-optic materials.

Health Infectious disease accounted for more hospital admissions in World War II, Korea, and Vietnam than combat injuries and non-battle injuries combined. The thrust of DOD health-related biotechnology research is to determine modes of action and transmission, diagnostic techniques, and vaccine design and development for diseases which have the potential to impact military operations. Work performed in laboratories and among troop populations is directed at prevention, diagnosis, and treatment of

viral, bacterial and parasitic disease—especially diarrheal diseases, meningitis, infectious hepatitis, typhus fevers, dengue fever, leishmaniasis, malaria, dental disease and, in recent years, HIV. One additional component of this research area is aimed at developing universal donor blood and blood substitutes.

Chemical/Biological Warfare Defense There are two research thrusts which all rely heavily upon advancements in biotechnology: detection, and decontamination. Detection of chemical and biological agents requires state-of-the-art detection schemes to provide real-time threat assessment. CBWD detectors currently depend upon several types of biotechnology: antibodies, receptors, enzyme reactions, and DNA/RNA probes. These technologies have been and continue to be developed almost exclusively under DOD sponsorship. Decontamination methodologies for personnel, gear, and waste-dump sites must act rapidly and selectively to maximize protection and minimize the effects of corrosive reagents currently available for this task. Schemes relying upon enzymes or "cocktails" of enzymes are most promising. Biotechnology research focuses on identifying reaction principles for decontamination and methods for designing appropriate enzymes or enzyme-like agents.

DEPARTMENT OF ENERGY

AGENCY OVERVIEW

The U.S. Department of Energy (DOE) carries out missions that include fundamental scientific research and development in energy technology, energy conservation, strategic weapons, energy regulation, energy data collection and analysis, Federal power marketing, and education in science and technology. In addition to its headquarters components, the Department has an extensive field structure of laboratories, research facilities, regional operations and support offices. Of particular relevance to biotechnology research are the 9 National Laboratories and 30 additional specialized research facilities. The National Synchrotron Light Source, the Fermi Accelerator and the Superconducting Super Collider projects, lasers, electron microscopes, advanced robotics, and supercomputers are examples of some of the unique tools that DOE employs and provides to the scientific community in exploring research frontiers. Nobel laureates and other eminent scientists employed in DOE laboratories have accomplished landmark work in physics, chemistry, biology, materials science, and other disciplines. The Department of Energy oversees an unparalleled collection of scientific and technical facilities and equipment with extraordinary potential for advancing interdisciplinary knowledge and application in biotechnology.

DOE also funds significant and extensive research programs at universities, industrial laboratories, and research institutes.

BIOTECHNOLOGY RESEARCH MISSION

The goal of biotechnology research at DOE, from structural biology research at national user facilities to enhanced production of ethanol by bacteria, is to improve production and utilization of energy in a way that is consistent with the National Energy Strategy.

Biotechnology will be applied to understand and to minimize the consequences to the environment and human health of energy production and use. Thus the



biotechnology research programs are focused on these long-term objectives as well.

The Department has a number of offices and programs that support biotechnology research. Most of the activity and support occurs in the Office of Energy Research, with additional programs located in Fossil Energy, Conservation and Renewable Energy, and the Office of Environmental Restoration and Waste Management. The principal biotechnology research programs at DOE are genome projects; structural biology; environmental mitigation, remediation, and restoration; biological processing of fossil fuels; biological solar energy conversion; biomass conversion to fuels and chemicals; and bioprocess engineering.

ONGOING PROGRAMS AND NEW INITIATIVES

DOE has ongoing programs in all areas of biotechnology research but most programs are in the areas of energy and general foundations research. Environmental research is also becoming increasingly important.

Agriculture

DOE agricultural biotechnology research programs are primarily involved with plant-microbe interactions and include mechanistic/structural studies of nitrogen fixation and the genetics of symbiotic relationships. Low-cost biomass species that can be used as economical feedstocks for large-scale production of renewable liquid fuels are also being examined.

Energy

A large fraction of biotechnology research at DOE focuses on energy and is ultimately related to the National Energy Strategy. For example, considerable activity is focused on biological solar energy conversion, especially in the development of cost-effective alternative transportation fuels. The five millionth U.S. patent was granted last year to a DOE investiga-



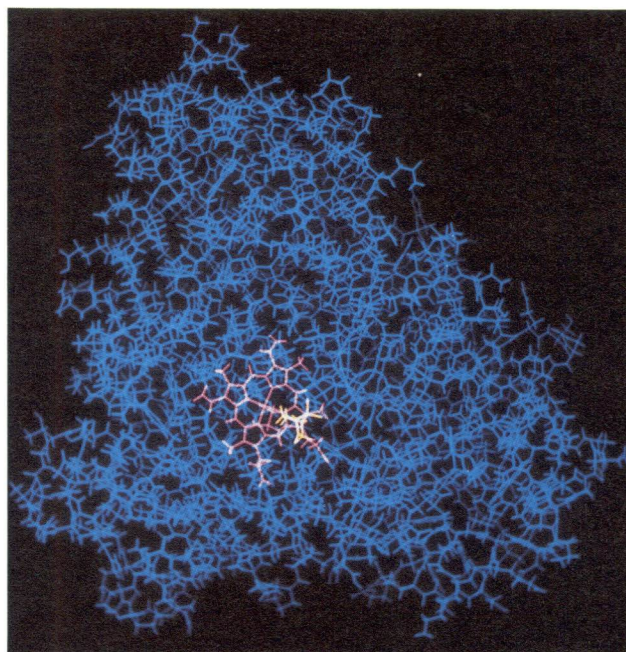
tor who optimized ethanol production in a bacterium. A promising long-term area of research targeted toward the production of diesel fuel substitutes is the use of biochemistry and molecular genetics to develop algae with rapid cell growth and high oil (lipid) content. In addition, DOE supports research on conversion of wastes to useful product; for example, cellulase genes are being inserted into new hosts, so as to obtain organisms with enhanced ability to breakdown cellulose.

Environment

Biotechnology holds great promise for mitigating environmental disturbances associated with energy exploration, production, and use. For example, many DOE waste disposal sites are polluted with complex mixtures of chemicals and radionuclides for which conventional treatments (e.g., removal) are either impractical or impossible. Biotechnology research will produce microorganisms and methods that can stabilize wastes within disposal sites. In the Ocean Margins program, for example, investigators will apply molecular biological methods to problems associated with determining the mechanisms of the carbon cycle on the continental shelf. The Subsurface Science Program has isolated new microbes with novel properties that may be useful in undertaking the subsurface environment and in devising remediation techniques.

General foundations

General foundations research is strongly supported by the Department, primarily through the Structural Biology and Human Genome Programs. Structural biology draws its strength from the large and unique user facilities operated by DOE, the synchrotron light sources, pulsed and steady-state neutron sources, and scanning/transmission electron microscopes. The Human Genome Program aims to develop the analytical means to understand the organization and structure of the human genome and to improve our understanding of the molecular basis of disease and of how genetic information is stored and expressed. Areas within the Human Genome Project



The x-ray crystal structure of cytochrome P450cam (blue), with its centrally located heme (magenta), is shown attached to a substrate, camphor (yellow). Using protein engineering, research is in progress to redesign the enzyme and thereby enhance the specificity and efficiency of this natural, biodegradative enzyme for remediation of DOE-site contaminants.

that are receiving special emphasis include new sequencing and mapping technologies, automation of molecular genetic techniques, and computational analysis and assembly of sequence and mapping data.

Health

DOE has a strong tradition of pioneering research in nuclear medicine. This tradition is now being continued through the application of biotechnology in the DOE Nuclear Medicine Program. This program seeks to develop new approaches to disease treatment and analysis such as the use of monoclonal antibodies labeled with a variety of radioisotopes. Spin-offs from the Human Genome Program, like chromosome painting, will make increasing contributions to the health area.



Manufacturing/Bioprocessing

Several DOE programs support this emerging area of biotechnology research, primarily through research in biocatalysis and bioreactor design. Some highlights of these programs include the use of computational models to predict the structure and function of biocatalysts, thereby providing information for the design of new, energy-efficient biocatalysts.

The Alternative Feedstocks Program, proposed for initiation in FY 1993, will produce high-volume chemicals from biobased feedstocks and will include bioconversion pathway opportunities. This program will expand the technology base in bioremediation and biobased fuels to higher-value chemicals, a vital link in the development of a competitive biobased fuels and chemicals industry.

Social Impact Research

DOE currently supports projects on the social impact of human genome research. This is a small but important area of biotechnology research, and its role in DOE's total biotechnology program will increase in the coming years.

Infrastructure Support

Beamlines for x-ray and neutron crystallography, new NMR spectrometers, Alexander Hollaender Fellowships, a microbial culture collection, databases and new approaches to informatics are all ways in which DOE supports its biotechnology research. While much of this support is used to facilitate DOE research, most of the facilities are made available to the entire scientific community.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

The Department of Health and Human Services (DHHS) is the Federal Government's principal agency for promoting the health of Americans and providing essential human services. The Public Health Service (PHS), a component of DHHS, is the principal health agency of the Federal Government and the largest public health program in the world today. The mission of the PHS is to protect and advance the health of the American people by conducting and supporting biomedical and behavioral research, helping prevent and control disease, monitoring the adequacy of health facilities and staffing, helping to deliver health care services to the medically underserved, ensuring the safety and effectiveness of drugs and medical devices, ensuring the wholesomeness of foods, and addressing global health issues in cooperating with other nations and international agencies.

Comprising the PHS are the Centers for Disease Control (CDC); the Food and Drug Administration (FDA); the Health Resources and Services Administration; the National Institutes of Health (NIH); the Alcohol, Drug Abuse; and Mental Health Administration (ADAMHA); the Agency for Health Care Policy and Research; the Indian Health Service; and the Agency for Toxic Substances and Disease Registry. Four of these agencies—ADAMHA, CDC, FDA, and NIH—conduct biomedical or behavioral research and all use the tools of biotechnology.

ALCOHOL, DRUG ABUSE, AND MENTAL HEALTH ADMINISTRATION

AGENCY OVERVIEW

The mission of ADAMHA is to find scientifically based solutions to health problems and issues associated with the use and abuse of alcohol and drugs, and with mental illness and mental health. Under its research mandate, ADAMHA and its three institutes—the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Drug



Abuse (NIDA), and the National Institute of Mental Health (NIMH)—support cutting-edge biomedical and behavioral research relating to mental illness and substance abuse and support training of basic and clinical research scientists.

BIOTECHNOLOGY RESEARCH MISSION

Historically, research on addictive and mental (ADM) disorders, ADAMHA's primary mission, has faced monumental difficulties because of the complexity and inaccessibility of the brain; the dearth of noninvasive research tools; and problems in distinguishing among biology, behavior, and biology-behavior interactions. There currently is a sense among neuroscientists that many research obstacles will be surmountable through biotechnology research methods. Applications of biotechnology to neuroscience research are therefore increasing rapidly.

ONGOING PROGRAMS AND NEW INITIATIVES

Biotechnology has provided a most important stimulus and tool for research in neurogenetics. Efforts to identify genes or groups of genes which control or influence the transmission in families of mental illnesses, alcoholism, or vulnerability to drug abuse are currently in progress and will increase in the future. Other molecular- and animal-level biotechnology research includes identification and cloning of genes for specific ADM disorders and understanding the heritability and expression of these genes; studies on the contributions of specific genes to neural function, morbidity, and mortality in order to elucidate fundamental neurobiological mechanisms; and development of potential gene therapies.

A technique which is proving particularly valuable in neurogenetics is the construction of transgenic animal models. Once a gene of interest has been cloned, it can be inserted into the mouse genome,



with or without modification, and studied under controlled conditions. Neurogenetic research is providing exciting leads to understanding the biological bases of addictions and serious mental disorders, as well as the influences of behavior and psychosocial factors on gene expression.

CENTERS FOR DISEASE CONTROL

AGENCY OVERVIEW

The CDC leads the efforts to prevent unnecessary infectious disease morbidity and mortality through applied research in vaccine development and evaluation, diagnostics development, and etiologic agent characterization. CDC utilizes advances in molecular biology and genetic engineering to develop and monitor safe, efficacious vaccines and sensitive specific assays for the early diagnosis and typing of infectious agents. Vaccine development includes genetic analysis of candidate vaccine strains at the molecular level, epitope mapping, three-dimensional analysis of potential immunogens, vaccine-challenge studies in experimental animals, and post-marketing evaluation in field situations.

ONGOING PROGRAMS AND INITIATIVES

Vaccine Biotechnology

Advances in molecular biology now permit the development of vaccines by recombinant DNA technology, offering promise for control of numerous infectious diseases and a substantial impact on the world's public health problems. Vaccine development at CDC has targeted diseases where current vaccines have proven ineffective or where CDC's biocontainment facilities provide a unique environment for scientists to work safely with hazardous microorganisms. Diseases include Lassa fever, Ebola, Japanese encephalitis, Venezuelan equine encephalitis, *Haemophilus influenzae* Type b dengue, pneumococcal disease, gonorrhea, malaria, and measles.

Diagnostic Biotechnology

CDC's extensive collection of data and specimens, its diagnostic systems, resources, and expertise give it outstanding capabilities in developing diagnostic reagents and techniques and in applying these techniques worldwide. New, precise assays are constantly being developed, and evaluation and adaptation of these techniques in field situations permit their widespread use in promoting public health and providing impetus for further research.

BIOSAFETY LEVEL IV FACILITY

CDC's new 95,000 square-foot, 6-story high-containment laboratory is one of only two facilities in the United States that allow work with hazardous microorganisms. Current work in the facility includes molecular characterization of viruses and vaccine development.

BIOTECHNOLOGY CORE FACILITY

CDC's new Biotechnology Core Facility consolidates highly specialized equipment and professional staff for molecular biologic, analytic, and synthetic technology. Work includes oligonucleotide synthesis, protein analysis, and peptide synthesis and analysis. The facility supports CDC's biotechnologic programs and its contributions to worldwide databases.

NRC Postdoctoral Fellowship Program

CDC, through the National Research Council, makes awards to outstanding postdoctoral and senior scientists for tenure as guest researchers. The outstanding contributions to biotechnology that are realized through this program, as well as the benefits to both CDC staff and researchers, are immeasurable. Currently, seven to ten fellowships are awarded each year.



Biotechnology Repositories and Databases

CDC, in its 25 World Health Organization Collaborating Centers for Reference and Research on infectious diseases, probably has the largest and most diverse collection of microorganisms in the world. Repositories of epidemic and endemic strains and databases that describe these strains are essential to ongoing and future research.

FOOD AND DRUG ADMINISTRATION

AGENCY OVERVIEW

The FDA is a scientific regulatory agency responsible for ensuring that drugs, biological products, medical devices, and diagnostic products are safe and effective; food is safe and wholesome; cosmetics are safe; the use of radiological products does not result in unnecessary exposure to radiation; and all of these products are honestly labeled and that prescription drugs are honestly advertised.

FDA reviews new products before they enter the marketplace, inspects manufacturing facilities, and takes corrective action to remove products from commerce when they are unsafe or ineffective. To accomplish these activities, FDA must maintain up-to-date expertise in many scientific areas. For example, FDA's research must develop rapid, accurate, sensitive, and reproducible methods that can be applied in response to public health emergencies such as microbial contamination of foods or contaminants in drugs.

The new biotechnology has led to the development of many products to improve the health of the American public. More than 630 FDA-approved biotechnology diagnostic devices, as well as a number of significant biotechnology-derived drugs, vaccines, and food ingredients, are already on the market, and over 800 clinical trials of new biotechnology products are in progress (figure 1). In the next century, biotechnology will exert a stronger influence

than ever on the direction and level of product development in FDA-regulated industries.

For many FDA research programs, the personnel responsible for laboratory research also perform evaluations of applications to market products. Consequently, the level of resources available for the research function directly affects the Agency's product review activities. The pharmaceutical, device, and food products of the new biotechnology are rapidly filling the review pipeline at the FDA. In its role as product reviewer, the FDA functions as the "gatekeeper" for the entry of important products into the marketplace. To sustain the commercialization of innovative products emerging from biotechnology research and development, the FDA must have the necessary science and research base to evaluate the safety, efficacy, and quality of these products.

ONGOING PROGRAMS AND AREAS OF EMPHASIS

The Food and Drug Administration will enhance its research capability in biotechnology and the associated enabling technologies in order to address the safety and efficacy of existing and emerging products and to provide the information needed for science-based regulatory decision-making regarding both premarket approval and postmarket surveillance.

Biotechnology research at the FDA focuses on the Agency's regulatory responsibilities in five broad areas: therapeutics, vaccines, diagnostics, devices, and food-borne contaminants and toxins.

- **Therapeutics** — The impact of biotechnology on therapeutic product development has demanded the establishment of sound scientific programs that address a multitude of novel and considerably complex issues, including the fundamentals of molecular biology, toxicology, structure-function relationships, standardization, and analytical methodology. Studies are being performed to understand the mecha-



FIGURE 1
Biotechnology products approved by the FDA.

BIOTECHNOLOGY PRODUCTS APPROVED BY FDA					
DRUGS AND VACCINES					
Product Name	Number	Indication(s)			
Human insulin	1	Diabetes			
Human growth hormone (HGH)	2	HGH deficiency in children			
Interferon alfa*	3	Hairy cell leukemia; genital warts; AIDS-related Kaposi's sarcoma; non-A, non-B chronic hepatitis			
Interferon gamma	1	Chronic granulomatous disease			
Tissue plasminogen activator (TPA)	1	Acute myocardial infarction; acute pulmonary embolism			
Erythropoietin (EPO)	1	Anemia of chronic renal failure and of AZT-related HIV-infected patients			
G-colony stimulating factor	1	Chemotherapy-induced neutropenia in non-myeloid malignancy			
GM-colony stimulating factor	1	Autologous bone marrow transplantation			
Muromonab-CD3	1	Reversal of acute kidney transplant rejection			
Hepatitis B vaccine	2	Hepatitis B			
IN VITRO DIAGNOSTICS					
Product Type	Number	Indication(s)			
		Infectious Disease Bacterial, Viral, Fungal	Tumor-Marker	Analyte & Drug Monitoring	Blood Screening
Monoclonal antibody	571	127	2	433	9
DNA probe	53	42		11	
Recombinant DNA	13	11	1	1**	
FOOD INGREDIENTS					
Product Name	Number	Use			
Chymosin	1	Cheese production			

*indications vary by company

**Gene rearrangement



nisms of action of products for FDA's review of safety and efficacy considerations and in the development of laboratory assays which are used in control testing of these products.

- **Vaccines** — Biotechnology methodologies allow for the development of vaccines that were not previously feasible or which may be safer or more effective than existing vaccines. FDA research programs focus upon evaluating the safety, purity, potency, and efficacy of vaccines, the development of methods for control testing and evaluating the immune response, as well as identifying antigens which may lead to new vaccine development. The Children's Vaccine Initiative, the aim of which is to develop a stable, oral, single-dose multicomponent vaccine that will produce life-long immunity when administered at birth is an example of an important disease-prevention program.
- **Devices** — Biotechnology has had a significant impact on medical device development, resulting in a variety of products such as biomaterial-based and biosensor products, as well as drug delivery and extracorporeal perfusion devices. Existing and new biomaterials are being increasingly incorporated into medical devices such as implants, prostheses, and encapsulated cellular transplants. FDA research programs focus upon the development of *in vitro* methodology, which includes computer modeling techniques, for assessment of cellular and molecular mechanisms of biomedical materials degradation and performance and of host system-device interactions.
- **Diagnostics** — Biotechnology has provided significant improvement in the sensitivity, specificity and reproducibility of diagnostic tests. Research has concentrated in several areas including blood donor screening tests, drug monitoring tests, detection of infectious agents, evaluation of markers for cancer and other diseases and the use of monoclonal antibodies for *in vivo* diagnostic imaging.



Computer-assisted analysis of monoclonal antibody-directed immunoscintigraphy by FDA scientists. Image enhancement enables clear and unambiguous localization of an adenocarcinoma in the left posterior ankle. Computer-assisted review helps to expedite FDA regulatory approval of novel products such as these.

- **Food-borne Contaminants and Toxins** — FDA biotechnology research has concentrated on the development of rapid, sensitive, and accurate methods to detect food-borne contaminants and toxins. With the use of these detection methods and other biotechnology tools, we have begun to analyze the distribution and movement of food-borne pathogens and the role food-borne pathogens play in chronic disease processes. At the new National Center for Food Safety and Technology—a unique consortium of government, industry, and academia—programs for biosensor development and the assessment of new food processing and packaging systems are under way.



NATIONAL INSTITUTES OF HEALTH

AGENCY OVERVIEW

From inauspicious beginnings as a one-room Laboratory of Hygiene in 1887, the National Institutes of Health (NIH) have grown into one of the foremost health research centers in the world and serves as the focal point for biomedical research. The primary mission of the NIH is to discover new knowledge that can be translated into better health for all Americans. To achieve this goal, NIH supports research of non-Federal scientists in universities, medical schools, hospitals, and research institutions throughout the U.S. and abroad; conducts research in its own laboratories; supports the training of research investigators; and supports biomedical communication.

NIH has played the dominant role in the evolution of modern biotechnology primarily through support of basic research which has been and remains the underpinning of biotechnology's applications. The first cloning of a gene in 1973, the development of DNA sequencing, and the experiments in recombinant DNA genetics were all supported by NIH. In recent years, NIH has supported the commercial research which led to the development of pulsed field gel electrophoresis for separating large DNA fragments and of high efficiency expression vectors for producing necessary quantities of the desired proteins. These technologies have found immediate applications.

Commercial biotechnology is characterized by its close linkage to the research base since progress in biotechnology is strongly dependent on the flow of new ideas. NIH support for research has been, and continues to be focussed on the fundamental underlying disciplines of genetics, structural biology, chemistry, pharmacology, and immunology. Some examples of particular commercial importance are analysis of chromosomal organization and function, instrument development, production of transgenic animals, development and

application of monoclonal antibodies, targeted drug design, immunobiology and vaccine development, gene therapy, and DNA technologies that involve fundamental processes for separating, cloning, and manipulating DNA.

ONGOING PROGRAMS AND NEW INITIATIVES

New Technology for DNA Manipulation

Much of biological science is becoming based upon DNA analysis and molecular genetics. Understanding of many diseases, ranging from cancer to diabetes to psychiatric illnesses, is being pursued by isolating the genes involved in the underlying biological function. The availability of relatively easy, reliable methods for handling DNA and mapping genes has been the technological base for this fundamental new approach to biomedical research.

Developing new technology for handling DNA is of particular importance. Better methods are needed for the biochemical and physical manipulation of DNA, such as isolating and characterizing individual chromosomes and large chromosome fragments, cutting DNA at rare and/or pre-determined locations, cloning very large fragments, and cloning important genes. Improved capabilities for DNA manipulation will increase the rate and decrease the costs required for construction of genetic maps. Development of improved technologies for handling large DNA fragments is essential to continued progress in this field.

Development of Novel Computing Approaches

Molecular genetics and structural biology are rapidly becoming data-bound disciplines in which the ability to produce data has overwhelmed the facilities for their analysis. For these data to be useful, powerful analytical techniques must be developed. As the wealth of genome data increases, the quantitative problem of deducing knowledge from the data will increase. Generation of high-resolution genetic and



physical maps requires more efficient analytical and data management systems. Other areas such as macromolecular structure and dynamics and the rational design of drugs will depend upon computational tools.



Computer analysis of DNA sequence data in an NIH laboratory.

Transgenic Animal Models

There are numerous important applications of transgenic technology and this approach has broad utility for solving a variety of experimental problems. Transgenic technology can be used for the study of carcinogenesis, developmental biology, and for the generation of model systems for environmental monitoring.

One of the major barriers to the development of new strategies for the treatment of AIDS has been the absence of suitable animal models. Transgenic mice have recently been developed in which non-replicating HIV-1 genes have been introduced. It has been established that viral gene products, in the absence of replicating virus, appear to be capable of causing several complications associated with the AIDS syndrome. In addition, these models can be used to test gene therapies directed at specific viral gene products.

In searching for systems capable of large-scale protein production, the mammary gland has been evaluated as a "bioreactor," and is seen to present a number of advantages. During lactation, the mammary

gland synthesizes large amounts of a limited range of proteins. Because the proteins are then secreted into milk, they can be harvested easily without harm to the host and without elaborate separation techniques. By targeting the expression of pharmaceutically active proteins to the mammary gland in transgenic animals, it may be possible to produce large quantities of desired proteins in milk, without secondary effects on the other tissues of the animal.

Therapy

Under the broad rubric of therapy there are a number of biotechnology-related approaches which have the potential to enhance patient treatment, revolutionize drug design and drug delivery, and improve approaches to disease related problems. Representative examples are presented here.

Gene Therapy

Insertion of genes into human cells to direct the expression of genes not usually expressed by the recipient cells is a powerful technique that may allow the correction of inherited genetic defects. Genetic alteration of certain cells has the potential to treat cancer by enhancing their capability to kill malignant cells or by enhancing the ability of normal cells to resist the effects of high-dose chemotherapy.

While gene therapy has already been used for a certain type of immunodeficiency disease, there are a number of conditions for which this mode of treatment may soon be possible. Familial hypercholesterolemia, which is caused by the absence of a receptor gene, causes high levels of blood cholesterol that can lead to heart attack by age five. It is anticipated that gene therapy for this disease will be initiated in 1992. The cloning of the gene for cystic fibrosis and its successful expression in a rat model system were significant steps toward definitive treatment of the most common lethal genetic disease in Caucasians in the U.S.



The current inability to insert new genes into bone marrow stem cells for persistent expression constitutes a significant barrier to gene therapy for immune-related diseases. There is a need for improved methods of stem cell purification, routine isolation of highly purified populations, and identification of factors regulating growth of stem cells. There is also a need to develop delivery systems for gene therapy targeted to cells other than blood cells. This work must proceed before gene therapy can assume a role as a widely applicable form of disease treatment.

Novel Delivery Systems

The lack of understanding of the pharmaceutical properties of large biomolecules, such as proteins, polypeptides, and oligonucleotides, is a major roadblock to product development for pharmaceutical industries. For example, the impressive *in vitro* promise of bioactive peptides and proteins is rarely applied to the whole organism. To achieve a therapeutic effect, drugs must reach the site of action in sufficient quantity, but little is known about how this happens for large biomolecules. Cellular processing of administered macromolecular biomolecules is not fully understood and such issues as stability of the molecule, clearance from the body, and delivery technologies require basic research. Research in this area needs to address: 1) the pharmacokinetics of large biomolecules; 2) the disposition and metabolism of those molecules in the whole organism; 3) the mechanisms by which the liver clears the molecules; 4) ways to engineer proteins and peptides to increase their therapeutic half-lives in the body; 5) ways to modify smaller molecules to eliminate undesirable effects while retaining desirable ones; 6) delivery systems that simulate endogenous secretion, and 7) the design of biosensors and biomaterials that can be incorporated into drug delivery systems.

Several novel drug delivery systems have been developed and some are very promising. Various types of liposomes or fat-containing bodies have been designed for carrying drugs. Biocompatible polymers

that incorporate a drug as an integral part of the matrix and release it at a constant rate, or one that is predefined and variable, are now available. Transdermal patches, attached to the skin, are increasingly common as a means of administering many drugs. The incorporation of magnetic beads in a polymer matrix to enable the release of a drug in response to a predetermined external magnetic signal has been tested. Photodynamic therapy, using a specific wavelength of light to activate a therapeutic molecule, is being tried in patients with skin disease and cancer. However, none of these new methodologies has yet been tried using a protein or a large biomolecule as the drug. While some existing methods may be adaptable, new methods must also be devised.

Biohybrid Devices

The use of biohybrid devices containing genetically modified cells is another innovative approach to therapy. For this technology to be successful, it will be necessary to select for cell lines that can survive for long periods of time when encapsulated within membrane-delimited compartments. Such compartments must be in the form of arrays of thin tubes or surfaces to permit vascularization and oxygenation of confined cells. These membranes must permit nutrients to reach the cells while being sufficiently permeable to allow release of protein products. The transplanted cells must be protected from the host immune system while ensuring that any cells which might escape confinement will not cause tumors. Recent preliminary results with an animal model suggest that diabetes can be effectively treated with a biohybrid device containing insulin-secreting cells.

Vaccines

The new techniques of biotechnology are being used in the identification and development of new and improved vaccines that are as safe or safer than those currently used. Many currently used vaccines are produced by growing the bacteria or virus, purifying



it, and inactivating it. These vaccines contain many contaminating materials that are not necessary to elicit a fully protective immune response.

There has been an explosion of new information on the antigenic determinants of infectious agents. Using this information it has been possible to clone and express these antigens in amounts that were previously not possible. This has made it possible to purify these antigens and to remove possibly toxic substances. In addition, it has been possible to enhance the immunogenicity of many important antigens, particularly polysaccharides, by generating protein carrier protein-polysaccharide conjugates (glycoconjugate) vaccines. This technology has made it possible to develop a vaccine to prevent *Haemophilus influenzae* type B meningitis in infants.

Other new types of vaccines involve the synthesis of synthetic lipopeptides, the synthesis of fusion proteins, or the synthesis of immunologically potent virus-like particles. Further, the introduction of foreign genetic information into selected viruses provides a means for constructing vaccines active against multiple diseases.

SUMMARY

Advances in biotechnology will continue to depend on support of basic research, but recent developments have emphasized that there is a need to stimulate growth of interdisciplinary research areas. Although it is difficult to make precise predictions about directions in research, it is clear that future results of biotechnology research will continue to provide substantive benefits to the health and economy of this country.



CLINICAL HIGHLIGHTS

“On September 14, 1990, at 12:52 p.m., a four-year-old girl with adenosine deaminase (ADA) deficiency received an infusion of autologous T cells into which a normal ADA gene had been inserted. The procedure took place in the Pediatric Intensive Care Unit of the Clinical Center of the National Institutes of Health; she received a billion cells; the infusion took 28 minutes; the entire undertaking was clinically uneventful.

“And so began human gene therapy.

“The event itself- the intravenous infusion of blood cells- was routine by hospital standards. So routine, in fact, that the child, who has experienced many needles in her short life and expected something special to happen this time, just played in her bed throughout the infusion. When it was over, she was still waiting for something out of the ordinary to occur.

“With the initiation of the ADA protocol, our society is now beginning to adjust to the new reality of genetic engineering. Although it will be a number of years before gene therapy will have any significant impact on the lives of most people, the technique does have the potential for accomplishing immense good by reducing the suffering and death caused by disease. We can look forward to the time when, with proper safeguards imposed by society, this important new therapeutic procedure becomes widely available.”

W. French Anderson, Human Gene Therapy, 1: 371-372, 1990



AGENCY OVERVIEW

As the nation's principal conservation agency, the Department of the Interior has responsibility for most of our nationally owned public lands and natural resources. This includes fostering the wisest use of our land and water resources, protecting our fish and wildlife, preserving the environmental and cultural values of our national parks and historical places, and providing for the enjoyment of life through outdoor recreation. The component Bureaus of the Department of the Interior use biotechnology in conducting research in their areas of responsibility; this requires research and development of specific tools or applications.

ONGOING PROGRAMS

U.S. Fish and Wildlife Service (FWS)

Fishery Research. The FWS supports research to develop methods for breeding, growth promotion, and hybridization. Growth enhancement has been achieved in higher animals in a variety of ways and positive results have also been shown in fish by administering growth hormones, by creating unisex populations where the faster growing sex is produced, and by producing species hybrids and triploids (animals with an extra set of chromosomes). Increased egg production has also been achieved by treating genetic males with estrogen to produce all female populations.

Efforts to detect and control fish diseases are vital to maintaining healthy fish under culture conditions. Biotechnology offers detection methods of greater specificity and sensitivity than previously available techniques. Examples include the use of monoclonal antibodies and DNA probes to detect fish pathogens. Particularly important to the detection of low levels of infection is the use of the polymerase chain reaction to amplify small amounts of pathogen DNA.

The FWS also supports studies on immunostimulants, compounds which, in small doses, stimulate both specific and nonspecific immune responses in fish. Stimulants have application for mitigation of stress (prior to handling fish) and enhancing efficacy of immunization. Research is also conducted on immunotoxins as potential measures and an early warning technique for exposure to aquatic contaminants.

As in higher animals, immunization of fish and birds to prevent disease outbreaks is preferable to treatment with an antimicrobial agent after the disease is manifest. Stimulation of antibodies in birds against the cilia of ciliate parasites is a unique technique being examined.

Contaminants Research. In both the terrestrial and aquatic environment it is important to recognize subtle effects of contaminants. With animals, these effects can be measured using changes in the immune response, shifts in enzyme activities, and presence of specific antibodies. Chemical assays for contaminants can be very complicated, time consuming, and expensive, and they cannot generally be conducted in the field. Development of monoclonal antibody methods specific for particular contaminants would be a great aid in environmental enhancement. Combined with cell culture techniques, the potential effects of a contaminant would be more easily and quickly determined.

Use of an artificial membrane which acts like a semipermeable cell membrane will greatly enhance the determination of potentially toxic compounds in an environmental situation. Such techniques are selective for compounds which can enter animal cells and are less complicated than chemical analyses.

Wildlife And Endangered Species Research. Development of enzyme-linked methods for identification of migratory waterfowl diseases are currently aimed at botulism in birds. Development of mutation and subcellular techniques for vaccine preparation avoids the objection to use of live mutant bacte-



ria which might regain their virulence in the environment. Development of manipulation methods to increase reproductive potential, is focusing on cryopreservation of avian blastodermal cells. Finally, molecular and immunological methods are being developed to address avian tuberculosis in endangered whooping cranes.

National Park Service (NPS)

Tissue culture responses to the toxin produced by the Dutch Elm Disease organism are being evaluated. The method will be used to screen the American elm for resistant individuals.

Bureau of Mines (BOM)

Some metals can be removed from ore by biological leaching. The biological systems involved can be improved and new ones developed through understanding of complex biological processes. Proper use of naturally occurring organisms and genetic engineering of organisms designed for specific uses will provide the basis for these improvements. Higher plants may also prove useful in the extraction of metals from low-grade ores.

Mining waste is a very significant problem which may be mitigated by biological detoxification. Microbial reduction of metals and sulfates, and neutralization of acid, as well as other detoxification systems, are being evaluated.

U.S. Geological Survey (USGS)

A variety of USGS research projects are investigating the biological and microbiological processes that affect solute composition and solute transport in surface and subsurface waters. Microbial processing of hazardous substances, including selenium, organic compounds, and iron, are being studied. Anaerobic microorganisms are receiving attention for removal of uranium. Genetically modified organisms are being investigated for control of groundwater contamination. Over 20 research grants are funded in the areas of biotransformation, biodegradation, biomonitoring, and bioremediation of contaminants and wastes.



AGENCY OVERVIEW

The Department of Justice (DOJ) administers a small but significant Biotechnology Research Program conducted by the research staff of the FBI Laboratory's Forensic Science Research and Training Center. The program is divided into two research initiatives: Forensic DNA Analysis for Identity Testing and the Development of a Combined DNA Index System (CODIS).

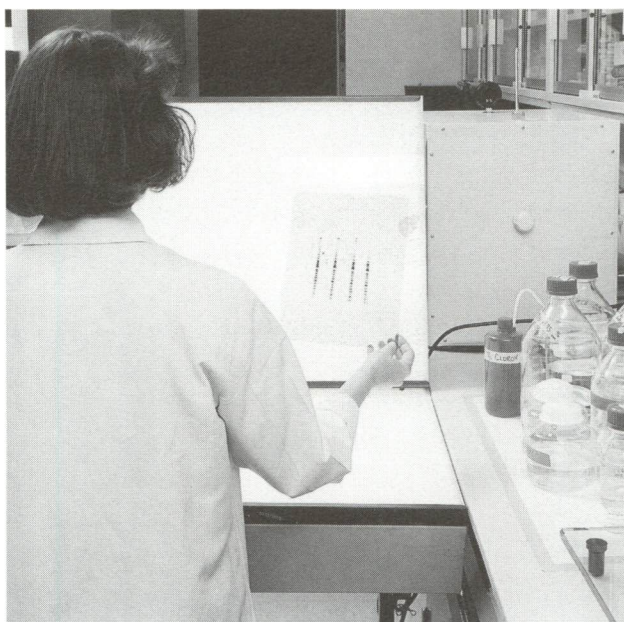
The mission of the DOJ's Biotechnology Research Program is to develop reliable and valid methods for conducting DNA profiling of biological evidentiary materials obtained from scenes of violent crimes for the purpose of identifying the source (victim/suspect) of the materials and to provide an automated mechanism for the reliable exchange of DNA profiling data within the nation's law enforcement community. This mission fits nicely into the overall mission of the DOJ, and more specifically the FBI, whose mission it is to investigate violations of Federal criminal law and to provide forensic technical assistance in investigations of violent crimes for other Federal, state, and local law enforcement agencies.

ONGOING PROGRAMS

DNA profiling may be the most significant breakthrough in forensic science since the development of fingerprinting. The FBI is working to enhance DNA profiling techniques and to establish a National DNA Index. This will allow crime laboratories to exchange DNA profiles for known violent criminals, providing a valuable new weapon for both the investigator and prosecutor.

Forensic DNA Analysis for Identity Testing.

In late 1985, English and American scientists, working independently, reported that specific, highly variable regions of human DNA could be used as a personal identifier. These scientists proposed that DNA extracted from blood or semen stains found at the

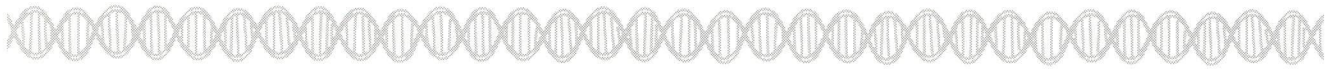


An analyst in the FBI Laboratory reviews a DNA profiling result.

scenes of violent crimes would yield DNA profiles that could uniquely identify the source of the stain.

Several methods of building DNA profiles from DNA extracted from body fluid stains have been investigated. One method is referred to as the restriction fragment length polymorphism (RFLP) method of DNA analysis. The DNA indices produced by these analyses provide the potential for building statistical and investigative DNA profile databases which can assist law enforcement in identifying individuals who commit violent crimes. The RFLP procedure has become the standard protocol for forensic DNA typing in most laboratories.

RFLP analysis has certain limitations. Some evidentiary samples do not contain enough DNA for RFLP analysis. In addition, the RFLP procedure can take 6 - 8 weeks to complete. Accordingly, the research staff of the FBI Laboratory Division have undertaken research to develop alternative methods of DNA analysis. The use of the polymerase chain reaction (PCR) allows for the amplification of specific fragments of DNA and allows a scientist to obtain



large amounts of DNA from a very small sample in a short period of time. A number of DNA loci which are variable among individuals are being evaluated for suitability for PCR amplification and typing. The PCR-based DNA analysis methods can be run in one or two days and may prove to be a powerful alternative to RFLP DNA analysis.

Combined DNA Index System (CODIS).

The FBI Laboratory is developing CODIS to support law enforcement operations only, and the database system will initially include one statistical and one investigative support database. The investigative support database would include open case, convicted violent offender and missing person/unidentified body DNA profiles. Only information relevant to law enforcement requirements will be maintained in the National DNA Database. The database will be limited to profiles of persons convicted of violent crimes or those involved in unsolved cases. No names of individuals or other identifying or characterizing data will be stored with the DNA profiles.

The statistical database would include DNA profiles produced from the examination of DNA from randomly selected unrelated individuals from a minimum of five populations, e.g., Blacks, Caucasians, Orientals, Hispanics and American Indians, and yet to be deter-

mined subpopulations. This information would be used to establish allele frequencies for the DNA probes being used by forensic scientists.

The open case part of the CODIS investigative database would contain DNA profiles obtained from body fluid stains recovered from violent crime cases having no suspects. These indices would allow for the grouping of serial rape cases based on DNA profiles and the tracking of serial rapists.

The convicted violent offender part of the investigative database would contain the DNA profiles of individuals who have been convicted of violent offenses. An important example of the benefit of this type of index will occur when DNA profiles obtained from evidence in unknown subject sexual assault cases can be checked against a set of sex offender DNA indices to determine if the offense was committed by a repeat offender.

The missing persons/unidentified bodies part of the database would contain DNA profiles from unidentified bodies, body parts, and bone fragments. DNA profiles from immediate relatives (parents) could be used to reconstruct the DNA profile for a missing person which could be compared with the missing person/unidentified body DNA profile database.



AGENCY OVERVIEW

The Veterans Health Administration of the Department of Veterans Affairs has as its mission the provision of high quality medical care to veteran patients. Each VA medical center has an investigator-initiated research program. The overall program is administered in VA's Central Office by the Associate Chief Medical Director for Research and Development.

BIOTECHNOLOGY RESEARCH MISSION

Current biotechnology research in the VA is disease-oriented and employs techniques such as cell fusion, recombinant DNA/RNA, DNA/gene transfer, and gene therapy. The techniques of biotechnology are employed in numerous investigations conducted in state-of-the-art laboratories across the VA system.

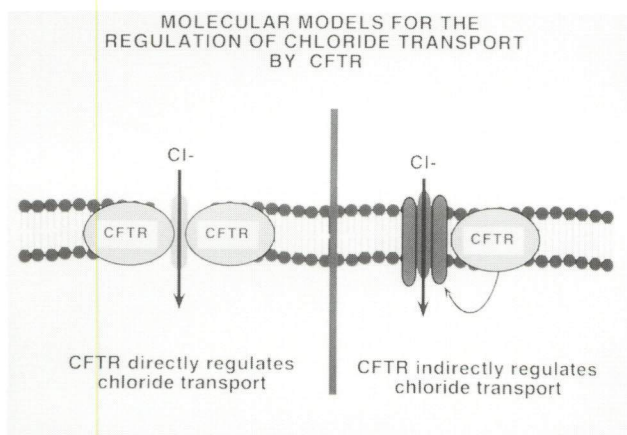
VA sponsored research in biotechnology is divided among well-defined programs. The Merit Review Program, based on peer review, represents 73% of the R&D budget and is the principal mechanism for research funding of VA clinician and non-clinician scientists. The Career Development Program is available to clinicians possessing a doctoral degree

and supports research training of clinicians seeking a career as a clinician-researcher within the VA system. The Cooperative Studies Program allows investigators from two or more VA medical centers to study collectively a selected health-related problem in a uniform manner using a common protocol with central coordination. Special Research Initiatives are developed when a perceived urgency arises or when concentrated efforts promise to hasten a breakthrough in disease treatment and diagnosis; included in this category are specified research centers focusing on AIDS, geriatrics, alcoholism, nerve regeneration, and schizophrenia.

ONGOING PROGRAMS

VA sponsored research programs involving biotechnology cut across all biomedical disciplines. Following are noteworthy examples of biotechnology application in VA sponsored research.

- Retrovirus infection of the central nervous system (e.g., HTLV I as an etiological agent) is being investigated in animal models. The goals are to determine mechanisms of neurologic disease induction and to develop novel treatment schemes.
- The growth of human tumors is being analyzed by the regulation of expression of specific growth factors influencing tumorigenesis. The objective is to correlate growth factor expression, vis-a-vis oncogenes, with clinical prognosis in cancer patients.
- Research on Graves disease is utilizing biotechnology to study the receptors associated with this autoimmune disorder. This research is anticipated to provide insight to the development of treatments against Graves disease and perhaps additional autoimmune disorders.



DVA scientists apply biotechnology to develop disease models that describe potential mechanisms of action. These two models illustrate how the cystic fibrosis gene product, CFTR, might affect membrane transport of chloride ions.



- Innovative instrumentation such as digitally processed, electrocardiographic wall motion analysis, is being assessed for clinical application to predict heart attack initiated by non-cardiac surgery. The goal is to reduce the incidence of heart attack in patients who undergo non-cardiac surgery and possess coronary disease.

AGENCY FOR INTERNATIONAL DEVELOPMENT



AGENCY OVERVIEW

The Agency for International Development (A.I.D.) is the foreign assistance arm of the U.S. Government. Technology development and transfer, including biotechnology, is one of the basic components in the Agency's strategy to achieve its goals.

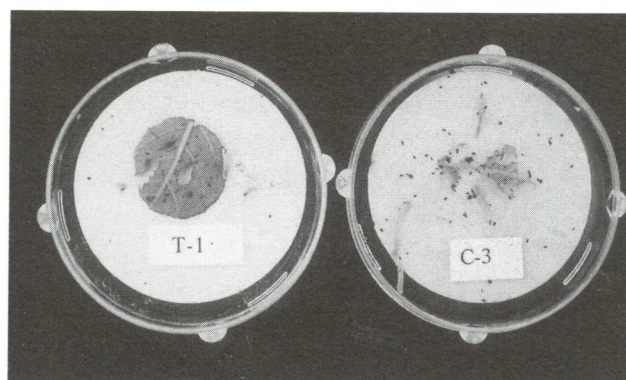
In accordance with its mission, research supported by A.I.D. is clearly directed to the development of specific products or systems that will be useful in improving human health conditions, enhancing agricultural efficiency and environmental compatibility, and expanding rural development in the developing world. Projects are supported both in the United States and in the developing world. In general, the Agency finances research that is expected to produce results in three to five years.

The overall research portfolio comprises projects supported from several offices within the Bureau for Research and Development, including the Office of Agriculture, the Office of Health, and the Office of the Science Advisor. Major expenditures in biotechnology are in the areas of agriculture and health.

INITIATIVES IN AGRICULTURE

The challenges of global agricultural research in the coming decade are to provide for the changing food needs of mankind, to promote greater efficiency and productivity in resource use, and to maintain environmental integrity. Two strategic thrusts follow from these goals. First is the need to build institutional capabilities to better manage the agricultural resource base for agricultural development. Second is support for research and development activities providing technological innovations for maintaining and enhancing productivity and agricultural performance in global markets.

A.I.D. is funding biotechnological research that will help identify and classify new strains of crops and livestock that can be grown in the harsh climates of



Research on agricultural for developing countries takes advantage of biotechnology. T-1 is the leaf of a potato plant engineered to be resistant to tobacco hornworm. C-3 is the leaf of a control potato plant. Both have been exposed to the feeding of tobacco hornworm larvae for 24 hours.

many developing countries. At the opposite end of production, A.I.D. also assists in providing support so that harvest storage methods can be developed that use more sensitive biotechnology screens for spoilage prevention and detection.

Biotechnological methods are also being brought to bear in A.I.D.-funded livestock production projects, and in aquaculture improvement efforts. Similarly, under A.I.D. sponsorship, developing country biotechnologists are enhancing conversion of agricultural wastes to useful materials. For example, a project in the Philippines attempts to convert cellulosic biomass into ethanol using recombinant microbes, while microbial fusion methods are used in Thailand to hasten fermentation of molasses mash.

Institutional areas are also in need of support, especially those relating to biosafety, protection of intellectual property rights, and more comprehensive training and networking. Expanding the critical mass of scientists, within the U.S. and abroad, involved in collaborative, product-oriented research is necessary. This will advance new technologies through better global relationships. Resources are needed to develop a better understanding of environmental interaction with the use of genetically modi-



fied plants in tropical agroecosystems. Such research would be of major importance in planning the use of new crop varieties and increasing our understanding of managing genetic resources available for crops through genetic engineering.

INITIATIVES IN HEALTH

In the past decade, there has been tremendous progress in international efforts on behalf of the health of the world's children. In particular, immunization efforts have made great strides. Today more than forty developing countries, with assistance from AID, have attained 80 percent immunization coverage with vaccines against common diseases of childhood.

Even with these efforts, mortality rates from vaccine-preventable and potentially vaccine-preventable diseases are still unacceptably high. Some 14 million children under five still die worldwide, nearly 2 million of them from measles alone. In addition, many diseases of childhood also affect the health of adults in the working-age population. Malaria is an important example, accounting for 1 million child deaths annually in Africa alone, but also reducing the prospects for survival and productivity of adults. For diseases that are not vaccine-preventable, there is an urgent need for better diagnostic tools to guide efforts for prevention and treatment.

Biotechnology offers important opportunities to improve immunization programs so as to reduce the toll of diseases such as pneumonia, measles and other respiratory diseases, cholera and other diarrheal diseases and malaria. In the case of malaria, A.I.D. is supporting investigators during the discovery phase and coordinates closely with the National Institutes of Health. A.I.D.'s plan to participate in the global

Children's Vaccine Initiative is also meant to help realize those opportunities. The goal of a "single-shot children's vaccine" - one that is affordable, heat stable, administered orally at or soon after birth and that would provide broad, long-term protection against a range of childhood diseases - is a distant dream. However, A.I.D. is committed to the development of new and improved vaccine products that require fewer doses, can be given earlier in life, can be combined, are more heat stable, are effective against a broader range of childhood diseases, and are affordable and realistically usable in the developing world.

In its participation in this initiative, A.I.D. is working closely with the Department of Health and Human Services, complementing the basic biotechnology research being carried out at the National Institutes of Allergy and Infectious Disease. Because of its focus on vaccine development, A.I.D. will focus its efforts on downstream, international aspects of the initiative including field testing, product development, and related policy studies and supporting activities.

A.I.D. will also continue its product development work on applied diagnostics directed at the principal causes of childhood mortality in the developing world, principally malaria, diarrhea, and respiratory infections. Early detection of illness is considered a key to correct and effective treatment. A number of projects have as their goal the quick, easy, and accurate diagnosis of tropical diseases. Tests kits suited to the conditions of an African field health station, for example, could provide the health worker with an assured means of diagnosing dengue fever, leprosy, leishmaniasis, schistosomiasis, malaria, or onchocerciasis at early treatable stages.

ENVIRONMENTAL PROTECTION AGENCY

AGENCY OVERVIEW

The United States Environmental Protection Agency (EPA) is charged to protect human health and the environment. It is EPA's responsibility to identify environmental and human health risks of various activities or substances and take actions to reduce or manage these risks. Because identifying harmful substances or activities and solving pollution problems often require investigation and research, EPA maintains an active research program to support these needs.

BIOTECHNOLOGY RESEARCH MISSION

The goals of EPA's biotechnology research are to establish the scientific and technical foundation for the implementation of biological solutions to environmental problems, to accelerate the transfer of biotechnology research discoveries to environmentally safe commercial applications, and to realize the benefits of biotechnology for protecting and restoring the environment.

ONGOING PROGRAMS AND NEW INITIATIVES

Biological approaches to pollutant clean-up operations, waste minimization, and pollution prevention are receiving increased attention as viable environmental technologies. They provide great promise as economically attractive, environmentally safe techniques that will be applied into the next century. The interest is due in part to the incredible advance of biological sciences in the last fifteen years. The EPA will play a significant role in the developmental stages of these technological advances as a regulatory agency sufficiently knowledgeable in the scientific underpinnings to develop new approaches and techniques for pollution remediation, to provide opportunities for the transfer of new technologies, and to provide credible evaluations of products that will ensure their safe application but not unduly burden the biotechnology industry. EPA currently has two major research programs specifically



Test plots at Snug Harbor, Alaska, demonstrating the potential for use of bacteria capable of degrading oil in cleaning up of oil spills.

identified as Biotechnology Risk Assessment and Biosystems (bioremediation).

The Biotechnology Risk Assessment Research Program is structured to provide the necessary scientific tools for identifying risks and assessing the safety of biotechnology product development, distribution, and use. These tools will allow sound evaluations to ensure appropriate oversight without interfering with commerce. The program is conveniently divided into environmental exposure, environmental effects, and control strategies.

Environmental Exposure: Microbial, serological, biochemical, physiological, and genetic methods for detection and enumeration are being tested and refined under a variety of laboratory conditions to maximize their sensitivity and specificity for microbes in soil, water, air, sewage, and intestinal tracts. The mechanisms and dynamics of transport within and between various environmental media are being studied. Cellular properties and relevant environmental factors that influence microbial survival and colonization are being identified and described. Analyses of microbial genetic exchange focus on environmental, genetic, organismal, and taxonomic factors which affect gene stability and the rate of genetic exchange.



Environmental Effects: A major objective is to develop conceptual and experimental frameworks that may be used to identify and describe perturbations to natural microbial communities and their predators. A portion of this research uses laboratory animal tests to examine the genetic and molecular bases of infectivity, pathogenicity, and host range of microbial pest control agents.

Control Strategies: Containment and monitoring strategies that may be used for limiting the dispersal and dissemination of microbial products are being evaluated under laboratory and field conditions. Process equipment design, decontamination technology, worker exposure and protection, and loss prevention techniques used in large scale fermentation facilities are being characterized to facilitate product reviews.

The objective of the **Biosystems Technology Development/Oil Spills Research Program** is to develop and demonstrate biological treatment systems and bioremediation technology for oil and other pollutants that have been accidentally or deliberately released into the environment. The Biosystems program has six general components including: 1) the identification, characterization and modeling of biodegradation processes occurring in surface water, sediments, soils, and subsurface materials that may be improved and used in biological degradation systems for contaminants at hazardous waste sites; 2) the development and enhancement for treatment biosystems using traditional and new (molecular biology) approaches; 3) the determination, evaluation, optimization, and demonstration of engineering factors necessary for the application of biological agents for pollutant degradation in reactors or *in situ*; 4) the determination of the environmental fate and potential effects of biological agents used in biotreatment systems and the metabolic products formed as a part of that process; 5) the development of means for mitigating adverse effects from the implementation of biotreatment technology; and 6) the transfer of information on the technology to promote its environmentally safe application.

The biosystems research program has included a variety of biotreatment configurations and field demonstration projects have been incorporated into the program. Under the oil spills program, a concerted effort has been made to test and evaluate biostimulation through nutrient addition and bioaugmentation to contaminated shorelines. This approach has been shown to accelerate the degradation of the easily degradable and acute toxic fractions of crude oils.

In FY 1993, the Agency will expand its current research program to facilitate the development of predictive risk assessment tools that take advantage of recent advances in molecular biology, microbiology, genetics, toxicology, and environmental sciences. A program expansion directed toward fundamental scientific and engineering issues relevant to remediation of complex waste mixtures, *in situ* bioremediation of contaminated sediments, and ground water contaminated with agricultural chemicals is proposed. Additional resources will support the exploration of innovative biotechnology to prevent pollution from industrial manufacturing operations and for the conversion of industrial wastes to useful products.



scientific advances into a form more appropriate for public dissemination.

AGENCY OVERVIEW

The environment of space offers unique opportunities for the scientific community to participate in cutting-edge scientific discoveries. It is the access to the microgravity environment that sets NASA's scientific contributions apart from the Earth-bound science efforts. However, in life sciences and materials sciences research, there is a strong connection between what is being learned both in space and on Earth. Biotechnology research programs at NASA complement comparable efforts being performed by a host of other institutions by offering a look at specific biological phenomena under conditions of microgravity. By eliminating gravity's effects (e.g., convection, sedimentation, and structural deformation forces), one is able to understand the role that gravity plays in the determination of the structure and function of biological systems.

NASA's biotechnology research efforts are located within the Office of Space Science and Applications (OSSA) and the Office of Commercial Programs. Within OSSA, the Life Sciences Division sponsors programs that relate to NASA's efforts to develop a Closed Ecological Life Support System (CELSS) that will be used to enable long-duration human space flight, and the Space Biology Program, a research program directed toward the examination of basic science questions related to cell and developmental biology for both animals and plants. Also within OSSA, the Microgravity Science and Applications Division sponsors a Microgravity Biotechnology Program with the primary research areas being protein crystal growth, separation technologies for biological materials, and cell culture studies.

Within the Office of Commercial Programs, two efforts are being undertaken to enable NASA discoveries to more easily flow into the mainstream of the commercial market. Both the Technology Utilization Program and the Centers for the Commercial Development of Space (CCDS) sponsor projects in NASA's biotechnology programs that transfer the

ONGOING BIOTECHNOLOGY PROGRAMS

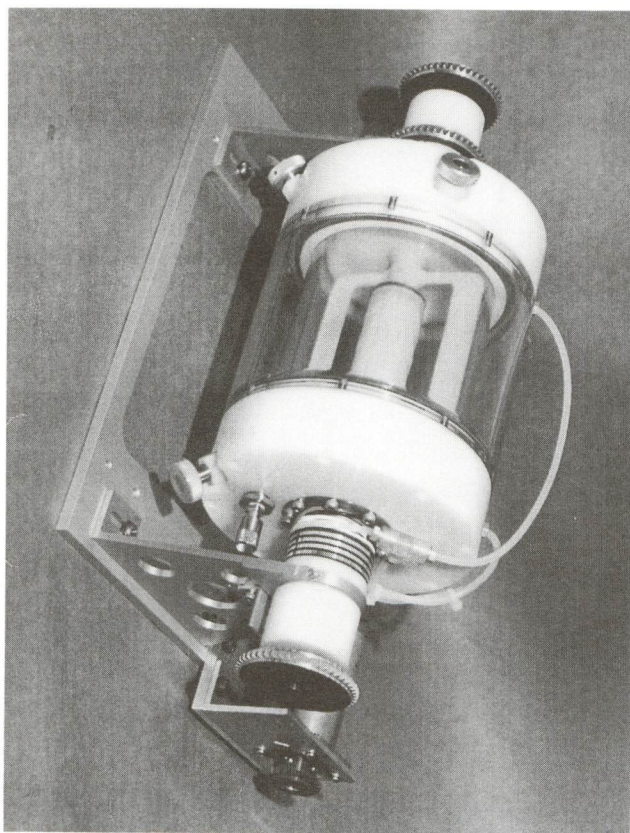
Closed Ecological Life Support System (CELSS) Program

The goal of the CELSS Program is to design, construct, and operate life support systems in space which are independent of major resupply. Food, water, and a breathable atmosphere are three elements fundamental to human survival. A system that regenerates these elements will require scientific research and development in the areas of plant growth, food processing, waste processing, sensing, and control systems.

A successful CELSS will involve the import and careful management of the nutrients, air, water, and energy needed to recreate the cycles of nature in a closed system. Volume, weight, and energy are all at a premium on a closed spacecraft, and the desirability of different food crops is judged partly on the basis of how much edible food can be continually produced in a given volume, and the amount of light, nutrients and growing time required. Although CELSS crops to date have been chosen for their high ratio of edible food to total biomass, researchers continue to explore methods of converting nonedible biomass to food. Research also continues in the areas of food processing, air and water reclamation, and systems controls.

Space Biology Program

The Space Biology Program uses the microgravity environment of space as a unique biotechnology tool to understand basic biological processes and effects of gravity and microgravity on living systems. Gravity, as perhaps the "first" environmental factor, may serve as a model for understanding the perception and transduction into physiological responses of a range of other environmental factors. Improvement



A ground laboratory prototype of a rotating-wall clinostat that suspends mammalian cell cultures in nutrient solutions, allowing them to grow in three dimensions. Tests at NASA Johnson Space Center have shows the ability to cultivate large aggregates of cells and encourage differentiation.

of the characteristics of plants and animals through an understanding of the effects of gravity - and its absence - on cellular, molecular, and genetic processes is an important component of the Space Biology Program.

The five major scientific disciplines involved in this program are cell and developmental biology, plant biology, neuroscience, musculoskeletal systems, and regulatory biology. Research priorities include: identifying how single cells "sense" gravity, including the dissection of both direct and indirect (environmentally mediated) effects; identifying how this information (alterations in gravitational force) is

transduced; identifying how cells respond to both acute and long-term variations in gravitational force; determining any commonality in mechanisms of g-sensing and transduction with perception of other environmental stimuli; determining control mechanisms for production and release of secretory products by cells; understanding how to manipulate cell differentiation and phenotype by environmental manipulation; understanding how molecular arrangement of cell organelles and cell products are and can be manipulated environmentally; and explaining if increased chromosomal disruption can be utilized effectively for biotechnology purposes.

Microgravity Biotechnology Program

The areas of emphasis for the Microgravity Biotechnology Program include macromolecular crystal growth, separations processes related to biological materials, and cell culture. In each of these fields, gravity has an acknowledged or soundly hypothesized role in the performance or production of a process, and space experiments coupled with theoretical research can result in the creation of unique products in space or new insights into biotechnological processes.

An example of the use of space to produce a product is the protein crystal growth project. Protein crystals are highly complex arrays of large molecules held together by very weak forces. Current understanding of the detailed physics underlying the growth of protein crystals is very limited, but the importance of protein crystals for the determination of protein structures through x-ray diffraction analysis drives a strong demand for improved technologies for growing protein crystals. Knowledge of a protein's structure opens the possibility of modifying the function of the protein by introducing compounds with the appropriate molecular characteristics to interact with the protein, and, for example, block access to the protein by other molecules. This strategy is the basis of rational drug design, a concept which has awakened interest in structure determination throughout



the pharmaceutical industry. The simplest aim of protein crystal growth research in NASA is to utilize the space environment to produce crystals for use in research and technology. The broader scientific purpose is to understand the processes that create and order these complicated molecular structures, and to learn to control these processes to grow crystals of previously uncrystallized proteins.



AGENCY OVERVIEW

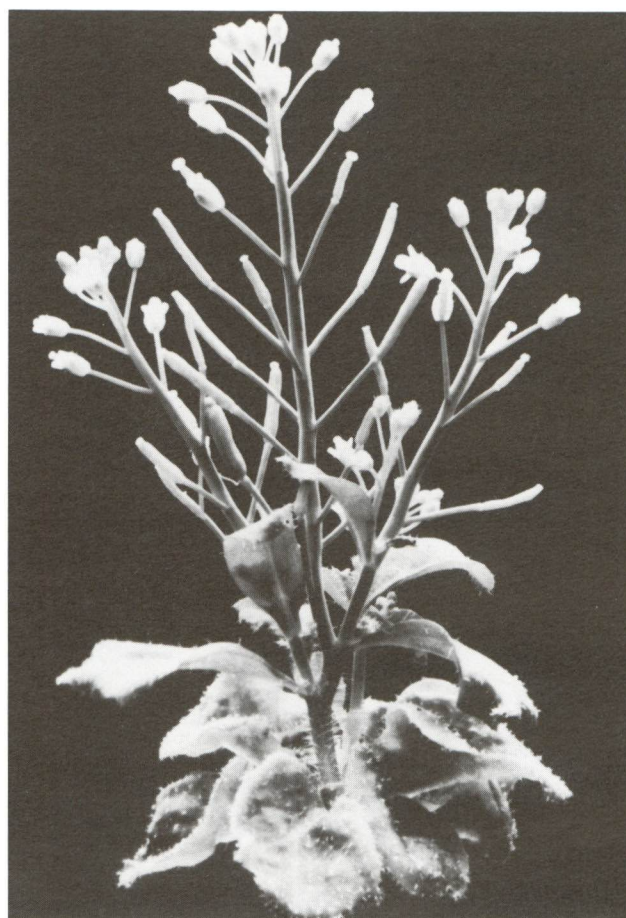
The mission of the National Science Foundation is to foster research and education in all fields of science and engineering, and to promote the interchange of information among scientists and engineers in the United States and internationally. A primary component of its activity is support of basic research in U.S. colleges and universities.

The NSF mandate to ensure a continuing flow of fundamental knowledge without the constraint of a goal-directed mission is unique among government agencies involved in support of science and engineering. Also unique to the NSF is the inclusion within its charge of all disciplines of science and engineering. This provides an environment in which disciplinary boundaries can readily be crossed in pursuit of new opportunities. Biotechnology represents such an opportunity.

The NSF is organized into seven major units called Directorates, all of which are actively involved in the support of research and education in scientific and engineering areas critical to biotechnology. Individual Directorates play specific but complementary roles in the NSF Biotechnology effort.

BIOTECHNOLOGY RESEARCH MISSION OF THE DIRECTORATES

The Directorate for Biological Sciences (BIO), through its disciplinary programs in the biological sciences, supports research on genetics, biochemical, cellular, and physiological traits, and on taxonomic and ecological relationships of a broad range of organisms. This research, which includes studies of macromolecular structure and function, gene transfer, metabolic pathways, cellular processing and secretion of proteins and metabolites, symbioses, and adaptation to environmental extremes, provides the underpinnings for applications related to the environment, bioprocessing and bioconversion, biomolecular materials, and agriculture. Studies of the molecular, physiological, and integrative



Model plant. Because of its relatively simple genome structure, *Arabidopsis thaliana* is being used for genome mapping to enhance fundamental understanding of plant processes. The National Science Foundation is the lead agency in this effort.

properties of neurons and neural networks, in conjunction with behavioral, and cognitive sciences, provide the framework for future applications in bioelectronics and bionetworks. Other, specifically targeted programs support acquisition of instrumentation and instrumentation and technique development as infrastructure for biotechnology research activities.

The Engineering Directorate (ENG) plays an important role in support of biotechnology research in the areas of bioprocessing and applied biotechnology, including research at several Engineering Research Centers. Research directed toward engineering solutions to health-related problems is addressed



in the Bioengineering Program. Research on living tissue development in the context of fundamental process engineering with the goal of producing large amounts of functional tissue for research and applications (Tissue Engineering) is an area of emphasis. The Environmental and Ocean Systems Program supports projects using microorganisms for detoxification of contaminated water sources. Programs in Industrial Science and Technology Innovation support biotechnology research and infrastructure.

The **Directorate for Mathematical and Physical Sciences (MPS)** supports research that provides the chemical and mathematical underpinnings of biotechnology, and that uses the methods of biotechnology in the formulation of new biomolecular materials. The Chemistry Division supports research on topics such as models for enzyme active sites, semi-synthetic enzymes and catalytic antibodies, biomimetic chemistry, bioanalytical chemistry, and theoretical studies of shapes and function of biomolecules. The Division of Materials Research supports studies including electrophoretic phenomena, gels and microemulsions, molecular self-assembly, production of new materials (primarily proteins) by methods of molecular biology, and materials properties of membranes, surfaces, and interfaces. The Division of Mathematical Sciences supports research in applied mathematics, biostatistics, and theoretical and computational biology.

The **Directorate for Computer and Information Science and Engineering (CISE)** supports research in the areas of bioelectronics and bionetworks and computational biology. Support is provided for work in computer algorithms, techniques, and software tools pertinent to biomolecular data modeling and management in high-performance, networked computing environments. Research in informatics and robotics also has important implications for biotechnology.

The **Geosciences Directorate (GEO)**, primarily through its Oceanography Division, supports research

on the biochemistry and physiology of organisms from extreme environments such as hydrothermal vents, studies of chemically mediated interactions between organisms (chemical ecology and natural products chemistry), and identification and characterization of marine algae, bacteria, and viruses.

The **Directorate for Social, Behavioral and Economic Sciences (SBE)** programs in behavioral and cognitive sciences contribute to applications in bioelectronics and bionetworks while programs in Ethics and Values Studies, History of Science, and Social and Economic Sciences support research leading to better understanding of the impact of biotechnology on society. Programs in Science Resources Studies and the Division of International Programs conduct many activities in support of biotechnology research and infrastructure.

The **Directorate for Education and Human Resources** addresses needs for training in science and engineering upon which the future of biotechnology depends.

ONGOING BIOTECHNOLOGY ACTIVITIES AND PROGRAMS

Recognizing its unique position in the U.S. effort in biotechnology, the NSF has monitored its biotechnology spending since 1985, using a set of criteria and subject areas set up within the agency at that time. Data from these prior inventories indicated that a substantial fraction of the research supported by a number of NSF organizational units was viewed as contributing to biotechnology.

To anticipate the accelerating pace of activity in biotechnology, the NSF has, in the past year, established a broadly based, agency-wide Biotechnology Working Group which convened a University-Industry Advisory Panel on Biotechnology Opportunities. The report of that Panel has recently been published as part of a larger document entitled, "Biotechnology Opportunities: The NSF Role."¹ This document



has helped to guide planning for future NSF activities in support of biotechnology.

NSF BIOTECHNOLOGY RESEARCH PROGRAMS

***Biomaintenance
Bioremediation
Waste Treatment and Management
Environmental Diagnostics
Bioprocessing
Tissue Engineering
Bioelectronics and Bionetworks
Neurobiotechnology
Genetics of Economically Important
Traits
Plant and Microbial Metabolism
Pest and Pathogen Control/Protection
Responses to Environmental Signals
Bioenergetics
Biomass Conversion
Cell Regulators and Mediators
Molecular Design and Engineering
Biomolecular Materials
Instrumentation Development
Informatics Research and Development
Biochemical and Biophysical
Techniques
Molecular Genetics Techniques
Cellular Techniques
Biomimetic Chemistry
Mathematical Modeling
Marine Biotechnology
Social Impact Research
Infrastructure programs***

NEW BIOTECHNOLOGY INITIATIVE

A Biotechnology Initiative is proposed beginning in FY 1993. It is focused on five areas of biotechnology in which the NSF has established strengths, which represent growth areas of the future, and which are currently underfunded relative to their promise. These areas are environmental biotechnology, bioprocessing, bioelectronics and bionetworks, agricultural biotechnology, and marine biotechnology.

The approach will be cross-Directorate and interdisciplinary, with an emphasis on fundamental and "proof of concept" research, training, instrumentation, research resources, and university-industry cooperation. A variety of funding modes will be utilized including interdisciplinary groups and centers and individual investigator awards. A very significant component will be small interdisciplinary groups. In supporting biotechnology research, NSF will continue to rely on the scientific and engineering communities to develop specific projects within the five identified areas.

These areas and approaches are consistent with the Strategic Objectives and Implementation Strategies of the Biotechnology Research Initiative.

¹NSF Publication NSF 91-56, April 10, 1991.



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TABLE 1. U.S. Biotechnology Research Initiative - FY 1993
(\$ Million)

Agency	Agricul.	Energy	Environ.	General	Health	Manufac.	Social	Infrastr.	Total
AID	12.7	0	0	0	18.0	0	0	0	30.7
DHHS	30.8	2.3	0.5	1354.7	1502.7	17.7	5.2	211.1	3125.0
NIH	12.4	2.3	0.5	1354.7	1346.6	17.7	5.2	204.5	2943.9
FDA	18.4	0	0	0	17.8	0	0	0	36.2
CDC	0	0	0	0	27.1	0	0	6.6	33.7
ADAMHA	0	0	0	0	111.2	0	0	0	111.2
DOC	3.0	0	0.6	2.4	1.8	3.5	0.1	1.6	13.0
DOD	0	0	11.5	26.5	30.2	18.4	0	0	86.6
DOE	2.1	91.1	18.5	69.5	14.0	13.2	1.9	32.4	242.7
DOI	0	0	4.3	0	0	0.7	0	0	5.0
DOJ	0	0	0	1.4	0	0	0	0.9	2.3
DVA	0	0	0	0	88.4	0	0	0	88.4
EPA	0	0	18.3	0	0	0	0	0	18.3
NASA	4.4	0	0.6	4.9	5.3	3.7	0	25.8	44.7
NSF	35.0	8.8	20.5	35.4	19.5	43.0	1.3	42.0	206.0
USDA	119.5	4.7	8.5	4.9	0.5	23.6	0.7	5.3	167.7
TOTAL	207.5	106.9	83.3	1499.7	1680.4	123.8	9.2	319.6	4030.4



**TABLE 2. U.S. Biotechnology Research Initiative
(\$ Million - % Increase)**

Agency	FY 1991	FY 1992	FY 1993
AID	19.0	21.5 ¹ (13%)	30.7 (43%)
DHHS	2662.7	2963.0 (11%)	3125.0 (5%)
DOC	12.7	13.0 (2%)	13.0 (0%)
DOD	79.6	81.0 (2%)	86.6 (7%)
DOE	152.7	181.9 (19%)	242.7 (33%)
DOI	5.9	5.2 (-12%)	5.0 (-4%)
DOJ	1.8	2.2 (22%)	2.3 (5%)
DVA	80.6	85.6 (6%)	88.4 (3%)
EPA	14.3	15.9 (11%)	18.3 (15%)
NASA	26.5	36.6 (38%)	44.7 (22%)
NSF	162.0	174.0 (7%)	206.0 (18%)
USDA	161.6	179.4 (11%)	167.7 ²
TOTAL	3379.4	3759.3 (11%)	4030.4 (7%)

¹Number is from the FY 1992 Presidential budget; no appropriation for 1992 has yet been passed

²Number does not include possible Congressional actions on facilities and special grants which may increase the final appropriation for FY 1993



TABLE 3. U.S. Biotechnology Research Areas
(\$ Million - % Increase)

	FY 1991	FY 1992	FY 1993
Agriculture	174.2	190.5 (9%)	207.5 (9%)
Energy	65.5	80.4 (23%)	106.9 (33%)
Environment	62.3	68.6 (10%)	83.3 (21%)
General Foundations	1259.5	1417.5 (13%)	1499.7 (6%)
Health	1421.3	1593.8 (12%)	1680.4 (5%)
Manufacturing/Bioprocessing	88.9	98.8 (11%)	123.8 (25%)
Social Impact Research	6.5	9.0 (38%)	9.2 (2%)
Infrastructure			
Research Facility	35.0	37.2 (6%)	30.4 (-18%)
Training/Career Development	139.3	145.0 (4%)	161.4 (11%)
Instrumentation	80.2	66.5 (-17%)	74.0 (11%)
Repositories	16.5	18.0 (9%)	19.1 (6%)
Data Bases	<u>30.2</u>	<u>34.0 (13%)</u>	<u>34.7 (2%)</u>
Subtotal	301.2	300.7	319.6 (6%)
TOTAL	3379.4	3759.3 (11%)	4030.4 (7%)

TABLE 4. Department of Agriculture¹
(\$ Million)

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	106.4	114.5	119.5
Energy	3.6	3.9	4.7
Environment	7.8	8.2	8.5
Manufacturing/BioProcessing	17.6	18.8	23.6
Health	0.5	0.5	0.5
General/Foundations	<u>4.6</u>	<u>4.8</u>	<u>4.9</u>
*Subtotal	140.5	150.7	161.7
Social Impact Research	0.8	0.7	0.7
Infrastructure			
Research Facility	15.1	22.7	0.0
Training/Career Development	1.1	1.1	1.1
Instrumentation	0.0	0.0	0.0
Repositories	0.0	0.0	0.0
Data Bases	<u>4.1</u>	<u>4.2</u>	<u>4.2</u>
*Subtotal	20.3	28.0	5.3
AGENCY TOTAL	161.6	179.4	167.7

¹The USDA budget figures for FY 1993 do not include possible Congressional actions on facilities and special grants which may increase the final appropriation.

TABLE 5. Agricultural Research Service
Department of Agriculture¹
(\$ Million)

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	54.2	56.3	57.2
Energy	0.5	0.6	1.4
Environment	4.2	4.3	4.4
Manufacturing/BioProcessing	14.5	14.8	19.5
Health	0.5	0.5	0.5
General/Foundations	<u>3.4</u>	<u>3.5</u>	<u>3.6</u>
*Subtotal	77.3	80.0	86.6
Social Impact Research	0.0	0.0	0.0
Infrastructure			
Research Facility	0.0	0.0	0.0
Training/Career Development	0.0	0.0	0.0
Instrumentation	0.0	0.0	0.0
Repositories	0.0	0.0	0.0
Data Bases	<u>3.8</u>	<u>3.9</u>	<u>3.9</u>
*Subtotal	3.8	3.9	3.9
AGENCY TOTAL	81.1	83.9	90.5

¹The USDA budget figures for FY 1992 and FY 1993 do not include funds traditionally added by Congress for facilities and special grants.



**TABLE 6. Cooperative State Research Service
Department of Agriculture¹
(\$ Million)**

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	48.4	54.0	54.8
Energy	3.1	3.3	3.3
Environment	3.2	3.4	3.4
Manufacturing/BioProcessing	3.0	3.8	3.8
Health	0.0	0.0	0.0
General/Foundations	<u>1.2</u>	<u>1.3</u>	<u>1.3</u>
*Subtotal	58.9	65.8	66.6
Social Impact Research	0.6	0.5	0.5
Infrastructure			
Research Facility	15.1	22.7	0.0
Training/Career Development	1.1	1.1	1.1
Instrumentation	0.0	0.0	0.0
Repositories	0.0	0.0	0.0
Data Bases	<u>0.3</u>	<u>0.3</u>	<u>0.3</u>
*Subtotal	16.5	24.1	1.4
AGENCY TOTAL	76.0	90.4	68.5

¹The USDA budget figures for and FY 1993 do not include funds traditionally added by Congress for facilities and special grants.

**TABLE 7. Economic Research Service
Department of Agriculture
(\$ Million)**

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	0.0	0.0	0.0
Energy	0.0	0.0	0.0
Environment	0.0	0.0	0.0
Manufacturing/BioProcessing	0.0	0.0	0.0
Health	0.0	0.0	0.0
General/Foundations	<u>0.0</u>	<u>0.0</u>	<u>0.0</u>
*Subtotal	0.0	0.0	0.0
Social Impact Research	0.2	0.2	0.2
Infrastructure			
Research Facility	0.0	0.0	0.0
Training/Career Development	0.0	0.0	0.0
Instrumentation	0.0	0.0	0.0
Repositories	0.0	0.0	0.0
Data Bases	<u>0.0</u>	<u>0.0</u>	<u>0.0</u>
*Subtotal	0.0	0.0	0.0
AGENCY TOTAL	0.2	0.2	0.2

**TABLE 8. Forest Service
Department of Agriculture
(\$ Million)**

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	3.8	4.2	7.5
Energy	0.0	0.0	0.0
Environment	0.4	0.5	0.7
Manufacturing/BioProcessing	0.1	0.2	0.3
Health	0.0	0.0	0.0
General/Foundations	<u>0.0</u>	<u>0.0</u>	<u>0.0</u>
*Subtotal	4.3	4.9	8.5
Social Impact Research	0.0	0.0	0.0
Infrastructure			
Research Facility	0.0	0.0	0.0
Training/Career Development	0.0	0.0	0.0
Instrumentation	0.0	0.0	0.0
Repositories	0.0	0.0	0.0
Data Bases	<u>0.0</u>	<u>0.0</u>	<u>0.0</u>
*Subtotal	0.0	0.0	0.0
AGENCY TOTAL	4.3	4.9	8.5

**TABLE 9. Department of Commerce
(\$ Million)**

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	3.0	3.0	3.0
Energy	0.0	0.0	0.0
Environment	0.9	0.6	0.6
Manufacturing/BioProcessing	3.5	3.5	3.5
Health	1.2	1.8	1.8
General/Foundations	<u>2.4</u>	<u>2.4</u>	<u>2.4</u>
*Subtotal	11.0	11.3	11.3
Social Impact Research	0.1	0.1	0.1
Infrastructure			
Research Facility	1.0	1.0	1.0
Training/Career Development	0.0	0.0	0.0
Instrumentation	0.0	0.0	0.0
Repositories	0.0	0.0	0.0
Data Bases	<u>0.6</u>	<u>0.6</u>	<u>0.6</u>
*Subtotal	1.6	1.6	1.6
AGENCY TOTAL	12.7	13.0	13.0

TABLE 10. National Institute of Standards and Technology
Department of Commerce
(\$ Million)

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	0.0	0.0	0.0
Energy	0.0	0.0	0.0
Environment	0.0	0.0	0.0
Manufacturing/BioProcessing	2.7	2.7	2.7
Health	0.0	0.0	0.0
General/Foundations	<u>2.1</u>	<u>2.1</u>	<u>2.1</u>
*Subtotal	4.8	4.8	4.8
Social Impact Research	0.0	0.0	0.0
Infrastructure			
Research Facility	0.0	0.0	0.0
Training/Career Development	0.0	0.0	0.0
Instrumentation	0.0	0.0	0.0
Repositories	0.0	0.0	0.0
Data Bases	<u>0.6</u>	<u>0.6</u>	<u>0.6</u>
*Subtotal	0.6	0.6	0.6
AGENCY TOTAL	5.4	5.4	5.4

TABLE 11. National Oceanographic and Atmospheric Administration
Department of Commerce
(\$ Million)

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	3.0	3.0	3.0
Energy	0.0	0.0	0.0
Environment	0.9	0.6	0.6
Manufacturing/BioProcessing	0.8	0.8	0.8
Health	1.2	1.8	1.8
General/Foundations	<u>0.3</u>	<u>0.3</u>	<u>0.3</u>
*Subtotal	6.2	6.5	6.5
Social Impact Research	0.1	0.1	0.1
Infrastructure			
Research Facility	1.0	1.0	1.0
Training/Career Development	0.0	0.0	0.0
Instrumentation	0.0	0.0	0.0
Repositories	0.0	0.0	0.0
Data Bases	<u>0.0</u>	<u>0.0</u>	<u>0.0</u>
*Subtotal	1.0	1.0	1.0
AGENCY TOTAL	7.3	7.6	7.6

**TABLE 12. Department of Defense
(\$ Million)**

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	0.0	0.0	0.0
Energy	0.0	0.0	0.0
Environment	9.6	12.3	11.5
Manufacturing/BioProcessing	12.7	17.4	18.4
Health	35.0	26.2	30.2
General/Foundations	<u>22.3</u>	<u>25.1</u>	<u>26.5</u>
*Subtotal	79.6	81.0	86.6
Social Impact Research	0.0	0.0	0.0
Infrastructure			
Research Facility	0.0	0.0	0.0
Training/Career Development	0.0	0.0	0.0
Instrumentation	0.0	0.0	0.0
Repositories	0.0	0.0	0.0
Data Bases	<u>0.0</u>	<u>0.0</u>	<u>0.0</u>
*Subtotal	0.0	1.0	0.0
AGENCY TOTAL	79.6	81.0	86.6

**TABLE 13. Department of Energy
(\$ Million)**

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	1.7	1.8	2.1
Energy	53.8	66.6	91.1
Environment	11.3	12.5	18.5
Manufacturing/BioProcessing	5.3	6.4	13.2
Health	12.3	12.7	14.0
General/Foundations	<u>54.3</u>	<u>63.2</u>	<u>69.5</u>
*Subtotal	138.7	163.2	208.4
Social Impact Research	1.4	1.8	1.9
Infrastructure			
Research Facility	3.1	5.9	20.2
Training/Career Development	2.1	2.2	2.7
Instrumentation	1.9	2.2	2.3
Repositories	2.8	3.0	3.2
Data Bases	<u>2.7</u>	<u>3.6</u>	<u>4.0</u>
*Subtotal	12.6	16.9	32.4
AGENCY TOTAL	152.7	181.9	242.7



**TABLE 14. Department of Health and Human Services
(\$ Million)**

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	25.6	28.9	30.8
Energy	1.9	2.1	2.3
Environment	0.3	0.4	0.5
Manufacturing/BioProcessing	16.7	17.0	17.7
Health	1258.5	1431.7	1502.7
General/Foundations	<u>1143.8</u>	<u>1284.3</u>	<u>1354.7</u>
*Subtotal	2446.8	2764.4	2908.7
Social Impact Research	3.3	5.2	5.2
Infrastructure			
Research Facility	9.0	7.4	9.0
Training/Career Development	122.0	126.4	141.0
Instrumentation	54.6	30.6	31.9
Repositories	10.4	10.5	11.0
Data Bases	<u>16.6</u>	<u>18.5</u>	<u>18.2</u>
*Subtotal	212.6	193.4	211.1
AGENCY TOTAL	2662.7	2963.0	3125.0

**TABLE 15. Alcohol, Drug Abuse and Mental Health Administration
Department of Health and Human Services
(\$ Million)**

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	0.0	0.0	0.0
Energy	0.0	0.0	0.0
Environment	0.0	0.0	0.0
Manufacturing/BioProcessing	0.0	0.0	0.0
Health	79.0	94.0	111.2
General/Foundations	<u>0.0</u>	<u>0.0</u>	<u>0.0</u>
*Subtotal	79.0	94.0	111.2
Social Impact Research	0.0	0.0	0.0
Infrastructure			
Research Facility	0.0	0.0	0.0
Training/Career Development	0.0	0.0	0.0
Instrumentation	0.0	0.0	0.0
Repositories	0.0	0.0	0.0
Data Bases	<u>0.0</u>	<u>0.0</u>	<u>0.0</u>
*Subtotal	0.0	0.0	0.0
AGENCY TOTAL	79.0	94.0	111.2

**TABLE 16. Centers for Disease Control
Department of Health and Human Services
(\$ Million)**

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	0.0	0.0	0.0
Energy	0.0	0.0	0.0
Environment	0.0	0.0	0.0
Manufacturing/BioProcessing	0.0	0.0	0.0
Health	22.6	27.1	27.1
General/Foundations	<u>0.0</u>	<u>0.0</u>	<u>0.0</u>
*Subtotal	22.6	27.1	27.1
Social Impact Research	0.0	0.0	0.0
Infrastructure			
Research Facility	2.4	3.0	3.0
Training/Career Development	1.4	1.4	1.4
Instrumentation	0.0	0.0	0.0
Repositories	1.1	1.1	1.1
Data Bases	<u>1.1</u>	<u>1.1</u>	<u>1.1</u>
*Subtotal	6.0	6.6	6.6
AGENCY TOTAL	28.6	33.7	33.7

**TABLE 17. Food and Drug Administration
Department of Health and Human Services
(\$ Million)**

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	15.3	17.6	18.4
Energy	0.0	0.0	0.0
Environment	0.0	0.0	0.0
Manufacturing/BioProcessing	0.0	0.0	0.0
Health	13.5	17.1	17.8
General/Foundations	<u>0.0</u>	<u>0.0</u>	<u>0.0</u>
*Subtotal	28.8	34.7	36.2
Social Impact Research	0.0	0.0	0.0
Infrastructure			
Research Facility	0.0	0.0	0.0
Training/Career Development	0.0	0.0	0.0
Instrumentation	0.0	0.0	0.0
Repositories	0.0	0.0	0.0
Data Bases	<u>0.0</u>	<u>0.0</u>	<u>0.0</u>
*Subtotal	0.0	0.0	0.0
AGENCY TOTAL	28.8	34.7	36.2



**TABLE 18. National Institutes of Health
Department of Health and Human Services
(\$ Million)**

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	10.3	11.3	12.4
Energy	1.9	2.1	2.3
Environment	0.3	0.4	0.5
Manufacturing/BioProcessing	16.7	17.0	17.7
Health	1143.4	1293.5	1346.6
General/Foundations	<u>1143.8</u>	<u>1284.3</u>	<u>1354.7</u>
*Subtotal	2316.4	2608.6	2734.2
Social Impact Research	3.3	5.2	5.2
Infrastructure			
Research Facility	6.6	4.4	6.0
Training/Career Development	120.6	125.0	139.6
Instrumentation	54.6	30.6	31.9
Repositories	9.3	9.4	9.9
Data Bases	<u>15.5</u>	<u>17.4</u>	<u>17.1</u>
*Subtotal	206.6	186.8	204.5
AGENCY TOTAL	2526.3	2800.6	2943.9

**TABLE 19. Department of the Interior
(\$ Million)**

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	0.0	0.0	0.0
Energy	0.0	0.0	0.0
Environment	4.9	4.4	4.3
Manufacturing/BioProcessing	1.0	0.8	0.7
Health	0.0	0.0	0.0
General/Foundations	<u>0.0</u>	<u>0.0</u>	<u>0.0</u>
*Subtotal	5.9	5.2	5.0
Social Impact Research	0.0	0.0	0.0
Infrastructure			
Research Facility	0.0	0.0	0.0
Training/Career Development	0.0	0.0	0.0
Instrumentation	0.0	0.0	0.0
Repositories	0.0	0.0	0.0
Data Bases	<u>0.0</u>	<u>0.0</u>	<u>0.0</u>
*Subtotal	0.0	0.0	0.0
AGENCY TOTAL	5.9	5.2	5.0

**TABLE 20. Department of Justice
(\$ Million)**

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	0.0	0.0	0.0
Energy	0.0	0.0	0.0
Environment	0.0	0.0	0.0
Manufacturing/BioProcessing	0.0	0.0	0.0
Health	0.0	0.0	0.0
General/Foundations	<u>1.2</u>	<u>1.3</u>	<u>1.4</u>
*Subtotal	1.2	1.3	1.4
Social Impact Research	0.0	0.0	0.0
Infrastructure			
Research Facility	0.0	0.0	0.0
Training/Career Development	0.0	0.0	0.0
Instrumentation	0.0	0.0	0.0
Repositories	0.0	0.0	0.0
Data Bases	<u>0.6</u>	<u>0.9</u>	<u>0.9</u>
*Subtotal	0.6	0.9	0.9
AGENCY TOTAL	1.8	2.2	2.3

**TABLE 21. Department of Veterans Affairs
(\$ Million)**

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	0.0	0.0	0.0
Energy	0.0	0.0	0.0
Environment	0.0	0.0	0.0
Manufacturing/BioProcessing	0.0	0.0	0.0
Health	80.6	85.6	88.4
General/Foundations	<u>0.0</u>	<u>0.0</u>	<u>0.0</u>
*Subtotal	80.6	85.6	88.4
Social Impact Research	0.0	0.0	0.0
Infrastructure			
Research Facility	0.0	0.0	0.0
Training/Career Development	0.0	0.0	0.0
Instrumentation	0.0	0.0	0.0
Repositories	0.0	0.0	0.0
Data Bases	<u>0.0</u>	<u>0.0</u>	<u>0.0</u>
*Subtotal	0.0	0.0	0.0
AGENCY TOTAL	80.6	85.6	88.4



**TABLE 22. Agency for International Development
(\$ Million)**

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	7.6	9.4	12.7
Energy	0.0	0.0	0.0
Environment	0.0	0.0	0.0
Manufacturing/BioProcessing	0.0	0.0	0.0
Health	11.4	12.1	18.0
General/Foundations	<u>0.0</u>	<u>0.0</u>	<u>0.0</u>
*Subtotal	19.0	21.5	30.7
Social Impact Research	0.0	0.0	0.0
Infrastructure			
Research Facility	0.0	0.0	0.0
Training/Career Development	0.0	0.0	0.0
Instrumentation	0.0	0.0	0.0
Repositories	0.0	0.0	0.0
Data Bases	<u>0.0</u>	<u>0.0</u>	<u>0.0</u>
*Subtotal	0.0	0.0	0.0
AGENCY TOTAL	19.0	21.5	30.7

**TABLE 23. Environmental Protection Agency
(\$ Million)**

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	0.0	0.0	0.0
Energy	0.0	0.0	0.0
Environment	14.3	15.9	18.3
Manufacturing/BioProcessing	0.0	0.0	0.0
Health	0.0	0.0	0.0
General/Foundations	<u>0.0</u>	<u>0.0</u>	<u>0.0</u>
*Subtotal	14.3	15.9	18.3
Social Impact Research	0.0	0.0	0.0
Infrastructure			
Research Facility	0.0	0.0	0.0
Training/Career Development	0.0	0.0	0.0
Instrumentation	0.0	0.0	0.0
Repositories	0.0	0.0	0.0
Data Bases	<u>0.0</u>	<u>0.0</u>	<u>0.0</u>
*Subtotal	0.0	0.0	0.0
AGENCY TOTAL	14.3	15.9	18.3

**TABLE 24. National Aeronautic and Space Administration
(\$ Million)**

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	4.3	4.2	4.4
Energy	0.0	0.0	0.0
Environment	0.6	0.6	0.6
Manufacturing/BioProcessing	2.6	2.6	3.7
Health	4.5	4.6	5.3
General/Foundations	<u>1.8</u>	<u>3.7</u>	<u>4.9</u>
*Subtotal	13.8	15.7	18.9
Social Impact Research	0.0	0.0	0.0
Infrastructure			
Research Facility	0.2	0.2	0.2
Training/Career Development	0.6	0.7	0.7
Instrumentation	11.9	20.0	24.9
Repositories	0.0	0.0	0.0
Data Bases	<u>0.0</u>	<u>0.0</u>	<u>0.0</u>
*Subtotal	12.7	20.9	25.8
AGENCY TOTAL	26.5	36.6	44.7

**TABLE 25. National Science Foundation
(\$ Million)**

	FY 1991	FY 1992	FY 1993
Research			
Agriculture	25.6	28.7	35.0
Energy	6.2	7.8	8.8
Environment	12.6	13.7	20.5
Manufacturing/BioProcessing	29.5	32.3	43.0
Health	17.3	18.6	19.5
General/Foundations	<u>29.1</u>	<u>32.7</u>	<u>35.4</u>
*Subtotal	120.3	133.8	162.2
Social Impact Research	0.9	1.2	1.3
Infrastructure			
Research Facility	6.6	0.0	0.0
Training/Career Development	13.5	14.6	15.9
Instrumentation	11.8	13.7	14.9
Repositories	3.3	4.5	4.9
Data Bases	<u>5.6</u>	<u>6.2</u>	<u>6.8</u>
*Subtotal	40.8	39.0	42.5
AGENCY TOTAL	162.0	174.0	206.0

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