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THE WHITE HOUSE
WASHINGTON

To The Congress of the United States:

A passion for discovery and a sense of adventure have always driven this Nation forward. These deeply rooted American qualities spur our determination to explore new scientific frontiers and spark our can-do spirit of technological innovation. Continued American leadership depends on our enduring commitment to science, to technology, to learning, to research.

Science and technology are transforming our world, providing an age of possibility and a time of change as profound as we have seen in a century. We are well-prepared to shape this change and seize the opportunities so as to enable every American to make the most of their God-given promise. One of the most important ways to realize this vision is through thoughtful investments in science and technology. Such investments drive economic growth, generate new knowledge, create new jobs, build new industries, ensure our national security, protect the environment, and improve the health and quality of life of our people.

This biennial report to the Congress brings together numerous elements of our integrated investment agenda to promote scientific research, catalyze technological innovation, sustain a sound business environment for research and development, strengthen national security, build global stability, and advance educational quality and equality from grade school to graduate school. Many achievements are presented in the report, together with scientific and technological opportunities deserving greater emphasis in the coming years.

Most of the Federal research and education investment portfolio enjoyed bipartisan support during my first Administration. With the start of a new Administration, I hope to extend this partnership with the Congress across the entire science and technology portfolio. Such a partnership to stimulate scientific discovery and new technologies will take America into the new century well-equipped for the challenges and opportunities that lie ahead.

The future, it is often said, has no constituency. But the truth is, we must all be the constituency of the future. We have a duty — to ourselves, to our children, to future generations — to make these farsighted investments in science and technology to help us master this moment of change and to build a better America for the twenty-first century.

William J. Clinton

SCIENCE: THE ENDLESS RESOURCE

Underpinning Our Nation's Economic Well-Being, Health, and National Security

"Cutting back on research at the dawn of a new century where research is more important than it has been for even the last fifty years would be like cutting our defense budget at the height of the Cold War."

Unpredictability

—President Bill Clinton



Throughout time, humans have pondered the nature of the universe and the laws that order it, seeking to understand our world and our place in the cosmos. Curiosity and the quest for understanding punctuate all human growth and learning, beginning with our childhood questions: "What is it?" "How does it work?" "What happens if . . . ?" Basic (or fundamental) research seeks to answer these and other questions in all scientific fields. Basic research usually does not have a specific practical benefit in mind; it simply helps us understand the way things are and generates new ideas and questions about the unknown. It has taught us about the evolution of the physical universe, the evolution of life, and a wealth of other topics.

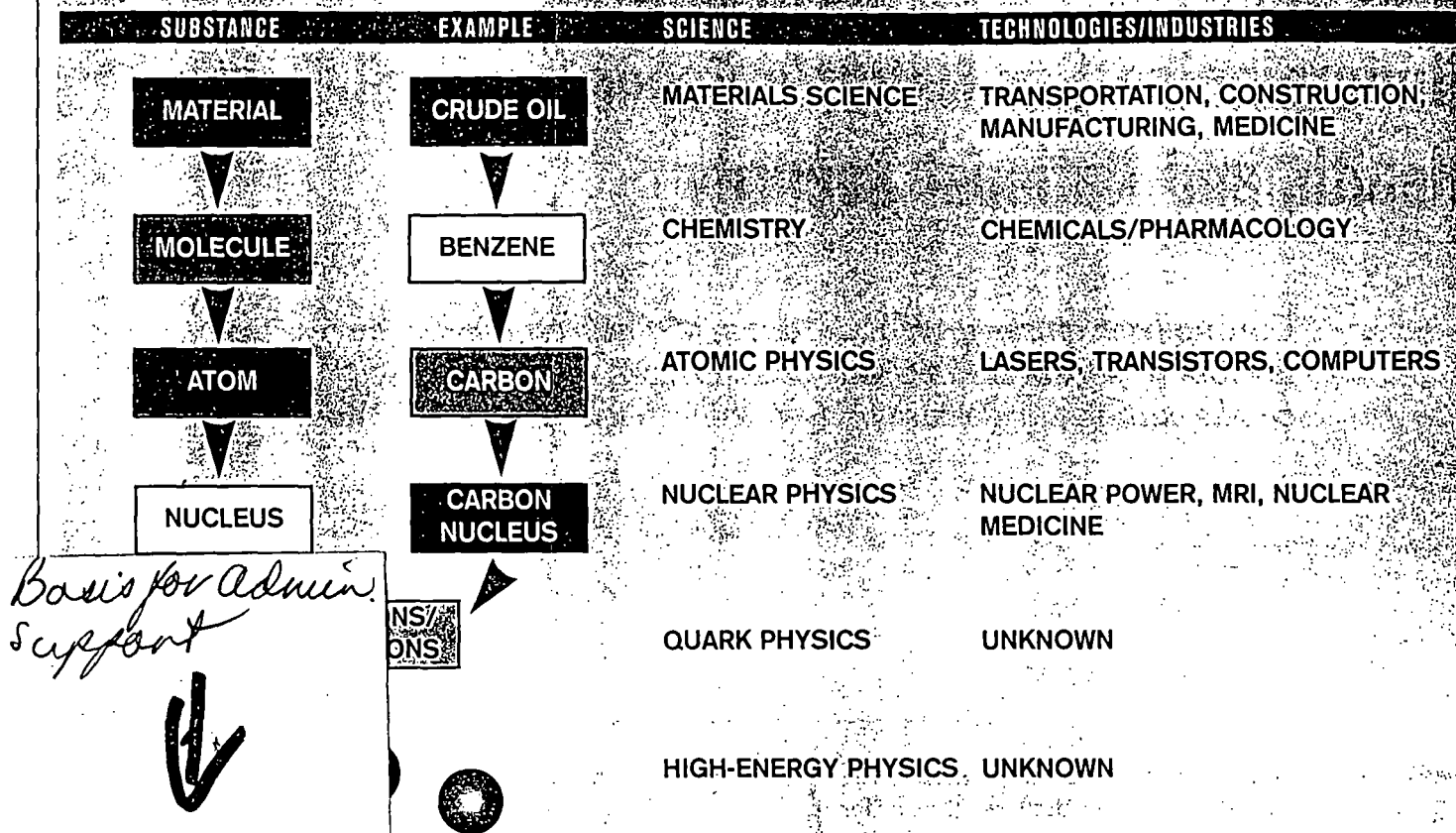
Inevitably, however, the results of basic research are prerequisites for many advances that substantially improve our lives. No one could anticipate that:

- early studies of the DNA molecule would lead to genetic engineering to develop new and effective drugs, more productive crops, and more nutritious foods;
- ultra-precise atomic clocks invented to test the laws of physics would become the heart of the Global Positioning System — now a multi-billion-dollar business used for navigation, emergency rescue, tracking commercial vehicles, and perhaps soon for air traffic control;

- basic research on the way liquids pass through holes would lead to improved fuel injection systems for cars, ink-jet printers, and artificial heart valves;
- basic studies of the attitudes and behaviors of tens of millions of military personnel over decades would lay the foundation for many of today's high-performance business management practices;
- engineering experiments on microelectromechanical systems would create a billion-dollar industry providing acceleration sensors for automobile air bags, and many other products;
- fundamental research on magnetism would transform our society, making our information age possible through tape recorders, video cassette recorders, and everything else that records and stores information; or
- decades of research in basic physics and chemistry would provide the sophisticated tools essential for molecular biology, genome sequencing, and advanced medical diagnosis and treatment.

Although it is virtually impossible to predict specifically how today's basic research results will eventually improve our quality of life, or to imagine the new industries and markets that will emerge, there is no question that such improvements and industries will arise. America's scientists and engineers are working

Technologies/Industries Derived from Fundamental Science



Basic science studies matter at all levels of aggregation, from the materials we experience everyday down to their most fundamental constituents. This progress leads to new scientific and technical knowledge and, years later, to innovative products and lucrative commercial markets. These advances have generated millions of high-skilled, high-wage jobs and significantly improved the quality of life for Americans.

in universities, industrial laboratories, research institutes, and national laboratories on important research. Their results will transform our lives in the twenty-first century, just as we now reap the harvest from past discoveries. Our children and grandchildren will look back with the same wonder we experience today at the myriad ways frontier basic research has advanced society.

The Administration's commitment to basic research derives from a clear and positive vision for the future prosperity of our nation and a strong belief that by creating knowledge and a well-educated citizenry, we gain the power to shape our future. Therefore, the Administration has championed Federal investments in science and technology, stressing repeatedly that science fuels technology's engine — the engine of economic growth that creates jobs, builds new industries, and improves our standard of living. Moreover, a significant component of Federally sponsored research is performed in colleges and universities, where young scientists and engineers are trained in the process of creating new knowledge.

OUR NATIONAL GOALS FOR SCIENCE

To advance America's interests in science, mathematics, and engineering, the Administration set forth the following goals in its 1994 science policy statement, *Science in the National Interest*:

- To sustain leadership across the frontiers of scientific knowledge.
- To enhance connections between fundamental research and broad national goals.
- To stimulate partnerships that promote investments in fundamental science and engineering and effective use of physical, human, and financial resources.
- To produce the finest scientists and engineers for the twenty-first century.
- To raise the scientific and technological literacy of all Americans.

Achieving these goals will ensure that our nation has the specialized human resources as well as the modern infrastructure needed for cutting-edge science and technology. The science and technology enterprise weaves a vast and variegated fabric of knowledge, ideas, devices, and questions that covers a broad range of human curiosity and innovation.

This report is organized around these science policy goals, and this chapter focuses on leadership in the generation of fundamental knowledge that defines basic science. The chapters on technology, health, environment, and national security capture the partnerships and connections that harness new knowledge, helping us reach those overarching national goals. The chapter on human resources addresses the production of the world's best scientists and engineers, and the need to improve public literacy in science and technology.

SUSTAINING LEADERSHIP ACROSS THE FRONTIERS OF SCIENTIFIC KNOWLEDGE

Leadership across the frontiers of scientific knowledge is not merely a cultural tradition of our nation — today it is an economic and security imperative. Creative

le working in diverse fields generate new knowledge — rich in wonder and often leading to unexpected applications. The range of our research spans all major fields of science and engineering and is one of its most powerful attributes.

There is a solid consensus that maintaining the human resources and modern infrastructure essential for scientific leadership is a fundamental Federal responsibility. Thus, public funding of research and development traditionally has enjoyed strong, bipartisan support. Government investments provide world-class facilities, promote scientific breakthroughs and interdisciplinary linkages among the major science and engineering fields, and train talented people to tackle emerging scientific challenges. As corporate R&D laboratories have increasingly favored applied research and development projects likely to improve competitiveness in the near term, the Federal government has become

the dominant sponsor of the nation's long-term, basic research portfolio. The Administration has embraced this role by continuing to support the basic science programs of the National Institutes of Health (NIH) in the Department of Health and Human Services (HHS), the National Science Foundation (NSF), the Department of Energy (DOE), and the National Aeronautics and Space Administration. These programs are vital to our nation's future, as are those at the Department of Defense (DOD), and the Departments of Agriculture (USDA), Commerce (DOC), Interior (DOI), and other Federal agencies with targeted missions. Between FY 1993 and the Administration's FY1998 budget request, Federal investment in basic research has risen from \$13.36 billion to \$15.30 billion — an increase of 14.5 percent.

This diversity of Federal sources of research funding and the rich variety of institutions and organizations conducting the research are two of the strengths contributing to U.S. leadership across the scientific frontiers. Universities and colleges — where education proceeds synergistically with the creation of new knowledge — consistently perform about one-sixth of all Federally funded R&D, and over half of our basic research. Federal laboratories, nonprofit research institutes, and industrial firms are also major players. The laboratories of DOE, NIH, NASA, and USDA, particularly, are deeply integrated into America's fundamental science enterprise in their mission areas. Rich in human talent and engineering capability, these Federal laboratories are renowned for unique, state-of-the-art scientific facilities, instruments, and other resources, operated for and made available to the national scientific community. Of course, a major component of the R&D portfolios of these laboratories, as well as those of DOD, DOC, and other agencies, serves their overriding missions to ensure national security, and to promote technological progress, health, environmental quality, and food supply as described in the other chapters of this report.

Most important, the people actively engaged in the quest to understand the unknown power our innovation system. They recognize, pursue, and exploit breakthroughs, no matter where in the world they are made.

America's Best: Our 1993-1996 Nobel Prize Winners

In each of the last four years, American scientists funded by the U.S. government have won Nobel prizes. These awards reflect the enormous dividends of specific research investments included years ago in our national research and development portfolio by the National Science Foundation, the National Institutes of Health, the Department of Energy, and the Department of Defense.

Nobels



Nobel Prize Winners 1993-1996

1993

NOBEL PRIZE IN PHYSICS awarded jointly to:

Russell A. Hulse, Princeton University, Princeton, NJ, and
Joseph H. Taylor, Jr., Princeton University, Princeton, NJ

for the discovery of a new type of pulsar, a discovery that has opened up new possibilities for the study of gravitation

NOBEL PRIZE IN CHEMISTRY awarded for contributions to the developments of methods within DNA-based chemistry with one-half to:

Kary B. Mullis, La Jolla, CA, for his invention of the polymerase chain reaction (PCR) method and one-half to:

Michael Smith, University of British Columbia, Vancouver, Canada, for his fundamental contributions to the establishment of oligonucleotide-based, site-directed mutagenesis and its development for protein studies

NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE awarded jointly to:

Richard J. Roberts, (UK), New England Biolabs, Beverly, MA, and
Phillip A. Sharp, Massachusetts Institute of Technology, Cambridge, MA
for their discoveries of split genes

BANK OF SWEDEN PRIZE IN ECONOMIC SCIENCES IN MEMORY OF ALFRED NOBEL awarded jointly to:

Robert W. Fogel, University of Chicago, Chicago, IL, and

Douglass C. North, Washington University, St. Louis, MO,

for having renewed research in economic history by applying economic theory and quantitative methods in order to explain economic and institutional change

1994

NOBEL PRIZE IN PHYSICS awarded for pioneering contributions to the development of neutron scattering techniques for studies of condensed matter with one-half to:

Bertram N. Brockhouse, McMaster University, Ontario, Canada, for development of neutron spectroscopy and one-half to:

Clifford G. Shull, Massachusetts Institute of Technology, Cambridge, MA, for the development of the neutron diffraction technique

NOBEL PRIZE IN CHEMISTRY awarded to:

George A. Olah, University of Southern California,
for his contribution to carbocation chemistry

NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE awarded jointly to:

Alfred G. Gilman, University of Texas Southwest Medical Center, Dallas, TX, and

Martin Rodbell, National Institute of Environmental Health Sciences, Research Triangle Park, NC,
for their discovery of G-proteins and the role of these proteins in signal transduction in cells

BANK OF SWEDEN PRIZE IN ECONOMIC SCIENCES IN MEMORY OF ALFRED NOBEL awarded jointly to:

John C. Harsanyi, University of California-Berkeley, Berkeley, CA,

John F. Nash, Princeton University, Princeton, NJ, and

Reinhard Selten, Rheinische Friedrich Wilhelms Universität, Bonn, Germany,
for their pioneering analysis of equilibria in the theory of non-cooperative games

1995

NOBEL PRIZE IN PHYSICS awarded for *pioneering experimental contributions to lepton physics* with one-half to:

Martin L. Perl, Stanford University, Stanford, CA, *for the discovery of the tau lepton*,

and one-half to:

Frederick Reines, University of California-Irvine, Irvine, CA, *for the detection of the neutrino*.

NOBEL PRIZE IN CHEMISTRY awarded jointly to:

Paul J. Crutzen (Netherlands), Max Planck Institute for Chemistry, Mainz, Germany,

Mario J. Molina, Massachusetts Institute of Technology, Cambridge, MA, and

Sherwood F. Rowland, University of California-Irvine, Irvine, CA, *for their work in atmospheric chemistry, particularly concerning the formation and decomposition of ozone*.

NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE awarded jointly to:

Edward B. Lewis, California Institute of Technology, Pasadena, CA,

Christiane Nüsslein-Volhard, Max Planck Institut für Entwicklungsbiologie, Germany, and

Eric F. Wieschaus, Princeton University, Princeton, NJ, *for their discoveries concerning the genetic control of early embryonic development*.

BANK OF SWEDEN PRIZE IN ECONOMIC SCIENCES IN MEMORY OF ALFRED NOBEL

awarded to:

Robert E. Lucas, Jr., University of Chicago, Chicago, IL, *for having developed and applied the hypothesis of rational expectations, and thereby having transformed macroeconomic analysis and deepened our understanding of economic policy*.

1996

NOBEL PRIZE IN PHYSICS awarded jointly to:

David M. Lee, Cornell University, Ithaca, NY,

Robert C. Richardson, Cornell University, Ithaca, NY, and

Douglas D. Osheroff, Stanford University, Stanford, CA, *for discovery of superfluidity in helium-3*.

NOBEL PRIZE IN CHEMISTRY awarded jointly to:

Robert F. Curl, Jr., Rice University, Dallas, TX,

Richard E. Smalley, Rice University, Dallas, TX, and

Sir Harold W. Kroto, University of Sussex, Brighton, U.K., *for their discovery of fullerenes*.

NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE awarded jointly to:

Peter C. Doherty (Australia), St. Jude's Hospital Memphis TN, and

Rolf M. Zinkernagel, University of Zürich, Switzerland, *for their discoveries concerning the specificity of the cell mediated immune defense*.

BANK OF SWEDEN PRIZE IN ECONOMIC SCIENCES IN MEMORY OF ALFRED NOBEL

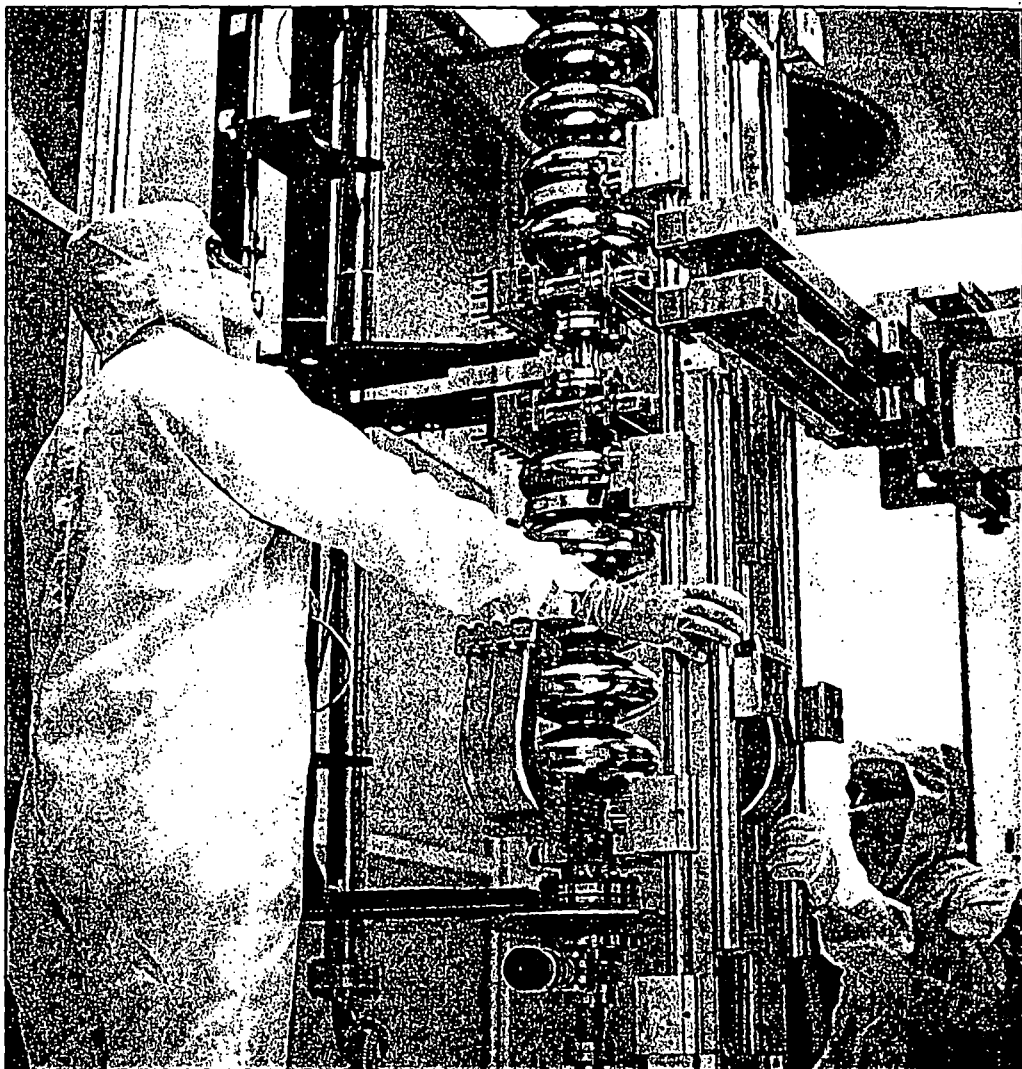
awarded to:

James A. Mirrlees, University of Cambridge, U.K., and

William Vickrey, Columbia University, New York, NY, *for their fundamental contributions to the economic theory of incentives under asymmetric information*.

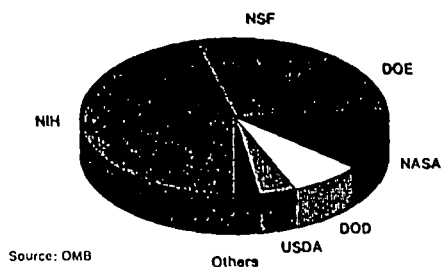
For example, in the mid-1980s European scientists discovered high-temperature superconductors. Immediately, American investigators with the requisite expertise turned their energies with great success to extending and exploiting this discovery, both in terms of fundamental understanding and engineered applications.

Given the growing linkages among the scientific and technical disciplines, it is impossible to predict what expertise will be indispensable for future developments. As with any investment portfolio, certain areas will be emphasized at any given time because of special opportunities for progress and impact. The Federal portfolio, however, must remain broad-based and accommodate the high-risk investments that may have enormous long-term impact. It is increasingly evident that the major fields of science and engineering mutually catalyze one another — strengthening the fabric of science and, with it, the entire science and technology enterprise. By advancing all frontiers of knowledge, creative American scientists and engineers, along with their students, enrich the present and shape the future.

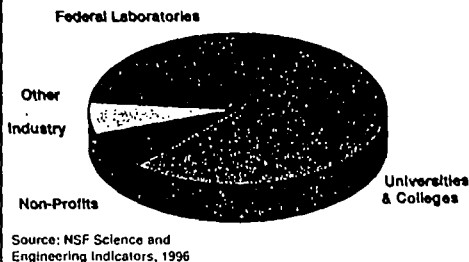


Scientific breakthroughs spur new technologies that, in turn, enable improved scientific capabilities to explore the unknown. It was not until the mid-1980s that physics understanding, niobium purity, and ultraclean manufacturing and processing techniques made it feasible to build a superconducting electron accelerator needed to explore the innermost structure of the atom's nucleus. The world's largest assembly of superconducting accelerator cavities is now at the Department of Energy's Thomas Jefferson National Accelerator Facility in Newport News, Virginia.

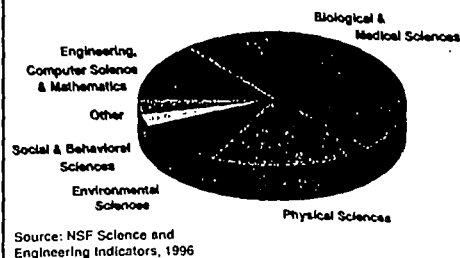
BASIC RESEARCH FUNDING BY AGENCY
FY 1998 Budget Request \$15.3 Billion

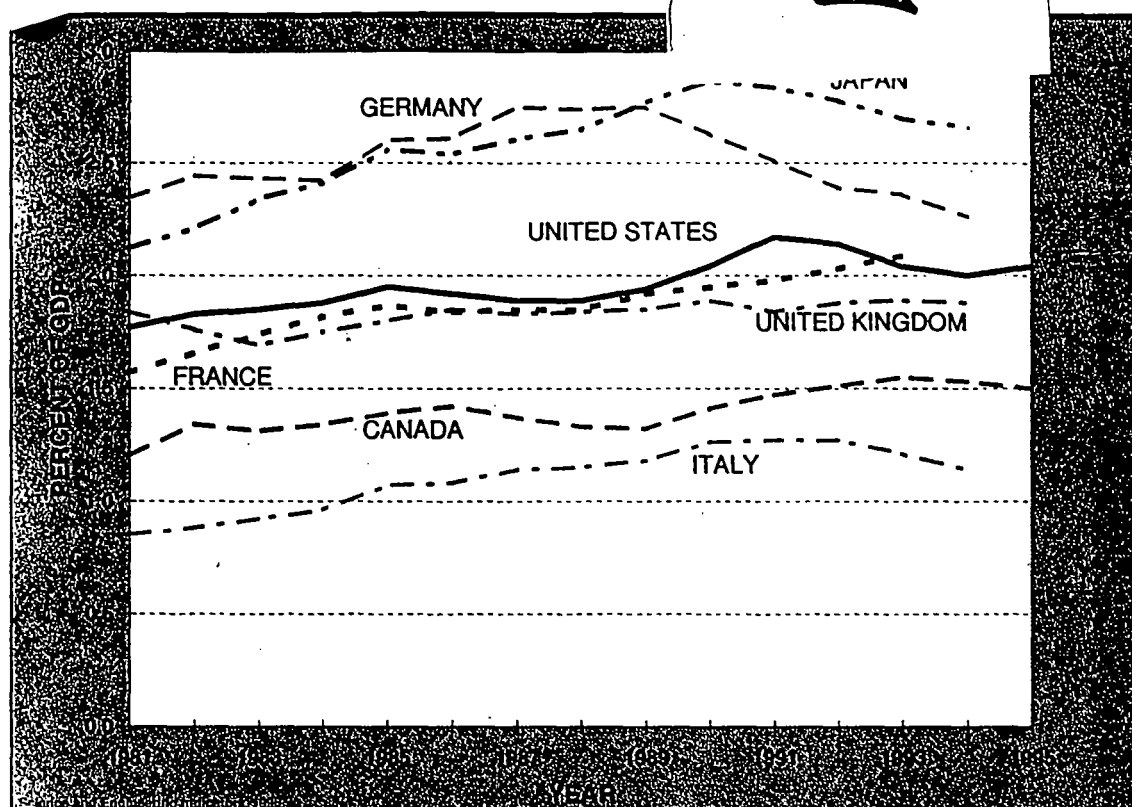


BASIC RESEARCH PERFORMERS
FY 1995 \$14.2 Billion



FEDERAL BASIC RESEARCH PORTFOLIO
FY 1995 \$14.2 Billion





nondefense R&D/GDP ratios of both Japan (2.7 percent) and Germany (2.4 percent) considerably exceeded that of the United States (2.0 percent) in 1993 and have done so for years. The non-defense R&D ratio of France matched the ratio of the United States; the ratios of the United Kingdom (1.9 percent), Canada (1.5 percent), and Italy (1.3 percent) were somewhat lower.

In this time of constrained resources, some have argued that less emphasis should be placed on basic research, since its results are typically available to anyone in the world. Japan, for example, has developed strong market positions for some products, particularly consumer electronics, for which American scientists did much of the original research and development. The Administration rejects this simplistic argument. The dominance of our basic research enterprise is a core American strength that must be preserved. This enterprise, in addition to producing new knowledge that is indeed appropriable by others, generates the physical and human infrastructure that underlies our national innovation system and our society's resourcefulness in the face of rapid technological change.

We also must remember that basic research repays society in the near term through newsworthy discov-

(Left) The diversity of Federal sources of basic research funding, and the variety of institutions and organizations conducting the research contribute to U.S. leadership across the scientific frontiers spanned by the Federal scientific and technical research portfolio.

eries that inspire our children and society at large. This ability to uncover and understand nature's secrets is a uniquely human accomplishment. Only the Federal government can supply the truly "patient capital" for the long-term investment in basic research.

The human infrastructure — creative scientists and engineers, trained at the research frontier and able to move boldly in response to new opportunities and challenges — positions America at the forefront of the "brainpower industries" of the future. Such industries — high technology, health-care technol-

ogy and biotechnology, business technologies, multimedia technologies, and others — increasingly support expansion of our export economy. America's economic resilience, as demonstrated in the rapid recovery of our leadership in semiconductors over the last five years, is clearly tied to our strength in science and technology, especially the basic and applied research capacity and human capital that spring from our research universities. Indeed, it is noteworthy that Japan's decision to dramatically increase research funding emphasizes strengthening its research universities.

Competitive advantages clearly accrue to nations fashioning the future through investments that return new, basic knowledge. Although our total investment in non-defense research and development remains the highest in the world, it is only 75 percent that of Japan and 85 percent of Germany's as a fraction of Gross Domestic Product (GDP). We must not let our position erode and thus compromise our future.

Medicine

breakthroughs with impacts comparable to those of the transistor, optical fiber, and solid-state laser. Continued progress and innovation in materials research lies at the heart of our scientific and technological future.

FROM MOLECULES TO MEDICINE

The human genome is the complete set of genetic instructions found in the nucleus of most cells on 23 pairs of chromosomes that are long strands of DNA. Each gene is a segment of DNA that carries the blueprints for a specific molecule, usually a protein.

When there is a mistake in the order of chemical bases that comprise the DNA coding for a specific protein, that protein may be altered, missing, or ineffective in the family members carrying the error. The methods for locating such disease genes include the construction of detailed maps to identify the position of the gene on a chromosome, sequencing the DNA in the area where the gene is localized, and comparing the gene sequence in individuals who have the disease with those who do not. For a newly isolated gene, the researcher can quickly gather from on-line databases everything that has already been determined about its identity, function, and protein product.

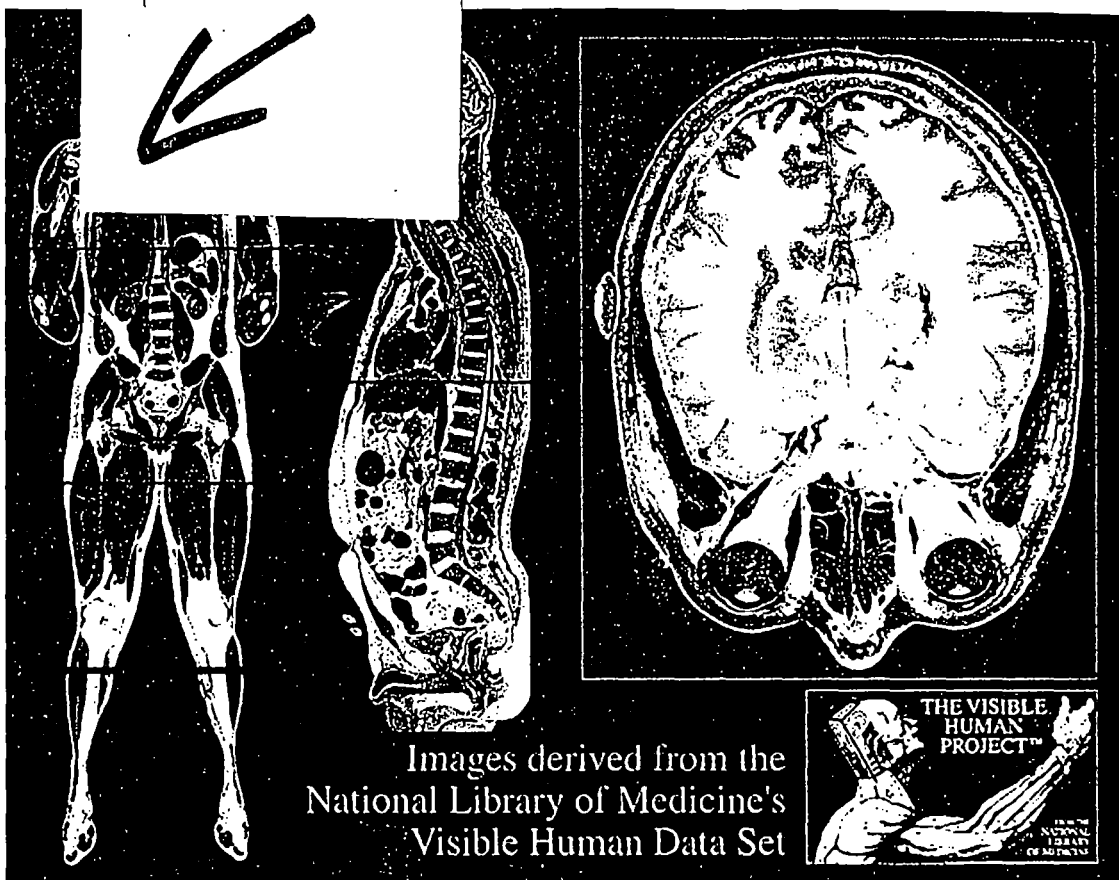
Over many years, the list of human diseases that result from known defects in a single gene has grown to about 4,000. Many of these conditions are rare and afflict only a fairly small number of people; sickle cell disease is an exception, affecting more than 50,000 individuals in the United States. However, it has also become clear that many complex afflictions, such as cardiovascular disease, diabetes, Alzheimer's disease, some forms of cancer, and other diseases, have a strong

Images derived from the
National Library of Medicine's
Visible Human Data Set

"Visible Humans" have transformed the teaching and practice of medicine. A 59-year-old female and a 39-year-old male donated their bodies to science, and became immortalized as the first digitized cadavers, available to the public and the medical community over the Internet. Images obtained from computerized tomography, magnetic resonance imaging, and high-resolution photographs were compiled into a database, providing complete, anatomically correct, three-dimensional views. The uses of these "recyclable" bodies include rehearsal of surgery, repeated dissection, computerized crash testing, and numerous other medical simulations.

genetic component. By developing and making widely available the tools for locating and rapidly sequencing genes, the Human Genome Project — an ambitious international research effort — is accelerating the progress of molecular medicine.

The Human Genome Project, funded by NIH, DOE, and several international partners, is helping scientists gain a genetic understanding of disease and also of healthy processes, such as growth, development, and how the immune system recognizes a foreign invader. Once the genetic basis of a disease is discovered, scientists have a better chance of defeating it. One example is prevention based on detection of a genetic predisposition to an inherited disorder such as colon cancer. Individuals who inherit certain mutations on chromosomes 2 or 3 have a 70 to 80 percent chance of developing a particular type of colon cancer. They may benefit from eating a high-fiber, low-fat diet and from scheduling annual colon exams starting at



THE NATIONAL SCIENCE FOUNDATION'S NEW MAJOR SCIENTIFIC FACILITIES

National Nanofabrication Users Network (Nodes in California; New York; Pennsylvania; Washington, D.C.); operational in 1994. Network providing electronic access to fabrication equipment and expertise on nanoscale materials and devices.

Gemini Observatories (Hawaii, Chile); to be completed in 2000. New-generation 8-meter optical/infrared telescopes with matching facilities in Northern and Southern Hemispheres.

National Radio Astronomy Observatory/Greenbank Telescope (West Virginia); to be completed in 1998. World's largest and most versatile steerable radio telescope.

National Optical Astronomy Observatories (NOAO)/WIYN Telescope (Arizona); completed in 1993. Telescope for optical and infrared astronomy.

NOAO/Global Oscillation Network (worldwide); completed in 1995. Network of telescopes to monitor the Sun.

National Astronomy and Ionosphere Center (Puerto Rico); to be completed in 1997. Upgrade for planetary astronomy and upper atmosphere studies.

National High Magnetic Field Laboratory (Florida; New Mexico); began operations in 1993. Science and engineering research on materials.

Cornell Electron Storage Ring (New York); to be completed in 1999. Upgrade for high energy physics and synchrotron radiation experiments.

Laser Interferometer Gravitational Wave Observatory (Louisiana and Washington); to be completed in 2001. Will study gravitational waves to test Einstein's theory of gravitation and to open a new type of astronomy.

age 30, an age considerably younger than that recommended for the general population.

Another disease that can now be detected by testing a blood specimen is cystic fibrosis, the most common lethal hereditary disease among Caucasians. The first human gene therapy trials are under way in Federally approved clinical trials. Understanding the course of cystic fibrosis at its most elementary level already has led to the development and approval of a drug that dramatically lessens its severity and improves the quality of life for those suffering from it.

The ethical, legal, and social issues associated with human genome research are being addressed in parallel with the scientific exploration and in a manner that encourages maximum public involvement. In addition, President Clinton established the National Bioethics Advisory Commission and charged it to consider as one of its first priorities the appropriate use and management of genetic information. Our policies and regulations need to keep pace with knowledge that promises such great rewards in disease prevention and cure.

LEARNING AND HUMAN POTENTIAL

The current revolution in information and communications technologies is creating demands for new human

learning skills and interaction modes. Merely being able to read, write, and calculate is no longer sufficient. Everyone needs to master the skills required to extract and integrate relevant information and use it for complex decision-making and problem-solving.

The Federal government has supported much of the research on how humans learn, process information, and then use that information to solve problems. Recent decades have seen dramatic advances in our understanding of human learning, from the level of neurochemistry and brain structure to the whole person. Neuroscientists, engineers, and computer scientists have developed new tools to provide insights into how human memory organizes different kinds of information. Psychologists and linguists are characterizing cognitive phenomena and mental processes ever more thoroughly. Artificial intelligence researchers have replicated mechanisms for learning and decision-making that have widespread applicability. Education researchers have developed cognitive-based methods that significantly improve students' thinking skills through research-based teaching. Engineers and computer scientists have developed intelligent systems that can learn from their environments and operate complex systems safely and reliably. All this progress has applications in education reforms, medicine, psychotherapy, and management.

Chapter 5

HEALTH



Improving Health Through Research for Better Medical Care and a Safe and Abundant Food Supply

"Our strategy for continuing to improve America's health, safety, and food emphasizes investing in the fundamental research necessary to assure our future well-being, promoting prevention in the areas of both health care and environmental protection, and educating Americans so they can improve their own health and safety decisions."

— President Bill Clinton

Improving the health of our nation's citizens continues to be a major goal of our Federal investment in science and technology. Starting in 1862 with the financial support for our Land Grant institutions and State Agricultural Experiment Stations (SAESs), and through the establishment in 1887 of the laboratory that became the National Institutes of Health (NIH), the United States has developed a system of intra- and extramural support for health-related research that is the envy of the world. Clearly, Federal support for biomedical and agricultural research has resulted in enormous improvements in the overall health and well-being of our nation's citizens. Today, average life expectancy of 76 years is 60 percent greater than the typical life expectancy of 47 years nearly a century ago. Much of that increase is due to better food, better sanitation, and medical advances including vaccinations to reduce or eliminate many childhood diseases.

Federal funding for biomedical and agricultural research is multifaceted. Although the primary performers are university and Federal scientists supported by the Department of Health and Human Services (HHS) and the Department of Agriculture (USDA), other Federal agencies, such as the National Science Foundation (NSF), National Aeronautics and Space Administration (NASA), the Environmental

Protection Agency (EPA), and the Departments of Energy (DOE), Defense (DOD), Veterans Affairs (VA) and Commerce, sponsor research programs that contribute greatly to improving the health and food security of all Americans.

In addition to improved health, this Federal investment contributes to an economically robust agriculture and health care industry. The production of food and fiber is the nation's largest industry, accounting for about 15 percent of Gross Domestic Product (GDP) and approximately 16 percent of all civilian jobs in the U.S. economy. Our nation's agricultural exports contribute over \$100 billion in business activity with a positive trade balance of approximately \$20 billion. Likewise, health care and related activities are estimated to account for up to one trillion dollars in annual expenditures in the United States, with 7.4 percent of the U.S. workforce making its living in the health care industry.

Even though our past investment strategy has been enormously successful, the economic, scientific, and social context for future science and technology investments in health has changed dramatically in the last decade. With these changes, it is imperative that we reassess our Federal investments and make changes to reflect new realities.

- In health care, major shifts are occurring in the age distribution of the U.S. population. For example, in 1990, 12.5 percent of our citizens were age 65 and older. In 2030 half of the baby boomers will reach 65, resulting in over 20 percent of the nation falling in the 65 and older age category. (U.S. Census Bureau projections). This will increase the prevalence of diseases that are associated primarily with the elderly, such as some types of cancer, Alzheimer's disease, and osteoporosis. Shifts also are occurring in how healthcare is financed, with more and more people participating in managed care programs. We must determine the impact this will have on basic and clinical research that underlies future medical advances. In an attempt to keep down costs of long-term care, as well as improve the overall quality of life, greater attention is now being given to research leading to better methods of preventing diseases.

- In agriculture, growing environmental and human health concerns coupled with new trade agreements and commodity price support policies require the Federal government to reassess its science and technology priorities and strengthen its partnerships with the states and private sector. In order to keep agribusiness strong and to ensure a safe and reliable food supply, the Federal government must maintain its research investments that produce new knowledge to improve environmental and human health and expand economic opportunities.

In February 1996, President Clinton released a report of the National Science and Technology Council entitled, *Meeting the Challenge: A Research Agenda for America's Health, Safety, and Food*. This report takes into account the numerous changes that we are experiencing in both health care and agriculture. It offers research strategies to contain health care costs while preserving access to high quality health care services, to develop sustainable agriculture and environmental management, and to contribute to our national security by enhancing international disease surveillance and access to food.

The breadth and diversity of our Federally supported research activities related to improving health range from fundamental research in molecular biology to crop breeding programs for improved pest resistance. This chapter highlights a number of the Administration's accomplishments spanning the breadth of our health-related research portfolio, and describes key areas of opportunity that merit enhanced support consistent with the strategic goals articulated in *Meeting the Challenge*.

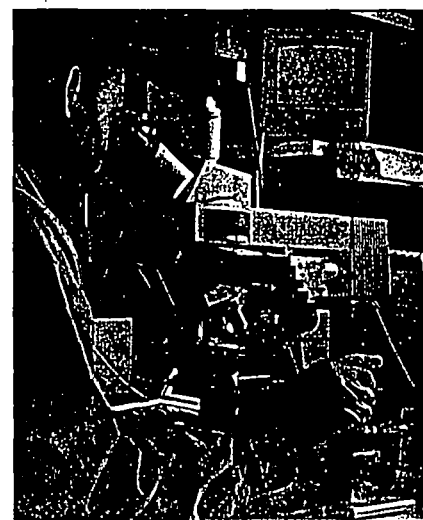
THE ADMINISTRATION'S COMMITMENT TO BIOMEDICAL RESEARCH

This Administration has strongly backed biomedical research investments. Since 1993, the NIH budget has been increased by \$2.4 billion (23 percent), representing significant new investment in biomedical research, in an era of constrained budgets. This commitment recognizes the need for stability to protect our long-term investment in the biomedical sciences. Living cultures or animal strains must continue to be fed, patients enrolled in clinical trials must be cared for, and the search must be continued for better methods for preventing, diagnosing, and treating disease. The Administration continues to sustain this critical investment in order to reap the benefits of better health and quality of life.

NEW APPROACHES TO UNDERSTANDING DISEASE PROCESSES

Scientific and technological breakthroughs are providing new approaches to solving many of the long-standing mysteries of life and its damaging diseases. We now have very powerful tools, developed through advances in computing, instrumentation, and recombinant DNA techniques, to help us understand what happens when normal biological processes go awry. We are beginning to apply this knowledge to developing ambitious strategies to bolster our natural protection systems and speed recovery. These tools have myriad applications that may lead to new disease treatments and new methods of disease prevention. Learning how healthy cells, organs, and organ systems operate when

Using tools emerging from the Human Genome Project, an international team tracked the gene for hereditary nonpolypoid colon cancer to a region of chromosome 2. Gene-based therapies may be designed to augment the immune system's response to cancer or to boost the effectiveness of chemotherapeutic agents.



...they are fully functional allows us to attempt to replicate, or add back defective pieces when necessary. For example, radiation or the sun's rays can damage DNA within the cell's nucleus, sometimes leading to skin and other cancers. If we can recreate DNA repair mechanisms, perhaps we may be able to prevent such damage in the future.

Although disease has always been part of life, certain behaviors and activities associated with the modern world present numerous new health challenges. For example, greater use of modern transportation can rapidly spread infectious disease, unhealthy diets can lead to osteoporosis and other diet-related diseases, and smoking can result in cancer and heart disease. A greater understanding of the behavioral factors and related activities underlying many conditions may lead to more effective methods of intervention and prevention.

HIV/AIDS

Acquired immunodeficiency syndrome (AIDS) is now the leading cause of death among Americans aged 25-44. As of June 1995, more than 500,000 cases of AIDS had been reported in the United States. It is estimated that over 20 million people world wide might be infected with the human immunodeficiency virus (HIV). Researchers must answer some very basic questions about how the virus behaves within the context of the human immune system before they can hope to design effective therapeutic and protective measures.

HIV infection is so different from the majority of infectious diseases that scientists must develop innovative and diverse approaches to learning how the virus functions and how the body responds to it. In most cases of infection, the immune system recognizes that a microorganism has invaded or damaged body cells and quickly destroys the intruder. In the case of HIV, however, the target of the virus is a type of cell known as CD4; a part of the immune system itself. CD4 cells are named for a protein receptor on the cell surface which is used by HIV to bind to the cell. Researchers have recently confirmed that the CD4 receptor is not sufficient for the virus to fuse with and infect the immune cells. NIH-supported scientists and others have recently discovered two cell surface proteins, fusin and CCR5, that act as "cofactors," or coreceptors, with CD4 that assist HIV in binding to and infecting immune cells.

These discoveries are important for developing new anti-HIV drugs to block or interfere with the binding of HIV to the receptors. At the same time, they may also explain why some people are seemingly immune to HIV, despite repeated exposure. Scientists have determined that two such individuals had inherited defective genes

for a fusion cofactor; in effect, the defect was a lifesaver. HIV was unable to gain entry into the immune system because the cells lacked the needed receptor protein.

NIH-supported basic biomedical research on HIV has allowed researchers to elucidate the viral life cycle and identify three specific enzymes critical to HIV replication. One of these critical enzymes is HIV protease. This enzyme is involved late in the HIV replication process at the stage of viral particle formation, release, and maturation.

X-ray crystallography and structure-based drug design programs have been used to determine both the structure of HIV protease and other molecules that might inhibit its activity. Preventing viral replication would potentially stop the spread of infection from HIV-infected cells to uninfected cells, ultimately halting disease progression in the patient. HIV protease inhibitors are achieving dramatic results in some AIDS patients.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) already affects four million Americans and that number will increase dramatically as the baby boomers reach the age of highest risk. NIH scientists have identified four genes that play a role in this devastating illness. Defects in either of two of these genes, PS1 and PS2, may be responsible for up to 80 percent of a subtype of AD that strikes before age 65. Recent progress in the field of protein structural biology is being applied to better understand neurodegeneration and other diseases of the aging nervous system, including AD. Sophisticated imaging technologies are being used to develop structural maps and to visualize molecular interactions in the aging brain. Understanding the functional consequences of changes in the 3-D structure of brain proteins has the potential to identify new treatments for AD and other neurodegenerative disorders.

NEW PREVENTIVE STRATEGIES AGAINST DISEASE AND DISABILITY

It is obvious that preventing disease is preferable to treating it after it occurs. Disease and disability prevention offer the patient and the community-at-large better quality of life and the economic benefits attendant to higher productivity. Ideally, prevention measures also incur lower health care costs, as in the case of vaccines. Some prevention measures, such as education, may be more costly or involve greater effort, but the scales are tipped in their favor in terms of

Pertussis Vaccine — Collaborations between NIH-supported scientists, vaccine manufacturers, and investigators around the world recently have resulted in a new class of vaccines for pertussis, or whooping cough, which each year claims 350,000 lives worldwide, primarily infants. The pertussis vaccine type that has been the "gold standard" for nearly 50 years is made from whole, killed pertussis-causing bacteria. It is extremely effective, but has been associated with adverse effects more frequently than any other vaccine in general use for infants. Many years of collaboration between NIH-supported basic scientists and the pharmaceutical industry have led to the development of so-called acellular pertussis vaccines that use only parts of pertussis bacteria instead of the whole organism. NIH-supported trials have demonstrated that three new acellular pertussis vaccines markedly reduce the frequency of side effects without diminishing the vaccines' effectiveness.

Rotavirus Vaccine — NIH intramural scientists recently developed and patented the first vaccine against rotavirus, the cause of infections that annually result in an estimated 130 million cases of diarrhea in infants and children. Moderate to severe dehydration occurs in 18 million of these episodes, and more than 870,000 children world-wide die as a consequence. In the United States alone, rotaviral infections incur costs of \$500 million annually in doctor visits and hospitalizations. The new vaccine protects against four different strains of human rotavirus. Clinical trials have shown the vaccine to safely achieve significant reductions in the incidence of rotavirus diarrhea. It is 80 percent protective against severe rotaviral disease and completely effective in preventing dehydrating illness. Routine childhood vaccination against rotavirus could quickly alleviate this major public health problem.

Hemophilus influenzae type b Vaccine — The vaccine against *Hemophilus influenzae* type b (Hib) meningitis provides the means to completely eliminate this disease from the United States within the next few years. For years, this disease had devastated our children, affecting 15 to 20 thousand of them each year, almost as many as polio at its peak. Hib killed 10 percent and left one third deaf and another one third mentally retarded, making it this country's leading cause of acquired mental retardation. Fortunately, two NIH scientists were instrumental in developing a safe and effective vaccine which, together with three other licensed Hib vaccines, has reduced the incidence of Hib by 95 percent since their use began in 1988. With greater use across the country, we have the hope of completely eliminating Hib meningitis.

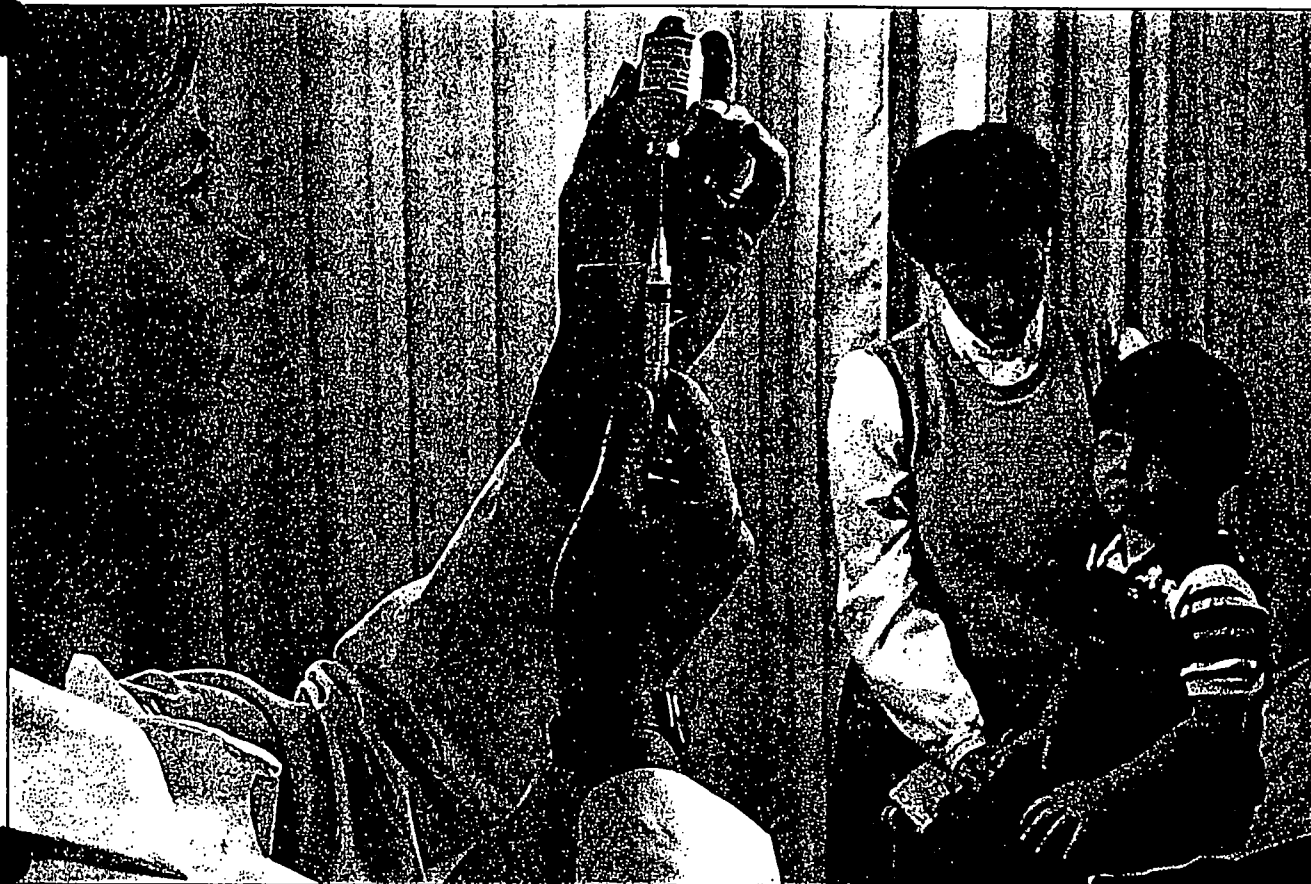
societal benefits. For these reasons, prevention research is a high priority and spans the full range of biomedical and behavioral research. The latest technologies, such as protein engineering and recombinant vaccine development as well as social and behavioral sciences, are being put to good use in erecting effective barriers against disease and disability.

Rising health care costs increase the importance of research to prevent disease and minimize the impact of illness and injury. New preventive strategies against disease involve investigations of emerging infections, as well as the prevention and treatment of drug and alcohol abuse. Vaccines against cancer and infectious diseases such as HIV, otitis media (ear-aches), herpes, chicken pox, pneumococcus, *Shigella* and *Salmonella*, are being studied. Prevention also entails the behavioral, genetic, and environmental aspects of risk assessment. The control of transmission of infectious disease by, for example, microbicide or behavioral changes, is an important aspect of prevention research. Prevention research across all

stages of life includes reducing sudden infant death syndrome (SIDS) and early diagnosis of osteoporosis. In addition, bionutrition, including the genetic basis of eating disorders and pathological consequences of particular diets, has become an important area for study in prevention of disease.

EMERGING INFECTIOUS DISEASES

To ward off pathogenic microbes, we are critically dependent on research to identify infectious diseases and to provide improved drugs and new vaccines. Both basic and clinical research are key, as the speed with which we develop the new antibiotics, new vaccines, and effective treatments will depend upon our understanding of the human immune system and the ever-growing number of pathogens that threaten human health. Research must also focus on the relationships and linkages among disease and climate, ecological change, population growth, and human behavior.



Vaccines are our strongest form of preventive medicine. Scientists supported by the National Institutes of Health have developed new vaccines for pertussis, rotavirus, and Hemophilus influenzae type b. The latter vaccine provides the means to completely eliminate this disease from the United States in the next few years.

BETTER HEALTH THROUGH VACCINES

Since Vice President Gore announced the President's policy directive on emerging infectious diseases (EID) in July 1996 (see vignette on Combating Ebola Hemorrhagic Fever, Chapter 3), the National Science and Technology Council launched a number of new research initiatives. To expand EID research, for example, NIH has funded ten international EID training awards and provided funding to expand four ongoing research and training efforts related to EIDs. The VA and DOD are investing jointly in research on emerging pathogens. NASA is supporting an NIH effort to study emerging viral diseases using remote sensing, and the Centers for Disease Control and Prevention are cooperating with NIH on epidemiologic surveys. NIH also has initiated long-term programs to study hepatitis C, hantavirus, the infectious origins of gastric ulcers, and Lyme disease. NIH and DOD are cooperating on the synthesis and testing of a new drug against the Ebola virus.

New recombinant DNA tools, advanced gene transfer techniques, and monoclonal antibody production are greatly improving public vaccination efforts. Vaccines now in development will provide greater protection for our nation's children against a wide range of infections and will lead to reduced disease and lower health care costs. For example, development of a vaccine against otitis media is under way. Such a vaccine would benefit millions of American children who suffer from this often chronic disease, which is responsible for more than \$3.5 billion worth of visits to doctors' offices, clinics, and emergency rooms annually.

In response to a comprehensive evaluation of the NIH AIDS research program, NIH has established an AIDS Vaccine Research Committee, a highly distinguished group of outside advisors in immunology, virology, and vaccinology. The committee, chaired by Nobel Laureate David Baltimore, will address key scientific questions in vaccine development, including new vaccine designs, efforts to understand the mechanisms of protection in animal models, and potential new targets for vaccines.

CRAYOLA® CHROMOSOMES

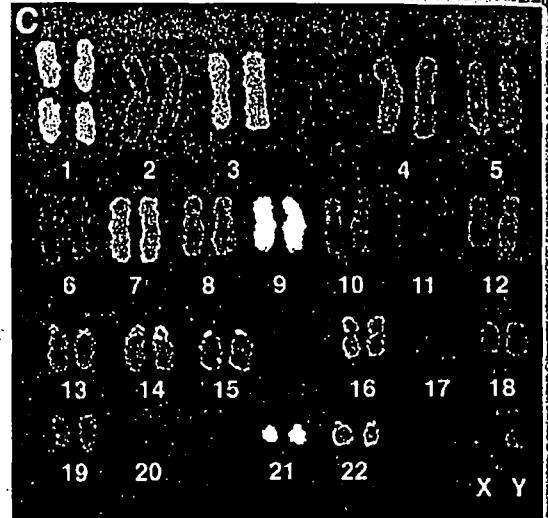
*"Toto, I have a feeling we're not in Kansas anymore.
We must be over the rainbow."*

Nearly 60 years after Dorothy left grey Kansas for the vibrant land of Oz, wizards of a different sort have concocted a powerful new way to visualize the full set of human chromosomes in a rainbow of colors. The new technique, called "spectral karyotyping," translates computer-gathered light waves into a full-color palette and assigns each chromosome its own distinct hue. With all 23 pairs of human chromosomes identified by a different color, scientists can more easily examine the entire set of chromosomes for changes that could lead to a disease, such as missing or extra pieces, or parts from different chromosomes that have swapped places. The technique could prove to be extremely valuable in diagnosis of disease based on chromosomal alterations.

"The value of chromosome examination in understanding the changes that take place during disease progression could be greatly enhanced if we could study the entire genome at once, and clearly distinguish genetic material belonging to one chromosome from that of another," said National Human Genome Research Institute scientist Thomas Ried, who led one of two groups that developed the technique. David Ward led a Yale University team in creating a different method that reached the same endpoint in chromosome analysis.

The power of the current diagnostic techniques is limited in examining whole chromosome sets, called karyotypes, for changes, because the methods rely on chemical stains that reveal only shades of gray. Pieces moved from one chromosome to another — a process called "translocation" that is often associated with disease — cannot easily be detected. And in diseased cells containing several badly distorted chromosomes, tracking the multiplication or exchange of genetic material is often impossible with conventional black-and-white banding.

Chromosome banding was first developed in the early 1970s, when it was observed that each human chromosome portrayed a characteristic pattern of bands when exposed to chemical stains. This allowed researchers to identify and sort out human chromosomes under the microscope not only by their size but also by their characteristic staining patterns.



This image shows the full complement of 23 pairs of human chromosomes, each painted a different color using the new labeling technique called "spectral karyotyping."

PREVENTING DISABILITY AMONG OLDER AMERICANS

Preventive health care for older Americans has a high payoff. More than \$108 billion is spent annually on long-term care for the elderly in the United States.

Researchers are studying risk factors for disability, improving screening processes to identify at-risk populations, and designing and evaluating interventions specifically targeted to at-risk individuals. The research is paying off:

- Three short tests of physical performance abilities can strongly predict the occurrence of disability as much as four years in advance.
- Older persons with three selected risk factors — such as mental impairment, low physical activity, and foot prob-

lems — are nearly 8-fold more likely to be involved in automobile accidents or traffic violations compared to those with no risk factors.

- Research showed a 44 percent reduction in serious falls among older persons through the use of interventions focused on physical risk factors, such as bone fragility, muscle weakness, use of sedatives or multiple medications, and balance and walking problems.
- Elderly patients who were cared for in a special hospital unit that focused on rehabilitation, prevention of disability, and preparation for the patient's return to home were significantly more able to perform basic activities of daily living and less likely to need institutionalized long-term care than individuals who

As staining techniques evolved, scientists used them to link chromosome changes to disease; missing bands indicated a deletion of genetic material, as in some inherited diseases, whereas extra bands, or translocations, indicated altered or additional genetic material, as is the case in many cancers.

Higher-resolution molecular techniques for visualizing chromosome regions, particularly fluorescence *in situ* hybridization, or FISH, later improved the process. FISH uses DNA probes labeled with fluorescent dyes to identify specific chromosomal regions. Spectral karyotyping is a new way to interpret data from FISH experiments and has distinct advantages over conventional microscopy.

Ried and his coworkers applied spectral imaging, a technology used in remote sensing devices, to chromosomes isolated from cells. First, they applied different molecular "paints" to the chromosomes.

The wavelengths of light, or emission spectra, emitted by each painted chromosome provided a unique "thumbprint" for that chromosome. Although to the eye, the thumbprints are difficult to distinguish from one chromosome to the next, computers rapidly detect differences in emission spectra and assign each chromosome its own easy-to-see color. In a spectral karyotype from a healthy cell, for example, computers translate the emission spectrum for chromosome 1 into yellow, chromosome 2 red, 3 gray, 4 turquoise, and so on.

Spectral karyotyping has already been applied successfully to analysis of cells from leukemia patients. Ried collaborated with Janet Rowley from the University of Chicago to locate a predicted chromosomal abnormality. In the process, several additional translocations were identified. These types of studies will improve scientists' understanding of the genetic basis of cancer and may ultimately assist the development of new methods for cancer treatment and prevention.

In addition to its role in identifying chromosome changes related to the progression of disease, the authors report that spectral karyotyping may be valuable in comparing genomes from different species to determine how genetic composition evolved over hundreds of thousands of years.



This technique highlights broken and rearranged chromosomes in a breast cancer cell line, a method that may lead to early diagnosis of disease.

received standard hospital care. This was accomplished without increasing in-hospital or post-discharge costs.

GENETIC MEDICINE

Genetic medicine is the application of DNA technologies to the diagnosis, treatment, and prevention of disease. It also includes analysis of complex diseases such as diabetes and assessment of genetic risk. The mapping and sequencing of entire genomes (human, as well as yeast, worm, fruit fly, and mouse) are critical components of genetic medicine. The technological tools developed in recent years — mapping techniques, various methods for sequencing the genome, and others — have accelerated

the discovery of human disease genes and are now widely used by researchers. For example, obesity genes, genes for aging, neurological disease genes, and cancer genes, such as BRCA-1 and 2, are being identified and characterized. Once the consequences of altered genes are understood, rational therapies may be able to be designed. Gene therapy to replace missing or defective genes, is one such approach that is under investigation. It has proven difficult to insert genes that operate properly and produce adequate protein products.

Most complicated diseases of modern life — cancer, heart disease, diabetes, arthritis, and a host of neuropsychiatric disorders — seem to result from the activities of several genes and the interactions between the human body and its environment. The direct causes of

these disorders have been difficult to discover. Research at the NIH Center for Inherited Disease Research will specialize in applying computer-based technology and robotics to conduct large-scale, rapid genetic analysis of these diseases, leading to the identification of the genes involved. Developments are currently under way to enable simultaneous analysis of thousands of DNA strands on a single silicon chip. These micro-machines greatly speed up research and lower its cost.

CANCER GENETICS

December 1996 marked the twenty-fifth anniversary of the war on cancer. Since 1971, scientists have discovered the causes of many cancers and have proven that cancer can be cured. Today, more than ten million of our family members, friends, neighbors and coworkers owe their lives to cancer research. Cancer survivors are alive today and enjoy a better quality of life because the years of research in prevention, diagnosis, and treatment methods have given doctors better information and more accurate tools. America's youth have received the greatest benefit from this country's investment in cancer research. For example, most cases of childhood leukemia are now curable. Death rates from children's cancers have declined by more than 62 percent. Cancer research has also brought about dramatic improvements in the survival rates for adults. The death rate for testicular cancer, for example, has declined 66 percent and five-year survival is now 95 percent. Today, most Hodgkin's disease patients can be cured.

Gene-based therapies are one class of exciting new approaches under investigation in cancer treatment. These methods are designed to augment the immune system's response to cancer or to boost the effectiveness of chemotherapeutic agents. They may involve administration of genes for immune factors, either in the patient or in cells taken from the patient and then returned. Another method is to give the patient genes that will increase the tumor's sensitivity to an anti-cancer drug, thus reducing harmful side effects on normal cells. Yet another technique involves the use of drug-resistance genes that protect the vulnerable bone marrow from highly toxic chemotherapy. Important goals for the future include the development of better viral vectors for delivering genes to their intended target cells and regulating production of the introduced genes' protein products.

A new project of the National Cancer Institute (NCI) provides another exciting example of the application of

this technology to the understanding of disease. The Cancer Genome Anatomy Project seeks to define all the genes that play a critical role in the development of cancer. The project will develop high volume, cost effective technologies to analyze the molecular mechanics of cancer cells and put those technologies in the hands of clinical researchers. Coupling these technologies with clinical investigation will provide a better understanding of the basis of disease, as well its detection, diagnosis, prognosis, development of treatments, and selection of therapy.

Breast Cancer — In 1995, in the United States alone, 182,000 new cases of breast cancer were diagnosed. Forty-six thousand women died from the disease. Health care costs of breast cancer exceed \$12 billion per year. In an extension of the exciting discovery in 1994 of a gene that confers susceptibility to breast and ovarian cancer, NIH scientists and collaborators discovered a specific mutation in the BRCA-1 gene in nearly 1 percent of samples of blood from women of Ashkenazi Jewish descent. This finding identifies a particular subgroup of the population that may benefit from genetic testing for the BRCA-1 mutation. Epidemiologists have hypothesized that this mutation may account for as much as 16 percent of breast and 39 percent of ovarian cancers among Ashkenazi Jewish women age 50 and under. Studies of families with inherited alterations of BRCA-1 suggest that more than half of the women who inherit mutations in BRCA-1 will be diagnosed with breast cancers by age 50, and more than 85 percent will have breast cancer by age 70.

OBESITY

In the United States, obesity is second only to tobacco as a risk factor for disease and accounts for about 300,000 deaths per year and an economic cost of \$50-\$100 billion. Obese individuals suffer increased risk for numerous chronic diseases, such as diabetes mellitus, cardiovascular disease, hypertension, gallbladder disease, and certain cancers. Fortunately, opportunities to attack obesity at the molecular level have multiplied. NIH-supported scientists have made important new discoveries regarding the obese (ob) gene, its protein product (leptin), its receptors, and its interactions with other regulators of energy expenditure and food intake.

This year, the diabetes (db) genetic mutation in the mouse and the fatty (fa) mutation in the rat (which cause diabetes in these animals) have been shown to be mutations of the leptin receptor gene. This is crucial evidence of the link between diabetes and obesity.

Although it appears unlikely that leptin deficiency causes obesity in most humans, the discovery of leptin and its receptor has already deepened our understanding of metabolism, and will continue to lead to fundamental research in the relationship between food intake, energy expenditure, and the regulation of body weight.

BIOLOGY OF BRAIN DISORDERS

As we are past the midway point in the Decade of the Brain, it is appropriate to highlight research and progress in the neurosciences. This discipline recently joined other areas in reaping the benefits of modern biology by coming one step closer to deciphering the molecular basis of memory and behavior. Two NIH-funded groups, using different but related genetic techniques, reported advances in understanding how mice create a mental map of a new environment. Using sophisticated imaging equipment, researchers are able to detect activity in individual brain cells as the mice investigate their surroundings. From these data, a map of the cells responsible for forming memory about space and time can be constructed. This work illustrates the interdisciplinary nature of neurobiology, marrying genetics with electronics to analyze cellular and biochemical processes as they occur in living organisms.

The biology of brain disorders encompasses studies of the basic biology, chemistry, and anatomy of the brain, including the physiology of the neuron, its receptors and the neurotransmitters that are responsible for relaying messages between cells. This area of research extends studies that seek to understand the development of the normal brain and the changes in development which may underlie brain disorders. The research employs animal models, neuro-imaging, and clinical studies in an effort to understand many disorders, such as pain, addiction, mental illness, neurodevelopmental disorders of children, neurodegenerative disease, diseases of the aging brain, and damage to the sensory system.

New or expanded NIH-supported research programs within this area include studies on the development of the nervous system, which have implications for the ability of the adult brain to repair and reorganize itself following injury from stroke, trauma, or degenerative processes such as Parkinson's disease; and studies related to spinal cord injury and neuroregeneration.

Studies related to Alzheimer's disease in addition to those in genetics will focus on:

- different aspects of the theory that components of the amyloid plaques that characterize AD trigger an inflammatory immune response that is the actual cause of neurodegeneration;
- different approaches to determine whether proteins known as kinases, which have an important role in normal cell function, also contribute to the formation of the abnormal protein filaments and plaques seen in Alzheimer's; and
- understanding of the process by which amyloid is deposited in brain blood vessels, as a part of AD or the normal aging process.

Stroke — Four out of five strokes suffered by a half million Americans each year are caused by a blood clot that blocks blood flow to the brain. With the brain starved for oxygen and other nutrients, damage follows quickly, often with devastating consequences. Researchers recently discovered that the clot-dissolving drug TPA is an effective emergency treatment for this type of stroke when given within three hours of initial symptoms. Given the narrow window for administering the drug after a stroke, the challenge now is to alert physicians about this finding and, more critically, to educate the public about the symptoms of stroke and the importance of seeking emergency help.

ACADEMIC HEALTH CENTERS AND THE CHANGING HEALTH CARE ENVIRONMENT

Academic health centers (AHCs), medical schools, affiliated hospitals, and schools of allied health professions are the principal places in the United States for combining medical technological development, basic and clinical biomedical research, and clinical education. In AHCs, education, research, and patient care are inextricably intertwined; patients are able to receive innovative medical care using the most modern techniques and can participate in research activities, and medical education is conducted. AHCs also provide a disproportionately large share of this country's care of the indigent and uninsured.

PEREGRINE: BETTER TREATMENT FOR CANCER PATIENTS

Cancer patients may soon receive dramatically more effective radiation therapy as researchers refine and test a revolutionary new tool for analyzing and planning treatments. The program, known as Peregrine, draws on technologies originally developed by the national laboratories for military applications — and turns them to life-saving use.

Peregrine addresses a straight-forward problem: Doctors have had no accurate means with which to assess how radiation travels through the body. Each year, roughly one third of the 300,000 cancer patients doctors hope to cure by radiation therapy die because the radiation failed to kill the original tumor. Improving the success of radiation therapy is exceedingly difficult because without reliable, detailed information showing how radiation is transported through tissues of different type and density, such as bone and lung, a physician trying to cure cancer tumors with radiation is like a surgeon operating in a dimly lit theater.

The Peregrine program takes advantage of increases in the speed and performance of computers, sophisticated computational techniques, and comprehensive nuclear and atomic physics databases residing in the national laboratories. It is being developed by scientists at the Lawrence Livermore National Laboratory, in collaboration with colleagues in medical physics and radiation oncology, and is expected to be commercially available within two years. It will provide doctors better information about where radiation is directed in the body, greatly improving the therapy's effectiveness, raising the prospect of saving as many as 100,000 lives each year in the United States alone.

Treatment planning based on Peregrine begins with a computer-aided three-dimensional (CT) scan that provides information about the exact location, composition, and density of the tumor and sensitive organs. These data are subjected to a sophisticated computational technique known as Monte Carlo that calculates the probabilities of random molecular interactions. The method enables doctors to track the path of an x-ray as it moves through the body, interacting with atoms much as balls in a pinball machine bounce randomly as they encounter obstacles in their path. The result is a detailed three-dimensional model that simulates the physical processes involved in radiation transport.

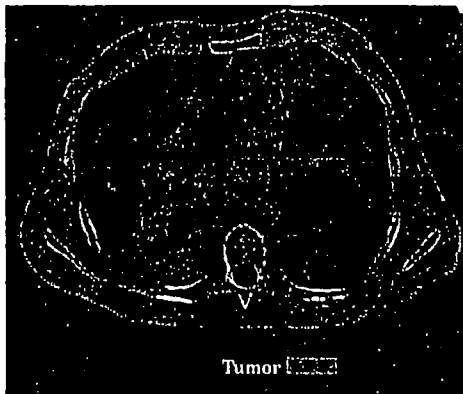
Current methods of calculation only approximate radiation dose distribution to the patient, which can result in underdosing of the tumor. In the tumor shown here, for example, current methods of calculation assured the radiation oncologist that the entire tumor would be treated. But Peregrine calculations show that the prescribed radiation targeted only a fraction of the tumor, making the treatment less effective.

Inaccurate dose calculations can have other unintended consequences, causing radiation to be directed where it is not needed, potentially damaging healthy cells. Peregrine will allow clinicians to administer more precisely

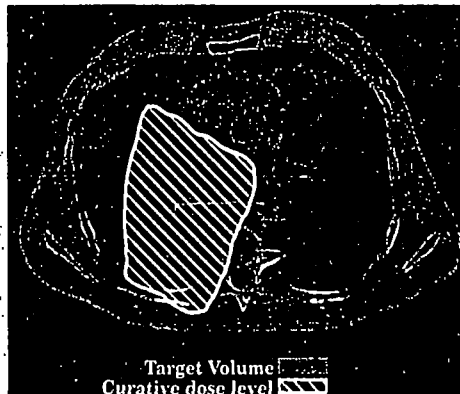
System-wide changes in the financing and delivery of health care are having substantial effects on basic and clinical research and medical education in AHCs. Patient care costs historically have been higher at AHCs because of the added research and education missions. Yet, the latter are clearly an important and broadly distributed public good for the future of quality health care in this country. The marketplace changes are raising important issues with respect to the ability of AHCs to attract the patient base needed to support their research and education missions:

- A decrease in the ability of AHCs to attract research subjects would affect the rate at which new treatments are developed, tested, and applied.
 - A decrease in the ability of AHCs to subsidize research and teaching costs would have a negative impact on the nation's research infrastructure and on the training of the next generation of researchers and clinicians.
- In November 1995, the President's Committee of Advisors on Science and Technology wrote to the President relaying their concerns about the future vitality of our AHCs. The research and educational capacity of our AHCs will continue to be a factor in the Administration's efforts to improve our health care system. It is important to continue to evaluate data to determine what impact recent changes in the health care system are having on AHCs.

lung Tumor- What they were treating



Planned Treatment: What they thought they were doing



Actual Treatment- What they really did



Cancer patients may soon receive dramatically more effective treatment through Peregrine. This revolutionary new technique is used to target radiation on tumors more precisely than current methods, and raises the odds of survival of the hundreds of thousands of cancer patients treated every year, while reducing harmful side effects. In a planned lung tumor treatment using current techniques, the Peregrine calculation (right panel) shows that the intended dose misses much of the tumor. The Peregrine program will allow more precise planning of radiation therapy.

targeted beams of radiation, giving them the confidence they need to treat tumors more aggressively, while minimizing risk to healthy cells.

Monte Carlo techniques have long been recognized as the best way to calculate dose distributions for radiation therapy, but such calculations often took hundreds of hours. Recent advances in computational techniques and computer architecture mean dose calculations now take only minutes, not days. Peregrine brings high-speed, highly accurate, and high resolution Monte Carlo treatment planning to desktop computers through simple network connections, much like file servers in an office environment. Cost should thus not be a limiting factor for hospitals who want to utilize the new treatment planning approach.

Researchers currently are examining Peregrine's application to a variety of patients and tumor types, including tumors of the lung, head and neck, larynx, and breast. So far, researchers have assessed how well the method would work using data only from patients who have already completed their radiation treatment. Once cleared by the Food and Drug Administration, physicians will be able to use it for patients preparing to undergo treatment, raising the odds of survival for hundreds of thousands of cancer patients, while reducing harmful side effects.

FOOD AND HUMAN HEALTH

There is a direct link between our health and the food we eat. Poor diet is a significant underlying contributor to illnesses that lead to death. In addition to the critical relationship between diet and health, it is estimated that each year millions of individuals become ill and that thousands of people die from eating food contaminated with microbial pathogens such as *Salmonella* and *E. coli* O157:H7. Research supported by the Federal government in the area of diet and nutrition and food safety has greatly improved the overall health of our nation's citizens. However, additional research is needed to guide efforts to improve the diets of Americans and to ensure that our food supply is free from harmful pathogenic microorganisms.

NUTRITION

Nutrition plays a pivotal role in optimizing health and productivity, while reducing the risk of diet-related diseases. The annual cost in the United States of treatment and care for individuals with diseases linked strongly to diet, such as cardiovascular disease, obesity, osteoporosis, and cataracts, exceeds \$200 billion. Fortunately, over the last half of this century, we have witnessed remarkable improvements in the dietary patterns of the U.S. population and those of several other western industrialized nations. Most notably these changes have brought about a decline in deaths from coronary heart disease, the leading cause of death in the United States. However, poor diet continues to be a leading contributing factor to numerous illnesses.

TOUGHER STANDARDS FOR SAFE MEAT

In July 1996, President Clinton announced sweeping reform of the nation's food safety rules, for the first time bringing science to the task of meat and poultry inspection. The new sanitation standards and requirements for scientific tests are designed to reveal the presence of deadly bacteria, and to maintain food safety from "farm to table." While previous methods for inspecting meat and poultry were based on how the food looks, feels, or smells, the new methods rely on technology to detect the bacteria *E. coli* and *Salmonella*, which are invisible without a microscope. A similar program for seafood inspection was adopted a year earlier.

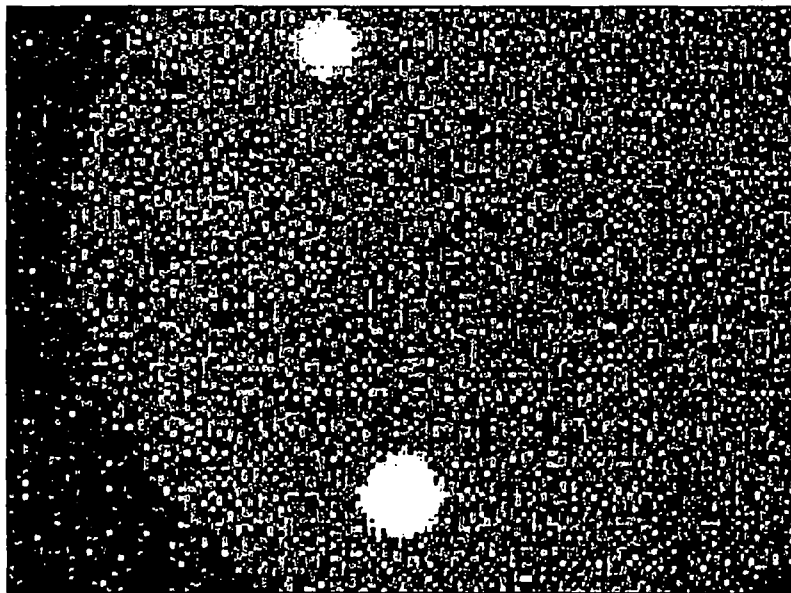
The heart of the reform is a Hazard Analysis and Critical Control Points, or HACCP (pronounced "hazup"), system. Unlike many federal regulations, the new rules do not dictate specific steps industry must take. Instead, packers and slaughterhouses are required to identify points in the process, such as cutting and grinding, where contamination can occur, and then come up with remedies that prevent the contamination. To verify that the preventive steps are effective, slaughterhouses and plants that produce raw, ground meat and poultry are required to meet standards for *Salmonella*, and also to conduct microbial testing for generic *E. coli* (a form of *E. coli* that is common in the intestinal tracts of food animals). *E. coli* often indicates fecal contamination, which is the main pathway for contamination of meat and poultry.

The inspection reforms reflect recommendations during the past decade by external bodies including the National Academy of Sciences, the General Accounting Office, and the National Advisory Committee on Microbiological Criteria for Foods. Like many observers, they urged modernizing the inspection system to address the growing hazards presented by microbial pathogens. For all our technological advances, the inspection system was virtually unchanged for nearly a century, since muckrakers in the early 1900s exposed filthy conditions in the nation's meat packing plants. In response, the government set up a manual system that relied on the senses of federal inspectors to protect the public from unsafe food.

Over the years, only incremental changes were made. Then, in 1993 tragedy struck people who ate undercooked fast food hamburgers at a restaurant in the western United States. Four children died from the outbreak, and hundreds became ill. The nation's — and the President's — attention was riveted on the threat posed by deadly strains of *E. coli*, in this case *E. coli* O157:H7. It was clear that the inspection procedures needed to be revamped, and government and industry began to work together in earnest to devise an effective system.

As the changes are phased in over the next few years, industry and scientists will continue to need additional, and more reliable, information, and faster, more accurate test results. Advances in biotechnology promise to provide earlier detection of contamination. Scientists from the U.S. Department of Agriculture have trimmed the time required to detect disease-causing bacteria on meat from the typical 48 hours to just five minutes. They have also developed tests specifically to detect hemorrhagic *E. coli* O157:H7 in less than eight hours, compared to the traditional three-day test.

None of this negates personal responsibility for handling raw meat and poultry safely, and for making sure it is well-cooked before it is served. But the progress is real. As President Clinton observed in announcing the inspection reforms, "Parents should know that when a teenager borrows the car to get a fast food hamburger, the hamburger should be the least of their worries. Our new food safety initiative will give families the security to know that the food they eat is as safe as it can be."



*New scientific technology reforms meat and poultry inspection. Microbial testing will be implemented in the Hazard Analysis and Critical Control Points program that requires the development and implementation of rapid tests to detect microorganisms. The two light areas are a deadly strain of *E. coli* O157:H7 among colonies of non-pathogenic strains.*

We still have much to learn about the prevention or management of diet-related diseases. In particular, we need to develop a better understanding of nutrient-gene interactions so that we can produce healthier food and better detect and prevent nutrition-related disease. An expanded human nutrition knowledge base will lower health care costs and raise the effectiveness of federal food assistance programs, such as food stamps. Since the causes of malnutrition and nutrition-related disease within the United States are complex, it is important that nutrition-related research include a multidisciplinary perspective.

The development of science-based programs that promote healthier eating habits will remain a high priority for the Administration. One such effort, based on a three-year trial involving 96 elementary schools in four states, has shown that children can be taught behaviors that may protect them against heart disease. Schools successfully lowered the fat content of school lunches, and physical education instructors increased the amount of vigorous exercise. Students reported lower daily caloric intake from fat at home. This program worked equally well among ethnically diverse populations and represents a cost-effective, easily implemented program that can have profound positive effects on children's eating habits and activity levels.

Fat Substitutes — The Federal government contributes to the development of a more healthful food supply — food that is more nutritious and low in fat. For example, Z-Trim, a new no-calorie, high-fiber fat replacement developed by U.S. Department of Agriculture (USDA) scientists, could soon find a place in foods such as cheese products, hamburger, and baked goods. Z-Trim is made from low-cost agricultural byproducts such as hulls of oats, soybeans, peas and rice, or bran from corn or wheat. The hulls or bran are processed into microscopic fragments and purified, then dried and milled into an easy-flowing powder. When the fragments absorb water they swell, forming a gel that provides foods with an enjoyable smooth texture like that of fat.

FOOD SAFETY

The Centers for Disease Control and Prevention estimate that as many as 6.5 million cases of food-borne illnesses occur annually in the United States, and that these illnesses contribute to approximately 9,000 deaths. USDA's Economic Research Service estimates that the annual overall economic

impact of food-borne illnesses in this country is \$6-9 billion. The safety of the wide variety of food we consume each day starts with its production on farms, ranches, ponds, lakes, and oceans, and ends at the table. Further research into food production, harvesting, and handling practices that will reduce human exposure to microbial pathogens, chemicals, and biotoxins — as well as into improved methods to detect and survey these hazards — can eliminate or significantly reduce an important cause of illness in the United States.

Enhancing our strong research program in food safety will further ensure public health and safety and reduce the prevalence of food-borne diseases. However, we also need a system that integrates prevention, detection, and intervention throughout the food production cycle, making use of technological advances in food processing and packaging, and pest control. Such a research program will build the scientific foundation for sound food safety regulation and policy, spur innovation in food safety and production, and help educate consumers to improve their food safety practices and increase their understanding of the relative risks and benefits.

Scientists are developing new ways to reduce the microbial contamination of food products. Hazard Analysis and Critical Control Point (HACCP) systems are one such approach. HACCP is based on the premise that for overall reduction of microbial pathogen contamination of food, it is better to reduce the level of pathogen contamination at key points in the food production, slaughter, and processing pathways rather than to simply inspect the finished processed product. The Administration has established over the last two years new regulations that require the implementation of HACCP principles for meat, poultry, fish, and shellfish. Research and disease surveillance are needed to guide the implementation of HACCP. In particular, research must be conducted that generates data needed to conduct quantitative risk assessments.

The Departments of Agriculture, Health and Human Services, and the Environmental Protection Agency have begun a comprehensive food safety initiative which will provide an integrated federal strategy to help ensure the microbiological safety of our nation's food supply. Key elements to this initiative are improved research, surveillance, risk assessment, and education, all done in full cooperation with state governments and the private sector.

SUSTAINABLE FOOD AND FIBER PRODUCTION

Agricultural productivity in the United States has grown dramatically at a rate of nearly 2 percent per year. Production has more than doubled since 1950

while total input use (use of energy, water, fertilizers, etc.) has actually fallen slightly over this same period. However, due to the new economic, environmental, and health demands being placed on our food and fiber production systems, we need to reassess our science and technology investments in agricultural research. Maintaining and enhancing rates of growth in food and fiber productivity in this new environment will be the major science and technology challenge for agricultural and natural resource scientists in the twenty first century.

Global food security remains a challenge for the next century. Significant uncertainties, however, remain in projections of future world food requirements and the ability of poor countries to achieve sustainable economic and agricultural development. Scientific and technical advances that improve agricultural productivity can help combat the human and social deterioration associated with hunger and poverty. In addition to traditional aid programs, U.S. support for international agricultural research centers helps build the research infrastructure in many regions of the world with persistent food production problems. U.S. Land Grant universities train significant numbers of agricultural scientists from the developing world, who in turn contribute to their national research programs. Working with other nations to develop the scientific tools and infrastructure they need to provide for the nutritional needs of their own people, the United States can help alleviate the pain of hunger that afflicts 800 million people daily.

INTEGRATED MANAGEMENT OF FARMS, RANGELANDS, FORESTS, AND COASTAL WATERS

Our nation's farms, rangelands, forests, and coastal waters must be managed in a fashion that allows for their long-term, sustainable use for production purposes while preserving other vital functions, such as habitat for wildlife, watershed protection, and recreation. To achieve sustainable production practices, we should view our farms and forests as integrated systems with a variety of inputs and outputs. Scientific knowledge, generated through research, has been and will continue to be the most important factor in any sustainable production system. Greater scientific understanding of the inter-relatedness of the multiple components of our nation's food and fiber production systems, ranging from geochemical and biological to social and economic interactions, will help farmers and natural resource managers understand what is necessary to maintain or restore the economic, social, and natural attributes of the system.

An excellent example of an integrated approach to natural resource management is the USDA Forest Service's Wine Spring Basin demonstration project in North Carolina's Nantahala National Forest. It encompasses about 4,500 acres and contains a mix of hardwood forest types, streams with native brook trout, and old growth timber stands. The purpose of the project is to develop, test, and demonstrate ecologically based concepts and technologies to restore the native mixed pine forest, its diverse understory, and stream habitats, as well as to achieve a sustainable forest community. Early project development has centered on reintroduction of fire under prescribed conditions, testing improved regeneration techniques for oak forest, restoring stream habitats with addition of woody debris, and a socioeconomic assessment of public attitudes and values.

Our coastal waters are as productive as the richest American farmland. Significant strides have been made in restoring the living marine resource habitat value to areas that have been degraded through catastrophic events such as oil spills or ship groundings, or as a result of cumulative human activities, such as water diversions or land use changes. Projects eventually benefiting upwards of 48,000 acres of coastal wetlands were initiated or under way by the end of 1996. As part of the efforts to recover Pacific salmon populations, removal of barriers to fish migration and restoration of historic spawning streams have been undertaken, in many cases by members of the fishing industry displaced as a result of reduced harvest levels due to habitat losses and other factors. These restorations generally represented partnerships among Federal, state, and local governments, tribes, industry, and non-governmental organizations.

ENVIRONMENTAL QUALITY

Reducing negative impacts on the environment or even improving its overall health is now a major consideration for American food and fiber producers. This is a significant shift from our traditional approach to farming and forestry in past decades. Since the end of World War II, farming was geared toward optimizing production using chemical pesticides and fertilizers or through management techniques that may have solved one problem but often created other, more serious ones. Excessive tillage to control weeds, for example, often led to unacceptable rates of erosion of valuable topsoil. Forestry was practiced in many cases with little regard for endangered species or the water quality of streams and rivers. Today we are investing in science and technology to produce more from our food and fiber production systems while protecting our environment.

Tillage and Global Change: Keeping organic matter tucked away in soil — where it is needed most for agricultural productivity — benefits the earth and the atmosphere. As organic matter is plowed up, carbon dioxide loss from the soil into the air dramatically increases. Measurements of a range of soil types, tillage methods, and climatic conditions indicate that deep plowing results in a much greater loss of carbon dioxide than all other forms of tillage. Such information is vital in quantifying the effects of tillage on soil quality and productivity and provides data for validating agriculture's role in global warming. These findings offer agricultural producers a way to help counteract global change by altering their cultivation practices.

Water Quality — Water pollution from agricultural chemicals must also be prevented. Combining wetlands, ponds, and underground irrigation could result in water conservation and bigger yields for farmers. USDA scientists built such a system in Ohio to demonstrate the benefits of recycling runoff and drainage water from fields. It reduces sediment and agricultural chemical flow to streams, improves water quality, enhances wildlife habitat, increases wetland acreage, and improves crop yields. The wetlands remove sediment and agricultural chemicals from field runoff. The water is then stored in a pond until it is needed to irrigate a field. Finally, it is pumped back through underground pipes to reduce water stress in crops. The overall result is that less pesticide and fertilizer runs off into surface waters.

Precision farming, such as site specific application of pesticides and fertilizers, holds considerable promise for the future. Using powerful tools such as the global positioning system, scientists are developing techniques to accurately place agricultural chemicals where they are needed most. Current methods of chemical application are more "broad brush," with chemicals being applied throughout an entire field. New precision farming techniques will reduce costs by eliminating unnecessary chemical application, and will protect the environment by reducing the amount of chemicals applied.

New biotechnology-derived crops also have the capability to improve management practices. For example, plants are being developed that require fewer applications of pesticides, that require less tillage (therefore reducing soil erosion), and that require less irrigation. While new genetic traits and the use of genetically engi-



Protecting surface and ground water from contamination by agricultural activities requires knowledge of land use, soil properties and hydrogeology as exemplified by the Mahantango Creek watershed near Klingerstown, Pennsylvania.

neered crops may be environmentally beneficial in many circumstances, a continuing strong research program is important to identify and minimize any potential long-term negative impact this technology may have on the environment.

GLOBAL MARKETS AND TRADE

Recent trade agreements such as GATT and NAFTA are creating significant opportunities to expand international markets for U.S. agricultural products. However, with the increased trade liberalization, U.S. agriculture faces a transition away from a system of commodity price supports to market-driven pricing. To succeed in this new environment, U.S. farmers will have to rely on the latest information and newest technology. Economic research also is needed to support decision-making at multiple levels from what to plant on the family farm to negotiations of international trade agreements.

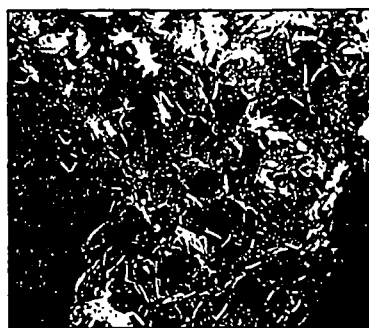
Where are the most promising growth markets for U.S. agricultural products? Will developing countries achieve sustainable agricultural practices or economic development that allows them to participate in world trade markets? Or will they stumble, fostering conditions for hunger, malnutrition, and political unrest? How can we overcome unfair trade barriers to U.S. agricultural products? These questions must be addressed if agriculture and its related activities are to continue to be major contributors to our nation's economy. Only through scientific and technological advances, coupled with sound economic decision-making, can our nation's farmers successfully compete in global markets.

USDA has developed new models to aid in assessing complex trade interactions. These models effectively measure and evaluate tariff barriers to trade and estimate the economic consequences of freer trade for U.S. agricultural producers and consumers. This allows economists to identify such key growth markets for U.S. agriculture as China, Korea, Indonesia, Mexico, and Saudi Arabia. Further, USDA research shows that growth in demand for U.S. exports is likely to be greater for high-valued products, such as processed foods and meats, than for bulk commodities. Such analysis not only identifies opportunities for U.S. agricultural exporters, but provides forward-looking information that can smooth out world prices when unexpected events disrupt world markets.

ANIMAL HEALTH

Animal diseases cost the United States billions of dollars each year, which is why the USDA supports research addressing the health concerns of important livestock, poultry, and aquatic species. Much of the research conducted by the biomedical programs of the NIH, DOD, and VA is directly relevant to improving animal health. New vaccines, drugs, and other approaches to disease prevention need to be continuously added to the veterinarian's disease fighting arsenal.

Production practices that result in healthy food animals not only improve agricultural profitability and the well-being of the animals, but also improve human health. Animal pathogens may play a larger role in human health than previously thought. Some human health concerns, such as *E. coli* O157:H7 or *Salmonella* infection, can be drastically reduced through improved animal health. Recent data indicate a degenerative disease of the human nervous system may have been transmitted from cattle infected with bovine spongiform encephalopathy (BSE), also known as "mad cow disease." Unknown in the United States, it has had a devastating effect on the British beef industry. USDA scientists have developed a new test for the prion protein believed by some to be linked to BSE. This test may be a promising tool to test live animals for the presence of scrapie (a related disease of sheep) or BSE. Scientists at the National Institute of Neurological Disorders and Stroke have also developed an assay for transmissible spongiform encephalopathies for use in humans and non-human mammals. Ensuring the safety of the American beef supply will help keep U.S. agriculture competitive in world markets.



Using science and technology to control pests is one goal of the Department of Agriculture's integrated pest management research. The brown citrus aphid is just one example of a new pest that is threatening U.S. agricultural production.

PLANT HEALTH AND INTEGRATED PEST MANAGEMENT

Farmers generally lose 10 to 30 percent of their crops to pests, costing them nearly a third of their production. In addition to existing pests, farmers are continually challenged by new pests such as the Karnal bunt fungus, new races of the fungus causing potato late blight, sweet potato whitefly with associated gemini viruses, and the brown citrus aphid with the associated citrus tristeza virus. These and other pests not only reduce profitability but often threaten export markets. The sweet potato whitefly has become a devastating pest of cotton, vegetables, melons and ornamentals in the United States, causing an estimated \$500 million in crop losses annually in this country. In Imperial County, California, alone, crop losses to sweet potato whitefly have been estimated at \$100 million. USDA scientists have teamed with USDA's Animal and Plant Health Inspection Service, Texas A&M University, and private industry to develop an EPA-approved fungal pathogen that kills up to 90 percent of whiteflies in vegetables and melons. Large-scale cooperative field tests have begun to refine pest management strategies that use the pathogen in conjunction with other biological controls. The fungal pathogen reduces producers' dependence on chemical pesticides and contributes to USDA's target of 75 percent of U.S. agricultural acreage being under integrated pest management (IPM) practices by the year 2000.

The goal of USDA's IPM research is to reduce the use of synthetic pesticides by placing greater emphasis on natural controls, host resistance, cultural practices, biological controls, and biopesticides. The aim is to produce high-quality food and agricultural products, while maintaining farmers' profitability and protecting human health and the environment. Research at Texas A&M University has saved the economy \$1.5 billion per year and spared the environment from 17.3 million pounds of insecticides alone. At the same time, 20,000 new jobs in Texas are associated with IPM. One IPM program in the Rio Grande Valley for carrots destined

baby food, soup, and frozen foods reduced insecticide use by 66 percent while increasing individual farmer profits by \$22,000.

More than 40,000 farmers have significantly reduced their use of chemical pesticides on row crops, fruits, and vegetables. USDA scientists, working with their counterparts in the Land Grant university system, have provided farmers with science-based information on new pest management practices that meet agricultural production, human health, and environmental goals. Fortunately, recent scientific advances, such as in molecular biology and computer science, hold great promise for further improvements in approaches to pest management. Where effective tactics have been developed, they are widely and rapidly implemented by farmers. IPM methods are used on about half of all fruit and nut, vegetable, and major field crop acreage in the United States.

IPM in Oregon has been proven to reduce greatly the amount of pesticides applied to crops. Twenty thousand acres of Oregon apples have gone from a maximum of three miticide applications per year to less than one under IPM. Each application costs growers \$3 per acre. Determining the pest status on a regular basis of 6,000 acres of pears in southern Oregon has helped eliminate 18 pounds of active pesticide ingredient per acre for a savings of more than \$600,000 per year. An Oregon mint IPM program adds \$500,000 to the value of the crop, since processors will not buy peppermint oil with pesticide residues.

GENETIC RESOURCES

Over a century of genetics research and breeding has led to many successful improvements in plants and animals. Virtually every foodstuff and many forest species have benefited from such improvements. Recent developments in genetic manipulation and the rapid mapping of genes are opening new possibilities, from improved disease resistance, to better taste, to longer shelf life. Access to genetic resources, such as gene sequencing and mapping data, and genetic material, such as cloned genes, novel strains, wild relatives and other plant, animal and microbial germplasm, are vital to the future health of American agriculture and forestry. The development of economically, environmentally, and nutritionally important traits will be possible only if the scientific community has ready access to needed genetic resources.

The majority of agriculturally important species produced in the United States did not originate in North

America. Therefore, we need to continue to rely on other countries for valuable germplasm, which underpins our nation's crop and livestock improvement efforts. We must preserve the incredibly diverse gene pool of all plants and animals now in existence, or we risk missing important future opportunities for progress. Preservation of existing genetic diversity is integral to improving our crops and livestock. Future work in germplasm preservation and maintenance must focus on improving access to existing worldwide collections and identifying gaps that exist in these collections.

A future challenge is to establish international agreements that ensure access to genetic resources. For example, potato germplasm maintained in one country should be accessible to the global research community so that new traits, such as resistance to the fungus that causes late blight, can be incorporated into potato cultivars in areas threatened by this pathogen. Although countries have rights over genetic resources within their borders, the Administration believes that open access to such resources is important to improve agricultural species critical to global food security.

Research leading to improved storage and regeneration of germplasm in a manner that ensures its genetic integrity is of paramount importance. We must also continue to develop appropriate databases that document germplasm availability, quality, and traits. To enhance germplasm traits that contribute to improved productivity and environmental sustainability, we should encourage multidisciplinary research approaches that combine the traditional tools of breeding and selection with the new tools of molecular genetics. The public and private sectors need to collaborate on research, development, and technology transfer to ensure an adequate flow of improved germplasm for major food and fiber species.

The genetic base of some important food species is dangerously narrow. This is particularly true of fish and shellfish stocks used in aquaculture farming, including catfish, shrimp, oysters, and salmonids. For example, the ancestry of most of the farmed catfish stocks in the southern United States can be traced to a single source of fish in Oklahoma. This greatly increases the chance of susceptibility to new or reemerging diseases and limits the possibility of genetic improvements through breeding.

In 1995, the National Plant Germplasm System, under the auspices of USDA's Agricultural Research Service, distributed approximately 120,000 samples of seed and clonal germplasm to both U.S. (85,000 samples) and foreign (35,000 samples) requestors.

GENOMICS

Gene maps are powerful tools with which to genetically improve plants, livestock, and other beneficial organisms. Such maps and their associated DNA markers are useful for improving the accuracy of selection of desirable new genotypes, moving new genes into populations, and characterizing potentially valuable germplasm populations. USDA scientists, working in collaboration with researchers from State Agricultural Experiment Stations, have produced genetic maps of important animals (cattle, swine, sheep, and poultry) and plants (corn, soybean, loblolly pine, wheat and others), which can be accessed electronically.

In general, the quality of these maps must be improved before their full potential can be brought to bear on new crop and breed development. The focus of USDA research in the area of animal genome mapping for the next five years will be on the development of markers for use in selection schemes for each of the livestock species. For plant gene mapping efforts, continued work is needed on improving the resolution of various maps and on the isolation of genes that confer desirable traits. In addition, considerable effort needs to be given to database development and the development of libraries of large genome fragments to facilitate gene identification and isolation.

Intellectual property rights associated with genetic resources need to be addressed. While promoting technology transfer and application in major crops, such as corn and wheat, patenting genetic resources and methods of genetic modification may actually impede the commercialization of biotechnology-derived minor crops, such as vegetables. Companies holding patents on enabling biotechnologies and genes may not be inclined to issue licenses for minor uses. We need to ensure that breeders of minor crops have access to the genetic resources and techniques needed to maintain the competitiveness of the minor crops industry.

The livestock gene maps developed at the U.S. Meat Animal Research Center in Clay Center, Nebraska, have over 1,300 markers for cattle, 1,100 for swine, and 500 for sheep. The poultry map developed in cooperation with Michigan State University has over 600 markers, and is being integrated with the United Kingdom's poultry map.

USDA is supporting research, through the National Research Initiative and the Agricultural Research Service, on gene mapping, identification, and characterization of over 40 crop species.

INVESTING IN A BALANCED AGRICULTURAL RESEARCH PORTFOLIO

Agricultural research supported by the federal government requires a balanced science and technology portfolio that encompasses a broad range of activities from fundamental to applied and developmental research. Private sector research spending in agriculture has grown more rapidly than that of the public sector and now accounts for more than the combined level of federal and state funding. While private sector research spending has taken over an increasing share of the developmental research (that portion of research that promises adequate economic returns to investors), the opportunities for developmental research and continuing technology advances depend on advances in research funded by the Federal government and primarily conducted by the USDA's Agricultural Research Service and State Agricultural Experiment Stations.

As in other research areas, the Administration has made a clear commitment to enhancing the quality and accountability of Federally funded agricultural research. Rigorous peer-review, the hallmark of American science, has been promoted annually by the Administration through the budget-setting process; science programs that are based on merit review with peer evaluation are a priority. The new Fund for Rural America, supported by the President and established in the Federal Agriculture Improvement and Reform Act of 1996, has strong merit-review provisions. These provisions are written into the program's authorizing language and will be implemented through peer evaluation. The National Research Initiative (NRI) utilizes excellent competitive peer-review procedures. Peer review procedures used by other USDA research programs (intramural and formula funds) are being assessed to determine how they can be improved.

SUPPORT FOR FUNDAMENTAL AGRICULTURAL RESEARCH

Increased support for fundamental research programs in molecular and cellular biology, physiology, and ecology has expanded our understanding of fundamental processes such as pathogenesis, genetic disorders, nutrition, photosynthesis, nitrogen fixation, and evolution. Better understanding of these and other biological processes leads directly to a more secure and economically competitive food and fiber supply. In addition to basic research in the biological sciences, it is important to recognize the important contributions that research in chemistry, physics, engineering, and social sciences

like in agriculture through the development and adoption of new enabling technologies and instrumentation. There is a clear need to maintain our Federal investment in the full range of agriculture-related science and technology activities, but investments in fundamental research are expected to generate the highest yield. Therefore, the Administration will continue to provide strong support for the NRI and other programs supporting fundamental agriculture research.

SUPPORT FOR APPLIED AGRICULTURAL RESEARCH

Agricultural problems often are based on specific soil, climate, or production systems that are unique to a particular region of the country. Therefore, much applied agricultural research needs to be conducted at the local or regional level, and funding should be based on priorities set regionally or locally. In addition to USDA's geographically dispersed intramural programs, support of applied research has been achieved primarily through state support and through various formula programs where Federal funds are distributed directly to State Agricultural Experiment Stations. Although this system of Federal support for applied research has substantially leveraged Federal investments, it has come under growing stress because Federal formula funds have not grown as fast as research costs and because research funds have declined in some states.

Several steps could be taken, and in some cases are under way, to improve the effectiveness of the current formula-based funding programs. State Agricultural Experiment Stations are downsizing. Downsizing requires careful attention to priorities, with most institutions supporting existing specific areas of excellence. Severe reduction or elimination of programs is forcing institutions to take a more regional approach to addressing the needs of their clientele. Often, they rely on expertise found in a neighboring state. In addition to downsizing, experiment stations are improving their use of formula funds through creative local funding mechanisms. For example, some experiment stations have established competitive peer-reviewed funding programs with their formula funds. Others use these funds to support young investigators or special projects.

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Urea is widely applied as a nitrogen fertilizer because of its cost-effectiveness, ease in handling, and high nitrogen content. However, it is not efficiently used by plants. Most of what is applied to fields is degraded by soilborne microorganisms into volatile ammonia, which is often toxic to plants. USDA's National Research Initiative has supported research on the enzyme responsible for the degradation, urease, to determine how the enzyme works as well as its molecular structure. A better understanding of urease sets the stage for developing safe, effective inhibitors of the enzyme to improve the efficient use of urea by plants.

Ethylene is a chemically simple gas that acts as a plant hormone, regulating multiple plant processes ranging from stem elongation to root growth and fruit ripening. Work on the ethylene signal transduction pathway supported by the Department of Energy's Division of Energy Bio-sciences has led to the first isolation of a plant hormone receptor. These studies show that plants sense this gaseous hormone through a combination of proteins that resemble signal transduction pathways previously described in bacteria and yeast. Genetic manipulation of these proteins will provide new tools for modifying plant growth and development for increased crop and biomass productivity.

The Departments of Energy and Agriculture and the National Science Foundation have cooperated to fund the effort to sequence the entire genome of the flowering plant *Arabidopsis thaliana*. When completed, this will be the first complete DNA sequence for any flowering plant. *Arabidopsis* is the leading model organism for the study of genetic traits that relate to plant growth and development and therefore to traits related to crop productivity. The goal is to complete the sequence by the year 2004.

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Mentoring minorities

Although our research universities remain unmatched, there have been numerous indications that stress on these institutions is increasing. The sources of stress are varied, reflecting the broader societal transformations affecting many institutions. Given the importance of the research universities and of the strong university-government partnership aimed at advancing science and technology in the national interest, the Administration is heeding a call from the President's Committee of Advisors on Science and Technology (PCAST) for a government-wide policy and administrative review of the partnership. That partnership — extending deep into the past century, when the Land Grant universities were founded — has been transformed over the last half century into the core element of our world-leading science and technology enterprise.

A multi-agency task force convened under the auspices of the National Science and Technology Council (NSTC) will: (1) identify major stresses in the areas of research, education, and administrative regulations; and (2) determine what the Federal government's role should be in addressing issues raised by this examination. The task force findings and recommendations will be presented in the summer of 1997.

The study may also review the mechanisms used to support graduate students, since the Federal government supports 20 percent of those enrolled in U.S. institutions. Since the late 1960s, the form of graduate support has shifted significantly from fellowships and traineeships, to research assistantships. Each of these mechanisms vests responsibility for the graduate training experience in different system participants. The portability of fellowships is attractive to the recipients, while assistantships delegate responsibility for the graduate research experience to faculty principal investigators. Traineeships provide funds to departments or programs with the expectation that a cadre of faculty will share responsibility for training new Ph.D.s, typically in emerging interdisciplinary research specialties or in areas of national need as identified by Federal agency missions. The optimal mix for developing the nation's scientific and engineering human capital needs to be revisited.

As we work to develop the finest scientists and engineers for the twenty-first century, human resources policy must move beyond simply the supply and demand of personnel and address the composition of the science and engineering workforce. Achieving diversity throughout the ranks of the scientific and technical workforce presents a formidable challenge; the number of women and minorities in science and engineering, relative even to professions such as medicine and law, remains low. We need to draw upon the full talent pool.

In most science fields, women receive a disproportionately smaller number of degrees than men. By the early 1990s, women were awarded 28 percent of the doctorates in science and engineering combined, with great variations by broad field — one of every two awarded in the social and behavioral sciences, one in four in the natural sciences, one in ten in engineering. Predictably, this translates into under-representation of women in the academic workforce, again with wide variations by field and institution type. At research and doctoral institutions, women represent 35 percent of the non-science and engineering faculty. Among science and engineering fields, women's faculty presence ranges from less than 6 percent in engineering and 8 percent in the physical sciences to over 20 percent in the biological and social sciences and over 40 percent in psychology. The picture in 1993 is similar in comprehensive and liberal arts institutions and in public and two-year institutions, except that the women are better represented in all fields.

Participation of racial and ethnic minorities and persons with disabilities leaves much room for improvement and continued policy considerations. At all degree levels in U.S. science and engineering, African-Americans, Hispanics, and Native Americans remain under-represented. In any given year of this decade, minorities awarded the Ph.D. in a science or engineering field still number in the tens. The trend in minority admissions and degree awards is not encouraging. Thus, the pool of prospective faculty is not increasing fast enough.

Today, the science and engineering workforce hardly reflects the face of America. But by 2010, about half of America's school-age population will be from minority groups, emphasizing the importance to the nation of broader participation in science and engineering careers. Expanding such participation will require drawing on and developing talent at all stages of educational preparation leading to advanced study. For example, only a small fraction (perhaps one-eighth) of all high school graduates have the mathematics and science preparation that would permit advanced study in a technical field; for under represented minorities, the fraction is only half as much.

The work of individuals and organizations to inspire and mentor young people, and offer role models is crucial. To recognize this, the annual Presidential Awards in Science, Mathematics, and Engineering Mentoring were established in 1996. Ten individuals and six organizations were honored for their outstanding mentoring efforts that have encouraged significant numbers of minorities, women, and disabled persons to succeed in these fields.



The first recipients of the Presidential Awards for Excellence in Science, Mathematics, and Engineering Mentoring. At the White House in September 1996, the honorees included ten individuals and six institutions that have been exemplary in their encouragement of minorities, women, and people with disabilities to pursue careers in scientific and technical fields. President Clinton noted that they would "serve as examples to their colleagues and will be leaders in the national effort to train the next century's scientists, mathematicians, and engineers."



1996 PRESIDENTIAL AWARDS FOR EXCELLENCE IN SCIENCE, MATHEMATICS, AND ENGINEERING MENTORING

INDIVIDUALS

Martha G. Absher, Duke University, Durham, NC
Howard G. Adams, National Institute on Mentoring,
 Georgia Institute of Technology, Atlanta, GA
Diola Bagayoko,
 Southern University, Baton Rouge, LA
Joaquin Bustoz, Arizona State University, Tempe, AZ
Carlos G. Gutierrez, California State University-Los
 Angeles, Los Angeles, CA
Janet S. Herman, University of Virginia,
 Charlottesville, VA
Susan J. S. Lasser, Clemson University, Clemson, SC
Melvin B. Robin, Science High School, Newark, NJ
Walter S. Smith, University of Akron, Akron, OH
Richard A. Tapia, Rice University, Houston, TX

INSTITUTIONS

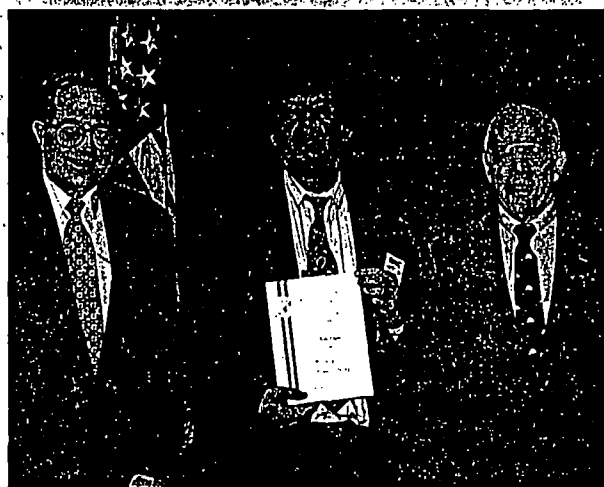
Columbia University Double Discovery Center,
 New York, NY
Dartmouth College Women in Science Project,
 Hanover, NH
**National Action Council for Minorities in
 Engineering, Inc. (NACME)**, New York, NY
New Mexico MESA, Inc., Albuquerque, NM
**Oregon Graduate Institute of Science &
 Technology Saturday Academy Program**,
 Portland, OR
University of Maryland Baltimore County,
 Baltimore, MD

TELL THEM, "YES, IT'S POSSIBLE."

As a poor Mexican American child, Richard Tapia knew he excelled in math and science, but how his technical abilities could lead him out of inner city Los Angeles seemed uncertain. "I just needed someone to tell me, 'Yes, it's possible.'"

Tapia, now director of Rice University's Department of Computational and Applied Mathematics, recalls several teachers who went the extra mile and encouraged him to "take your talent and love of math and make a career out of it." While building impressive academic and professional achievements, including nomination by President Clinton to the National Science Board that governs the National Science Foundation (NSF), Tapia has never forgotten that one positive statement can change someone's life forever.

In addition to teaching and research, Tapia began and now directs all outreach programs of the NSF-funded Center for Research on Parallel Computation at Rice. In less than ten years, these programs have trained and encouraged more than 750 students and 700 teachers, especially under-



Honored for his mentoring efforts, Richard Tapia of Rice University is flanked by Neal Lane, National Science Foundation Director (L) and John Gibbons, Assistant to the President for Science and Technology.

represented minorities and women, to pursue careers in mathematics and science. He is as comfortable speaking to a class of second-graders as to a graduate school seminar. All the while, he is urging his network of teachers, students, and community leaders to interact with each other to make the world a better place.

Today, the importance of role modeling and mentoring is recognized at the highest levels. In 1996, Tapia, along with nine other individuals and six institutions, received a Presidential Award for Excellence in Science, Mathematics, and Engineering Mentoring. The awards are bestowed by the White House Office of Science and Technology Policy through the National Science and Technology Council. They recognize outstanding mentoring efforts and programs that enhance the participation of individuals from groups under-represented in these fields, namely minorities, women, and persons with disabilities.

effect of social policy changes on child well-being and service delivery and data sources needed to monitor change.

- **Longitudinal Studies.** The 1998 budget requests additional funding for an Early Childhood Longitudinal Study (ECLS), which is to provide a comprehensive and reliable set of data that may be used to describe and better understand children's preparation for school, key transitions during their educational careers, their experience in kindergarten, pri-

mary, and elementary grades, and how their experiences relate to their likelihood of succeeding in school. The study would encompass both a birth and kindergarten cohort.

Long-term follow-up studies of children provide the best means for assessing how child development in "normal" conditions compares to what occurs in adverse conditions, and how childhood and adolescent interventions can best be targeted to the childhood antecedents of adult disease to prevent or delay the onset of problems in adult life.

Tapia's example is remarkable, but it is not unique. He and his co-recipients share President Clinton's belief that the nation's future prosperity depends on producing the finest scientists and engineers for the twenty-first century, and that we cannot afford to ignore the talents of people who may be outside the economic and social mainstream.

Another award winner, Martha Shumate Absher, firmly believes that outreach is done one individual at a time. Absher is director of outreach for the NSF Engineering Research Center for Emerging Cardiovascular Technologies at Duke University. She recalls a deaf undergraduate student she met when she visited Washington, D.C. to interview Gallaudet University candidates for her summer program. He was a "superb computer scientist," she recalls; but he was discouraged and worried about how to support his wife and the child they were expecting. He needed a job and was considering dropping out of school. She arranged a paid research internship for him in industry for one semester and, after the baby was born, brought the young father to Duke for the summer program. "He did a wonderful job," and was inspired to apply to the University of Maryland Computer Science Department, where he is now enrolled. Without her program's support, "who knows if he could have continued?" Absher muses. "He might have been lost to the whole educational system."

Absher's program provides laboratory research experience, and develops mentoring relationships with students from six universities, including Gallaudet and five Historically Black Colleges and Universities. Students from her program often become mentors to other students. She concentrates on follow-up because students who face challenges, such as disabilities, are often unable to turn one positive experience into continued career development.

Absher and Tapia believe that government support has literally changed the lives of students who otherwise would be unable to make the move from high school to undergraduate school to graduate school. Both express surprise that their award has made a difference to them but say that the personal recognition, and the visibility brought to their programs, helps them toward their goal of developing a pool of highly trained scientists and engineers that reflects our diverse population. Especially for those students who must overcome long odds to pursue a technical career, mentors such as Tapia and Absher can be all-important figures because they believe it when they say, "Yes, it's possible."



Martha Shumate Absher of Duke University was honored at a White House ceremony for her outstanding efforts to encourage minorities and persons with disabilities to pursue scientific and technical careers.

Scientific research must be linked to policy. The Administration will establish, under the joint auspices of the Domestic Policy Council and the National Science and Technology Council, a multi-agency working group to help shape the Federal research portfolio on the health, education, and well-being of American

children to provide systematic research input to policy development, and to assist in outcome evaluation. We owe this to our children, our families, and our nation as a sound investment in the national interest.

Moreover, during the Florio years, New Jersey experienced a sharp drop in property values, leaving owners with the worst of all possible worlds: falling property values and rising property taxes.

Since I assumed office, the state budget has risen 3 percent, a noteworthy accomplishment in a state in which, historically, the budget has doubled every six years.

The former governor is disingenuous at best and misleading at worst when he claims that my

So Florio's advice to President Clinton that he shouldn't underestimate the impact of tax cuts is well-intentioned. After all, in New Jersey, tax cuts have put \$1.2 billion back into paychecks of working men and women, have helped create 140,000 new jobs and have kept property tax increases at some of the lowest levels in years. None of that should be underestimated.

The writer is governor of New Jersey.

Jessica Mathews

The Aliens Among Us

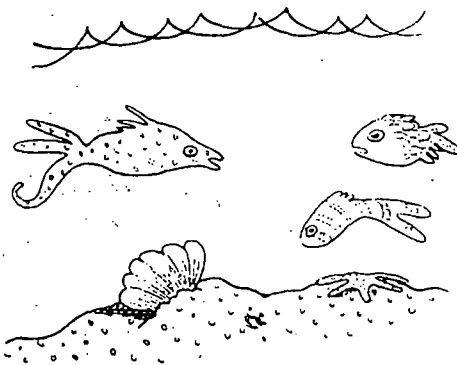
Last month, headlines blared the apparent discovery of fossils of bacterial life from Mars. Reporters couldn't write enough about it. Philosophers and clergy pondered the ultimate mysteries on uncounted talk shows.

No surprise in all that; I guess, though the depth of our cosmic loneliness was strikingly evident in how little attention was paid to the discoverers' cautions about the uncertainty in their claim or to the fact that, if real, these were fossils of life that existed billions of years ago.

What is surprising, weird in fact, is how little attention was paid to the more recent announcement of the discovery of a new form of life here on Earth, one whose chief author believes opens "a wholly new view of the universe." Media that headlined the Mars story buried the Earth story or ignored it.

The announcement was of the sequencing of the entire genome of a strange organism discovered near a place on the ocean floor where superheated water pours out of a vent. This eccentric beast flourishes at near boiling temperatures under pressures of 200 atmospheres, far beyond the sun's reach. All it needs to live is nitrogen, carbon dioxide and hydrogen, from which it makes methane (natural gas).

Its gene sequence revealed that this methanococcus is in fact a member of a previously postulated form of life called archaea. The two living domains that schoolchildren are taught about—prokaryotes, bacteria with no nucleus; and eukaryotes, complex organisms from yeast to humans whose cells have a nucleus—are now



BY MARGARET SCOTT

joined by a third. Textbooks will have to be rewritten. The gene sequence proved a 20-year-old hypothesis that until now has been considered highly controversial, if not downright nutty.

More than half of the genes of this amazing organism turned out to be unrelated to any previously known genes, a staggering result. Even odder, while some are closely related to bacterial genes, others, that direct the cell's information processing, are similar to eukaryote genes, even to human genes. Archaea, it seems, partake of both the known domains and may be either their common ancestor or a giant step on the way to the discovery of the root of life.

In this kingdom are creatures that seem like pure science fiction. They violate many of the

failed '70s socialist policies, are witholding millions in desperately needed assistance until Meles changes or is replaced. The absence of democracy thus undermines the very goals the international community seeks to preserve.

Asrat and his followers—despite state-sponsored murders, frame-ups, torture, arrests and "disappearances"—have pledged themselves to nonviolence. This rarity in African

painful, messy and may cost lives, but these small dictators have a way of coming entrenched.

The longer the inevitable confrontation is delayed, the higher will be the ultimate price in violence and suffering.

The writer is an American adviser to the All Amhara People's Organization, an opposition party in Ethiopia.

Jack, We can work some of this (Science 23 Aug. 12) primary source into your crisis in Science at GW

supposed requirements for life. Some archaeons can live at zero degrees centigrade. Others thrive above the temperature of boiling water. Another can survive more than a million rads of radiation, making it the likely victor had the Cold War ever erupted in nuclear holocaust.

All this would be enough to stop us in our mental tracks with the realization of how little we know about life on Earth, even if the archaea comprised only a few, peculiar organisms. As it turns out, living under our noses on this planet we think we know so well is a previously unrecognized form of life that accounts for an eye-popping one-third to one-half of all the biomass on Earth, much of it in the oceans.

There are several dimensions to this. First, of course, is the tremendous excitement, mystery and scope of discovery that lies ahead in the natural sciences. Biology is going to be the revolutionary science of the next century, as physics has been for this one. Genome sequencing will provide a more powerful tool for understanding the origin of life than the hit-or-miss search for fossils. Behavioral science and molecular genetics will converge, yielding unimagined insights. Ecology is now only in its infancy.

There's no end to the mind-bending possibilities. You thought that natural gas was a fossil fuel? Well, the genes of this organism and other methane-producing archaeons might make it possible to produce natural gas as a renewable energy supply.

Discovery of the archaea also underlines, in a way no sane person can ignore, the scope of what we don't know about our planet. We know

more about the surface of the moon than about Earth's deep oceans. We do not know to within a factor of 10 how many species live with us (most of the uncertainty involves the number of insects) or, therefore, what percentage are being lost.

Environmentalists agonize over the resulting dilemma: They fear that greater public awareness of what we don't know might encourage inaction rather than be understood as the reason for greater precaution in human activities that could be changing who knows what. That a species can create a continent-sized hole in the stratosphere and not realize it for more than a decade is reason to worry about what we might inadvertently do next.

The final irony in our enormous excitement about extinct life on Mars and indifference to new life on Earth is that the archaea, with their preference for extreme conditions and their independence of the sun's energy, are the perfect candidate for alien life. "I would be surprised," says Craig Venter, leader of the gene-sequencing team, "if we don't find organisms similar to this at some stage on other planets." Perhaps archaea or something like them on a falling meteor from Mars first seeded Earth's primeval hot oceans. Perhaps these organisms will be Earth's first colonists to other planets.

One thing we know for sure. We don't need to look to outer space for heroic science: There's plenty right here.

The writer is a senior fellow at the Council on Foreign Relations.

Program
#2

inner-city areas is about 50 percent. Public health measures require an immunization rate of 80 to 90 percent of all children to prevent the spread of outbreaks.

IMMUNIZATION

One of the greatest public health success stories for children is development of vaccines against the infectious diseases of childhood. Work continues today to develop more vaccines and assure that they are used for maximum benefit.

NIH- and FDA-supported research has led to the creation of important vaccinations that have been instrumental in reducing childhood illness. For example, Hemophilus influenza type b meningitis used to infect 15,000 children yearly, and was the leading cause of acquired mental retardation in the United States. The vaccine these agencies developed has nearly eliminated the disease in just six years.

NIH serves as the lead agency within the Public Health Service on the Children's Vaccine Initiative, a global effort launched in 1990 to accelerate the development of safe, inexpensive, orally administered vaccines. Work is under way on redesigning existing vaccines and developing new vaccines against rotavirus diarrhea, pneumococcus, meningococcus, Shigella dysentery, and other diseases.

CDC research showed that linking immunization services with WIC clinics could significantly increase immunization coverage of low-income children. In 1994, CDC and USDA developed a coordinated strategic plan to improve the immunization and general health status of WIC participants under two years of age. CDC also helped to develop immunization registries, a critical tool to achieve the National Goal for the Year 2000 of having at least 90 percent of two-year-old children fully up-to-date with their recommended immunizations. These and related efforts have brought us to the highest levels of immunization of children in the Nation's history.

I. Introduction

By the mid-1950s, the threat of infectious diseases appeared to be receding in the United States. Deaths from infection, commonplace in our grandparents' time, were no longer a frequent occurrence. American physicians used fast-acting, effective drugs to combat often fatal bacterial diseases such as meningitis and pneumonia. The incidence of childhood diseases such as polio, whooping cough, and diphtheria, was declining due to the use of vaccines. Meanwhile, in other parts of the world, chemical pesticides like DDT were lowering the incidence of malaria, a major killer of children, by controlling populations of parasite-carrying mosquitoes.

As it turned out, our collective — and quite understandable — euphoria did not take into account the extraordinary resilience of microbes, which have a remarkable ability to evolve, adapt, and develop resistance to drugs in an unpredictable and dynamic fashion. Moreover, disease-carrying insects have developed resistance to pesticides in a very short time.

Today, most health professionals agree that new microbial threats are appearing in significant numbers, while well-known illnesses thought to be under control are re-emerging. Most Americans are aware of the epidemic of the acquired immunodeficiency syndrome (AIDS) and the related increase in tuberculosis (TB) cases in the United States. In fact, there has been a general resurgence of infectious diseases throughout the world, including significant outbreaks of cholera, malaria, yellow fever, dengue, and diphtheria, as well as illnesses caused by antibiotic-resistant bacteria. There has also been a resurgence of fungal infections for which there are very few treatments. Furthermore, the incidence of AIDS is increasing in many countries.

New diseases have also appeared within the United States, including Lyme disease, Legionnaires' disease, and most recently, hantavirus pulmonary syndrome (HPS). HPS was first recognized in the southwestern United States in 1993 and has since been detected in more than 20 states and in several other countries in the Americas. Other new or

re-emerging threats in the United States include multi-drug resistant TB, antibiotic-resistant staphylococcal, enterococcal, and pneumococcal infections, and diarrheal diseases caused by the parasite *Cryptosporidium parvum* and by certain strains of *Escherichia coli* bacteria. In fact, only one antibiotic remains consistently effective against common hospital-acquired staphylococcal infections. Meanwhile, the number of new antibiotics introduced into the U.S. market has declined; not one new

Savings Due to Vaccination

Smallpox: The economic benefits of the Smallpox Eradication Program have been substantial for all of the countries in the world, as preventive measures and treatment facilities for smallpox are no longer needed. The cost to the United States for the successful 13-year campaign to eradicate smallpox throughout the world was about \$30 million. Since smallpox was eradicated in 1977, the total investment has been returned to the United States every 26 days.

Polio: Once a common cause of disabilities or death, polio has been eliminated from the Americas. The current drive towards global eradication is one of the great challenges of our generation. Once the global eradication program is completed (target date: 2000), the United States will save millions of dollars yearly on vaccination costs alone, since there will no longer be a need to immunize new births. Based on the current rate of progress towards eradication, WHO predicts a global savings of \$500 million by the year 2000, increasing to savings of \$3 billion annually by the year 2015.

Other Infectious Diseases of Childhood: Health economists estimate that for every dollar spent on the measles/mumps/rubella vaccine, \$21 are saved; for the diphtheria/tetanus/pertussis vaccine, \$29 are saved; and for the polio vaccine, \$6 are saved.

and CDC. Reliable lines of communication must be established to ensure that surveillance information is received promptly enough to control outbreaks before they spread. A list of clinical circumstances that require high-priority surveillance efforts is shown on page 23.

Diagnostic Tests. Work with WHO, national public health authorities, universities, and research centers to implement WHO's country-level objectives. This entails determining which "common" diseases should be diagnosed within a country and which "uncommon" ones should be referred to reference laboratories. It also requires that diagnostic tests be made available through a regional laboratory referral and distribution system.

Develop simpler, more cost-effective procedures to determine the causes of disease. Ideally, these procedures should be simple enough for use in the field when laboratory facilities are not available.

Support basic and applied research on infectious microbes, especially on pathogens for which there are no reliable diagnostic tests. The new tools of biotechnology should be exploited to speed these efforts.

Response. Enhance the capabilities of U.S. Government agencies and existing disease-specific networks (see page 50) to respond to recognized outbreaks identified through improved surveillance. Also, rebuild and coordinate the relevant technical resources of U.S. Government agencies such as CDC, DoD, USAID, and FDA.

Diseases that are transmitted by different routes will necessarily require different control strategies. Types of response may include sanitation and hygiene measures, controlling populations of disease vectors (for example, malaria-carrying mosquitoes or rabid raccoons), drug treatment, vaccination or post-exposure prophylaxis, or education to decrease human behaviors that cause spread.

Interdisciplinary Research to support Control and Prevention.

Form linkages between

- Experimental biologists and epidemiologists both here and abroad.
- The global infectious disease network and environmental and climatic research programs.

Encourage collaborative research to determine the causes of epidemics, devise strategies for control and prevention, and identify environmental and climatic conditions that favor the emergence of pathogenic microbes.

Prevention Through Immunization: The Search for an Effective Pneumonia Vaccine

The largest killer of infants and young children in developing countries are acute respiratory infections, mainly pneumonia, which claim the lives of an estimate 3.8 million children under age 5 every year. While appropriate case management using common antibiotics has been very successful in treating these diseases, the emergence of antimicrobial resistant strains suggest that this success may be relatively short-lived. One way to avoid problems with resistance is to prevent the infection from occurring using safe and effective vaccines.

Through its Children's Vaccine Initiative, Project USAID is initiating a major new program to evaluate newly developed vaccines that may protect children in underdeveloped countries. These vaccines are aimed against major bacterial and viral causes of pneumonia including *Streptococcus pneumoniae* and *Haemophilus influenzae* b. Studies in the industrialized world and preliminary studies in developing countries suggest that these vaccines, especially new conjugated versions, hold great promise.

efforts must be coordinated to prevent global pandemics, disease surveillance must be the responsibility of each sovereign nation. However, individual governments may not easily share national disease surveillance information, fearing losses in trade, tourism, and national prestige. Nevertheless, because U.S. experts are often consulted on problems of infectious disease recognition and control, the U.S. Government is usually informed about major disease outbreaks in other countries, although not always in an official or timely fashion. To ensure that we continue to be notified when an unusual outbreak occurs, we must encourage and support other countries' efforts in national disease surveillance and respond when asked for assistance. We must strive to develop a sense of shared responsibility and mutual confidence in the international effort to combat infectious diseases.

There is much room for optimism. If the United States takes the lead, we can expect that other nations will contribute resources to a global surveillance system. Both Canada and the European Union have recently decided — in spite of tight budgets — to provide substantial funds (\$7 and \$10 million per year, respectively) to strengthen infectious disease surveillance and control. It is also absolutely critical that developing nations be engaged in an international effort that is in their own interests. In May 1995, WHO passed a resolution urging member states "to strengthen national and local programmes of surveillance for infectious diseases, ensuring that outbreaks

of new, emerging, and re-emerging infectious diseases are identified." Soon after the resolution was drafted, WHO issued a report urging the strengthening of global disease surveillance and control, and encouraging greater use of WHO Collaborating Centers in this endeavor.

Are infectious disease surveillance and control cost-effective?

The direct and indirect costs of infectious disease are staggering (see Table 1). Clearly, public health measures that prevent infectious diseases can be extremely cost-effective.

In 1994 and 1995 two major U.S. health-care expenses have been for the treatment of tuberculosis and AIDS. The Public Health Service budget for fiscal year 1996 includes \$343 million to combat TB and nearly \$3 billion to combat AIDS. TB is a very old, well-known disease that has re-emerged sometimes in a drug-resistant or multidrug-resistant form. AIDS, on the other hand, is a new disease, unrecognized before the 1980s. When the first cases of AIDS and drug-resistant TB were detected in the United States, control measures were delayed, partly because of a lack of surveillance information and incomplete understanding of the epidemiology of these diseases.

Tuberculosis

For many years, the United States had in place a surveillance system to monitor cases of TB. However, during the 1980s, federal and local spending on infectious disease control

Table 1 Estimated costs of common infectious diseases in the United States, per year

Disease	Financial Cost
Intestinal infections	\$23 billion in direct medical costs and lost productivity
Food-borne diseases	\$ 5-6 billion in medical and productivity costs
Sexually-transmitted diseases (excluding AIDS)	\$ 5 billion in treatment costs
Influenza	\$ 5 billion (direct medical costs) and \$12 billion (lost productivity costs)
Antibiotic-resistant bacterial infections	\$ 4 billion in treatment costs and increasing
Hepatitis B virus infection	\$720+ million in combined direct and indirect costs

These costs, combined with dollars spent on AIDS and TB, exceed \$120 billion per year.

NEW MEDICINES

IN DEVELOPMENT FOR

HEART DISEASE & STROKE

Presented by the Pharmaceutical Research and Manufacturers of America

1997 Survey

New Medicines in Development Include 96 for Heart Disease and Stroke

Spending billions of dollars every year, pharmaceutical company research is tackling two of the nation's most vexing health problems: heart attack, the number one killer of both men and women, and high blood pressure, which afflicts about 50 million Americans.

Eighteen medicines are in development for heart attacks, which kill nearly 500,000 Americans every year, and 10 new drugs are being developed for high blood pressure, which plays a role in the more than 150,000 deaths a year from stroke. Beyond the human suffering, the illnesses brought on by uncontrolled high blood pressure cost billions of dollars annually.

Though more progress is clearly needed, great strides have been made. Heart attack deaths decreased more than 30 percent from 1981 to 1991, due in large part to better prevention, diagnosis and advancements in medicines. Treatment of heart attacks with clot-dissolving drugs, for example, has helped reduce deaths dramatically.

High blood pressure, meanwhile, is being controlled today by increasingly effective new medicines and more knowledgeable use of existing drugs.

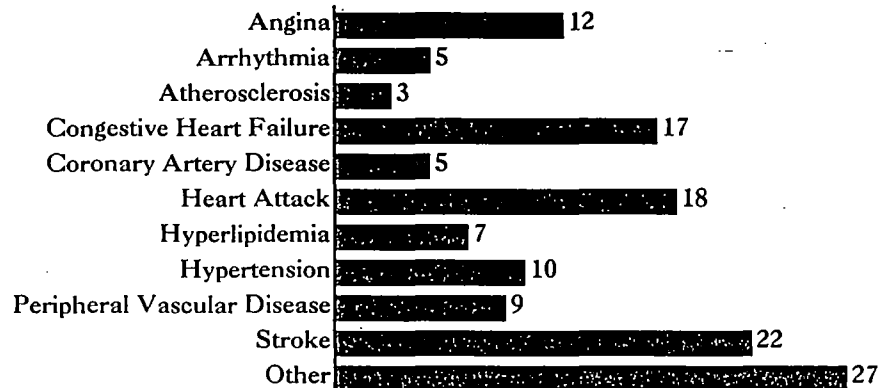
New Medicines in Development for Heart Disease and Stroke, a new report released by PhRMA, shows that 96 new drugs are in development for heart disease and stroke.

In addition to the new drugs for heart attacks and high blood pressure, other heart medicines in clinical testing or at the Food and Drug Administration (FDA) for final review include 12 medicines for angina, 9 for peripheral vascular disease, 5 for arrhythmia and 5 for coronary artery disease.

Preliminary estimates indicate that the pharmaceutical industry will spend \$3.1 billion on cardiovascular research in 1997.

The 22 medicines in development for stroke show researchers are trying to continue progress against that feared disorder.

1997 MEDICINES IN DEVELOPMENT FOR HEART DISEASE AND STROKE



In the past 30 years, the stroke death rate has declined by about 60 percent. Prevention and medicines have both played a major role in the reduction. With continued introduction of new stroke medicines and continued attention to reducing risk factors, scientists predict that Americans will be able to prevent 80 percent of all strokes by the end of the decade.

In an important step for better treatment, the FDA last June approved Activase, Genentech's genetically engineered clot-dissolving agent, as a new stroke medicine. Stroke patients, if treated with Activase within three hours, are 33 percent more likely to end up with little if any disability. The finding is based on a study conducted by the National Institute of Neurological Disorders and Stroke, published in the December 14, 1995 issue of the *New England Journal of Medicine*.

Pharmaceutical company researchers have learned more in recent years about the complex mechanisms at work before, during and after a stroke. This knowledge is leading to new and better ways to limit cell

death in the brain when a stroke occurs; helping to salvage damaged brain cells; and improving recovery efforts.

The commitment to battle heart disease and stroke is now shared by 63 companies as researchers strive to develop more effective medicines. When heart disease became the leading killer of Americans in 1921, few treatments were available to fight it. And development of new heart drugs, at first, was a slow process. When President Franklin Delano Roosevelt was diagnosed with high blood pressure in the early 1940s, doctors could only advise him to eat a low-salt diet and take sedatives.

Today, patients benefit from a wide range of medicines for heart-related ailments, including high blood pressure. And the 96 medicines now in development will lead to further progress against heart disease and stroke.

Alan F. Holmer
Alan F. Holmer
President
PhRMA

Facts About Heart Disease and Stroke in the United States¹

Heart disease is the leading cause of death in the United States; stroke is the third. These diseases together will cost Americans an estimated \$259.1 billion this year (in direct and indirect costs).

<i>Disease</i>	<i>Annual Incidence</i>	<i>Prevalence</i>	<i>Deaths</i>	<i>Hospitalizations and Discharges²</i>
Angina	350,000	7.1 million	*	152,000 discharges
Arrhythmias		4.5 million	43,431	398,000 hospitalizations 679,000 discharges
Atherosclerosis and Peripheral Vascular Disease		2.3 million	17,980	97,000 hospitalizations 265,000 discharges
Congestive Heart Failure	400,000	4.8 million	41,819 220,000**	874,000 discharges
Coronary Artery Disease		13.7 million		
Heart Attack	1.5 million		487,490	2.1 million discharges
Hyperlipidemia		97.2 million (cholesterol levels above 200)		
Hypertension (High Blood Pressure)		50 million (age 6+)	38,130 180,000**	372,000 discharges
Stroke	500,000	3.9 million	154,350	885,000 discharges

* Deaths from angina are included in total deaths from heart attacks.

** Number of deaths where disease was listed as a contributing cause of death.

Key Facts:

- An estimated 57.5 million Americans—more than one in five males and females—suffer from at least one form of cardiovascular disease.
- More than 954,000 Americans die from cardiovascular disease each year, representing nearly 42 percent of all deaths in the United States. More than 2,600 Americans die each day of these diseases—an average of one death every 33 seconds.
- One in two women (50 percent) will eventually die from heart disease or stroke.
- On average, someone suffers a stroke in the United States every minute; every 3.4 minutes someone dies from a stroke.
- An estimated 7.9 million Americans age 15 and older have disabilities resulting from cardiovascular conditions, representing 19 percent of all disabilities in the United States.
- Cardiovascular disease is the leading diagnosis in all hospital discharges—more than 5.8 million, almost equally divided between males and females.

Notes:

1. *1997 Heart and Stroke Statistical Update*, American Heart Association.
2. "Hospitalizations" refers to the number of patients admitted to the hospital for a specific cause; "discharges" refers to the number of inpatients—whether alive or dead—discharged from short-stay hospitals where some type of disease was the first listed diagnosis.

Improved Drugs Have Played a Key Role In Reducing Coronary Heart Disease Deaths

By John F. Beary, III, M.D.

Senior Vice President, Regulatory and Scientific Affairs, PhRMA

Deaths from coronary heart disease (CHD) in 1990 were 34 percent lower than in 1980, according to an article in the February 1997 issue of the *Journal of the American Medical Association (JAMA)*. The article attributes nearly half of the mortality decline to improved medicines and surgery techniques.

For many patients, heart disease risk factors are controlled by drugs that manage blood pressure, cholesterol and diabetes. Many other heart medicines are also available, including beta blockers, diuretics, antiplatelet drugs, thrombolytics and ACE inhibitors.

The JAMA article was written by a team of health policy and medical specialists from the Harvard School of Public Health, Harvard Medical School, the University of Groningen in the Netherlands and several other medical centers.

CHD is a result of atherosclerosis, which occurs when arteries become narrowed or clogged by deposits of hardened fat, cholesterol and plaque. The arteries are unable to supply enough blood for the heart's needs. This can lead to chest pain known as angina, heart attacks and

congestive heart failure (CHF).

The annual cost of CHD in the United States is close to \$80 billion and consumes about 15 percent of the U.S. health care budget. Left untreated, CHD can lead to myocardial infarction, or heart attack, the leading cause of death for both men and women in the United States. About a third of the 1.5 million Americans who suffer a heart attack each year die.

Nevertheless, the number of fatalities has decreased: treatment of heart attacks with clot-dissolving drugs, for example, has helped reduce heart attack deaths. The number of drugs for treating CHD, heart attacks and CHF has increased dramatically over the years.

Beta blockers block structures in the body called beta receptors. These drugs, by blocking the receptors, reduce heart muscle oxygen demands during physical activity or excitement. Beta blockers also help to reduce blood pressure. Additionally, the role of beta blockers in preventing second heart attacks is now well established.

Antiplatelet drugs, such as low-dose aspirin, help prevent clots from forming in coronary blood

vessels and are taken daily by many heart patients.

ACE inhibitors help regulate the heart's pumping action by preventing production of a substance that constricts blood vessels. These medicines dilate blood vessels, which helps to lower blood pressure in a phenomenon known as after-load reduction. ACE inhibitors are useful for both hypertension and CHF.

Biomedical researchers are now striving to move beyond today's arsenal of drugs for coronary heart disease and its complications. Pharmaceutical researchers are trying to develop new medicines based on gene therapy. Industry scientists are trying to find the genes responsible for myocardial cell growth in the heart so they can stimulate normal production of heart muscle and a return to normal functioning after heart attacks.

Research is also leading to a better understanding of the basic causes of atherosclerosis and vascular disease. This will lead to still more new treatments, such as targeted antibody therapies directed at reducing artery-clogging plaque.

SUDDEN INFANT DEATH SYNDROME

Sudden Infant Death Syndrome (SIDS) is the leading cause of death among infants from one month to one year of age. Though the causes of SIDS remain unknown, research efforts have facilitated scientific breakthroughs and enabled the development of public health strategies to combat it.

Research sponsored by the NIH over the last two decades has identified risk factors associated with SIDS, the effects of sleep position on infant health, and other related issues. This information led the American Academy of Pediatrics to recommend, in 1992, that babies be placed on their backs or sides to sleep. In addition, research conducted by the CPSC provided the first epidemiologic evidence that infants who sleep on their stomachs on top of soft bedding (e.g., pillows, comforters) are likely to rebreathe carbon dioxide. The research showed that rebreathing carbon dioxide trapped in bedding may have contributed to the deaths of as many as 30 percent of the infants initially diagnosed as experiencing SIDS. CPSC warned the public about the hazards of soft bedding through Safety Alerts, a national press conference, and by joining in the "Back to Sleep" public health campaign. The "Back to Sleep" campaign was launched in 1994 and sponsored by a coalition of Federal agencies, the American Academy of Pediatrics, the SIDS Alliance, and the Association of SIDS Program Professionals.

These events have been credited with lowering the percentage of babies placed on their stomachs to sleep from over 70 percent to less than 30 percent, and helping to reduce the death rate from SIDS by 30 percent in the two-year period from October 1993 to October 1995. This is a prime example of how research can be linked to practice and program development to achieve a national objective.

REDUCING CHILDHOOD LEAD POISONING: SIGNS OF PROGRESS¹⁴

Efforts to understand the extent of lead poisoning in America's children began to flourish in the 1950s, as people became more aware of the harmful effects of lead exposure and its sources. Lead poisoning adversely affects three major organ systems in the human body: the central nervous system (specifically, the brain), the kidneys, and the blood-forming organs. Children can experience lead exposure not only from lead-based house paint, but also from leaded gasoline, drinking water, and household products.

Numerous Federal agencies – the EPA, the NIH, the CDC, ASTDR, HUD, and the CPSC – have cooperated to generate the data needed to understand the consequences of lead exposure to infants and children as well as how to prevent and treat it. One of the greatest steps in protecting children's health occurred 20 years ago, when the EPA phased out lead in gasoline and the CPSC also banned lead in residential paint, coatings, and certain other consumer products.

In the 1980s, studies tracking children from birth showed that levels of lead in children's blood previously thought to be safe were, in fact, associated with serious neurological and behavioral problems such as impaired coordination, increased aggressiveness and hyperactivity, and lower IQ scores. CDC revised their screening guidelines for acceptable blood lead levels in children, from 60 g/dL in the 1960s to 10 g/dL today. In 1991, CDC recommended that virtually all children be screened for lead exposure and poisoning.

CDC, HUD, EPA and CPSC issued strategies for elimination of lead poisoning. Together, these efforts have led to a 98 percent reduction in lead levels in the air and protected millions of children against serious, permanent learning disabilities. From 1976 to 1993, the percentage of children ages one to five with blood lead levels higher than acceptable levels decreased from 88 to about 4 percent.

Though lead levels in children have significantly declined, this environmental health hazard currently affects as many as 0.9 million children age five and under. The fact remains that lead exposure is an entirely preventable childhood health problem. There is still much to be done to protect children – particularly those living in lower income areas or in older homes threatened by chipping or peeling paint and excessive amounts of lead-contaminated dust. What is more, there is a host of other environmental hazards, the effects of which on child and adolescent development are still not fully understood; even less is known about their *cumulative* effects and the risks they pose to children.

THE UNITED STATES EXPERIENCES DRAMATIC DECLINES IN CHILDHOOD IRON DEFICIENCY ANEMIA¹¹

Iron deficiency, a widely prevalent condition in America that causes anemia, has serious effects on the health and development of infants and children. Infants with iron deficiency anemia have been shown to score lower on tests of mental and motor development than their healthy counterparts. Evidence also points to long-term effects of iron deficiency at young ages including impairment in general intelligence, language capability, fine and gross motor skills, and visual integration.

Public policy efforts to reduce iron deficiency date back to the 1940s, when the NAS endorsed the addition of iron to white flour and the Food and Drug Administration (FDA) established Standards of Identity for enriched flour. By 1990, 95 percent of grain products in the food supply were enriched, contributing to a 50 percent increase in per capita consumption of iron.

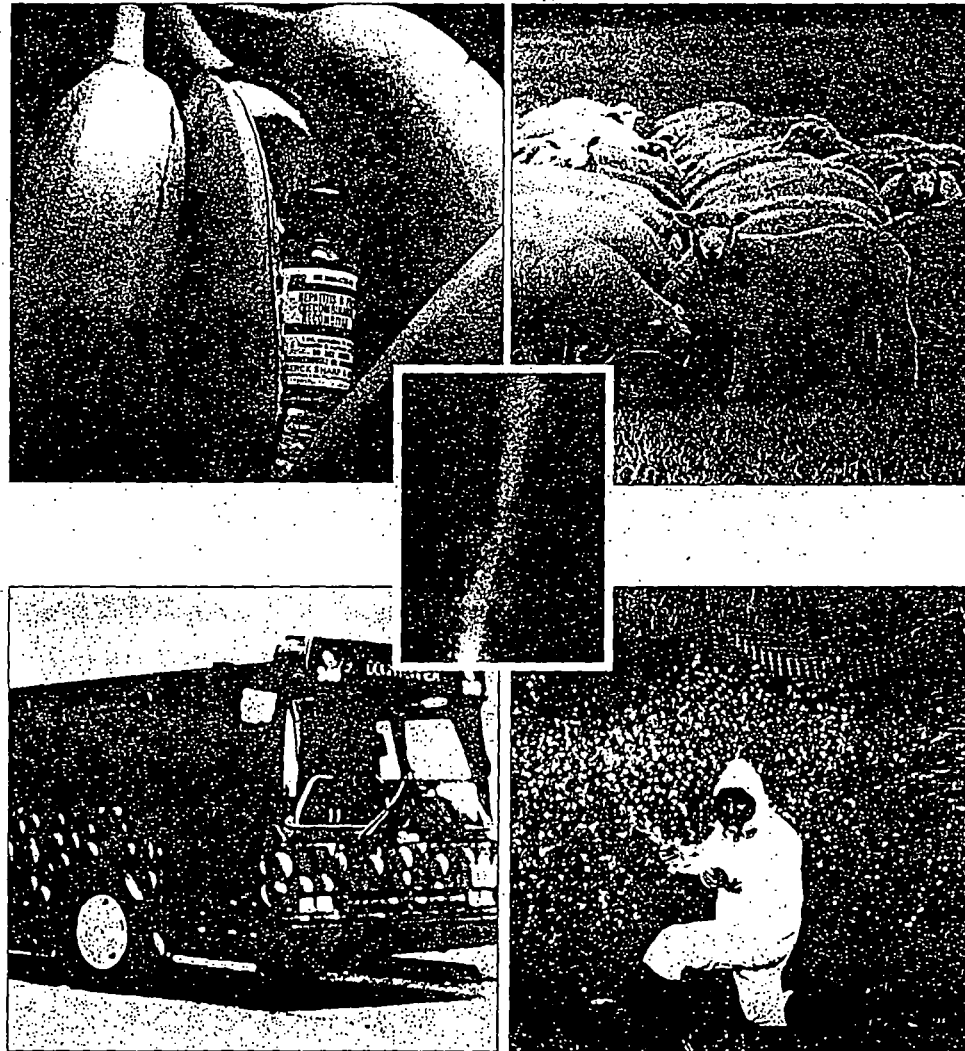
Food assistance programs directed toward specific populations have also succeeded in improving the iron status of these groups. The USDA's WIC program, established in the early 1970s, is especially noteworthy. WIC provides highly nutritious, iron-fortified food to low-income women who are pregnant or breast-feeding and to their children up to the age of five. The program also provides nutrition education and increased access to other health care and social services, including prenatal care. One of the goals of the WIC program is to reduce the incidence of iron deficiency among this high-risk population.

Research shows that the overall prevalence of anemia in children from low-income families who participated in WIC declined from 8 percent in 1975 to about 3 percent in 1985. Among inner-city infants who were given an iron-fortified formula during the first year of life, only 1 percent suffered from iron deficiency anemia as compared to about 9 percent of infants who did not receive an iron-fortified formula.

Despite these improvements, iron deficiency anemia in infants and children remains a public health concern. To assure the health and well-being of America's children and infants, continued monitoring of iron levels as well as dietary interventions are needed.

NABC REPORT 8

Agricultural Biotechnology: Novel Products and New Partnerships



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Genetic Engineering of Flavor and Shelf Life in Fruits and Vegetables

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Twenty years ago, consumers only ate fruit that was "in season." Fruit was not shipped long distances and supply was dependent on local production areas. Demand for year-round, inexpensive produce has led to consolidation of production where temperatures are warm, sunshine is plentiful, and labor is cheap. In most cases, produce is now shipped long distances before being consumed. Tomatoes grown in Mexico are trucked 3,500 miles, bananas grown in Ecuador travel 6,000 miles on a boat, bell peppers from Holland greenhouses are flown 5,000 miles to market. Unfortunately, fruit was not designed to be shipped long distances. In order to make it to market, fruit is picked before it is ripe (and before it has any taste). Despite harvesting immature fruits, post-harvest losses of fruits and vegetables still exceed 25 percent of crop production and the fruit that makes it to market has often been described as tasteless.

STRATEGIES FOR FLAVOR AND SHELF-LIFE IMPROVEMENT

Flavor can be addressed by increasing intensity (concentration) of an important chemical component of flavor. This can be accomplished by increasing production of a specific compound (e.g., sucrose), by shifting the balance of compounds (glucose versus sucrose), or by blocking production of undesirable compounds (such as starch). Genes have been isolated to explore increased sweetness. These include sucrose phosphate synthase (increased sucrose), invertase (interconversion of sugars), and ADPG-pyrophosphorylase (sugar to starch conversion).

Alternatively, flavor can be improved by delaying harvest until the fruit is ripe. Greater firmness or reduction in ethylene production can permit fruit to be retained on the vine until ripe, when it has achieved full flavor potential. Increased firmness through regulation to decrease fruit softening enzymes has met with limited success to date. Control of ethylene content appears to be more promising. Ethylene controls ripening and rotting in many fruits and vegetables. By reducing ethylene concentration in fruit, it is possible to arrest development of the fruit and permit the fruit to remain on the vine until ripe.

CASE STUDY: ETHYLENE REGULATED TOMATOES

Technology

Tomato fruits produce ethylene in high concentrations during ripening. There is a burst of ethylene production, called the climacteric, that occurs when the tomato fruit begins to turn from green to red (Grierson and Covey, 1988). The increased concentration of ethylene in tomato fruit is associated with color development, fruit softening, increased respiration, and sugar accumulation. Ethylene is a simple chemical. Its biosynthesis is understood well and the genes that are required for biosynthesis have been identified. In addition, genes have been identified that degrade intermediates in ethylene biosynthesis.

Ethylene formation is the result of a three-step biosynthetic pathway (Imaseki, 1991): Methionine is converted to S-adenosyl-L-methionine (SAM) by the enzyme methionine adenosyltransferase. SAM is converted to 1-aminocyclopropane-1-carboxylic acid (ACC) by the enzyme ACC synthase (ACC-S). ACC is converted to ethylene by the enzyme ACC oxidase. Genes encoding the enzymes involved in biosynthesis (ACC synthase and ACC oxidase) have been identified, isolated, and cloned. It is possible to use techniques to block expression of those genes, thereby blocking or reducing biosynthesis of ethylene. Alternatively, enzymes have been identified in microorganisms or viruses that metabolize the intermediates in ethylene biosynthesis. These include ACC deaminase, an enzyme capable of degrading ACC, and SAM hydrolase, an enzyme capable of degrading SAM.

The process for developing genetically engineered plants with reduced concentrations of ethylene in the fruit is complicated and requires several technologies that have been developed over the past twenty years. These technologies include gene introduction into plants, selection of transformed cells, regeneration of plants from genetically transformed cells, and gene expression.

Commercial Opportunity

The principle commercial benefit of ethylene-regulated tomatoes is long shelf-life. Tomatoes blocked for ACC-synthase can survive in laboratory conditions

for 90 days. At DNA Plant Technology Corp., we completed commercial tests on a hybrid tomato variety that was blocked for ACC-S using Transwitch™ technology. In commercial tests, these ethylene-regulated tomatoes have a 40 day shelf-life. This includes harvest, five to seven days ethylene treatment to complete color development, five to seven days to ship to market, five to seven days storage in the local market at a repacker, seven days in the supermarket, and 10 days with the consumer prior to consumption. This contrasts with the maximum of 20 days for current commercial tomato varieties.

The current commercial system works as follows (How, 1991):

1. Growers harvest a tomato field two or three times during a season. All tomatoes (unless red ripe) are harvested.
2. Tomatoes are brought from the field to a packing shed where they are sorted by size and color. Tomatoes with some red color are usually sold at a discount price in the local market because they are already beginning to soften and will not survive trucking over long distances. The 90+ percent green tomatoes are placed in 25 pound boxes and treated for one to three days with 100-150 ppm ethylene, then trucked to a repacker at a local market.
3. Upon receipt, the repacker sorts tomatoes for color. Tomatoes that developed color in transit are shipped to supermarkets (or food service outlets) immediately. The remaining tomatoes receive an additional two to seven days of ethylene treatment and then are shipped to market.

Extended shelf life provides a distinct advantage throughout the chain of commercialization.

Grower: The ACC-S regulated tomato reaches full size and flavor potential, begins to degrade chlorophyll, but does not turn red in the field. At this stage, the tomato can remain in the field for several weeks without rotting or softening. This attribute affords the grower two benefits. First, all the tomatoes are harvested, i.e., no over ripe tomatoes are left in the field. This increases field yield per acre. Second, harvest costs per pound are lower because fewer total harvests are required.

Packer: Over-ripe tomatoes are sold at a discount in local markets (Florida, California, and Mexico). Because all the ACC-S regulated tomatoes that are harvested can be shipped to remote markets, revenue per pound is increased. In addition, tomatoes left on the vine generally increase in size. Large tomatoes command an average premium price of four to six cents per pound.

Repacker: When tomatoes arrive at a repacker they are sorted based on stage of ripeness. Losses at the repacker range from six to ten percent of tomatoes shipped from production areas. These are discarded tomatoes that have rotted in route or are showing signs of impending deterioration. Ethylene-regulated tomatoes are superior, with decreased losses.

Retailer: Because current tomatoes rot in two to three days at retail, orders and shipment are made daily by most large supermarkets. Loss due to rotting can reach 20 percent of product at the retail store level. Both issues are addressed by a long shelf-life tomato. Moreover, better tasting tomatoes can be sold at a premium price, resulting in increased revenue and profit per square foot in the produce section of the supermarket.

Consumers: Because ethylene-regulated tomatoes are left on the vine until they reach full maturity, the consumer purchases a better tasting tomato. Moreover, there should be a significant reduction in the number of rotten tomatoes in consumer homes.

The commercial potential of a better tasting, longer shelf-life tomato that is sold at a premium price can be quantified as follows:

per 100 lbs. harvested	standard	ethylene controlled
Revenue	\$20.00	\$60.00
Costs	\$16.00	\$38.00
Margin	\$ 4.00	\$22.00
Margin %	20%	37%

INTELLECTUAL PROPERTY

The technology that is required to make an ethylene-regulated tomato is the subject of several patents and represents a mine field that must be successfully navigated prior to introducing a product to market. The present intellectual property situation is as follows:

Germplasm: Nearly all commercial acreage of fresh market tomatoes is grown using proprietary seed developed by a seed company. The open pollinated, publicly available varieties (e.g., Rutgers, Floradade) cannot compete with current hybrid varieties in yield and disease resistance, hence genetically engineered open pollinated varieties are not commercially viable. As proprietary seed is controlled by seed companies, relationships must be negotiated with seed companies to obtain access to parental seed for genetic engineering. The largest tomato seed companies are Seminis, Ferry Morse, and Sun Seeds. Other companies with breeding capability have developed proprietary tomato germplasm using breeding or cellular genetics (Morrison and Evans, 1996). In addition to hybrids and the protection inherent in segregation of hybrid seeds, most companies also seek Plant Variety Protection Certificates on one or both of the hybrid's parents. Those layers of protection, along with seed production capability, assure seed company involvement in commercialization of genetically engineered tomatoes.

Gene Introduction: There are two methods available for gene introduction into tomatoes. *Agrobacterium tumefaciens*-mediated gene transfer is the preferred method. *Agrobacterium* plasmids are modified to incorporate desired promoters and genes and the natural infection behavior of the bacterium is used to deliver the DNA into plant cells. Broad claims have not been issued on this technology. However, several components of this technology, such as the use of binary vectors, are the subject of patents. A secondary gene introduction method is ballistics. Ballistics uses some method to shoot DNA into plant cells. Variations on the type of microprojectile and the acceleration device have been optimized during experimentation for different crop plants and likely would need to be optimized for tomatoes. DuPont Corp. has claims in a U.S. patent that are directed to the ballistics technology. Other patents are issued or pending on various modifications of the ballistics approach for specific plant species.

Plant regeneration: Regeneration using standard tissue culture methods is routine in tomato. The method using leaf pieces of tomatoes as explant material has been used in several laboratories since the early 1980's. No broad patents cover the commonly used techniques for tomato regeneration.

Promoters: A wide range of promoters have been identified that will express DNA in plants. Some of these, including 35S, derived from cauliflower mosaic virus, are the subject of issued or pending patents (Fraley, et al., 1994). Much effort has been directed to isolation of tissue-specific promoters. Fruit-specific promoters in tomato would be ideal to ensure that ethylene regulation is directed to the tomato fruit and to ensure that ethylene production (involved in disease resistance) is not blocked in leaf and other tissue.

Selectable markers: Markers are foreign genes that are inserted into target plant cells at the same time as a segment of DNA that can modify ethylene. Because ethylene regulation cannot be selected in a test tube, the selectable marker permits transformed cells to proliferate while non-transformed cells die. Resistance to kanamycin (conferred by the nptII gene) is a preferred selectable marker that has received both EPA and FDA approval for use in tomatoes and other crop plants. Kanamycin resistance is the subject of an issued patent in the United States and a pending patent in Europe (Rogers and Fraley, 1991).

Genes: Segments of DNA can be patented in the United States. For ethylene, patents are issued or pending on each gene that has been identified in ethylene biosynthesis or degradation. For example, the USDA has a pending patent on the ACC-S gene that we have used. The gene isolation work was completed at the USDA in Albany, California (Oeller, et al., 1991). The USDA has licensed the gene to multiple companies within different fields to ensure broad commercialization of the government funded technology. Other genes have been isolated including ACC-oxidase (Hamilton, et al. 1990), ACC-deaminase (Klee, 1994), and SAM hydrolase (Good, et al., 1993).

Gene expression: In order to block ethylene biosynthesis using ACC-synthase or ACC-oxidase, the endogenous genes must be regulated to decrease their expression. Two methods have been used in tomatoes: Transwitch® and antisense. Transwitch® is a unique phenomenon in which some plants resulting from transformation with a homologous gene are suppressed for the target gene (Jorgensen, 1995). Antisense achieves a similar result, i.e., gene suppression, by inserting a gene sequence that is complementary to the target gene (Shewmaker, et al., 1992). Each technique is the subject of issued patents in the United States and Europe.

COMMERCIALIZATION IMPLICATIONS

Despite the demonstrated value of ethylene-regulated tomatoes, no one is presently in the market with such a product. This product has extremely high barriers to entry due to the intellectual property situation. The companies closest to market are DNA Plant Technology, Monsanto/Calgene, and Zeneca Plant Sciences. It is likely that each party will need licenses to intellectual property from other companies in order to successfully commercialize an ethylene-regulated tomato. While the current patent situation presents an additional commercialization hurdle to the three companies, it also tends to eliminate the prospect of future new entrants developing and marketing an ethylene-regulated tomato.

RESEARCH AND PLANNING IMPLICATIONS

Several general lessons have been learned from attempts to commercialize ethylene-regulated tomatoes that apply to all commercial projects using plant genetic engineering.

1. Many patents are still pending. Work initiated today using technology developed by others may never be commercialized in the absence of licenses. Many of the basic agricultural biotechnology patents have not been resolved, with broad patents still possible or likely for gene introduction and gene regulation technology.
2. In commercial or academic genetic engineering research, genes need to be inserted into the best existing germplasm. This affords an appropriate benchmark to value the technology and eases adoption of new varieties. Seed company and technology-provider alliances involving universities and research laboratories are more likely in the future.
3. The earliest product developed is not always the first to be commercialized. The complex business system of fresh market tomatoes and the complex patent situation have delayed commercialization. If a new genetically engineered variety requires modification of growing or handling practices, adoption is slow.

4. In a complex business system a novel trait may have multiple benefits. The ethylene-regulated tomato provides benefits to growers, packers, repackers, retailers, and consumers while originally targeted to increase shelf-life.

SUMMARY

The initial hurdles for commercialization of products of plant genetic engineering included technical, regulatory, and consumer acceptance. As the first products are now ready for market introduction, it is obvious that an additional major hurdle exists: intellectual property. Patents have been granted that cover a number of basic biotechnology methods and the use of specific genes for genetic engineering. For some technologies and genes, patents already have been issued and represent barriers to commercialization. For other technologies, the patents are still pending and represent an uncertainty. Indications from the first products being commercialized in cotton, corn, and soybean suggest that patents are being aggressively enforced and are being used to establish competitive advantage in the marketplace. Clearly, if broad patents are upheld by the patent office and the courts, alliances and cross licenses will be necessary for commercialization.

The modification of consumer-preferences traits could have implications for several, perhaps unintended, steps in the chain of commercialization. For example, ethylene regulation in tomato will primarily result in a tomato with longer shelf-life. However, the tomato will not be red when it reaches full maturity, can stay in the field for a longer period of time prior to harvest, requires post-harvest ethylene treatment, and results in delivery of a better tasting tomato to consumers. These features of the ethylene-regulated tomato require modification of harvest practices and modification of handling and packing procedures. Moreover, production trials and operation tests may suggest modification of pesticide practices, staking, and handling in the field; sorting, ethylene treatment, and shipping from the field; as well as packaging and pricing for the retailer. Ultimately, successful commercialization of new consumer-preference traits in fruits and vegetables requires more than simple insertion of a gene into a plant.

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Partnerships

Phytoremediation

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Phytoremediation is a new application of biotechnology — an exploitation of specific plants to clean up the environment. Plants are used to treat or remove environmental contaminants from soil and other solids like dredge spoils, water, other liquids, and air.

Plants may be viewed as the original polluters. Our earth was hospitable to methanogenic bacteria before the evolution of photosynthesis by plants, producing oxygen that now is 20 percent of our atmosphere. Oxygen forced the methanogens into anaerobic regions of the world. Now we plan to use plants to help us clean up toxic soils. Scientists at the Ag Biotech Center at Rutgers University, such as Ilya Raskin, have explored methods of using plants to treat organic and inorganic contaminants in soils, and have discovered that plants provide very effective biological processes for cleaning up and removing contaminants from the environment.

I will focus on the use of plants to remove and concentrate heavy metals. Heavy metal contaminants in the soil and water in all developed countries are a large and important worldwide problem caused by manufacturing processes and other activities of commerce dating back to the 1700s. One may view a plant as a solar driven concentrator of chemicals like metals that took 360 million years to build, test, and optimize. The scientists at the Ag Biotech Center enhanced that process so it is more rapid and useful for clean up at contaminated sites.

What is the appeal of phytoremediation? First, it is an elegant method of treating contaminated sites relative to conventional treatment methods in which contaminated soil is transferred to a landfill (which means simply moving it

somewhere), presumably for permanent storage, and then transferring uncontaminated soil to the original site. Plants leave the soil in place while removing the contamination. Phytoremediation is cost effective, while transfer of contaminated soils to a licensed hazardous waste site is expensive.

Even after 25 years of cleanup efforts and growing awareness of the dangers posed to the environment by contaminated sites, America still has a huge number of contaminated sites. The main reason for the slowness of the cleanup is the large expense of using conventional technology to clean up these sites. We must find more cost effective methods. The use of plants helps address the economic issue. This use offers owners a new method of remediating contaminated property at less cost, which presumably will accelerate the pace of remediation.

Phytoremediation is compatible with public concerns about technology. People have been concerned about biotechnology. They are frightened particularly about genetically engineered bacteria. They always will be. It is easy to frighten people about bacteria. For example, when you tell people how many bacteria there are in yogurt, it doesn't make them think better of the bacteria, it makes them quit eating yogurt. Plants are something that everyone can see; they are familiar and therefore comfortable with plants. Using plants to clean up a contaminated site is more acceptable to community members than the use of bacteria.

At the time of the Exxon Valdez oil spill, the state of Alaska decreed that no non-Alaskan micro-organisms could be used. This was the first microbial-immigration policy and it was useless. Bacteria travel on the wind, and in many other ways, and they didn't seek Alaskan regulators' permission before they entered Alaskan waters to eat the oil on the beach.

Phytoremediation is sophisticated scientifically. Technology must be developed so it can be safe, effective, and reliable.

Over the next five years the United States will spend \$43 million to treat only sites contaminated with heavy metals and heavy metals mixed with organics. That's not what would be needed to clean up all the sites. We need low-cost approaches so that we can accelerate the pace of remediation.

Phytoextraction is the subset of phytoremediation in which plants remove contaminating toxic or radioactive metals from a site by root uptake and accumulation in the plant shoots.

I will describe the use of a plant — Indian Mustard — to remove lead from a toxic site. The plants are watered with agricultural chemicals that make the lead water soluble. The water containing lead is taken up by the roots and moved into the stems and leaves where it evaporates, leaving the concentrated lead in the plant. The harvested plants may be sent to a smelter where the metal is recycled — a hazardous waste is removed from the environment and recycled to commerce. This technology, developed by the Ag Biotech Center, is the subject of a technology transfer agreement between Rutgers University and Phytotech.

Brassica juncea (Indian Mustard) has the special property of metal accumulation that was discovered at the AgBiotech Center by screening plants for metal uptake abilities. This metal uptake property is being expanded and enhanced by research including genetic engineering, mutagenesis, and selection at the Ag Biotech Center and at Phytotech. Most plants do not accumulate heavy metals in the stems or leaves and are not useful for phytoextraction. For most plants, some metal is taken up by the roots, but not much is transferred to the shoots and stems. Indian Mustard and *Amaranthis* accumulate cadmium, nickel, zinc, copper, lead, and chrome6, a widespread pollutant in New Jersey and a carcinogen.

To increase availability of lead, a biodegradable, short-lived chemical is added to the soil to cause the plants to take up the lead. An example is the metal chelator EDTA added to contaminated soil. There is a direct correlation between the amount of EDTA added and the metal uptake. We are also doing environmental impact rates and effect studies to evaluate the environmental impact, good and bad, of removing metal from the soil by growing the plants on site and adding chemicals to induce uptake and clean the site.

We are in the process of modeling, analyzing, and monitoring the impact of this approach to remediating contaminated sites. What do you do with the harvested plants following phytoextraction? We dry the plants, may incinerate them, may compost them, or may compact them by pressing followed by acid leaching and disposal, or recycling, of the heavy metal. The volume or mass of the plants that contain the extracted heavy metals is only about two percent of the volume or mass of contaminated soil. This is a 50-fold concentration.

Indian Mustard has many attractive characteristics for cleaning up toxic metal sites. It is inexpensive to grow and grows very rapidly to about five feet in about two months, producing 2-10 tons/hectare of dry weight with fairly rapid clean up of the site. We believe there are a significant number of contaminated heavy metal sites in the U.S. that could be remediated in about three years or less so that the Environmental Protection Agency or the state environmental agency would conclude that that site was safe for use. We have great hope that we will be able to use phytoremediation as an effective technology.

We have treated a site in the middle of an urban environment, Magic Marker, in Trenton, N.J. It was originally contaminated by a battery manufacturing and recycling facility located there since about 1950.

Other sites that we have examined in Trenton and other New Jersey towns were contaminated in the 1700s and 1800s by practices such as pottery making. Trenton was a big pottery making center at one time. Pottery glazes contained lead or cadmium and there is a large number of lead and cadmium contaminated sites in the city of Trenton.

The Magic Market site was blocked out, samples were taken to establish lead content, the site was plowed, and fertilizer was added. The soil on the site is dark, not because of humus, but due to the asphalt in the soil. The site was

on a parking lot. An irrigation system was installed and Indian Mustard was hydroseeded to evenly distribute the seeds without disturbing the soil.

We collaborated with the local residents. There was a Phytoremediation Day in Trenton. Through an organization called Isles Inc., we attended community meetings, told everybody that lived in the area (there are houses all around this site) what we were doing, and invited everyone to attend the first planting. The costs of those trials were paid by Phytotech, which had raised \$6 million of venture capital and has 16 employees.

As indicated in my presentation, we are enthusiastic about the role of phytoremediation in the cleanup of toxic sites.

Agricultural Biotechnology: A Farmer's Perspective

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I am particularly pleased and somewhat surprised to be a speaker today, given that I am neither a scientist nor an expert in biotechnology. Frankly, I have only a limited understanding of biotechnology. I'm just a plain ordinary family farmer from a long line of plain ordinary family farmers. However, this humble status has never prevented me from striving to make as much money as possible and I see exciting opportunities ahead to do just that: rapid improvements in the quality of crops, livestock, and livestock products; huge reductions in input usage and costs of production; and the creation of new consumer products. In fact, I expect that my family farming operation will be fundamentally changed over the next few years because of the things most of you are doing.

However, in the push to advance the field of agricultural biotechnology, farmers are often the last to be considered or consulted. Does the research always meet our production needs? Does the regulatory system provide for timely approvals of new technologies? Are farmers sought out to participate in forums like this?

At NABC 7, held in May, 1995, I met very few farmers, though I found our input in workshops much appreciated. This year, I doubt I'd see many hands raised if I asked how many people rely on farming for their income. Yet farmers are your critical link in the biotechnology path to market. We utilize the research and produce the product which then must be marketed and find public acceptance. And all this in a world where the anti-technology crowd is way out in front in shaping public opinion.

Most farmers are cautiously optimistic about agricultural biotechnology, but they need someone to take leadership in managing this controversial issue on their behalf.

of molecular genetic manipulations that have been so informative in other symbioses. It will be most interesting to determine whether any of the plant genes with a critical role in legume nodule initiation are also involved in the establishment of actinorhizal symbioses.

One significant difference between legume and actinorhizal nodules is the site at which root cells become reactivated to form nodule primordia. In rhizobial symbioses, cortical cells are activated to reenter the cell cycle, whereas in actinorhizal symbioses, pericycle cells are activated. The early phases of

initiation are therefore quite similar to lateral root development. We hypothesize that this developmental pro-

cess has an evolutionary origin of symbiosis. This review. Although Włowski and Bisseling involve from pathogenic to symbiotic? Why are nitrogen-fixing bacteria of two plant families,

whereas mycorrhizal associations are so widespread? Answers to these questions are of considerable practical value and may provide fundamental insight into the evolution and operation of many plant-microbe interactions.

CONCLUDING REMARKS

The rapid progress that continues to be made in our elucidation of plant-microbe interactions is contributing to major advances in our understanding of plant and microbe cell biology and biochemistry. On the pathogen side, studies reported in this issue provide illuminating information concerning the evolution of virulence, the signaling processes involved in symbiotic relationships, pathogenesis, and resistance responses, and the nature of protective mechanisms relevant to the ecology and survival of nonpathogenic microbes.

On the plant side, studies of plant-microbe interactions have led to the development of a wide range of model systems that can be used to probe normal cell biological processes. For example, the recent suggestion that plant pathogenic bacteria export virulence factors directly into plant cells is an exciting concept that impacts investigations of both plant and animal diseases. Similarly, identifying the host components that are involved in plant virus replication and movement should prove helpful for understanding the intricacies of plant nucleic acid metabolism. The same systems are also providing information about the role of the cytoskeleton in macromolecular targeting and the potential developmental impact of diffusion gradients that may be created by cell-to-cell transport of these macromolecules.

The practical utility of understanding plant-microbe interactions is obvious. For example, as the bases for the astounding specificity that is typical of most host resistance responses are unravelled, it should become possible to genetically en-

gineer crop plants that express novel or altered specificities and therefore exhibit broad spectrum resistance to disease. Disease control strategies based on a more detailed understanding of the intricate relationships among roots, pathogens, and beneficial microbes in the rhizosphere are also forthcoming. Strategies hinging on the deployment of decoy molecules that contribute to shifts in the expression of pathogen virulence genes or that affect the ability of rhizosphere pathogens to compete with benign soil organisms could well be realized.

It has been enormously satisfying to participate in the formulation and editing of this Special Issue of THE PLANT CELL. Collectively, the reviews in this issue offer an outstanding analysis of our current knowledge of plant-microbe interactions and the plant and microbial processes upon which they depend. The insight gained from these analyses are already impacting studies of plant development and responses to the environment. We fully anticipate that you will enjoy reading these reviews as much as we have enjoyed editing them!

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APHIS News

United States
Department of
Agriculture

Animal and
Plant Health
Inspection
Service

Rule published in FR 5-2-97
Ag Biotech

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USDA AMENDS REGULATIONS FOR GENETICALLY ENGINEERED ORGANISMS

WASHINGTON, May 1, 1997--The U.S. Department of Agriculture is amending its regulations pertaining to genetically engineered plants introduced under USDA's notification and petition regulatory processes.

"The amendment will simplify procedures for the introduction of certain genetically engineered organisms, expedite review for certain determinations of nonregulated status, and adjust procedures for the reporting of field tests conducted under notification to the biology of the test organisms," said John Payne, director for biotechnology and scientific services with the Animal and Plant Health Inspection Service, a part of USDA's marketing and regulatory programs mission area.

Developing and commercializing new genetically engineered plant varieties most often involves field testing under APHIS oversight, followed by submission of a petition for determination of nonregulated status by the agency.

APHIS grants nonregulated status to a new plant variety when it determines that the new variety has no potential to pose a plant pest risk and is as safe to grow as any other variety of the same plant.

The amended regulations will allow a broader application of existing simplified procedures for requests for movement or field testing of genetically engineered plants. They will also streamline the determination of nonregulated status for plant varieties that closely resemble other varieties that have already been through the determination process. This will enable APHIS, when appropriate, to extend the existing determination of nonregulated status for new products that do not raise new risk issues.

For plants that are being evaluated in field tests, reporting requirements have been made more consistent. For example, for trees and other long lived plants field data reports will only need to be provided upon the conclusion of the trial. However, applicants must apply to APHIS for yearly renewal to ensure appropriate measures are taken when plants become reproductively mature.

APHIS will also use appropriate guidelines to provide additional information to developers of regulated articles and other interested persons regarding procedures, methods, scientific principles, and other factors that could be considered for various aspects of its regulations. The first guidelines will provide information to help applicants on requests for extension of a determination of nonregulated status.

Payne added that USDA has the responsibility to ensure that, in releasing any bioengineered plant, no plant pest risk is presented. APHIS

- more -

*Req Ref
Streamlined
Based on Science
Speed notification process
Protect environment*

- 2 -

reviewers focus on the biology, propagation, and cultivation of the plant. The reviewers also consider the source of the engineered genes, the vector used to transfer them, and the stability of the insertion.

The original final rule which was printed in the April 24, Federal Register was retracted April 25, a month before it would have gone into effect. This final rule supersedes the previous one issued.

For further information on the regulatory changes, contact John Payne, director, biotechnology and scientific services, 4700 River Road, Unit 98, Riverdale, Md. 20737-1237; (301) 734-7602. For technical information, contact Michael Schechtman, biotechnology and scientific services, plant protection and quarantine, Unit 146, Riverdale, Md. 20737-1237, (301) 734-7601.

Notice of this action is scheduled for publication in the May 2 Federal Register and becomes effective June 2.

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NOTE: USDA news releases, program announcements, and media advisories are available on the Internet. Access the APHIS Home Page by pointing your Web browser to

<http://www.aphis.usda.gov> and clicking on "APHIS Press Releases." Also, anyone with an e-mail address can sign up to receive APHIS press releases automatically. Send an e-mail message to majordomo@info.aphis.usda.gov and leave the subject blank. In the message, type subscribe press_releases

Field Testing of New Agricultural Products Continues and Expands

Field testing of new agricultural products continues its rapid pace of expansion by approximately doubling each year. Since 1987 the Animal and Plant Health Inspection Service (APHIS) has approved or acknowledged 2,745 field trials at 11,291 field sites. The notification option, which simplifies regulatory requirements for certain field trials involving particular types of modified crops, has been in effect since 1993 and now accounts for approximately 85% of all current field testing. Since the beginning of 1994, 2,086 field trials (at 9,746 test sites) were approved or acknowledged, of which 1,781 were conducted under notification and 305 under permit. Derivatives of 48 different plant species have been field tested to date, with a wide variety of modifications (see right). Corn continues as the major crop being field tested under our regulations. In the past 2 years we have seen the first field trials involving *Arabidopsis thaliana*, barley, broccoli, carrot, chicory, cranberry, creeping bentgrass, eggplant, gladiolus, grape, pea, pepper, raspberry, strawberry, sugarcane, sweetgum, sweet potato, watermelon, and wheat.

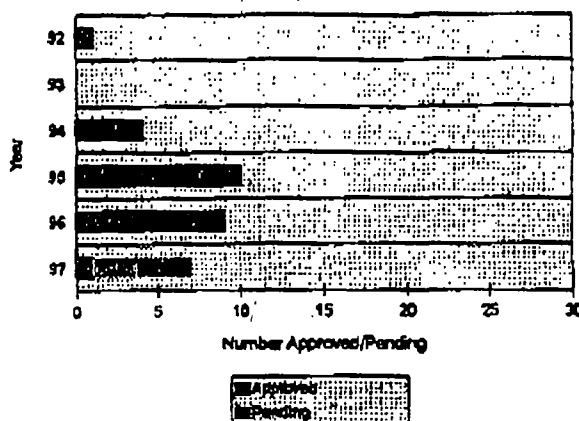
In an effort to expand public access and awareness of the progress in the development of work with transgenic plants, APHIS has made available on the Internet information on both field testing and commercialization of new varieties.

This information, which is updated daily and provides direct public access to information formerly available only upon written request, is proving useful both to companies and to individual researchers who wish to track the progress of agricultural biotechnology. The World Wide Web site can be accessed at <http://www.aphis.usda.gov/bbep/bpl>.

Some New Products No Longer Regulated

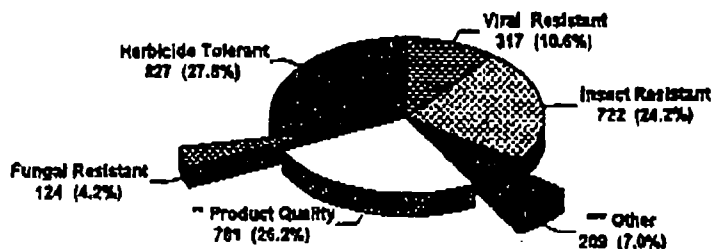
Over the past year, there has been a continuous flow of requests for determinations by APHIS that particular field-tested organisms have no potential for plant pest risk and should no longer be regulated (see right). These requests, from developers of new products produced through biotechnology, facilitate the entry of the products into the marketplace. Seventeen new products in six crop plants were the subject of such determinations in the past 23 months—

Petitions: Determination of Nonregulated Status approved and pending; as of 3/31/97



47/87

Field Releases*: Most Frequent Categories 1987 to 1997 (3/31/97)



* Permits Issued and Notifications Acknowledged

** Agronomic Properties
--- Marker Genes, Soluble Markers,
Bacterial Resistance and Herbicide Resistance

47/97

1. Insect-resistant corn, Ciba Seeds, May 1995.
2. Herbicide-tolerant corn, AgrEvo, June 1995.
3. Insect-resistant cotton, Monsanto Agricultural Co., June 1995.
4. Delayed-softening tomato, Zeneca Plant Science/Petoseed Co., Inc., June 1995.
5. Herbicide-tolerant cotton, Monsanto Agricultural Co., July 1995.
6. Insect-resistant corn, Monsanto Agricultural Co., August 1995.
7. Altered-ripening tomato, Monsanto Agricultural Co., September 1995.
8. Herbicide-tolerant corn, DeKalb Genetics Corp., December 1995.
9. Insect-resistant corn, Northrup King Co., January 1996.
10. Herbicide-tolerant cotton, DuPont Agricultural Products, January 1996.
11. Male-sterile corn, Plant Genetic Systems (America), Inc., February 1996.
12. Altered-ripening tomato, Agritope, Inc., March 1996.
13. Colorado potato-beetle-resistant potato, Monsanto Agricultural Co., May 1996.
14. Virus-resistant squash, Asgrow Seeds, June 1996.
15. Herbicide-tolerant soybean, AgrEvo, July 1996.
16. Virus-resistant papaya, Cornell University and The University of Hawaii, September 1996.
17. Insect-resistant corn, DeKalb Genetics Corp., March 1997.

Four types of products that have been approved merit particular mention here—

1. Virus-resistant squash, the first of which was approved in 1994, was the first crop considered for which there are populations of interbreeding wild relatives in the major areas of squash cultivation in the United States, and with a trait that has the potential in theory to alter the fitness of the crop plant or its wild relatives. The analysis demonstrated that there was no potential for increased woodiness of either the crop or its relatives as a result of cultivation in agriculture of the new squash variety.
2. Insect-resistant crops, of which a potato developed by Monsanto Agricultural Company was the first approved in March 1995, may have the potential to offer an alternative to the use of chemical insecticides.
3. The insect-resistant corn developed by Ciba Seeds was the first new corn variety that has been determined not to pose a potential plant pest risk. The modification in the corn line may offer the potential for control of European corn borer, which has not heretofore been effectively managed. Corn is the leading crop in terms of economic importance in the United States.
4. Virus-resistant papaya, which was approved in 1996, was the first new product developed by academic researchers in collaboration with USDA scientists.

Transgenic Arthropods and Nematodes—First Field Trials Approved

In February 1996 APHIS granted a permit for the first limited field trial release of a transgenic arthropod, *Metatetranychus occidentalis* (Acarid: Phytoseiidae), in Alachua County, Florida. This organism, a transgenic predatory mite, may be potentially useful for the control of spider mites in strawberries and other crops. The particular transgenic organism was modified only by the addition of marker DNA sequences, which are not expressed and do not alter any of its phenotypic characteristics. Upon receipt of the application, APHIS made it available to the public electronically and established an expert team for its review. An Environmental Assessment and Finding of No Significant Impact was prepared in support of the agency decision to authorize

the field trial, and these documents have also been made available electronically.

In April 1996 APHIS made available to the public a regulatory assessment and granted a courtesy permit for the controlled field testing of a transgenic nematode in Salem County, NJ after going through a similar process. The nematode, *Heterorhabditis bacteriophora*, is a native nonpathogenic organism widely distributed across the United States. It was modified with the addition of a gene encoding a fluorescent marker protein and another encoding a heat-shock response protein.

Regulatory and Policy Developments In Progress

We continually reexamine our regulations to keep abreast of the latest scientific developments to remain responsive to the demands of rapidly expanding technology and to the public. In the interest of such flexibility and responsiveness, new regulations were proposed in the Federal Register on August 22, 1995, which, if finalized, would

- Enable APHIS to extend an existing determination of nonregulated status to additional organisms that resemble the organism for which the determination was initially made
- Extend the notification system to enable field testing under performance standards of most crop plant species.

The proposed rule also announces APHIS' intent to develop guidelines on various topics relevant to our regulations to developers of new varieties and to other interested persons. In addition, the proposed rule would lessen certain paperwork requirements for the research community and for State agricultural officials. The comment period on the proposed rule closed on October 23, 1995.

International Harmonization of Regulatory Approaches

For the first time several new agricultural biotechnology products developed in the United States are entering the international marketplace as produce and as bulk commodities.

A key effort we have undertaken is to ensure that these products can enter existing export markets without the imposition of undue regulatory burdens. We are working on several fronts to bring about international harmonization of regulatory approaches for these products—

- Ongoing bilateral environmental consultations with the Commission of the European Union continue and we

have established a Permanent Technical Working Group on Biotechnology and the Environment. There are also other informal meetings with representatives of the Commission of the European Union and key trading partners to discuss policy developments on the commercialization of, and trade in, new agricultural commodities.

- Under the joint auspices of the OECD Environment and Agriculture Directorates, the United States has taken the lead in a project on the Commercialization of Agricultural Products Derived Through Modern Biotechnology. The aims of this project, which was initiated in 1994, are to assist member countries in their oversight of these organisms, specifically in their efforts to ensure safety, to make oversight policies more transparent, and to facilitate trade. A key area of work has been the development of scientific consensus documents on specific topics relevant to the environmental biosafety of transgenic plants, such as the biology of particular crop plants and issues associated with the introduction of particular traits into plants. One that has been completed concerns the use of coat protein genes from plant viruses to confer virus resistance on host plants.
- Regular meetings continue with Canada and Mexico to address safety issues relevant to biotechnology-derived commodities that are under regulatory review or already approved in one of our three nations, and to facilitate trade in these products.
- APHIS continues to be an active participant in discussions by the Conference of Parties (COP) to the Convention on Biological Diversity. The COP, of which the United States is not a member, decided to negotiate a binding protocol that may affect international transfer of certain biotechnology products, and set up an ad hoc working group to develop it. The United States is participating in those negotiations, which commenced in July 1996 in Aarhus, Denmark. The next meeting is to be held in May 1997 in Montreal, Canada. APHIS is working along with other Federal agencies to ensure that appropriate policies are agreed upon to guarantee the safe international use and development of new products derived through biotechnology.

Clinton Presidential Records Digital Records Marker

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Divider Title:
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EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20502

March 19, 1997



MEMORANDUM FOR FRANKLIN D. RAINES
DIRECTOR
OFFICE OF MANAGEMENT AND BUDGET

FROM: JOHN H. GIBBONS 
DIRECTOR

SUBJECT: AMENDMENT TO EXECUTIVE ORDER 12975 - Extending the
Charter of the National Bioethics Advisory Commission (NBAC)

The purpose of this memorandum is to seek a two-year extension of the charter for the National Bioethics Advisory Commission (NBAC). NBAC was established on October 3, 1995 by Executive Order 12975. As with other Federal advisory committees, the original charter provides for a two-year term, expiring on October 3, 1997, unless extended. Due to the length of time required for member selection and background reviews, the Commission did not meet until October 4, 1996, a full year after its establishment. (E.O. 12975, draft amendment and NBAC charter are attached.)

The President issued an initial charge to the Commission to consider protection of the rights and welfare of human research subjects, and issues in the management and use of genetic information. Then, on February 24, 1997, the President asked NBAC to take on an additional charge: thorough review of the ethical and legal issues associated with possible use of cloning technology to clone human embryos. The Commission's report on cloning is due at the end of May.

I understand that Federal advisory committee charters are customarily reviewed and extensions filed with the General Services Administration each September. However, in view of the special circumstances in this case, it seems reasonable and appropriate to take action on NBAC's charter immediately, thus facilitating the Commission's planning process for meeting the President's requests.

You should be aware of a potential complication regarding NBAC's financial support. The President delegated administrative responsibilities for NBAC under the Federal Advisory Committee Act to the Secretary of the Department of Health and Human Services (HHS). For the current fiscal year, HHS has explicit Congressional authority to seek funding for NBAC from other Executive branch agencies and has done so, resulting in an arrangement that spreads the estimated \$1.6 million budget over seven agencies, with HHS paying one-half of the total. (A list of the other agencies and their level of support is attached.) At a meeting on January 22, all the agencies supported a two-year extension of the NBAC term, as proposed by HHS, and agreed in principle to continue the current funding arrangement, subject to Congressional approval. The

Memo to Franklin D. Raines

March 19, 1997

Page two

President's FY 98 budget requests broad permission for multi-agency funding of Federal advisory committees or alternatively, permission limited to NBAC. NBAC's charter is not dependent on resolution of this issue since it leaves the matter of funding to HHS alone, subject to the availability of appropriations.

Extending NBAC's charter will enable the Commission to respond to the President's immediate request for advice and recommendations on the cloning of human beings, without unduly constraining resources to address the President's two original concerns: protection of human research subjects and proper use and management of genetic information, both important issues in their own right. The issue of delays in naming the NBAC members and obtaining support has been reported in the media as indicative of lack of attention from the Administration. While this is not the case, prompt action on extending the Commission's term might be one way to convey a more positive attitude and would support the Commission's efforts to provide thoughtful, astute responses to the President's requests.

Please contact me or Rachel Levinson of my staff if you require further information.

Attachments

ROSTER OF NBAC MEMBERS

Chair

Harold T. Shapiro, Ph.D.

President

Princeton University

One Nassau Hall

Princeton, NJ 08544-0015

(July 19, 1996 - July 18, 2000)

Patricia Backlar

Senior Scholar

Center for Ethics in Health Care

Oregon Health Sciences University

Portland, OR 97207

(July 19, 1996 - July 18, 1998)

Arturo Brito, M.D.

Assistant Professor of Clinical Pediatrics

University of Miami School of Medicine

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(July 19, 1996 - July 18, 1999)

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Co-Director

Pacific Center for Health Policy and Ethics

Univ of Southern California Law Center

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(July 19, 1996 - July 18, 2000)

Eric J. Cassell, M.D.

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Cornell Medical College

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(July 19, 1996-July 18, 1998)

R. Alta Charo, J.D.

Professor of Law

University of Wisconsin

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(July 19, 1996 - July 18, 2000)

James Childress, Ph.D.

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University of Virginia

Cocke Hall, Rm. 101

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(July 19, 1996 - July 18, 1999)

David R. Cox, M.D., Ph.D.

Professor of Genetics and Pediatrics

Stanford University School of Medicine

Department of Genetics, M-336

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(July 19, 1996 - July 18, 1999)

Rhetaugh Graves Dumas, Ph.D., R.N.

Vice Provost for Health Affairs

The University of Michigan

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(September 16, 1996 - September 15, 1999)

Ezekiel J. Emanuel, M.D., Ph.D.

Associate Professor of Medicine

and Social Medicine

Dana-Farber Cancer Institute

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(July 19, 1996 - July 18, 1998)

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Carol W. Greider, Ph.D.
Senior Staff Scientist
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(October 29, 1996 - October 28, 1998)

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(July 19, 1996 - July 18, 2000)

*ASIAN-
AMERICAN*

Lawrence H. Muike, M.D., J.D.
Director
State Department of Health
1250 Punchbowl Street
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HAWAIIAN

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(July 19, 1996 - July 18, 1999)

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(July 19, 1996 - July 18, 2000)

A-A

Federal Register

Vol. 60, No. 193

Thursday, October 5, 1995

Presidential Documents

Title 3—

Executive Order 12975 of October 3, 1995

The President

Protection of Human Research Subjects and Creation of
National Bioethics Advisory Commission

By the authority vested in me as President by the Constitution and the laws of the United States of America, it is hereby ordered as follows:

Section 1. Review of Policies and Procedures. (a) Each executive branch department and agency that conducts, supports, or regulates research involving human subjects shall promptly review the protections of the rights and welfare of human research subjects that are afforded by the department's or agency's existing policies and procedures. In conducting this review, departments and agencies shall take account of the recommendations contained in the report of the Advisory Committee on Human Radiation Experiments.

(b) Within 120 days of the date of this order, each department and agency that conducts, supports, or regulates research involving human subjects shall report the results of the review required by paragraph (a) of this section to the National Bioethics Advisory Commission, created pursuant to this order. The report shall include an identification of measures that the department or agency plans or proposes to implement to enhance human subject protections. As set forth in section 5 of this order, the National Bioethics Advisory Commission shall pursue, as its first priority, protection of the rights and welfare of human research subjects.

(c) For purposes of this order, the terms "research" and "human subject" shall have the meaning set forth in the 1991 Federal Policy for the Protection of Human Subjects.

Sec. 2. Research Ethics. Each executive branch department and agency that conducts, supports, or regulates research involving human subjects shall, to the extent practicable and appropriate, develop professional and public educational programs to enhance activities related to human subjects protection, provide forums for addressing ongoing and emerging issues in human subjects research, and familiarize professionals engaged in nonfederally-funded research with the ethical considerations associated with conducting research involving human subjects. Where appropriate, such professional and educational programs should be organized and conducted with the participation of medical schools, universities, scientific societies, voluntary health organizations, or other interested parties.

Sec. 3. Establishment of National Bioethics Advisory Commission. (a) There is hereby established a National Bioethics Advisory Commission ("NBAC"). NBAC shall be composed of not more than 15 members to be appointed by the President. NBAC shall be subject to the Federal Advisory Committee Act, as amended (5 U.S.C. App.).

(b) The President shall designate a Chairperson from among the members of NBAC.

Sec. 4. Functions. (a) NBAC shall provide advice and make recommendations to the National Science and Technology Council and to other appropriate government entities regarding the following matters:

(1) the appropriateness of departmental, agency, or other governmental programs, policies, assignments, missions, guidelines, and regulations as they relate to bioethical issues arising from research on human biology and behavior; and

- (2) applications, including the clinical applications, of that research.
- (b) NBAC shall identify broad principles to govern the ethical conduct of research, citing specific projects only as illustrations for such principles.
- (c) NBAC shall not be responsible for the review and approval of specific projects.
- (d) In addition to responding to requests for advice and recommendations from the National Science and Technology Council, NBAC also may accept suggestions of issues for consideration from both the Congress and the public. NBAC also may identify other bioethical issues for the purpose of providing advice and recommendations, subject to the approval of the National Science and Technology Council.

Sec. 5. Priorities. (a) As a first priority, NBAC shall direct its attention to consideration of: protection of the rights and welfare of human research subjects; and issues in the management and use of genetic information, including but not limited to, human gene patenting.

(b) NBAC shall consider four criteria in establishing the other priorities for its activities:

- (1) the public health or public policy urgency of the bioethical issue;
- (2) the relation of the bioethical issue to the goals for Federal investment in science and technology;
- (3) the absence of another entity able to deliberate appropriately on the bioethical issue; and
- (4) the extent of interest in the issue within the Federal Government.

Sec. 6. Administration. (a) The heads of executive departments and agencies shall, to the extent permitted by law, provide NBAC with such information as it may require for purposes of carrying out its functions.

(b) NBAC may conduct inquiries, hold hearings, and establish subcommittees, as necessary. The Assistant to the President for Science and Technology and the Secretary of Health and Human Services shall be notified upon establishment of each subcommittee, and shall be provided information on the name, membership (including chair), function, estimated duration, and estimated frequency of meetings of the subcommittee.

(c) NBAC is authorized to conduct analyses and develop reports or other materials. In order to augment the expertise present on NBAC, the Secretary of Health and Human Services may contract for the services of nongovernmental consultants who may conduct analyses, prepare reports and background papers, or prepare other materials for consideration by NBAC, as appropriate.

(d) Members of NBAC shall be compensated in accordance with Federal law. Members of NBAC may be allowed travel expenses, including per diem in lieu of subsistence, to the extent permitted by law for persons serving intermittently in the government service (5 U.S.C. 5701-5707).

(e) To the extent permitted by law, and subject to the availability of appropriations, the Department of Health and Human Services shall provide NBAC with such funds as may be necessary for the performance of its functions. The Secretary of Health and Human Services shall provide management and support services to NBAC.

Sec. 7. General Provisions. (a) Notwithstanding the provisions of any other Executive order, the functions of the President under the Federal Advisory Committee Act that are applicable to NBAC, except that of reporting annually to the Congress, shall be performed by the Secretary of Health and Human Services, in accordance with the guidelines and procedures established by the Administrator of General Services.

(b) NBAC shall terminate two years from the date of this order unless extended prior to that date.

(c) This order is intended only to improve the internal management of the executive branch and it is not intended to create any right, benefit, trust, or responsibility, substantive or procedural, enforceable at law or equity by a party against the United States, its agencies, its officers, or any person.

William Clinton

THE WHITE HOUSE,
October 3, 1995.

[FR Doc. 95-24821

Filed 10-3-95; 2:11 pm]

Billing code 3195-01-1'

EXECUTIVE ORDER

AMENDING EXECUTIVE ORDER NO. 12975

By the authority vested in me as President by the Constitution and the laws of the United States of America, and in order to extend the term of the National Bioethics Advisory Commission, it is hereby ordered that Section 7(b) of Executive Order No. 12975 is amended to read, "NBAC shall terminate on October 3, 1999, unless extended by the President prior to that date."

WILLIAM J. CLINTON

NATIONAL BIOETHICS ADVISORY COMMISSION CHARTER

Purpose

The National Bioethics Advisory Commission will provide advice and make recommendations to the National Science and Technology Council, other appropriate entities and the public, on bioethical issues arising from research on human biology and behavior, and the applications, including the clinical applications, of that research.

Authority

Executive Order 12975. This Commission is governed by the provisions of the Federal Advisory Committee Act (FACA), Public Law 92-463, as amended (5 U.S.C. Appendix 2), which sets forth standards for the formation of advisory committees, and implementing regulations (41 C.F.R. § 101-6.10).

Functions

The National Bioethics Advisory Commission shall advise, consult with, and make recommendations to the National Science and Technology Council, Federal agencies, and other appropriate entities, and also make available to the public the Commission's advice and recommendations. The Commission's purview includes the appropriateness of departmental, agency, or other governmental programs, policies, assignments, missions, guidelines, and regulations as they relate to bioethical issues arising from research on human biology and behavior, and applications, including the clinical applications, of that research. The Commission shall identify broad, overarching principles to govern the ethical conduct of research, citing individual projects only as illustrations for such principles. The Commission shall not be responsible for the review and approval of individual projects.

As a first priority, the Commission will direct its attention to consideration of:

- A. Protection of the rights and welfare of human research subjects; and
- B. Issues in the management and use of genetic information including but not limited to human gene patenting.

In addition to responding to requests for advice and recommendations from the National Science and Technology Council, the Commission also may accept suggestions for issues for consideration from both the Congress and the public. The Commission also may identify other bioethical issues for the purpose of providing advice and recommendations, subject to the approval of the National Science and Technology Council. The Commission shall consider four criteria in establishing priority for its activities:

- A. The public health or public policy urgency of the bioethical issue.
- B. The relation of the bioethical issue to the goals for Federal investment in science and technology.
- C. The absence of another body able to deliberate fruitfully on the bioethical issue.
- D. The extent of interest in the issue across the government. (The Commission ordinarily will not deliberate on a bioethical issue of interest to just one department or agency.)

Structure

The National Bioethics Advisory Commission shall consist of not more than 18 members including the Chairperson. Appointments shall be made by the President, who shall select from knowledgeable non-Government experts and community representatives with special qualifications and competence to deal effectively with bioethical issues. At least one member shall be selected from each of the following categories of primary expertise: (i) philosophy/theology; (ii) social/behavioral science; (iii) law; (iv) medicine/allied health professions; and (v) biological research. At least three members shall be selected from the general public, bringing to the Commission expertise other than that listed. The membership shall be approximately evenly balanced between scientists and non-scientists. Close attention will be given to equitable geographic distribution and to ethnic and gender representation.

Members shall be appointed for overlapping four-year terms. Initially, members will be appointed for two-, three- or four-year terms. Terms of more than two years are contingent upon renewal of the National Bioethics Advisory Commission by appropriate action prior to its termination. The Chairperson shall be appointed by the President. The term of office for the Chairperson shall be two years, renewable by appropriate action of the President.

If a vacancy occurs on the Commission, the President shall make an appointment to fulfill the term. Any member appointed to fill a vacancy occurring prior to expiration of the term for which his or her predecessor was appointed shall serve for the remainder of such term. Members may serve after the expiration of their terms until their successors have taken office.

The heads of executive departments and agencies shall, to the extent permitted by law, provide the Commission with such information as it may require for purposes of carrying out its functions.

The Commission may conduct inquiries, hold hearings and establish subcommittees, as necessary.

The Commission is authorized to solicit information from relevant human research subject groups.

The Commission is authorized to conduct analyses and develop reports or other materials. In order to augment the expertise present on the Commission, the Secretary of Health and Human Services is also authorized to contract for the services of non-governmental consultants who may conduct analyses, prepare reports and background papers or prepare other materials for consideration by the Commission, as appropriate.

In order to avoid duplication of effort, the Commission is encouraged to review the deliberations of other entities. The Commission may incorporate or otherwise use the results of the deliberations of other entities as it deems appropriate.

The Assistant to the President for Science and Technology and the Secretary of Health and Human Services shall be notified upon establishment of each subcommittee, and shall be provided information on the name, membership (including chair), function, estimated duration of the subcommittee, and estimated frequency of meetings.

To the extent permitted by law, and subject to the availability of appropriations, the Department of Health and Human Services (DHHS) shall provide NBAC with such funds as may be necessary for the performance of its functions. Management and support services shall be provided by the DHHS.

Meetings

Meetings of the Commission shall be held up to 10 times a year at the call of the Chairperson. Meetings of the subcommittee(s) shall be convened as necessary. A Federal Government official shall be present at all meetings.

Meetings shall be open to the public except as determined otherwise by the Assistant to the President for Science and Technology and the Secretary of Health and Human Services. Advance notice of all meetings shall be given to the public.

Meetings shall be conducted, and records of proceedings kept, as required by applicable laws and Federal regulations.

Compensation

Members may be compensated at a rate not to exceed the maximum pay authorized by 5 U.S.C. 3109, plus per diem and travel expenses as in accordance with standard government travel regulations.

Annual Cost Estimate

The estimated annual cost for operating the National Bioethics Advisory Commission is \$500,000.

Reports

Reports by the National Bioethics Advisory Commission on specific issues shall be submitted to the National Science and Technology Council, the appropriate committees of Congress, and other appropriate entities. The Commission may specifically identify the Federal department, agency or other entity to which particular recommendations are directed and request a response from the Federal department, agency or other entity within 180 days of publication of such recommendation.

Executive summaries of each report of the Commission shall be promulgated in the Federal Register. Such summaries shall specifically list the department, agency, or other entity to which any recommendations are directed and the date by which such responses are expected.

An annual report shall be submitted to the National Science and Technology Council and the appropriate committees of Congress. It shall contain, at a minimum, (i) the Commission's function; (ii) a list of members and their business addresses; (iii) the dates and places of meetings; (iv) a summary of the Commission's activities during the year; (v) a summary of the Commission's recommendations made during the year; and (vi) a summary of responses made by departments, agencies, or other entities to the Commission's recommendations during the year.

General Provisions

Notwithstanding the provisions of any other Executive Order, the functions of the President under the Federal Advisory Committee Act that are applicable to the Commission, except that of reporting annually to the Congress, shall be performed by the Secretary of Health and Human Services, in accordance with the guidelines and procedures established by the Administrator of General Services.

Termination Date

Unless extended by appropriate action prior to its expiration, this National Bioethics Advisory Commission will terminate October 3, 1997.

Approved:


John H. Gibbons
Assistant to the President for
Science and Technology

Date 26 July 1996

NBAC Funding Request - FY 97

Agency

Amount (\$\$ in 000's)

DHHS

800

DOD

200

DOE

150

VA

150

USDA

125

NASA

100

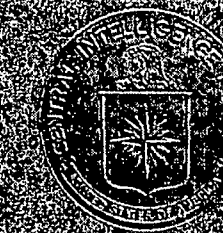
NSF

75



Building Public Trust

ACTIONS TO RESPOND TO THE
REPORT OF THE ADVISORY COMMITTEE
ON HUMAN RADIATION EXPERIMENTS



United States Government
Human Radiation Interagency Working Group

THE WHITE HOUSE

WASHINGTON

In January 1994, after accounts of Cold War-era experiments involving the effects of radiation on humans came to light, I established an independent Advisory Committee on Human Radiation Experiments to investigate these reports. I asked the Committee to determine the truth about this dark chapter in our nation's history.

After taking extensive testimony and conducting numerous public hearings, the Advisory Committee issued its report in October, 1995. The Committee's report included recommendations to make the record of these experiments open to the public, improve ethics in human research today, and right the wrongs of the past inflicted on unknowing citizens. In my remarks when I accepted the report, I promised that it would not be left on the shelf to gather dust. I made a commitment that we would learn from the lessons that the Committee's report offered and use it as a road map to lead us to better choices in the future.

This document -- my Administration's response to the Advisory Committee's report -- is a milestone in meeting that commitment. We have actively worked to respond to the important recommendations made by the Advisory Committee through a special interagency working group. This group includes representatives from the Executive Office of the President, the Departments of Energy, Defense, Health and Human Services, Justice, Veterans Affairs, the National Aeronautics and Space Administration, and the Central Intelligence Agency. The Environmental Protection Agency has also joined the effort. This report reflects the joint progress of these agencies to address the Advisory Committee's recommendations.

My Administration has made significant achievements in opening government and making information more easily available to the citizens to whom it belongs. Agencies have also improved the protections in place for subjects of future human research. Finally, the Federal government is providing redress to those who have suffered from radiation experiments, as recommended by the Advisory Committee.

I emphasize that this document is by no means the end of the journey. Much work remains to be done. I am confident that all of us -- the eminent committee that produced the original report, the Federal officials who worked so hard to support the Committee's efforts and now are implementing its recommendations, and most importantly, the citizens of this great country from whose experiences we have learned so much -- can together help ensure a better world for our children.

My thanks to all of you for a job well done, I pledge my strong support for your continued efforts.

Bill Clinton

The Administration has invested heavily in making documents accessible.

Key Actions

- The Administration has invested heavily in making documents accessible. ACHRE transferred more than 1 million pages of documents to the National Archives. The Administration has made 300,000 fully searchable pages of documents available on the Internet, and will add an additional 200,000 pages shortly. The Departments of Energy and Defense have published document search guides.
- The President signed Executive Order 12958 directing Federal agencies to review and declassify thousands of documents, including documents on radiation experiments.
- The National Archives and Records Administration is conducting an independent review of the Central Intelligence Agency's (CIA's) recordkeeping system and the CIA's Inspector General reviewed and reported on the CIA's human experiments.

Protecting Human Subjects in the Future

The Advisory Committee recommended steps to strengthen protections for human subjects and ensure the government does not repeat past mistakes.

Key Actions

- President Clinton is issuing a directive to strengthen protections for subjects of classified (secret) research. Agencies will propose new rules to eliminate waiver of informed consent; disclose the identity of the sponsoring agency; ensure a more independent review process; and require permanent records. Agencies will also report annually on the number of classified human research projects and the number of human subjects involved in each project.
- President Clinton established the National Bioethics Advisory Committee (NBAC) to examine bioethical issues, including human research issues. A subcommittee of NBAC will address certain broad questions raised by ACHRE, including how to strengthen Institutional Review Boards (IRBs)—the local ethics panels for federally sponsored research.
- President Clinton directed agencies to develop plans to improve oversight of ethics rules. NBAC will review these plans in the coming months.

A subcommittee of National Bioethics Advisory Committee will address certain broad questions raised by ACHRE, including how to strengthen Institutional Review Boards—the local ethics panels for federally sponsored research.

- Agencies have undertaken nationwide education efforts to raise the profile of ethical considerations, and are funding research to improve our understanding of ethical issues.

Righting Past Wrongs

The Advisory Committee recommended, among other things, that the government apologize to all subjects, compensate certain subjects, and consider modifying the Radiation Exposure Compensation Act, and its regulations, to compensate additional uranium miners.

Key Actions

- The President apologized to all subjects on behalf of the government; former Energy Secretary Hazel O'Leary made apologies in certain individual cases.
- ACHRE recommended that the government compensate the families of the 18 subjects of the plutonium injection experiments. The government has settled compensation claims with the 16 families who have come forward. ACHRE and the government have not been able to identify participants in additional experiments that ACHRE included in its recommendation for compensation.
- The Administration will propose legislative and regulatory changes to the Radiation Exposure Compensation Act to incorporate the latest science and better compensate affected uranium miners.
- The Administration will propose legislation to make veterans treated with nasopharyngeal radiation eligible for health screening under the Department of Veterans Affairs' Ionizing Radiation Program.

The actions and policies described in this report will help bring justice to those harmed by the mistakes of the Cold War, and prevent the recurrence of past wrongs. The report presents those actions that are completed or underway. The Administration will continue to take steps to open the government's records, raise ethical standards, and right the wrongs of the past.

The Federal government has settled the compensation claims of the 16 families of plutonium injection subjects who have come forward.

ACHRE Findings and Recommendations on Protecting Human Subjects in the Future

Based on its review of current human subject protections, the Advisory Committee found, among other things, that

[H]uman research involving radioisotopes is currently subjected to more safeguards and levels of review than most other areas of research involving human subjects. The Advisory Committee further finds that there are no apparent differences between the treatment of human subjects of radiation research and human subjects of other biomedical research. (Finding 20)

Responsibility for ethical conduct of research begins with researchers and extends to their institutions, and the Institutional Review Boards (IRBs).

[T]oday research involving human subjects sponsored by the government may be classified and conducted in secret, but it must comply with the provisions of the Common Rule. (Finding 21)

[I]n comparison with the practices and policies of the 1940s and 1950s, there have been significant advances in the protection of the rights and interests of human subjects of biomedical research. However, we also find that there is evidence of serious deficiencies in some parts of the current system for the protection of the rights and interests of human subjects. (Finding 22)

ACHRE Recommendation on the Centrality of Ethics

ACHRE recommended that active efforts on a national scale be made to ensure that human subjects researchers fully understand the ethical implications and responsibilities of their work, and the centrality of ethical decisions. (Recommendation 9)

Response

Responsibility for the ethical conduct of research begins with researchers and extends to their institutions and the Institutional Review Boards (IRBs). The Administration has multiple efforts underway to reach, educate, oversee, and hold accountable each layer of the research system. The Administration is also taking steps to promote understanding of, and consensus about, ethical issues.

National Bioethics Advisory Commission

The National Bioethics Advisory Commission (NBAC), a national deliberative body of private citizens, was established by the President to provide guidance to all Federal agencies on the ethical conduct of human behavioral and clinical research, and the applications of that research. NBAC was established, in part, to respond to ACHRE, and the Administration expects NBAC will choose to address the key issues identified in ACHRE's recommendations. NBAC will not be able to review all issues raised by ACHRE. The Administration has been careful to ensure that issues not taken up by NBAC will be addressed elsewhere.

As a first priority, NBAC will seek to improve protection of the rights and welfare of human research subjects. The Executive Order establishing NBAC, required each agency to review its current human subjects research in light of the Advisory Committee recommendations and report the results to NBAC. NBAC is currently reviewing these documents. Appendix C details specific activities currently being carried out by the agencies as a result of their reviews.

NBAC's meetings are public and provide a forum for dialogue on ethics issues. NBAC has heard presentations on issues related to genetic research, including cloning, as well as the broader area of human subjects research. Members of Congress, Congressional staff, and representatives from diverse organizations including the Task Force on Radiation and Human Rights, the College of American Pathologists, the Biotechnology Industry Organization, and Citizens for Responsible Care in Psychiatry and Research testified on ethics issues and on NBAC's mission. Further information can be obtained from the NBAC Web Site (www.nih.gov/nbac/nbac.htm).

Education

ACHRE's report made clear that a key to preventing the repetition of past mistakes is thorough and continuing education about ethics and how they apply to current human-subjects research. The Administration is responding to ACHRE's specific recommendations by co-sponsoring educational programs with external groups such as medical schools, universities, and scientific societies. The goals of these educational efforts are to strengthen human subjects protection, to provide a forum for addressing ongoing as well as emerging issues in human subjects research, and to familiarize professionals engaged in non-federally funded human subjects research with relevant ethical considerations.

Part of the ongoing educational process is a reinforcement of the importance of Institutional Review Boards (IRBs) at institutions conducting federally funded research. These IRBs are local groups

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whose membership and responsibilities are regulated by the Federal government. They are responsible for reviewing and approving the ethical content of all proposed human subjects research projects. IRBs are a linchpin in the protection of human subjects, and their credibility and effectiveness depend on adequate awareness of basic ethical topics.

Similarly, educational programs are also being targeted at government-regulated research that is not government-funded (e.g., FDA-regulated research sponsored by the pharmaceutical industry). In September of 1996, the FDA sponsored its first nationwide conference on human subjects protection.

Government employees who have responsibility for supporting or overseeing human subjects research are also targeted for educational programs. Thus, Federal agencies are implementing training programs to educate senior level officials on regulations and policies governing this research. For example, NASA is working with international research partners to develop common ethical principles that ensure the protection of human subjects. DOE educational efforts target laboratory staff, field office personnel, and program officials.

Despite the vigor with which all parties embrace the informed consent process, it is not well understood.

Information Gathering

ACHRE's report highlighted the limited state of knowledge regarding some key issues in human subjects research. Most importantly, NBAC will be reviewing and evaluating the IRB process.

In addition, Departments have pooled resources to sponsor research on the informed consent process. The informed consent process is intended to help each potential research subject decide whether to participate in research by providing advance information about the research. Information includes a description of the nature of the research, the subject's role and potential risks, and the subject's rights and responsibilities. Despite the vigor with which all parties embrace the informed consent process, it is not well understood. Much of the Advisory Committee's commentary on current human subjects research was centered on informed consent. The National Institutes of Health (NIH), VA, and DOE are committed to supporting research that will more fully illuminate the informed consent process. A Request for Applications (RFA) to conduct research on this issue was published in the fall of 1996, and Fiscal Year 1997 monies are earmarked to support this RFA.

ACHRE Recommendation on Institutional Review Boards

ACHRE recommended specific changes to IRBs in five critical areas (Recommendation 10):

- (1) mechanisms to ensure a stronger focus on studies that pose more than minimal risk to subjects;
- (2) better means of explaining to potential subjects the distinction between research and treatment, the realistic likelihood of medical benefit to the subject from participation, and the potential for discomfort and pain;
- (3) ensuring that potential subjects fully understand the sponsors and purposes of the research;
- (4) ensuring that potential subjects fully understand the financial implications of participation; and
- (5) recognition that the IRBs must decide if the quality of the science justifies the risk to the subjects.

The Administration anticipates specific recommendations from NBAC regarding reform of IRBs, including recommendations that address ACHRE's concerns.

Response

The Administration agrees that there are indications that the IRB system is not always adequate to ensure protection of human subjects. NBAC has undertaken to review the current IRB system and intends to finish that project within a year. The Administration anticipates specific recommendations from NBAC regarding reform of IRBs, including recommendations that address ACHRE's concerns.

In the interim, agencies are informing IRBs of ACHRE's recommendations and are working to improve IRBs.

The Office for Protection from Research Risks (OPRR), part of NIH, is undertaking a national effort to educate the research community about ACHRE's recommendations. OPRR and FDA support an annual public meeting for individuals interested in the governance of human subjects research. In addition, OPRR, in cooperation with FDA and local academic institutions, has held discussions of the recommendations at national workshops in Atlanta, Oklahoma City, Honolulu, Peoria, Houston, and San Diego.

OPRR and the FDA make extensive use of public meetings, forums, hearings, and electronic media to address evolving issues on human subject protection. OPRR and FDA also regularly mail information directly to IRBs and other interested parties. FDA seeks public input through the *Federal Register* and by mailing proposals to the IRB and clinical investigator communities. In October 1995, FDA issued

It might be a good time to develop an Administration on the Glenn bill (S. 193) with the thought of announcing support, if that is our conclusion. The major element of the bill is to extend protection to human subjects of research conducted outside PHS or FDA regs. Criminal penalties are authorized for violation of the Act. A relatively minor element of the bill is to elevate the status of the Office for Protection from Research Risks out of NIH and place it in the Office of the Secretary, DHHS.

As part of its deliberations on the adequacy of current protections for human subjects, NBAC is considering adopting a resolution that would have the same effect as the Glenn bill.

Response

The Administration agrees that extraordinary steps are needed to protect military personnel, and DOD is implementing ACHRE's recommendations. Among other steps, DOD is revising directives and Military Department regulations, and incorporating needed training into courses for commanders, senior leadership, and those involved in human subjects research. In the summer of 1997, DOD will publish a revised human subjects protection directive that includes policy changes recommended by the Advisory Committee. For example, to avoid undue command influence, the new policy will preclude officers and noncommissioned officers from playing a role in selecting volunteers for military tests. (See Appendix C for more details).

In the summer of 1997, DOD will publish a revised human subjects protection directive that includes policy changes recommended by the Advisory Committee.

ACHRE Findings and Recommendation on the Federal Oversight of Research

ACHRE found that oversight of human subjects research is limited and is constrained by practical considerations. ACHRE found that the "current mechanisms for oversight . . . do not provide a sufficient basis for ensuring that the current system is working properly."

ACHRE found that sanctions may be inadequate for violations of human subjects research protections. For example failure to obtain consent from subjects (who are not physically injured) is generally punishable only by the withdrawal of research funding.

ACHRE also found that "there is a need to assess the level of research performed outside [the Common Rule] and to consider action to ensure that all subjects are afforded the protections it offers." ACHRE recommended the improvement of three parts of the current Federal system for human research subject protection: oversight of the research process; sanctions for violations of human subjects protections; and protections for subjects of non-federally funded research. (Recommendation 13)

Response

The Administration agrees that there are important gaps in the current system of human subjects protection, and has identified, in testimony before Congress, examples of research that does not fall within the ambit of Federal protection. Congress has proposed the Human Research Subject Protection Act of 1997 (S. 193) to ensure that all human subjects are adequately protected. The Administra-

[Handwritten initials]

tion believes that Congress is also the appropriate place to consider whether additional civil or criminal sanctions for the violation of human subject protections are necessary and desirable. (Sanctions, including criminal liability, apply to investigators conducting FDA-regulated research who violate FDA regulations protecting human subjects.) Any legislation would need to protect research subjects and avoid deterring needed research.

In addition to exploring legislation, Federal agencies are undertaking specific activities to strengthen oversight, some of which are described in Appendix C. The Administration expects that NBAC will recommend additional actions to improve oversight of Federal research, and will identify the highest priority steps.

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ACHRE Findings and Recommendation on the Compensation of Subjects in the Future

ACHRE found that the Federal government lacks a "policy or guide for a fair system of compensation of research subjects."

ACHRE recommended that the government resolve the longstanding issue of whether and how all persons injured in the future from federally funded human subjects research should be compensated. ACHRE recommended that the Federal government consider a system of compensation for research subjects who suffer physical injury or dignitary harm as a result of federally funded research. (Recommendation 14)

Response

In the absence of a finding that a significant number of modern research subjects are unfairly denied compensation, the Administration is not prepared to propose a system outside the existing network of Federal and state liability and insurance systems.

The Administration does, however, view the debate over the extent and effectiveness of our current human subject protections to encompass this issue. The Administration would be open to considering any recommendations from NBAC or legislation from Congress that seek to address this issue.

The desire to spread the cost of research injury is a reason to consider a compensation scheme. The current tort system, though imperfect, provides one mechanism to seek compensation for injuries that arise from research. In addition, the tort system

REMARKS BY PRESIDENT WILLIAM J. CLINTON IN ACCEPTANCE OF HUMAN RADIATION FINAL REPORT

October 3, 1995
Old Executive Office Building

Let me begin with a simple thank you to everyone who participated in this extraordinary project and to everyone who supported them.

I want to thank Secretary O'Leary for her extraordinary devotion to this cause. And you heard in her remarks basically the way that she views this. It's a part of her ongoing commitment to finish the end of the Cold War. And perhaps no Energy Secretary has ever done as much as she has to be an advocate, whether it is for continued reforms within the Energy Department or her outspoken endorsement of the strongest possible commitment on the part of the United States to a Comprehensive Test Ban Treaty, which I believe we will achieve next year in no small measure thanks to the support of the Secretary of Energy.

And, of course, I want to thank Dr. Ruth Faden for her extraordinary commitment of about a year and a half of her life to this unusual but important task.

And all of you who served on the committee—I remember the first time we put this committee together. I do thank you so much for the work you have done.

I saw this committee as an indispensable part of our effort to restore the confidence of the American people in the integrity of their government. All of these political reform issues to me are integrated. When I became the President, I realized we had great new economic challenges, we had profound social problems, that a lot of these things had to be done by an energized American citizenry, but that our national government had a role to play in moving our country through this period of transition. And in order to do it, we needed to increase the capacity of the government to do it through political reform, but we also needed, as much as anything else, to increase the confidence of the American people that, at the very least, they could trust the United States Government to tell the truth and to do the right things.

So you have to understand that, for me, one reason this is so important is that I see it as part of our ongoing effort to give this government back to the American people—Senator Glenn's long effort to get Congress to apply to itself the same laws it imposes on the private sector—the restrictions that I imposed on members of my administration in high positions for lobbying for foreign governments; and when the lobby bill failed in the Congress, I just imposed it by executive order on members of the Executive Branch. All these efforts at political reform, it seems to me, are important.

But none of these efforts can succeed unless people believe that they can rely on their government to tell them the truth and to do the right thing. We have declassified thousands of government documents, files from second world war, the Cold War, President Kennedy's assassination. These actions are not only consistent with our national security, they are essential to advance our values.

So, to me, that's what this is all about. And to all those who represent the families who have been involved in these incidents, let me say to you, I hope you feel that your government has kept its commitment to the American people to tell the truth and to do the right thing.

We discovered soon after I entered office that with the specter of an atomic war looming like Armageddon far nearer than it does today, the United States government actually did carry out on our citizens experiments involving radiation. That's when I ordered the creation of this committee. Dr. Faden and the others did a superb job. They enlisted many of our nation's most significant and important medical and scientific ethicists. They had to determine first whether experiments conducted or sponsored by our government between 1944 and 1974 met the ethical and scientific standards of that time and of our time. And then they had to see to it that our research today lives up to nothing less than our highest values and our most deeply-held beliefs.

From the beginning, it was obvious to me that this energetic committee was prepared to do its part. We declassified thousands of pages of documents. We gave committee members the keys to the government's doors, file cabinets and safes. For the last year and a half, the only thing that stood between them and the truth were all the late nights and hard work they had to put in.

This report I received today is a monumental document—in more ways than one. But it is a very, very important piece of America's history, and it will shape America's future in ways that will make us a more honorable, more successful and more ethical country.

What this committee learned I would like to review today with a little more detail than Dr. Faden said, because I think it must be engraved on our national memory. Thousands of government-sponsored experiments did take place at hospitals, universities, and military bases around our nation. The goal was to understand the effects of radiation exposure on the human body.

While most of the tests were ethical by any standards, some were unethical, not only by today's standards, but by the standards of the time in which they were conducted. They failed both the test of our national values and the test of humanity.

In one experiment, scientists injected plutonium into 18 patients without their knowledge. In another, doctors exposed indigent cancer patients to excessive doses of radiation, a treatment from which it is virtually impossible that they could ever benefit.

The report also demonstrates that these and other experiments were carried out on precisely those citizens who count most on the government for its help—the destitute and the gravely ill. But the dispossessed were not alone. Members of the military—precisely those on whom we and our government count most—they were also test subjects.

Informed consent means your doctor tells you the risk of the treatment you are about to undergo. In too many cases, informed consent was withheld. Americans were kept in the dark about the effects of what was being done to them. The deception extended beyond the test subjects themselves to encompass their families and the American people as a whole, for these experiments were kept secret. And they were shrouded not for a compelling reason of national security, but for the simple fear of embarrassment, and that was wrong.

Those who led the government when these decisions were made are no longer here to take responsibility for what they did. They are not here to apologize to the survivors, the family members or the communities who's lives were darkened by the shadow of the atom and these choices.

So today, on behalf of another generation of American leaders and another generation of American citizens, the United States of America offers a sincere apology to those of our citizens who were subjected to these experiments, to their families, and to their communities.

When the government does wrong, we have a moral responsibility to admit it. The duty we owe to one another to tell the truth and to protect our fellow citizens from excesses like these is one we can never walk away from. Our government failed in that duty, and it offers an apology to the survivors and their families and to all the American people who must—who must be able to rely upon the United States to keep its word, to tell the truth, and to do the right thing.

We know there are moments when words alone are not enough. That's why I am instructing my Cabinet to use and build on these recommendations, to devise promptly a system of relief, including compensation, that meets the standards of justice and conscience.

When called for, we will work with Congress to serve the best needs of those who were harmed. Make no mistake, as the committee report says, there are circumstances where compensation is appropriate as a matter of ethics and principle. I am committed to seeing to it that the United States of America lives up to its responsibility.

Our greatness is measured not only in how we so frequently do right, but also how we act when we know we've done the wrong thing; how we confront our mistakes, make our apologies, and take action.

That's why this morning, I signed an executive order instructing every arm and agency of our government that conducts, supports, or regulates research involving human beings to review immediately their procedures, in light of the recommendations of this report, and the best knowledge and standards available today, and to report back to me by Christmas.

I have also created a Bioethics Advisory Commission to supervise the process, to watch over all such research, and to see to it that never again do we stray from the basic values of protecting our people and being straight with them.

The report I received today will not be left on a shelf to gather dust. Every one of its pages offers a lesson, and every lesson will be learned from these good people who put a year and a half of their lives into the effort to set America straight.

Medical and scientific progress depends upon learning about people's responses to new medicines, to new cutting-edge treatments. Without this kind of research, our children would still be

dying from polio and other killers. Without responsible radiation research, we wouldn't be making the progress we are in the war on cancer. We have to continue to research, but there is a right way and a wrong way to do it.

There are local citizens' review boards, there are regulations that establish proper informed consent and ensure that experiments are conducted ethically. But in overseeing this necessary research, we must never relax our vigilance.

The breathtaking advances in science and technology demand that we always keep our ethical watchlight burning. No matter how rapid the pace of change, it can never outrun our core convictions that have stood us so well as a nation for more than 200 years now, through many different scientific revolutions.

I believe we will meet the test of our times—that as science and technology evolve, our ethical conscience will grow, not shrink. Informed consent, community right-to-know, our entire battery of essential human protections—all these grew up in response to the health and humanitarian crises of this 20th century. They are proof that we are equal to our challenges.

Science is not ever simply objective. It emerges from the crucible of historical circumstances and personal experience. Times of crisis and fear can call forth bad science, even science we know in retrospect to be unethical. Let us remember the difficult years chronicled in this report, and think about how good people could have done things that we know were wrong.

Let these pages serve as an internal reminder to hold humility and moral accountability in higher esteem than we do the latest development in technology. Let us remember, too, that cynicism about government has roots in historical circumstances. Because of stonewallings and evasions in the past, times when a family member or a neighbor suffered an injustice and had nowhere to turn and couldn't even get the facts, some Americans lost faith in the promise of our democracy. Government was very powerful, but very far away and not trusted to be ethical.

So today, by making ourselves accountable for the sins of the past, I hope more than anything else, we are laying the foundation stone for a new era. Good people, like these members of Congress who have labored on this issue for a long time, and have devoted their careers to trying to do the right thing, and having people justifiably feel confidence in the work of their representatives. They will continue to work to see that we implement these recommendations.

And under our watch, we will no longer hide the truth from our citizens. We will act as if all that we do will see the light of day. Nothing that happens in Washington will ever be more important in anyone's life affected by these experiments, perhaps, than these reports we issue today. But all of us as Americans will be better off because of the larger lesson we learned in this exercise and because of our continuing effort to demonstrate to our people that we can be faithful to their values.

Thank you very much.

**The Administration Announces Actions
Responding to President Clinton's Advisory Committee on
Human Radiation Experiments
March 28, 1997**

Background

In January, 1994 President Clinton established the Advisory Committee on Human Radiation Experiments (ACHRE) to examine reports that the government had supported unethical human radiation experiments and releases of radiation during the Cold War. He asked ACHRE to uncover the truth, recommend ways to right past wrongs, and suggest ways to make sure the government will not repeat past mistakes.

In October, 1995 ACHRE issued its report. ACHRE found that the government had conducted several thousand human radiation experiments from 1945 to 1975 and that the majority advanced biomedical research. The Committee found, however, that some were conducted unethically. For example, scientists injected plutonium into 18 patients without their knowledge, and researchers conducted experiments on indigent patients and children. ACHRE made 18 recommendations to open the public record, protect human subjects of future research, and compensate those wronged by the government's actions.

In October, 1995 the President received the Advisory Committee's report and made it clear that the report would "not be left on a shelf to gather dust." He directed his Cabinet to "use and build on these recommendations." Over the past year and a half, the Administration has acted to implement ACHRE's recommendations to improve openness in government, strengthen ethics in human subjects research, and compensate individuals for the government's mistakes.

Today's Announcement

- **The Administration released *Building Public Trust*, outlining its comprehensive response to the President's Advisory Committee on Human Radiation Experiments (ACHRE). The report summarizes actions to address ACHRE's 18 recommendations.**
- **The Departments of Energy and Justice announced that the government has settled compensation claims with families of all of the known individuals ACHRE recommended for compensation. ACHRE recommended the government compensate the families of 18 subjects of plutonium injection experiments. The government has settled with all 16 families that came forward.**
- **President Clinton signed a memorandum to strengthen the rights and protections of people participating in secret, government-supported research. ACHRE recommended that subjects of secret experiments have special protections and information. Acting on that recommendation, the President directed agencies today to propose new rules for secret research that would require scientists to: obtain informed consent from all potential subjects of all secret experiments (current rules allow researchers to waive informed consent in certain cases); disclose the identity of the sponsoring agency to potential subjects; and tell potential subjects that an experiment is classified. The new rules**

would also establish a more independent review process; require the head of the agency conducting secret human research to approve each project; and require permanent records of secret experiments. The President also directed federal agencies to report annually on the number of classified human research projects and the number of subjects in each project. A preliminary review by the Administration's human radiation Interagency Working Group indicates that the government is not supporting any classified human research at this time; today's directive initiates a formal, routine accounting of secret human studies.

- The Administration announced proposed amendments to the Radiation Exposure Compensation Act of 1990 to compensate hundreds of uranium miners who would not be compensated under current law. ACHRE found that some deserving miners do not qualify for compensation under the Act. The amendments would establish fairer, science-based criteria for compensation. The Administration will also propose regulatory changes to RECA to facilitate claims processing.

Previous and On-going Actions Described in *Building Public Trust* Include:

Actions to Improve Openness in Government.

- ACHRE transferred more than 4,000 cubic feet of documents to the National Archives. The Administration has made 300,000 fully searchable pages of documents available on the Internet, and will add an additional 200,000 pages shortly. The Departments of Energy and Defense have published document search guides.
- The President signed Executive Order 12958 directing Federal agencies to review and declassify thousands of documents, including documents on radiation experiments.

Actions to Protect human subjects in the future.

- President Clinton established the National Bioethics Advisory Commission (NBAC) to examine bioethical issues, including human research issues. A subcommittee of NBAC will address certain broad questions raised by ACHRE, including how to strengthen Institutional Review Boards -- the local ethics panels for Federally-sponsored research.
- In October, 1995 President Clinton directed agencies to develop plans to improve their oversight of ethics rules. The agencies have completed their review and upgraded protections, and NBAC will review agency procedures in the coming months.
- Agencies have undertaken nationwide education efforts to raise the profile of ethical considerations, and are funding research to improve our understanding of informed consent.

Actions to Right Past Wrongs.

- In October, 1995 President Clinton apologized to subjects of radiation experiments and their families on behalf of an earlier generation of American leaders and citizens; former Energy Secretary O'Leary made apologies in certain individual cases.
- The Administration will propose legislation to make veterans treated with nasopharyngeal radiation eligible for health care services under the Veteran's Administration's Ionizing Radiation Program.

Senator John Glenn

News Release

For Immediate Release:
January 22, 1997

Contact:

Bryan McCleary (202) 224-9799
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New Law Proposed to Prevent Researchers from Conducting Experiments on Unsuspecting Americans

Glenn Calls on Administration to Put Human Research Issue on Front Burner

Tough new safeguards are needed to protect the rights of Americans who participate in medical research, Senator John Glenn (D-Ohio) said today. Glenn made his comments as he introduced comprehensive legislation aimed at ensuring that "informed consent" is obtained from potential research subjects, closing gaps which have allowed unethical human experiments, and creating first-ever criminal penalties for violators.

"I find it astounding that after horror stories like experiments described at Nuremberg, the thalidomide babies, and recent revelations about Cold War radiation experiments in Ohio and elsewhere, we still don't have a law on the books saying it is illegal to experiment on Americans without their permission.

Glenn said a large body of federal regulations has evolved to protect human research subjects, but he believes it is spotty, contains major gaps that invite abuse, often fails to give subjects an honest picture of risks, and lacks the force of law.

"There is more protection in existing statutes for animals than for humans," Glenn said, citing the Animal Welfare Act.

"Think about your own family, your son or daughter or parent or grandchild. The next time they go to the doctor or hospital, they could be the subject of some medical experiment or research they know nothing about. There can't be anything more un-American than that."

Glenn is also calling on the Clinton Administration to make this issue a higher priority. The Senator complained that a Presidential advisory commission charged with suggesting better protections for human research subjects is being hobbled by a lack of funding. In a letter last week to Dr. John Gibbons, President Clinton's science advisor and chief of the Office of Science and Technology Policy, Glenn called the issues to be addressed by the commission "among the most important, complex, and controversial of our time."

Glenn says President Clinton exhibited strong leadership in creating the National Bioethics Advisory Commission following revelations about radiation experiments on unsuspecting subjects during the Cold War. Now, he said, the Administration needs to

follow through on its commitments. The Senator said that more than 15 months after its establishment, the commission is having difficulty conducting its business because federal agencies have not fulfilled their pledges to support it. Glenn wrote to Gibbons that "past abuses have affected my constituents directly" and asked him to see that the commission is fully funded.

Dr. Gibbons is meeting today with representatives from agencies who agreed to support the commission with resources and staff.

Glenn, the senior Democrat on the Senate Governmental Affairs Committee, has long pushed the Government to disclose evidence about Cold-War era excesses. He was among the first to identify the environmental and health risks posed by U.S. nuclear production plants. More recently, he released information about how the U.S. government deliberately released radiation into the atmosphere during the 1940's and 50's. Finally, he has worked on the Governmental Affairs Committee to examine how it could happen that Americans became unwitting guinea pigs in experiments involving radiation and plutonium injections and exposure.

In the course of conducting hearings and spearheading Congressional probes into radiation experiments -- one of the most infamous sets having occurred at the University of Cincinnati -- Glenn continued to ask two questions. First: what protections are in place to prevent such abuses from happening again? Second: what law prohibits experimenting on people without their consent?

Today's legislation is an outgrowth of these two questions. A number of problems with the way in which research is conducted have been identified by Congressional investigators, the media, Glenn and government commissions. Some examples:

- * The "common rule" -- a guideline requiring that researchers fully inform tests subjects about experiments and submit them to a local ethics review board -- is not applied to all U.S. medical research. Some of private industry is exempted and not all government research is covered. What's more, the common rule is not law and no criminal penalties are on the books if it is violated.

- * The Cleveland Plain Dealer has identified cases where deaths have resulted from treatments patients were not told were experimental. In a comprehensive investigation, the paper also reported that since 1977, more than half of the 4,154 investigations the FDA has made of drug research have shown that researchers failed to clearly disclose the experimental nature of their work. They also showed cases where the federal government sponsored research where informed consent was not obtained.

- * Local ethics committees called Institutional Review Boards (IRB's) are supposed to approve experiments while ensuring that

researchers minimize risks, clearly inform subjects of the nature of proposed treatment or experimentation, and let patients know about alternative treatments. However, reports show IRB's often face an overwhelming workload, do not check up on experiments after they are approved, and do not receive sufficient guidance or oversight from the federal government. Glenn noted that no one even knows how many review boards are operating nationally or what kind of job many of them are doing.

* Consent forms approved by IRB's for distribution to potential subjects often gloss over the experimental nature of proposed treatment, blurring the distinction between therapy and research. The Advisory Committee on Human Research Experiments found such consent forms "flawed in morally significant respects" and concluded that over half the studies they reviewed raised "serious or moderate concerns."

Glenn's legislation, among other things, would: apply Common rule protections to all human subject research and put criminal sanctions on the books for violators; create new protections for classified federal experiments; provide additional protections to vulnerable populations such as children and pregnant women; and elevate the Office for Protection from Research Risks to newer, more independent watchdog status.

Glenn said his bill will be referred to the Senate Labor and Human Resources Committee. Later this week, he will introduce a narrower bill which will deal solely with public research and will be sent to the Governmental Affairs Committee on which Glenn serves as ranking Member.

The Senator said he expects that both committees will hold hearings on the issue in the near future. He said he would be working to gather support for the legislation from his colleagues and would also reach out to organizations representing patient rights, veterans, senior citizens, and others.

Glenn stressed that human research is absolutely critical to America and its development of new medicines and treatments to fight and cure diseases. "I don't think people mind being test subjects if they know the pros and cons." Still, he said, "people need to have all the facts. They need to make their decision based on good information -- not information that is selective or slanted or misleading."

For additional background on the issue, including a 1996 General Accounting Office report to Glenn, call 202-224-9799.

105th CONGRESS
1st Session

S. 193

To provide protections to individuals who are the human subject of research.

IN THE SENATE OF THE UNITED STATES

January 22, 1997

Mr. Glenn introduced the following bill; which was read twice and referred to
the Committee on Labor and Human Resources

A BILL

To provide protections to individuals who are the human subject of research.

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Be it enacted by the Senate and House of Representatives of the United
States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Human Research Subject Protections Act of
1997".

SEC. 2. FINDINGS AND PURPOSES.

(a) Findings.--Congress makes the following findings:

(1) The Constitution guarantees the right of the people to be secure
in their persons, and the Declaration of Independence asserts as self-
evident that all men have certain unalienable rights among these are
life, liberty and the pursuit of happiness.

(2) The first principle of the Nuremberg code states that with
respect to human research, the voluntary consent of the human subject is
absolutely essential. The Nuremberg code further asserts that such
consent must be competent, informed and comprehending.

(3) In 1974, the Department of Health, Education and Welfare
published regulations (45 CFR 46) governing the protection of human
subjects in research. These regulations applied only to research
sponsored by the Department. In 1991 these regulations were adopted by 16
additional Federal agencies to apply to any research which these agencies
may sponsor.

(4) Between 1974 and 1983, Congress enacted 2 Public Laws that
established ethical advisory bodies. Public Law 91-348 established the

National Commission for the Protection of Human Subjects of Biomedical Research and Public Law 95-622 established the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Each of these advisory bodies made recommendations to the President and Congress to expand protections for human research subjects. Some of these recommendations have been incorporated into the Federal regulation (45 CFR 46).

(5) In 1995, the President's Advisory Committee on Human Radiation Experiments found that there are significant deficiencies in some aspects of the current system for the protection of human subjects. In particular, the Committee found that some consent forms currently in use are flawed in morally significant aspects.

(6) The President's Advisory Committee on Human Radiation Experiments recommended the adoption of a Federal policy requiring the informed consent of all human subjects of classified research and that this requirement not be subject to exemption or waiver. The Committee further recommended that in all cases, potential subjects should be informed of the identity of the sponsoring Federal agency and that the project involves classified information.

(7) Some agencies of the Federal government sponsor research involving human subjects, but these agencies have not adopted the Common Rule as provided for in part 46 of title 45, Code of Federal Regulations.

(8) Private individuals or institutions that do not receive any Federal funding or that are not seeking the approval of the Food and Drug Administration for a drug or device, and that sponsor research involving human subjects, do not need to abide by the requirements of part 46 of title 45, Code of Federal Regulations.

(9) Many, but not all, research institutions that receive Federal sponsorship for research involving human subjects may voluntarily apply the protections of the Common Rule to all research conducted at the research institution.

(10) Notwithstanding paragraphs (1) through (9), no provision of United States law explicitly requires that informed consent and independent review of research involving human subject be obtained.

(11) The human research subject activities described in this section are either in interstate (or foreign) commerce or substantially affect such commerce or the free flow thereof, and the regulation of those activities as provided for in this Act is necessary to prevent and eliminate burdens upon such commerce and to effectively regulate such commerce, in order to insure that the rights and welfare of human research subjects are protected.

(b) Purpose.--The purposes of this Act are--

(1) to apply common rule protections to all human subject research and provide for criminal sanctions for violations of this Act;

(2) to prohibit the provision of Federal support for classified

research that is not reviewed by an institutional review board and require disclosure to human research subjects of certain information regarding classified research; and

(3) to address any potential regulatory conflict of interest within the Department of Health and Human Services and the National Institutes of Health, and establish an Office for Protection of Research Subjects within the Office of the Secretary of Health and Human Services.

SEC. 3. DEFINITIONS.

In this Act:

(1) Assurance.--The term "assurance" means a written agreement between the Secretary and a research facility, or an institution supporting the research facility, that such research facility will comply with all Federal ethical standards regarding human subject research, including the common rule protections. Such term includes a "single project assurance", "multiple project assurance", and "cooperative project assurance".

(2) Board.--The term "board" means an institutional review board established in accordance with and for the purposes expressed in this Act.

(3) Classified research.--The term "classified research" means research involving human subjects that is specifically authorized under criteria established by an Executive Order to be kept secret in the interest of national defense or foreign policy.

(4) Common rule protections.--The term "common rule protections" means the requirements and protections provided under part 46 of title 45, Code of Federal Regulations, as in effect on the date of enactment of this Act.

(5) Human subject.--The term "human subject" means a living individual about whom an investigator (whether professional or student) conducting research obtains--

(A) data through intervention or interaction with the individual;

or

(B) individually identifiable private information.

(6) Interstate commerce.--The term "interstate commerce" has the meaning given the term in section 201(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(b)).

(7) Office.--The term "Office" means the Office for Protection of Research Subjects established under section 102(a) or the Office designated under section 102(b).

(8) Research.--The term "research" means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge, and those activities for which a Federal department or agency has specific responsibility for regulating as research activities.

(9) Research facility.--The term "research facility" means any public or private entity, agency (including Federal, State, and other agencies) or person that--

(A) uses human subjects in research involving interstate commerce; or

(B) receives support under a grant, loan, contract, or other award from a department, agency, or instrumentality of the United States for the purpose of carrying out research using human subjects.

(10) Secretary.--The term "Secretary" means the Secretary of Health and Human Services.

(11) State.--The term "State" means a State of the United States, the District of Columbia, the Commonwealth of Puerto Rico, the Virgin Islands, Guam, American Samoa, or any other territory or possession of the United States.

TITLE I--GENERAL RESEARCH REQUIREMENTS

SEC. 101. APPLICATION OF COMMON RULE REQUIREMENTS AND PROTECTIONS.

(a) In General.--Except as provided in subsection (b), the requirements and protections provided under part 46 of title 45, Code of Federal Regulations, as in effect on the date of enactment of this Act, shall apply to research conducted by research facilities using human subjects.

(b) Exception When in Conflict with Act.--The provisions of this Act shall supersede any provision of part 46 of title 45, Code of Federal Regulations, if such provisions are in conflict.

SEC. 102. OFFICE FOR PROTECTION OF RESEARCH SUBJECTS.

(a) Establishment.--Not later than 90 days after the date of enactment of this Act, the Secretary shall establish within the Office of the Secretary an office to be known as the "Office for Protection of Human Research Subjects" or make the designation described in subsection (b).

(b) Designation.--Not later than 90 days after the date of enactment of this Act, the Secretary may reassign the Office for Protection from Research Risks to the Office of the Secretary and designate such Office to carry out the duties of the Office under this Act.

(c) Funding.--The Secretary shall ensure the availability of such sums as may be necessary to enable the Office to conduct all activities under this Act, as well as to conduct appropriate oversight and implementation activities.

SEC. 103. REGISTRATION OF FACILITIES.

(a) In General.--To conduct research using human subjects, a research facility shall have in effect a valid registration with the Secretary in accordance with this section and with such regulations as the Secretary may promulgate.

(b) Requirements.--An application for registration under subsection (a) shall include--

- (1) a statement of the principles of the applicant research facility with respect to the protection of the rights and welfare of humans subjects of research conducted or supported by the research facility;
- (2) a designation of the official responsible for all human subject research conducted or supported by the applicant research facility;
- (3) a designation of, and membership roster or rosters for, each board that is responsible for reviewing human subject research conducted or supported by the applicant research facility; and
- (4) an assurance that the applicant research facility is complying and will continue to comply with the requirements for--
 - (A) board membership;
 - (B) the functions and operations of the board;
 - (C) the review of research by the board;
 - (D) the approval of research by the board;
 - (E) the suspension or termination of board approval of research;
 - (F) the maintenance of records by the board; and
 - (G) obtaining and documenting informed consent from human subjects, consent from children, and permission from parents or guardians as provided for in the common rule protections.

(c) Period of Registration.--The registration of a research facility shall be valid for the 3-year period beginning on the date on which the Secretary approves the application for registration, except that such registration may be suspended, revoked or deemed to be incomplete or otherwise insufficient by the Secretary.

(d) Affect of Assurances.--Upon the notification of the Secretary by the official designated under subsection (b)(2), a research facility shall be deemed to be in compliance with the registration provisions of this section, if that research facility has in effect a valid assurance negotiated with the Department of Health and Human Services.

(e) Failure to Register.--A research facility may not conduct an activity covered by this Act if the facility is not registered with the Secretary under this section or an assurance described in subsection (d) is not in effect.

SEC. 104. INSPECTION AND INVESTIGATION.

(a) In General.--The Secretary may carry out such inspections or investigations as may be necessary to enable the Secretary to determine whether any research facility has violated or is violating any provision of this Act.

(b) Access to Facilities and Records.--To enable the Secretary to carry out subsection (a), the Secretary shall, after providing reasonable notice, be provided with access to a research facility and the records required to be kept by the facility pursuant to section 103(b)(4) and the common rule

protections.

(c) Penalties.--Title 18, United States Code, is amended by inserting after chapter 89 the following:

"CHAPTER 90--PROTECTION OF HUMAN SUBJECTS BY RESEARCH FACILITIES

"Sec. 1841. Protection of human subjects

"(a) In General.--Whoever forcibly assaults, resists, opposes, impedes, intimidates, or interferes with any person while such person is engaged in the performance of his or her official duties under the Human Research Subject Protections Act of 1997, or because such person has carried out such duties, shall be fined not more than \$10,000, or imprisoned not more than 3 years, or both.

"(b) Use of Weapon.--Whoever in the commission of an act that is a violation of subsection (a), uses a deadly or dangerous weapon shall be fined not more than \$25,000, or imprisoned not more than 10 years, or both.

"(c) Homicide.--Whoever kills any human being while that human being is engaged in the performance of his or her official duties under the Human Research Subject Protections Act of 1997, or because such human being has carried out such duties, shall be fined or imprisoned as provided for under sections 1111 and 1114."

SEC. 105. ENFORCEMENT.

(a) Suspension of Registration.--If the Secretary has reason to believe that any research facility registered under section 103 has violated or is in violation of any provision of this Act, or of any of the rules or regulations or standards promulgated by the Secretary under this Act, the Secretary may suspend the registration of that research facility for a period of not to exceed 30 days, and after notice and opportunity for a hearing, may suspend such registration for any additional period as the Secretary may determine appropriate. Upon a determination by the Secretary that such a violation has occurred the Secretary may continue such suspension or revoke the registration.

(b) Penalties.--Any employee of a research facility that knowingly violates any provision of this Act shall, on conviction thereof, shall be fined not more than \$10,000, or imprisoned not more than 3 years, or both. Such violation shall be referred by the Secretary to the United States Department of Justice for prosecution.

SEC. 106. REGULATIONS.

The Secretary may promulgate such regulations as the Secretary determines to be necessary to carry out this Act.

TITLE II--CLASSIFIED RESEARCH

SEC. 201. PROHIBITION.

Notwithstanding any other provision of law, no Federal funds shall be the performance of his or her official duties under the Human Research Subject Protections Act of 1997, or because such person has carried out such duties, shall be fined not more than \$10,000, or imprisoned not more than 3 years, or both.

"(b) Use of Weapon.--Whoever in the commission of an act that is a violation of subsection (a), uses a deadly or dangerous weapon shall be fined not more than \$25,000, or imprisoned not more than 10 years, or both.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Office for Protection from Research Risks
6100 Executive Boulevard, MSC 7507
Rockville, Maryland 20892-7507

Hand delivery or express mail:

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FAX: 301-402-2071

April 10, 1997

James F. Childress, Ph.D.
Chairman
Human Subjects Subcommittee
National Bioethics Advisory Commission
6100 Executive Boulevard, Suite 3C01
Rockville, MD 20892

*in support of
Megan Bell*

Dear Dr. Childress:

I am writing to respond to questions raised by some members of your Subcommittee regarding the nature and extent of human-subjects research taking place beyond the boundaries of existing protections. Subcommittee members have made repeated reference to human subjects involved in such activities as the "most vulnerable" of all human subjects.

In my October 4, 1996 remarks to the National Bioethics Advisory Commission, I noted that human subjects involved in research outside the perimeter of the existing protections are protected only by occasional state or local law or regulation, or at the discretion of the individuals or institutions undertaking the research. In other words, I am referring to human subjects research that is: 1) not conducted or supported by any of 17 Federal Departments or Agencies that adhere to the Federal Policy for the Protection of Human Subjects; 2) not regulated by the Food and Drug Administration (FDA); and 3) not voluntarily pledged to the Department of Health and Human Services' regulations at 45 CFR Part 46.

The Office for Protection from Research Risks (OPRR) receives a number of inquiries involving human subjects research over which it has no jurisdiction. Most are informal inquiries received over the telephone and are never pursued by OPRR. Each year, however, OPRR is presented with several formal, written complaints that can be reviewed in sufficient depth to confirm OPRR's lack of jurisdiction.

For example, parents of a young child who underwent experimental bone marrow transplantation alleged that they were not adequately informed about the procedure's reasonably foreseeable risks, including the severe brain damage which their child suffered. In a second example, it was alleged that women who had experienced multiple miscarriages were misled about

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the substantial financial cost of participating in research to enhance pregnancy. A third example involved a mid-level state university, where there was a considerable controversy about appropriate confidentiality protections for subjects involved in a study of adult literacy, as well as charges of conflict of interest among members of the university's Institutional Review Board (IRB). In a fourth example, a woman who had been treated for breast cancer alleged that identifiable private information from her medical record had been placed in a registry and made available to research investigators without her consent.

In each of these examples, OPRR was unable to pursue the allegations, because it was formally determined that the research was neither supported by the Federal government nor voluntarily covered under an institutional Assurance of Compliance submitted to OPRR.

OPRR also receives many less-formal inquiries and complaints involving individuals or institutions for which OPRR's lack of oversight authority is readily apparent.

For example, it is frequently alleged that patients have been subjected to "experimental" treatment procedures without appropriate informed consent and without IRB review. OPRR has received specific inquiries about the use of "experimental" techniques in gall bladder surgery; "experimental" psychotherapy techniques; and surgery research that was not subjected to IRB oversight, allegedly because the investigator generated a great deal of revenue for the hospital involved.

Other examples involve breach of confidentiality in research. In one instance, it was alleged that confidential, identifiable responses of nurses involved in research about lapses in patient care were made available to the nurses' employers. In another instance, it was alleged that an investigator utilized sensitive, identifiable drug abuse treatment information for research without informed consent or IRB review. In a third instance, it was alleged that several physicians provided a research investigator with confidential patient identity and medical record information without patient permission or IRB review.

The use of deception in research has also generated inquiries to OPRR. For example, one complainant described "team management" research in which unsuspecting individuals were subjected to a sham robbery, resulting in significant stress, fear, and anxiety. Another complainant described "fright response" research in which participants were subjected to unexpected and disturbing visual stimuli.

OPRR was also unable to pursue complaints alleging 1) a coercive structure of payment for participation in weight loss research which made it extremely unlikely that subjects would discontinue participation prior to completion of the research; 2) failure to characterize adequately the severity of reasonably foreseeable risks associated with a research comparison of two FDA-approved drugs; and 3) lack of parental consent and IRB review for survey research in which children were asked sensitive questions about their own behavior and that of their parents and friends.

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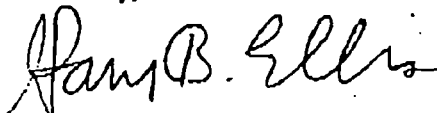
From time to time, OPRR is also made aware of media reports describing questionable involvement of human subjects in research. A November 9, 1995 University news release describes private-foundation funding of a dentist's study of removal and replacement of mercury amalgam from the dental fillings of approximately 30 patients. On October 10, 1994, the *New York Times* reported that a Manhattan gynecologist had successfully induced abortions in 121 of 126 patients with two FDA-approved drugs in an attempt "to show the medical community that there is a safe, simple, effective, legal technique of terminating pregnancies that is private and inexpensive." In another *New York Times* story (August 15, 1994), grade schools in North Carolina are described as permitting industry-sponsored survey of the height of children, so that short children could be identified for referral for potential treatment with genetically engineered human growth hormone. On June 13, 1996, the *San Diego Tribune* reported that "four African-American children were singled out for a race-related survey" by a local graduate student without the permission of their parents or of the school system.

The information contained in these 19 examples drawn from OPRR files may seem fragmentary. That is by necessity. With current authority, it is neither proper nor possible for OPRR to pursue these incidents and many other like incidents, and to fully describe and understand what is happening to the participants that are involved.

I hope that the details provided herein will put to rest any uncertainty among Subcommittee members as to the existence of a substantial problem: That is, the unwitting participation--with attendant possibility for physical or dignitary harm--of some of our fellow Americans in research. OPRR's experience indicates that there exists in 1997 a substantial reservoir of such research activity.

The Nation needs the tools necessary to insure that human subjects are protected by 1) initial and continuing IRB review, and 2) legally effective informed consent. As the Subcommittee proceeds with its consideration of protecting the rights and welfare of human subjects, please do not advance beyond what I would call Square One without articulating a meaningful standard of protection for all individuals who may be research subjects.

Sincerely,



Gary B. Ellis, Ph.D.

Director

Office for Protection from Research Risks

REVISED

**Testimony of
Harold E. Varmus, M.D.
Director, National Institutes of Health**

**Before the
Subcommittee on Human Resources and Intergovernmental Relations
Committee on Government Reform and Oversight
United States House of Representatives**

**Thursday, May 8, 1997
Rayburn House Office Building, Room 2247
10:00 a.m.**

FOR RELEASE UPON DELIVERY

Mr. Chairman and Members of the Subcommittee:

I am Harold Varmus, Director of the National Institutes of Health. I am pleased to appear before the Subcommittee to describe our system of protection of human research subjects, a responsibility of enormous weight. While the collection of scientific data to expand our knowledge of the causes of human ills is the ultimate aim of medical research, of importance is the protection of the individuals who assist us through their participation in research studies. Without these individuals, it would have been impossible for us to have made such remarkable progress in the development of effective treatment and prevention strategies for a host of human diseases and conditions.

History of Human Subjects Protection

May 30 marks the 22nd anniversary of the formal promulgation of the Department of Health and Human Services' (DHHS) regulations for Protection of Human Subjects in research (Title 45 Code of Federal Regulations Part 46). This vigorous system of protections, designed to preclude the very problems we will discuss today, is guided by a set of principles--respect for persons, beneficence, and justice--which are the three quintessential requirements for the ethical conduct of research involving human subjects. It is based on a succession of judgments made by a variety of individuals in the context of DHHS regulations. Scientists, ethicists, lawyers, advocacy group members, and, most importantly, public citizens look at research protocols and weigh risks and potential benefits.

Let me take a moment to give you some background on the development of human subjects protections. Our modern-day system began with the Nuremberg Code, which was developed for the Nuremberg Military Tribunal to provide standards by which to judge the human experimentation conducted by the Nazis. Many of the Code's principles regarding the ethical conduct of research involving human subjects still are followed today. It was followed in 1964 by the World Medical Association's *Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects*; and in 1966, NIH issued "Policies for the Protection of Human Subjects, which established the institutional review board (IRB) as one mechanism through which human subjects would be protected.

As I have mentioned, it was in May 1974 that the DHHS regulations were issued, elevating to regulatory status NIH's "Policies." Then in July 1974, the National Research Act was enacted, which established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The activities of the National Commission, which was active from 1974 to 1978, culminated in the development of the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. The Report set forth the three basic ethical principles underlying the acceptable conduct of research involving human subjects, mentioned above, which continue to guide us today. Over the years, the DHHS regulations have been revised six times, adding additional protections for vulnerable populations.

Whose Responsibility Is The Protection of Human Subjects of Research?

Who is involved in protecting human subjects? The architecture of the current system involves at least half a dozen levels of protection. Ultimately, protection depends on several principles. First, the clinical investigator must be scientifically well-trained and also aware of his or her ethical responsibilities as a researcher committed to both the advancement of knowledge and the welfare of research participants. The initial planning of the research protocol is a vital part of the protection of human subjects, during which time the researchers perform a thorough review of the literature in order to develop a research plan and also to identify any potential risks associated with the research. The investigators address both benefits and risks associated with the research, and formulate an appropriate process to inform potential participants, to obtain informed consent for participation, and to document the consent.

Second, there is review and approval of the research protocol by a local IRB, a requirement of the DHHS regulations for Federally-supported research. Although non-Federal research is not covered by these regulations, you should be aware that the DHHS regulations are in general use by others as well. Following IRB review, additional review responsibilities rest with 1) the executive official of the research site; 2) the scientific review group at the NIH (generally, within the Division of Research Grants, or within an NIH Institute or Center [IC]); 3) the Advisory Council or Board of the funding IC; and 4) the executive official of the funding entity. Each has the authority to raise concerns about human subjects issues and to request further evaluation and correction of any problems found.

Once multiple review of the proposed study design and informed consent documents has been accomplished, and the proposal is funded, there is the crucial interaction between the research volunteer and the research investigator. It is at this point that the informed consent process begins — when the research volunteer is apprised of what will be required for his/her participation in the study, including known associated risks. The informed consent document is only one component—the written component—of the informed consent process. I will describe the particulars of informed consent later. There also may be several individuals involved with the research volunteer during the process of obtaining informed consent, and throughout the course of the study, such as the nursing and scientific staff, as well as a physician. There also may be a consent auditor or monitor, or an advocate for the research subject to ensure that research subjects understand and are kept informed of any proposed changes or risks.

IRB Review

As I mentioned earlier, IRB review is required by DHHS regulations. The IRB must be established at the local level and have a minimum of five people, including at least one scientist, one nonscientist, and one person not otherwise affiliated with the institution conducting the research study. Having the IRB at the research site is the cornerstone of our system of protection of human subjects. IRB review is a prospective and continuing review of the research by a group of individuals with no formal interest in the particular research study, who are in the best position

to know the resources of the institution, the capabilities and reputations of the investigators and staff, and the prevailing values and ethics of the community and, thus, the likely subject population. No human subjects research may be initiated, and no ongoing research may continue, in the absence of an IRB approval. The NIH cannot provide funds for human subjects research unless an IRB approves the protocol for such studies.

Once research is initiated that involves human subjects, IRBs have continuing responsibilities. These include the conduct of continuing review at intervals appropriate to the degree of risk, but not less than once per year; the authority to observe or have a third party observe the consent process and the research; prompt reporting of any unanticipated problems involving risks to subjects or others, or any serious or continuing noncompliance with the IRB's requirements or determination, or with the regulations; and authority to suspend or terminate IRB approval of research that is not being conducted in accord with the IRB's requirements or that has been associated with unexpected serious harm to subjects.

Data Safety Monitoring Boards

An additional layer of review that is sometimes employed is an independent Data and Safety Monitoring Board, or "DSMB," appointed to oversee and to evaluate the research investigation. Size and make-up of DSMBs vary; however, most include physicians with expertise in the disease under study, gained either through patient care or in the conduct of research, statisticians, and experts in scientific specialities. A patient advocate also may be included among the members of a DSMB. At periodic intervals during the course of a research study, the Data and Safety Monitoring Board reviews the accumulated data and makes recommendations on the continuation, or modification, of the study. When a study is stopped prematurely because of a toxic effect or because a strong positive effect was seen, and it would be unethical to continue with some subjects not receiving the test article that has demonstrated benefit, it is likely due to the intervention of a Data and Safety Monitoring Board.

Institutional Officials

The final responsible party at the applicant/grantee institution is the institutional official, who signs-off on the research project when the application is submitted to the funding agency and assumes responsibility for the research project on behalf of the institution when the award is accepted.

Those directly involved with the protection of human subjects on behalf of the NIH are the members of peer review groups, the Director and other staff of the funding institute or center, and the Office of Protection from Research Risks (OPRR). Located administratively and logistically at the NIH, OPRR exerts extensive oversight of the entire process of human subjects protection for HHS-supported research. Among its many responsibilities, the OPRR develops and monitors, as well as exercises compliance oversight relative to, DHHS regulations; establishes criteria and negotiates for Assurances of Compliance with institutions engaged in

DHHS-supported research involving human subjects; conducts programs of clarification and guidance for both the Federal and non-Federal sectors with respect to the involvement of humans; and evaluates the effectiveness of DHHS policies and programs for the protection of human subjects. OPRR plays a major role in ensuring that human subjects of research are informed and protected and that thorough investigations of human subjects concerns are conducted. OPRR also investigates complaints from research subjects and others concerned with their welfare, and conducts a national program to educate the research community about human subjects protections.

Members of NIH scientific review groups and advisory councils evaluate the proposed involvement of human subjects in the research and identify comments or concerns regarding protections for human subjects. NIH program staff work with the principal investigator and the institution to resolve any human subject comments or concerns prior to award. Grants management staff confirm that an applicable Assurance of Compliance and IRB approval have been obtained prior to award. Once these steps are completed, the Institute or Center Director makes the decision whether or not to fund the research project.

A Perfect System?

While I have emphasized the multiple layers of protection inherent in this system, I know you are most concerned about the possibility that this system can somehow fail. We acknowledge that despite our best efforts, there are occasions when the systems for protection are not perfect or the individuals charged with ensuring adequacy of these protections are unable to foresee potential problems. What is the possibility of a failure in human judgment running through six or more layers of review? Certainly, the successes far outweigh the failures. Nevertheless, there have been research studies that have required further evaluation for human subjects concerns. To give you a sense of the kinds of problems we have encountered, I will relate brief accounts of selected research studies involving human subjects concerns and highlight actions taken to address them.

In one well-publicized instance, concern was raised about the proper explanation of risks in the informed consent process for a study involving research subjects with schizophrenia at the University of California at Los Angeles (UCLA). After extensive review of concerns voiced, and of the institution's informed consent practices in general, it was determined that the IRB did not exercise sufficient oversight of the informed consent process. The institution was directed to revise the informed consent process. In addition, OPRR instituted close monitoring of the institution's human subjects activities, and issued a report on the investigation of UCLA activities relative to this protocol. As a result of this occurrence, the Acting Director of the National Institute of Mental Health (NIMH), the funding entity for the study, sent correspondence to more than 200 clinical investigators to provide each with a copy of the OPRR report and to request that they carefully scrutinize all informed consent documents for full compliance with the OPRR recommendations. In 1995, the Institute released a program announcement--Informed Consent in Clinical Mental Health Research--to expand upon previously funded research on informed

consent. NIMH also has sponsored, and co-sponsored with advocacy groups, a number of workshops and conferences aimed at addressing issues specific to mental illness in clinical research.

In a second instance, concern was expressed about the misuse of an expedited IRB review process. OPRR identified failure of leadership within the IRB as the root of the problem, resulting in resignation of the IRB chairman. Sometimes, an OPRR review leads to a finding that the concerns were unfounded as in the case of another institution. OPRR followed up on concerns that were raised about whether a particular IRB was properly conducting the required annual review of continuing research. The institution demonstrated to OPRR that some 2,000 research protocols involving human subjects had, indeed, received continuing review by the IRB in accord with DHHS regulations.

Protection of Vulnerable Populations

Let me return briefly to the specific responsibilities of the IRB and the concerns IRBs must address. IRB review assures that risks are minimized; risks are reasonable in relation to anticipated benefits; selection of subjects is equitable; there is proper informed consent; and the rights and welfare of subjects are maintained in other ways, as well. This is particularly important when subjects are likely to be vulnerable to coercion or undue influence.

What populations are judged to be vulnerable? IRBs pay careful attention to research involving children, prisoners, pregnant women, individuals with mental disabilities, individuals who are economically disadvantaged, and individuals who are educationally disadvantaged.

The DHHS regulations provide extra protection for vulnerable subjects in several ways. If an IRB regularly reviews research that involves a vulnerable category of subjects, consideration must be given to including as IRB members one or more individuals who are knowledgeable about and experienced in working with the vulnerable population. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, IRBs must see that additional safeguards are included in the study protocol. Specific, detailed protections are actually written into DHHS regulations pertaining to pregnant women, fetuses, human ova fertilized *in vitro*, prisoners, and children. I would like to highlight a few additional protections in place for several of these vulnerable groups.

Children

Recognizing the need for special attention to pediatric subjects of research, it is assumed that children are incapable of providing informed consent. As such, special protections are mandated for this vulnerable population. As required by regulation, parents or legal guardians must give proxy consent for their children to participate in research protocols. In protocols involving only minimal risk or those involving greater than minimal risk but which have the prospect of direct benefit to the child, only one parent must give consent. In protocols involving

a minor increase above minimal risk or more than a minor increase above minimal risk in which the child stands not to benefit, both parents must sign a consent form.

As an additional protection, within the intramural program of the NIH--with specific, rare exceptions--children between the ages of 7 and 18 who are capable of understanding that they are involved in a research project are required to sign an "assent" form, which acknowledges their affirmative agreement to participate in a research protocol. Much care is given to writing assent forms in readily understandable language that is age-appropriate and to providing simple oral explanations, sometimes accompanied by visual demonstrations with dolls or by role-playing. Research investigators and nursing staff are often assisted in the "assent" process by patient advocates and assent auditors who are not involved in the research project in order to avoid any possibility of coercing the child into participating in the protocol.

Persons with Mental Illness or Dementia

Although there are no DHHS regulations providing specific protections for persons with mental illness or dementia, special attention is being given to informed consent issues related to their involvement in research studies. Recognizing the many issues surrounding patients with mental illness, the NIMH co-sponsored with the National Alliance for the Mentally Ill (NAMI) a series of meetings, including a symposium at the NAMI annual meeting, to discuss ethical issues concerning human subjects with mental illness in biomedical research. The NIMH and NAMI now are planning co-sponsorship of a meeting with a broader group of participants to develop a series of principles to guide informed consent with potentially cognitively impaired subjects. NIMH also sponsored a conference, *Ethical and Human Subjects Issues in Mental Health Research with Children and Adolescents*, to discuss the specific ethical challenges involved in this research. In addition, the NIMH and OPRR co-sponsor regional workshops to focus on issues specific to patients with mental illness in clinical research. These workshops, held throughout the country, are attended regularly by approximately 1,000 IRB members and researchers.

Issues of informed consent are of particular concern for the elderly population, particularly with regard to Alzheimer's disease patients and others with diminished cognitive capacities. The National Institute on Aging (NIA) is participating in a Request for Application on informed consent in research involving human subjects, which I will discuss later. NIA is particularly interested in the role of cognitive function in aging, and the ability of the elderly to understand and remember so that information related to the consent process is meaningful.

In addition, the NIA issued an announcement in the NIH Guide to Grants and Contracts, in October 1996 on "Implementation of Policies for Human Intervention Studies." This notice codifies additional oversight on the part of NIA Program Administrators to ensure the safety of participants in NIA-supported intervention studies.

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Beyond these guidelines and the general NIH-wide guidelines on protection of human subjects, the NIA has no formal written guidelines for informed consent for research with Alzheimer's disease patients. However, efforts are being made to maintain consistent practices across large multi-site clinical studies. For the Alzheimer's Disease Cooperative Studies Program, the Principal Investigator reviews the consent forms from each site for consistency and appropriateness.

In addition, the NIH Warren Grant Magnuson Clinical Center--together with the NIMH, the NIA, the National Institute of Neurological Diseases and Stroke, and other NIH institutes--has pioneered the concept of the durable power of attorney applied to research participation, whereby individuals, while competent, could identify someone to represent their best interest and provide informed consent should they later become cognitively impaired. The classic example of when this would be used is with participants in a study of progressive dementias.

Drug Users

The National Institute on Drug Abuse recognizes the importance of drug users to drug abuse research and the special attention that must be given to ensuring informed consent in this special population. In addition to the roles that the IRB and OPRR play in ensuring the protection of participants in NIDA research studies, the Institute adheres to the basic principle and provides guidance that the investigator has the primary responsibility for the protection of vulnerable subjects. The investigator must give adequate consideration to the mental and physical conditions and motives of the individuals in terms of their ability to fully understand the context of the informed consent. If there is a question about a potential subject's ability to give meaningful and informed consent, an independent clinician, ethical consultant, or uninvolved third party with appropriate qualifications should be asked to evaluate this ability if the subject is to be entered or continued in the study.

Those most necessary to drug abuse research are drug abusers. Recidivism is a key issue in drug abuse treatment research, and relapse cannot be studied without the use of individuals who have taken drugs. Research that requires administration of drugs to individuals who are addicted to drugs warrant special attention, however. There are a number of extremely important principles which need to be addressed by anyone considering or evaluating requests to conduct research using drug-addicted individuals. Medical and mental examinations and screenings must be made to ensure the absence of any medical or mental condition for which further drug exposure would be contraindicated. A thorough assessment of the risks entailed if the participant is to be exposed to a higher dose, rate of administration, and/or new route of administration than they would normally encounter by their own choice in their usual circumstance must be made. Finally and most importantly, investigators must make a serious and concerted effort to link these individuals to drug abuse treatment.

The effects of drug use on adolescents is a major issue in drug abuse research and children are often involved in drug abuse prevention research. If the hypothesis being tested

requires the involvement of individuals under age 18 and the risk/benefit assessment is favorable, the investigator must: (1) obtain the individual's consent and/or assent to participate in the study; (2) obtain permission from the parent(s) or guardian for the individual to participate in the study; and (3) comply with any applicable local laws governing such research.

Assurance of Compliance With Human Subjects Regulations

The DHHS regulations for Protection of Human Subjects are not a set of rules that can be applied rigidly to make determinations of whether a proposed research activity is ethically "right" or "wrong." Rather, they are a framework in which investigators, IRB members, and others can ensure that serious efforts have been made to protect the rights and welfare of research subjects.

OPRR oversees implementation of the regulations in all DHHS facilities as well as domestic and foreign institutions or sites receiving DHHS funds. OPRR requires that each DHHS agency and extramural research institution that conducts research involving human subjects set forth the procedures it will use to protect human subjects in a policy statement called an "Assurance of Compliance." An Assurance statement is a formal, written commitment to: 1) widely-held ethical principles; 2) the DHHS regulations for Protection of Human Subjects; and 3) institutional procedures adequate to safeguard the rights and welfare of human subjects. The terms of the institution's Assurance are negotiated with OPRR. The detailed, written Assurance statement becomes the instrument that OPRR uses to gauge an institution's compliance with human subject protections if there is a problem.

At OPRR's discretion, institutions with large research portfolios and demonstrated expertise in human subjects protection may be granted a Multiple Project Assurance (MPA). An MPA, as the term implies, is an institution's pledge of full human subject protections for multiple projects at the institution. More than 450 institutions currently hold an MPA. As an agency regulated by OPRR, the NIH Intramural Research Program, with 14 Institutional Review Boards overseeing research conducted at the NIH itself, has earned a Multiple Project Assurance from OPRR.

Informed Consent

All present today know how integral, and how crucial, the process of informed consent is to the protection of human subjects, whether in research or in other situations where medical assistance is necessary. Many have a general picture of informed consent, and it is useful to add higher resolution to that picture. DHHS regulations specify 14 elements of informed consent. Of these, eight are required and are designed to ensure that research subjects are fully informed

about the studies in which they are to enroll, the risks and benefits, if any, as well as their rights with regard to participation in DHHS-sponsored research. These are highlighted below.

- 1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental.
- 2) A description of any reasonably foreseeable risks or discomforts to the subject.
- 3) A description of any benefits to the subject or to others that may reasonably be expected from the research.
- 4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- 5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.
- 6) For research involving more than minimal risk, an explanation as to whether any compensation will be paid, whether any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained.
- 7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- 8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

A researcher who seeks to recruit an individual for research without conveying these elements of information in language understandable to the potential subject is not obtaining *informed* consent.

Implementing informed consent is a dynamic endeavor, and we are always seeking new perspectives. For example, a June 2, 1997, conference co-sponsored by the National Cancer Institute, the NIH Office of Research on Women's Health, the National Action Plan on Breast Cancer, and others, will seek to identify principles and models for prospectively obtaining, storing, and utilizing stored tissue specimens for research. Also, the National Bioethics Advisory Commission (NBAC), which is charged with providing guidance to Federal agencies on the ethical conduct of current and future human biological and behavioral research, is reviewing all

of the human subjects protections for their adequacy and appropriateness today. You will hear more about this from my HHS colleague, Dr. William Raub.

Special Considerations in Informed Consent

With any set of regulations, situations arise that require special consideration. DHHS regulations for Protection of Human Subjects do provide avenues for such occurrences, recognizing that certain consent procedures with IRB approval may not include or may alter some or all the elements of informed consent, or that a waiver of the informed consent requirement may be made. These avenues may only be used in certain narrow circumstances. The DHHS regulations (45 CFR 46.116(d)) provide for waiver of the requirements to obtain informed consent when all four of the following circumstances pertain:

- the research involves no more than minimal risk to the subjects; ("Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests [45 CFR 46.102(f)].)
- the waiver, or alteration, of consent will not adversely affect the rights and welfare of the subjects;
- the research could not practicably be carried out without the waiver or alteration; and
- whenever appropriate, the subjects will be provided with additional pertinent information after participation.

IRBs are required to make and document these judgments.

You will hear about waivers and informed consent in emergency situations from Mary Pendergast, Deputy Commissioner, Food and Drug Administration..

Research on Informed Consent

Despite the specificity of Federal regulatory language on informed consent, its endurance through many years, and the enthusiasm with which we all adhere to it, there is little empirical work in existence to document the degree of understanding achieved by research participants. There is a scarcity of data that bear upon, for example: 1) research subjects' comprehension of a study's methods and procedures; 2) subjects' understanding of relative risks and benefits of participation; 3) subjects' understanding of confidentiality and any exceptions to confidentiality; and 4) subjects' understanding of the implications of withdrawal from a study. Such data are needed to aid in designing informed consent procedures that are readily comprehended by prospective participants and, at the same time, impart all critical information.

In this vein, the NIH has joined with the Department of Energy and the Department of Veterans' Affairs in a Request for Applications (RFA) for original research proposals in the area of "Informed Consent in Research Involving Human Participants." The sponsoring organizations are jointly issuing this RFA because voluntary informed consent is the defining aspect of interactions between researchers and participants, and is integral to the conduct of the scientific research funded by all of these organizations. One of the goals of this RFA is to bring together perspectives of these different agencies, since their different research foci reflect a diversity of issues relating to informed consent. Of course, many facets of understanding the informed consent process are shared, and hence a combined effort is efficient for the agencies and scientists alike. Such data should be useful in designing informed consent procedures that are readily comprehended by prospective participants and impart all critical information. The goal of the present initiative is to develop and test alternative strategies for obtaining informed consent in diverse populations and determine optimal ways to obtain informed consent for research participation.

The three agencies have set aside funds in FY 1997 to support projects in response to this RFA. More than 80 proposals were submitted by the March 11, 1997, closing date for receipt of applications. These three agencies are igniting the engine of research in an area that has for too long been under explored.

Conclusion

In the final analysis, Mr. Chairman and Members of the Subcommittee, research investigators, institutions, NIH, and DHHS are stewards of a trust agreement with the people who volunteer to be research subjects. We have a system in place that to the greatest degree possible 1) minimizes the potential for harm; 2) enables and protects individual, autonomous choice; and 3) promotes the pursuit of new knowledge. By doing so, we protect the rights and welfare of our fellow citizens who make a remarkable contribution to the common good by electing to volunteer for research studies. We owe them our best effort.

Thank you, Mr. Chairman. I will be pleased to answer any questions you may have.