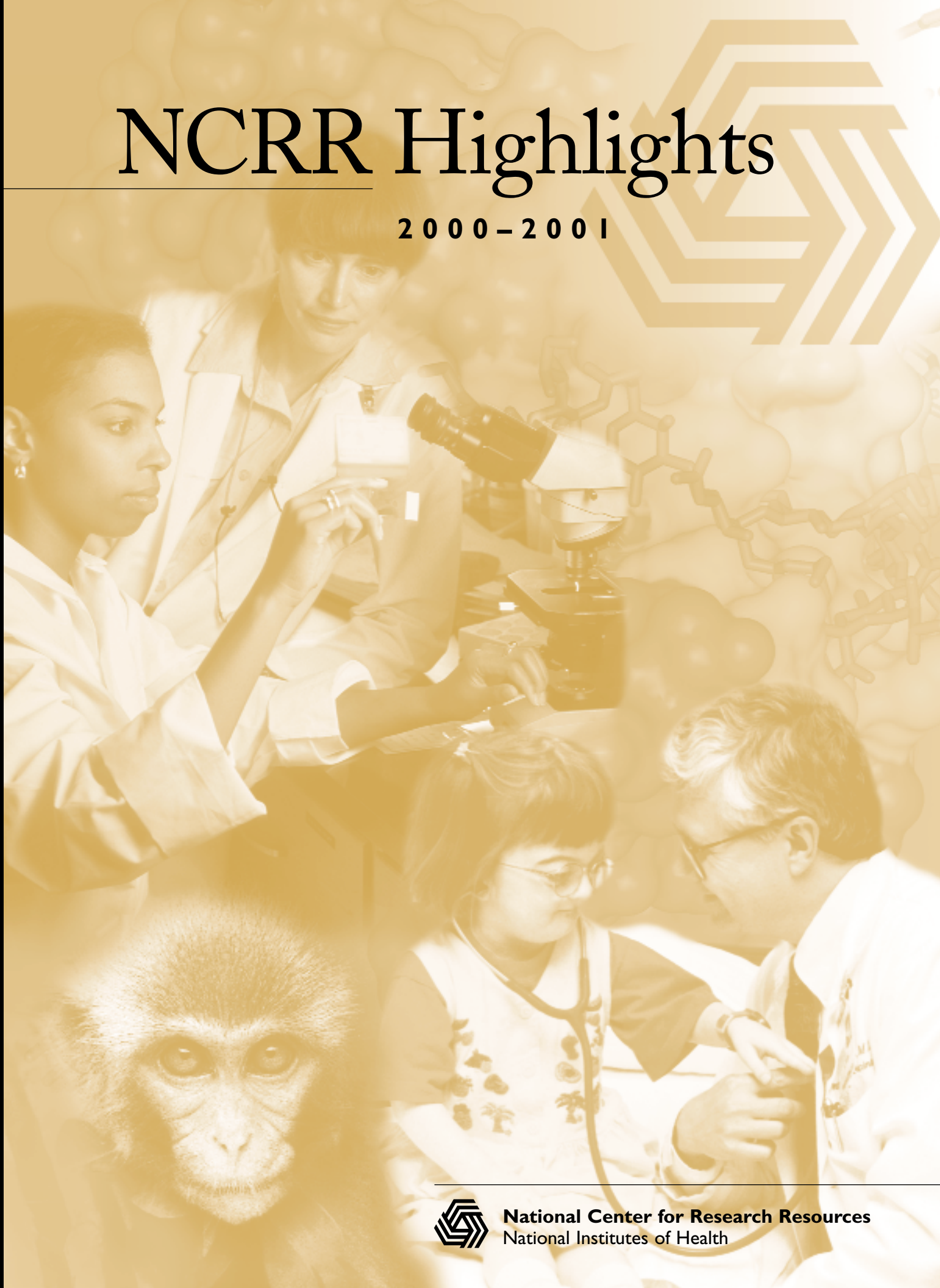
NCRR Highlights

2000–2001



National Center for Research Resources
National Institutes of Health

ON THE COVER **This collage illustrates the diverse human, animal, and technological resources that the National Center for Research Resources (NCRR) supports. Biomedical researchers who share these resources conduct basic and clinical investigations that improve human health.**

NCRR Highlights

2000–2001

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National Center for Research Resources
National Institutes of Health

MISSION

The National Center for Research Resources (NCRR) is a catalyst for discovery for NIH-supported investigations throughout the nation. NCRR creates, develops, and provides a comprehensive range of human, animal, technological, and other resources to enable biomedical research advances.

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NCRR HIGHLIGHTS

Introduction

ALTHOUGH IT'S NOT ALWAYS APPARENT, Americans today benefit in countless ways from the nation's long-term investment in biomedical research. We can now expect to live nearly 30 years longer than those born a century ago; vaccines and therapies have slashed the incidence of costly infectious diseases; and death rates from coronary artery disease and stroke have been halved in recent decades. Moreover, molecular and clinical studies have identified effective drugs for combating AIDS and armed us with new weapons in the fight against cancer.

These and other improvements to public health have depended in large part on the stewardship of the National Institutes of Health (NIH), the nation's leading supporter of biomedical research. More than 50,000 scientists, located at over 2,000 institutions nationwide, receive funding from NIH to conduct biomedical investigations. Their success relies not only on the ingenuity and resourcefulness of the researchers themselves, but also on the ready availability of critical research tools and resources, including clinical research environments, cutting-edge technologies, nonhuman models of disease, and other research infrastructure.

Providing these tools is the role of the National Center for Research Resources. NCRR is one of the few NIH components that has a cross-cutting mission—to enable all lines of scientific inquiry that NIH supports. To achieve this mission, NCRR works in trusted partnership with the biomedical research community and with other NIH institutes and centers in an effort to meet, and even anticipate, diverse needs for research infrastructure.

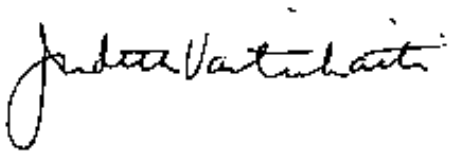
This publication, *NCRR Highlights 2000–2001,* provides examples of the many mechanisms by which NCRR supports the nation's research efforts. The "Research Divisions" section provides an overview of NCRR's four divisions—Biomedical Technology, Clinical Research, Comparative Medicine, and Research Infrastructure—and highlights each division's recent achievements. Each division's accom-

plishments over the past two years demonstrate NCRR's commitment to engaging in dialogues with the scientific community and responding rapidly to their ever-changing resource needs. For instance, after preliminary studies identified a cellular therapy that may offer diabetic patients respite from insulin injections, NCRR teamed with the Juvenile Diabetes Research Foundation International to create a network for producing these cells—known as pancreatic islets cells—for use in clinical studies. When investigators identified a need for enhanced funding of research instruments that were prohibitively expensive (in excess of $1 million), NCRR established the new High-End Instrumentation Program. That program awards up to $2 million in direct costs for cutting-edge instruments that might otherwise be impossible for research institutions to purchase on their own.

NCRR Highlights 2000–2001 also represents NCRR's commitment to helping NIH achieve its overarching goals in safeguarding the nation's health. In Fiscal Years 2000 and 2001, NIH identified seven broad categories of research that show extraordinary promise for addressing public health needs and taking advantage of new scientific opportunities. These seven areas of research emphasis—biology of brain disorders; new approaches to pathogenesis; new preventive strategies against disease; new avenues for development of therapeutics; genetic medicine; bioengineering, computers, and advanced instrumentation; and health disparities—receive top priority when NIH makes funding decisions. The "Research Highlights" section illustrates the many ways that NCRR-supported resources contribute to advances in these seven promising areas of study.

These research advances are only small steps, each moving us further along on the pathway of discovery. We do not yet know where each research avenue will ultimately lead. Discovery of genes in yeast and roundworms (described on page 49) may lead to discovery of comparable genes in higher organisms and possibly even provide clues for slowing the human aging process. Detailed understanding of the outer coat of the human herpesvirus (page 52) may lead to better treatment strategies.

Today's medical treatments are built on untold numbers of research contributions from seemingly unrelated fields. Each discovery—whether at the level of molecules, cells, or whole organisms—opens the door to new knowledge. By funding essential tools and other research infrastructure, NCRR helps scientists explore more complex research questions as they arise, and future generations will reap the rewards of these efforts.



JUDITH L. VAITUKAITIS, M.D.
Director, National Center for Research Resources

The Benefits of Shared Research Resources

TOOLS, LIKE LIVING SYSTEMS, EVOLVE OVER TIME. Hand tools made of stone gave way to metal 5,000 years ago, just as drums and smoke signals were replaced, in quick succession, by the telegraph, telephone, and computer as tools for two-way communication. The pace of change in the tools we use evolves rapidly over time, as new technologies and materials are developed and mastered. Nowhere is this more evident than in biomedical science.

Advances in technology have so quickened the rate of developing new biomedical tools that many labs now depend on research resources that were nonexistent only a decade ago. High-throughput microarray technologies, genetically modified biological models, advanced microscopies, synchrotrons for crystallography, and functional magnetic resonance imaging are just a few of the research tools that have evolved in recent years and are indispensable to biomedical research.

The goal of the National Center for Research Resources (NCRR) is to anticipate the ever-changing needs for research infrastructure and to ensure that the biomedical community has ready access to sophisticated, enabling tools and technologies. The critical research resources funded by NCRR include not only state-of-the-art technologies but also clinical research environments; biological models; career development programs for physicians, dentists, and veterinarians; and construction funds to build or renovate research laboratories. These cross-cutting resources enhance all lines of scientific inquiry supported by the National Institutes of Health (NIH), from studies of genes and cells to clinical evaluation of candidate vaccines and novel therapies.

NCRR's primary strategy for maximizing the effectiveness of Federal research dollars is to encourage investigators and institutions to share scarce or expensive institutional research resources. Shared resources are not only cost effective but also provide a setting in which research ideas may be exchanged and scientific collaborations initiated. Interdisciplinary teamwork is especially important today, as researchers strive to translate genome sequences and gene discovery into a deeper understanding of the proteins expressed by genes, their interactions, and the modulation of cellular mechanisms.

When making funding decisions, NCRR places particular emphasis on ensuring that the biomedical community has access to research resources that are:

- cost-saving, efficient, shared, and accessible;
- multidisciplinary and collaborative, often serving to integrate diverse research efforts; and
- at the cutting edge of innovation, including high-risk and long-term research that may have significant societal payoff.

NCRR programs are concentrated in four divisions: Biomedical Technology, Clinical Research, Comparative Medicine, and Research Infrastructure. Each division fills a unique niche in meeting the cross-cutting needs of NIH-funded researchers. The four divisions complement the research missions of other NIH components.

NCRR's Division of Biomedical Technology funds resource centers that develop advanced instruments and technologies, including those for computation, analyses, and imaging. Qualified scientists may seek expert advice from the scientific staff of the resource, gain access to unique technologies, or attend workshops that provide training sessions at these state-of-the-art resource centers. The Division of Biomedical Technology also awards grants for two different shared instrumentation programs, including equipment that costs up to $2 million. These grants provide funds to institutions to buy expensive instruments that can be cost-effectively purchased and shared among several researchers.

The Division of Clinical Research supports a nationwide network of 79 General Clinical Research Centers (GCRCs), which provide research environments for the study of human subjects. Usually located within major academic medical centers or teaching hospitals, each GCRC contains inpatient and outpatient facilities, laboratories for specialized tests, computer facilities, and a specially trained staff of research nurses and other personnel. Some GCRCs also include specialized facilities such as diet kitchens and metabolic study units. NIH-funded investigators are encouraged to use the cost effective, controlled environment of the GCRC to conduct human studies. Elsewhere such facilities might be prohibitively expensive or technically difficult to access and use. Other clinical research resources provide access to high-quality clinical-grade vectors

for human therapies; human pancreatic islets for transplantation; and human tissues and organs for research.

The Division of Comparative Medicine funds research resources and projects that provide the biomedical community with a broad array of high-quality animal and biologic models, ranging from yeast, *C. elegans,* and aplysia to genetically modified rodents and higher organisms. Nonhuman primates, in particular, are so closely related to humans that studies of these animals offer crucial insights into the pathobiology and treatment of devastating conditions such as AIDS, cardiovascular disorders, and drug addiction. The nationwide network of eight Regional Primate Research Centers offers opportunities for qualified investigators to study nonhuman primates and collaborate with primatology experts.

The Division of Research Infrastructure supports institutional development of new research capacity, minority research facilities, and science education. The Research and Animal Facilities Improvement Programs provide much-needed funds for the construction of new or renovation of existing biomedical research facilities. Through its Institutional Development Awards (IDeA), NCRR also helps to strengthen research infrastructure in specific geographic regions that traditionally have not received significant competitive funding from NIH. IDeA enables development of multidisciplinary research centers, facility renovation and purchase of laboratory equipment, and recruitment of established research faculty to institutions in IDeA-eligible states. Other programs—like the network of 18 Research Centers in Minority Institutions—enhance the biomedical research capacity at institutions that serve predominantly minority populations. And education programs like the Science Education Partnerships Awards target a variety of audiences to enhance understanding of biological sciences and perhaps even motivate future generations of biomedical researchers.

The diverse research resources and projects supported by NCRR's four divisions meet a trans-NIH need. By ensuring sufficient access to essential research tools, NCRR helps to move discoveries from bench to bedside. Whether these research tools are traditional or newly emerging, NCRR stands ready to meet the shifting requirements of the biomedical community, and the health of our nation's citizens will be the prime beneficiary.

Research Divisions

NCRR HIGHLIGHTS 2000–2001

THE NCRR DIVISION OF BIOMEDICAL TECHNOLOGY (DBT) provides access to cutting-edge technologies and instruments that play a critical role in health-related discoveries. At more than 65 Biomedical Technology Resource Centers—located at universities and research institutions nationwide—teams of scientists discover, develop, and disseminate technological innovations that can be applied to a broad spectrum of biomedical investigations. Each research resource center specializes in a particular type of research tool or technology such as synchrotron radiation, mass spectrometry, laser applications, flow cytometry, advanced microscopy, or simulation and computation. Biomedical investigators can gain direct access to these centers, some of which are testing new protocols for providing remote access to advanced technologies via high-speed Internet connections.

DBT also supports investigator-initiated research projects, including exploratory/development grants, to create new or improved instruments and technologies that may eventually evolve into full-fledged resource centers.

The DBT Shared Instrumentation Grant (SIG) Program allows three or more NIH-supported investigators to purchase sophisticated commercial instruments that cost at least $100,000. Instruments that cost more than $750,000 may be funded through the new High-End Instrumentation Program, which provides awards of up to $2 million.

DBT also participates in Federal grant programs that assist small businesses to develop new or improved biomedical technologies and to facilitate commercial development.

Accomplishments

- Funded five new Biomedical Technology Resource Centers. The new centers will enhance investigators' opportunities to access advanced research tools related to high-field magnetic resonance spectroscopy, synchrotron radiation, imaging mass spectrometry, electron spin resonance, and magnetic resonance imaging, to name a few.

- Launched a new multicenter collaborative project known as the Biomedical Imaging Research Network (BIRN), a scalable, shared network of neuroimaging databases that will serve as a testbed for development of hardware, software, and protocols for mining data in a site-independent manner for both basic and clinical research.

Biomedical Technology

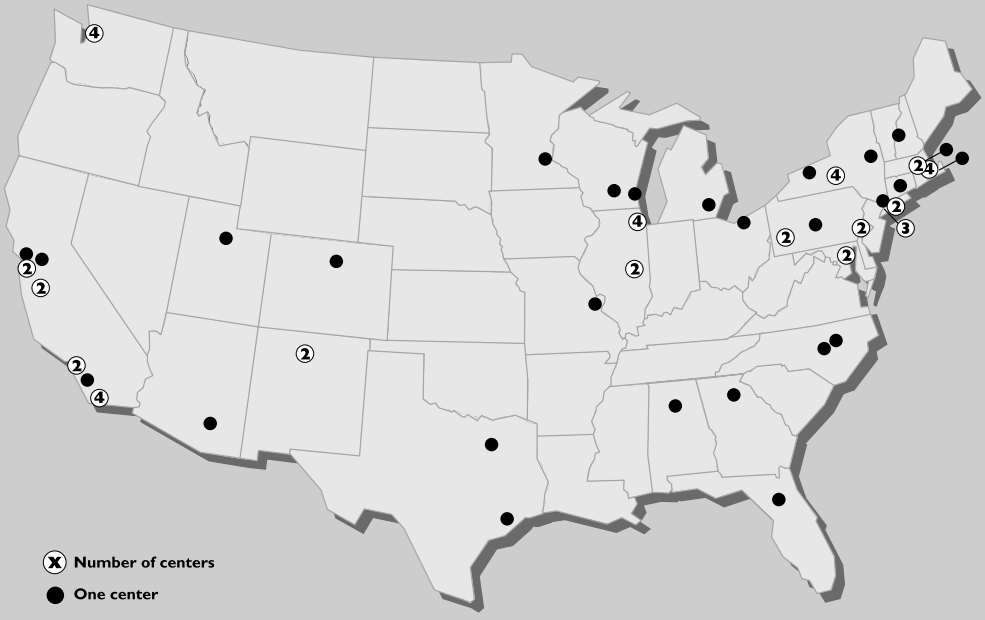
- Supported annual meetings of program directors and staff from the nationwide network of Biomedical Technology Resource Centers.

- Supported more than 300 SIG awards, which enabled the purchase of cutting-edge instruments that cost more than $100,000 each. By encouraging groups of NIH-supported scientists to share expensive instruments, NCRR helps to optimize the use of Federal research dollars. Such instruments include high-resolution and high-throughput DNA sequencers, high-performance computers, and scanning confocal microscopes.

- Raised the ceiling for SIG awards from $400,000 to $500,000, beginning with grants awarded in FY 2000.

- Established the first NIH-wide program that provides funding to purchase instruments that cost more than $1 million. The new High-End Instrumentation Program will award up to $2 million in direct costs for expensive equipment such as high-resolution mass spectrometers, supercomputers, and functional and structural imaging systems.

BIOMEDICAL TECHNOLOGY RESOURCE CENTERS



THE NCRR DIVISION OF CLINICAL RESEARCH (DCR) helps translate scientific knowledge into effective patient care through its network of 79 General Clinical Research Centers (GCRCs), located at academic medical centers and teaching hospitals nationwide. Each GCRC provides a specialized research environment for conducting patient-oriented studies of many diseases—including cardiovascular disease, cancer, diabetes, and AIDS—that affect adults and children. Among the research resources available at most GCRCs are specially trained staff, including research nurses, dieticians, and biostatisticians; computer hardware and software systems for data management and analysis; patient beds; and sophisticated laboratories vital for both inpatient and outpatient research. In addition, several GCRCs have satellite locations at nearby institutions that serve to expand the scope of outpatient investigations. DCR also supports clinical research career development.

Along with several NIH institutes, DCR supports the National Gene Vector Laboratories Program, which ensures that high-quality clinical-grade gene vectors are produced and disseminated for use as potential human therapies.

DCR also supports the Pancreatic Islet Cell Resource Centers Program, which isolates, characterizes, and distributes human pancreatic islets for transplantation into patients with type 1 diabetes. In addition, DCR supports the National Disease Research Interchange's Human Tissue and Organ Resource, which collects and distributes samples of human tissues and organs, both normal and diseased.

Accomplishments

- Funded two new GCRCs located at the University of Illinois, Chicago, and the University of Oklahoma Health Sciences Center, Oklahoma City.
- Established new GCRC satellite units at the University of California, Irvine, and the Children's National Medical Center, Washington, DC.
- Established and expanded GCRC core laboratory units at: University of Connecticut (DNA-RNA); University of California, Los Angeles (brain imaging); Yale University (informatics); University of Southern California (informatics); and University of Oregon (molecular genetics).
- Established a new program that provides salary support for Research Subject Advocates (RSA) at the GCRCs. To protect the safety of patients who participate in clinical research, RSAs will keep patients and volunteers informed about the research projects and clinical trials in which they participate and will facilitate the reporting of serious adverse events within a required timeframe to appropriate oversight boards and agencies.

Clinical Research

- Initiated a new program to establish Human Pancreatic Islet Cell Resource Centers, in collaboration with the Juvenile Diabetes Research Foundation International. These regional resource centers will isolate, characterize, and distribute human pancreatic islets for transplantation into patients with type 1 diabetes. The centers will be located at City of Hope National Medical Center and Beckman Research Institute (Duarte, California); Columbia University, College of Physicians and Surgeons (New York City); Joslin Diabetes Center (Boston, Massachusetts); Puget Sound Blood Center (Seattle, Washington); University of Colorado Health Science Center (Denver); University of Miami (Florida); University of Minnesota (Minneapolis); University of Pennsylvania (Philadelphia); University of Tennessee (Memphis); and Washington University (St. Louis, Missouri).

- Established five-year cooperative agreements to support the network of National Gene Vector Laboratories (NGVL). These NGVLs will produce clinical-grade vectors for human gene transfer protocols and perform related toxicology studies for Phase I and II human clinical gene transfer protocols. The NGVLs will be located at Baylor College of Medicine (Houston, Texas); City of Hope National Medical Center and Beckman Research Institute (Duarte, California); Indiana University (Indianapolis); Southern Research Institute (Birmingham, Alabama); and University of Florida (Gainesville).

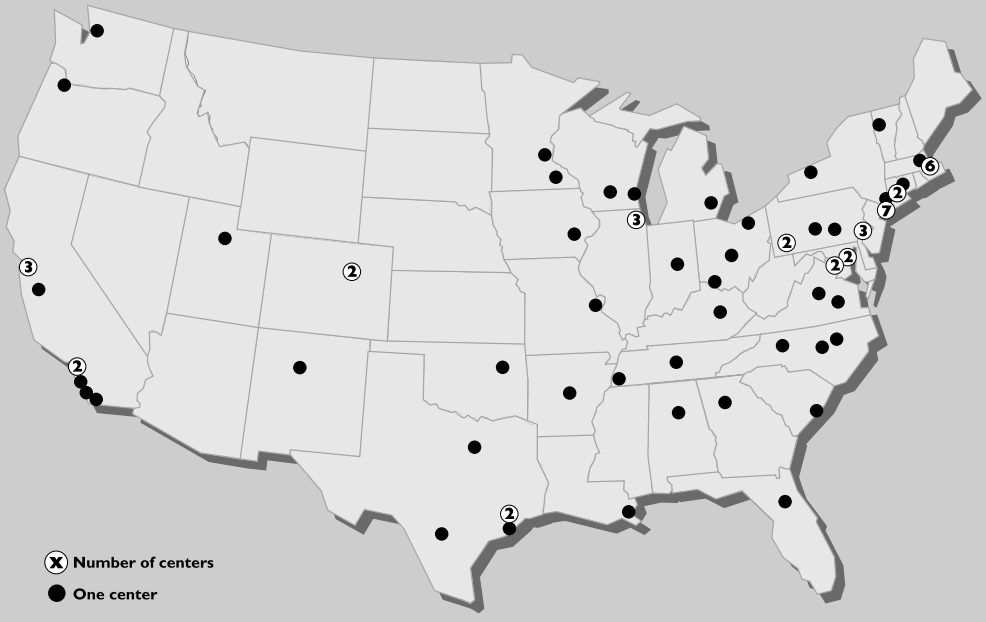
- Cosponsored a Gene Therapy Vector Production Conference, which focused on recent developments and guidelines related to vector production.

- Launched a series of meetings titled "Bioinformatics: An Enabling Technology for Clinical Research." Attendees from around the country discussed how bioinformatics might be most advantageously adopted in GCRCs.

- Increased funding to support Mentored Patient-Oriented Research Career Development Awards to help clinical researchers launch independent careers at the GCRCs, where they can benefit from the presence of mentors.

- Sponsored annual three-day meetings of program directors and staff.

GENERAL CLINICAL RESEARCH CENTERS



THE NCRR DIVISION OF COMPARATIVE MEDICINE (DCM) ensures that biomedical investigators have sufficient access to healthy research animals and animal-related materials that are critical to understanding human health and disease. DCM-supported animal resource centers, biomaterial and information resources, and career development awards enable investigators to carry out research and to create, preserve, or distribute a wide variety of high-quality animal and animal-related models.

Eight Regional Primate Research Centers and related resources maintain nonhuman primates and provide specialized research environments. Because these animals are so closely related to humans, they are optimal models for studying normal biological processes and devastating diseases. DCM also sponsors the national NIH Chimpanzee Management Program, which supports long-term, cost-effective housing and maintenance of chimpanzees that can be used in biomedical research.

DCM-supported Mutant Mouse Regional Resource Centers make available quality, genetically altered mice. Other rodent resources emphasize the discovery and preservation of naturally occurring and induced mutant mouse models of human disease.

Repositories and stock centers offer access to additional animal models, including wild-type, mutant, or genetically defined strains of zebrafish, fruit fly, and roundworm. Other animal-related resources provide specialized tissues, cells, and microorganisms; DNA arrays for analysis of gene expression; computer models; and comprehensive shared databases and resources.

Accomplishments

- Began implementing chimpanzee sanctuary legislation enacted late in 2000. Identified organizations interested in operating and maintaining sanctuaries and requested proposals for sanctuary contracts.

- Awarded a contract to operate and maintain the Alamogordo Primate Facility, located on the Holloman Air Force Base in New Mexico. The contract provides for the long-term care and husbandry of approximately 250 NIH-owned chimpanzees currently housed at the facility.

- Completed a full-scale evaluation of the Regional Primate Research Center (RPRC) program. The expert panel that conducted the evaluation concluded that the RPRCs are a national treasure that must be supported and strengthened. NCRR is acting on the panel's recommendations.

- Supported a workshop for experts in primatology and human genomics to determine future research directions related to primate genetics and genomics and to consider future contributions of the RPRCs.

- Funded six specific-pathogen-free (SPF) rhesus macaque colonies at NCRR-supported primate centers in Louisiana, Massachusetts, Puerto Rico, Texas, Oregon, Louisiana, and California. The colonies will help meet the increased demand for SPF macaques for AIDS research.

Comparative Medicine

- Funded a new grant to develop reference laboratories for major histocompatibility complex (MHC) typing of rhesus macaques. Animals with certain MHC types will play critical roles in the testing of potential AIDS vaccine candidates.

- Announced the opening of a Mutant Mouse Regional Resource Centers network, which provides a coordinated program for characterization and storage of mice with induced mutations. The network began accepting animals from researchers to add to its collection for broad dissemination to the biomedical research community.

- Established a Rat Resource and Research Center at the University of Missouri (Columbia). The resource will import, cryopreserve, and distribute various mutant rats and rat strains to the research community. The resource also emphasizes detailed analysis of the genotypes, phenotypes, and disease status of mutant rats.

- Established a National Stem Cell Resource at the American Type Culture Collection in Manassas, Virginia. The resource is devoted to acquiring and distributing cells, reagents, and information about nonhuman embryonic and postnatally derived stem cells from a variety of species.

- Funded the new Gene Library Resource for the Sea Urchin *Strongylocentrotus purpuratus* at the California Institute of Technology in Pasadena. The resource will distribute high-density macroarrays containing large cDNA libraries related to each stage of embryogenesis, several individual cell types, and specific adult tissues.

- Funded cooperative agreements, in collaboration with the National Human Genome Research Institute, to increase the national capacity to produce bacterial artificial chromosome (BAC) libraries from the DNA of organisms that are important to biomedical and biological research.

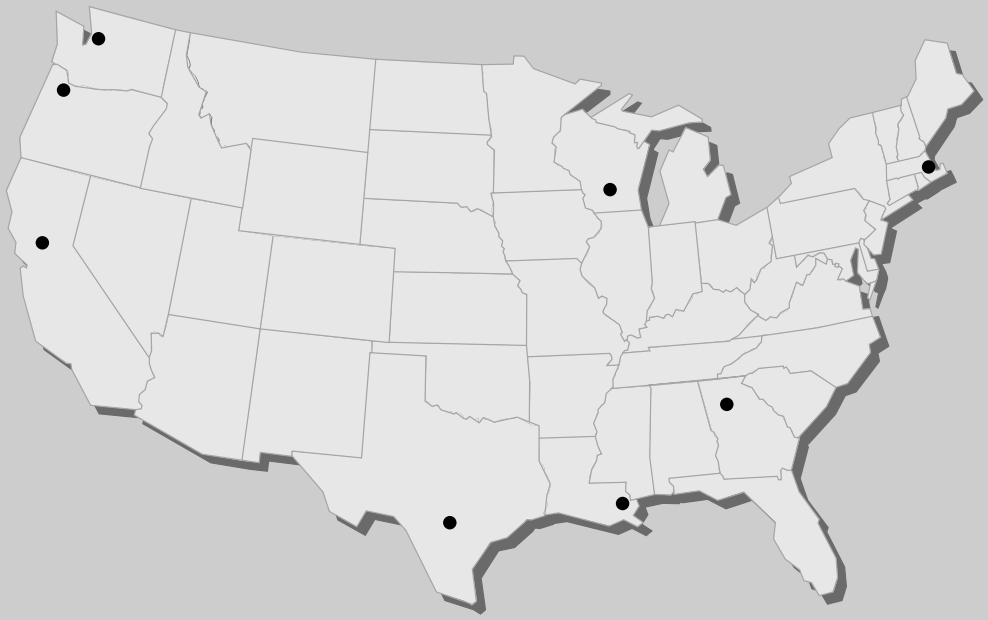
- Initiated a new program known as Centers of Veterinary Research Excellence (COVRE). The program will help address the shortage of research veterinarians by providing support for faculty, infrastructure, and recruitment of promising young investigators.

- Established a program that provides training grants to veterinary students who are pursuing animal-oriented, hypothesis-based research.

- Republished the Midcareer Investigator Award in Mouse Pathobiology Research. These grants support established pathobiologists and provide them with protected time to devote to mouse pathobiology research, and to serve as mentors for beginning investigators.

- Published the 2000 edition of the *Cost Analysis and Rate-Setting Manual for Animal Research Facilities*—last revised in 1979. This new manual was developed in collaboration with the Office of Management and Budget, the Department of Health and Human Services, and the Office of Naval Research, and was field-tested at eight biomedical research institutions.

REGIONAL PRIMATE RESEARCH CENTERS



THE NCRR DIVISION OF RESEARCH INFRASTRUCTURE (DRI) sponsors diverse programs and projects that develop, expand, and invigorate the nation's biomedical research infrastructure.

The Research Centers in Minority Institutions (RCMI) Program enhances the research capacity and infrastructure at minority colleges and universities that offer doctorates in the health sciences. Six of the 18 RCMI-supported institutions have clinical research centers. Supported by DRI funding through the RCMI Clinical Research Infrastructure Initiative, these centers encourage minority scientists to participate in clinical research.

The Research Infrastructure at Minority Institutions (RIMI) project supports minority institutions that offer bachelor's or master's degrees in health-related sciences. RIMI funding enhances biomedical research by facilitating collaborations with nearby research-intensive institutions that offer doctoral degrees.

The Research and Animal Facilities Improvement Programs provide institutional grants to construct new or renovate existing research laboratories and clinical facilities, and to renovate and repair existing animal facilities that support biomedical and behavioral research.

The Institutional Development Award Program (IDeA) targets institutions in states that historically have not had the capacity to successfully compete for NIH research grants. The program helps strengthen their infrastructure and ability to compete independently.

The Science Education Partnership Award (SEPA) Program encourages scientists to work with educators and community organizations to educate K-12 students, teachers, and the public about the life sciences.

Accomplishments

- Funded three new Specialized Neuroscience Research Programs (SNRPs), located at the University of Alaska in Fairbanks, Meharry Medical College in Tennessee, and Hunter College in New York. The SNRP initiative strengthens the research capabilities of faculty, students, and fellows at minority institutions by supporting the development of basic and clinical neuroscience research. With these new awards, a total of eight SNRPs have now been established through a collaborative effort between DRI and the National Institute of Neurological Disorders and Stroke (NINDS).

- Launched the RCMI Stroke Initiative to develop innovative strategies for reducing the burden of stroke and cardiovascular disease in high-risk populations. The initiative is a collaborative effort among DRI, NINDS, and the National Heart, Lung, and Blood Institute.

- Convened the Seventh RCMI International Symposium in San Juan, Puerto Rico, in November 2000. It was the first symposium in this series to address biomedical and scientific topics related to health disparities between minority and majority communities.

Research Infrastructure

- Established a new program, the Biomedical Research Infrastructure Networks (BRIN), to enhance research capacity in states that have not fully participated in NIH grant funding in the past. In 2001, NCRR awarded 24 BRIN grants, totaling more than $45 million in the first year of these three-year grants, to institutions in 23 eligible states and Puerto Rico.

- Enabled the opening and expansion of several state-of-the-art research facilities with funding provided by the Research Facilities Improvement Program (RFIP). Among the new facilities to open were a sophisticated gene and cell therapy core laboratory at the University of Washington General Clinical Research Center in Seattle and a molecular genetics core laboratory at the National Human Genome Center at Howard University in Washington, DC. In addition, RFIP funding supported the expansion of the Zebrafish International Resource Center at the University of Oregon in Eugene; biosafety levels 2, 3, and 4 containment areas at the Southwest Foundation for Biomedical Research in San Antonio, Texas; and biosafety levels 3 and 4 containment areas for cutting-edge viral immunology research at the University of Texas Health Science Center, San Antonio.

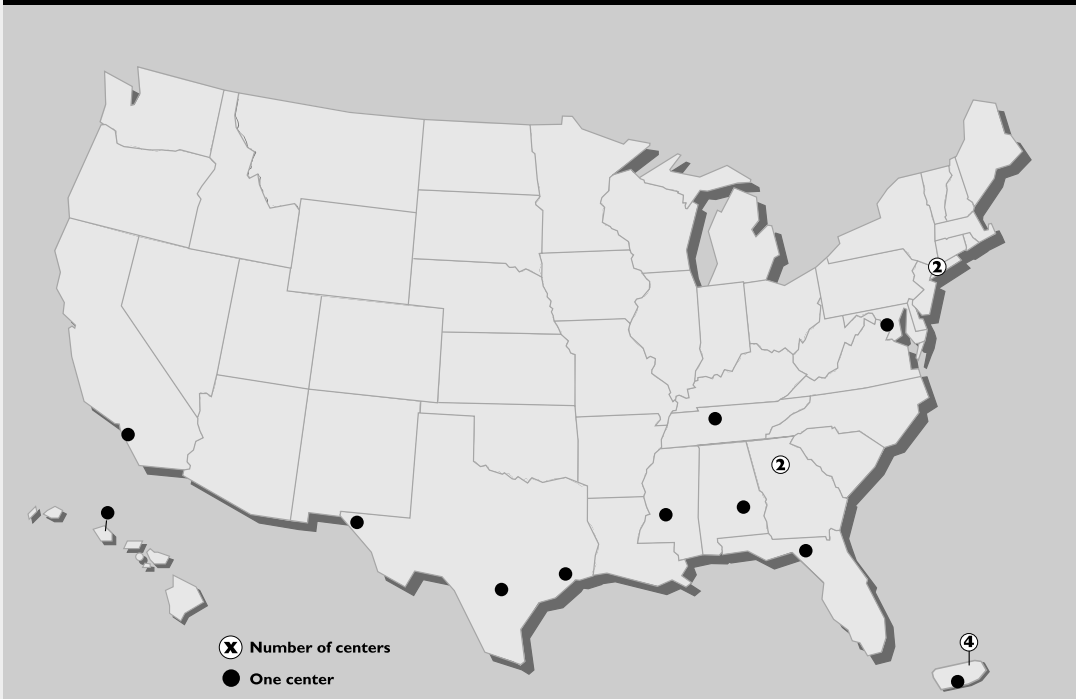
- Awarded 29 grants, totaling approximately $260 million over five years, as part of the Center for Biomedical Research Excellence (COBRE) Program in 2000 and 2001 to institutions that had not fully participated in NIH funding in the past. The grant enables each institution to establish a COBRE to be led by an established investigator who will direct a multidisciplinary effort to focus on a basic or clinical research theme.

- Increased the number of new grants awarded under the SEPA program. For the first time in SEPA history, grants were awarded directly to science centers and museums nationwide to enhance the reach of unique health-related education programs.

- Sponsored grantsmanship workshops for prospective or current recipients of SEPA grants, Institutional Development Awards, and Research Facilities Improvement grants.

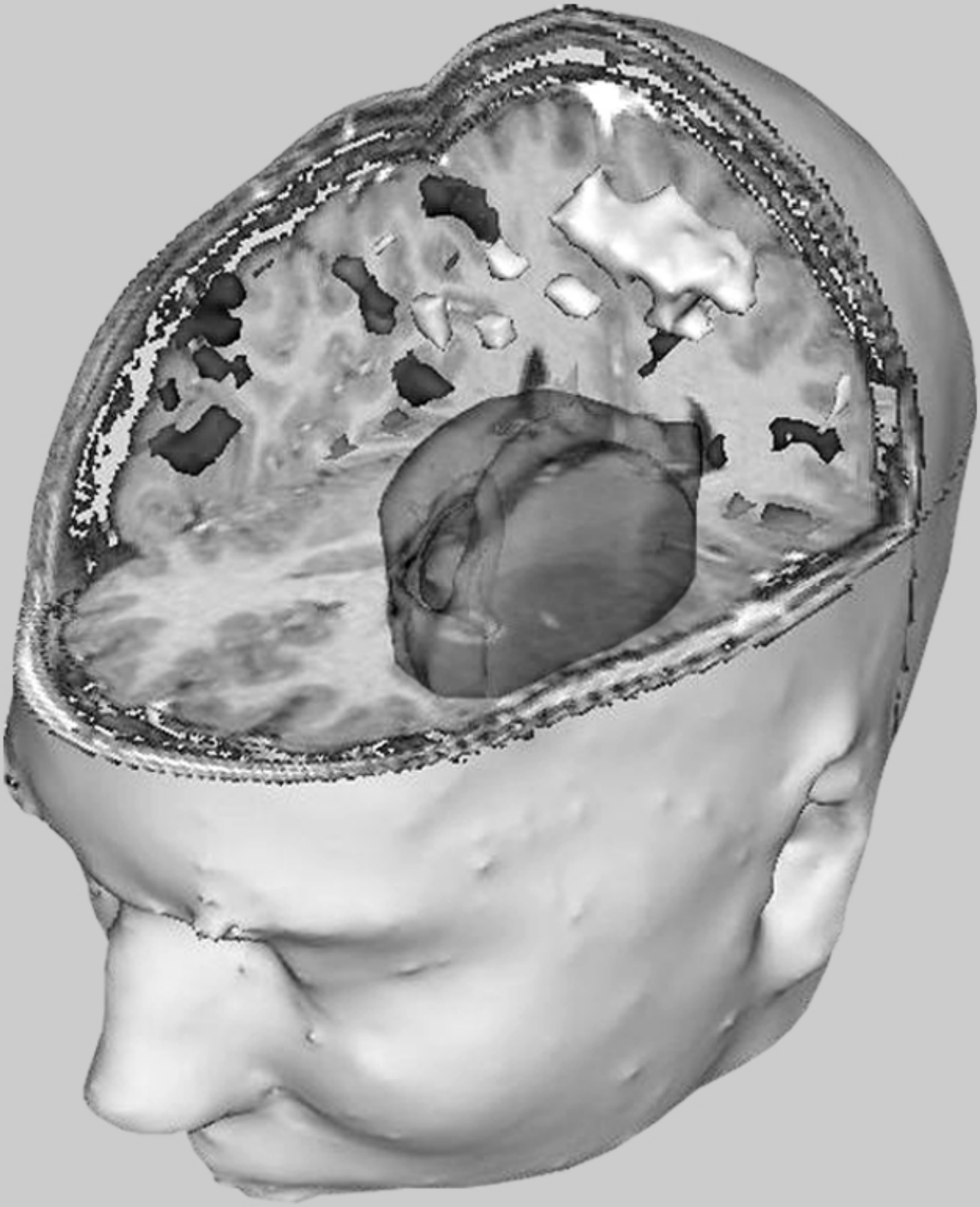
- Awarded new grants for the construction or renovation of biomedical research and animal facilities at more than 120 sites nationwide.

RESEARCH CENTERS IN MINORITY INSTITUTIONS



Research Highlights

NCRR HIGHLIGHTS 2000–2001



Biology of Brain Disorders

THE HUMAN BRAIN IS A COMPLEX NETWORK of more than 100 billion interconnected nerve cells that work in concert to direct the body's functions and thought processes. With recent advances in research tools and technologies, neurobiologists now have unprecedented opportunities to examine the nervous system from a variety of vantage points, ranging from the molecular and genetic to the integrated systems, organ systems, and tissues of the human body.

Advanced three-dimensional imaging techniques used during surgery can reveal the location of a deadly tumor (dark lump) at the center of a patient's brain. *Image courtesy of David Gehring and the Surgical Planning Laboratory, Brigham and Women's Hospital, Boston*

NCRR has launched several new initiatives and programs designed to strengthen investigations into neurobiology and enhance the sharing of data, technologies, and other resources across disciplinary boundaries. For instance, one NCRR program supports neuroscience research at minority institutions, another is establishing a state-of-the-art network for sharing brain imaging data across institutions, and a third is fostering development of neuroimaging and bioinformatics core laboratories in clinical research settings. These integrated efforts promise to provide the most detailed and informative picture yet of the workings of the human brain in health and disease.

Image-guided Neurosurgery. Using sophisticated image-processing and analysis techniques, scientists at the NCRR-supported Neuroimaging Analysis Center at Brigham and Women's Hospital are enabling precise planning for difficult brain surgery and improving diagnosis and even prediction of progressive brain disorders. In one application, known as image-guided surgery, neurosurgeons examine detailed three-dimensional (3D) reconstructions of a patient's brain prior to surgery to accurately locate internal structures, such as tumors. Surgery is then performed

MRI techniques developed by Drs. Ron Kikinis (left) and Ferenc Jolesz may enhance detection of Alzheimer's disease, even before conspicuous symptoms appear.
Photo courtesy of the Surgical Planning Laboratory, Brigham and Women's Hospital, Boston

in an open MRI magnet, which allows frequent acquisition of two-dimensional images to evaluate the operation's progress. Ultimately, the NCRR-supported scientists hope to accelerate the speed of 3D image processing to enable near-real-time acquisition of complete images during surgery. These advanced imaging tools also have the potential to enhance diagnosis of brain-related disorders such as Alzheimer's disease, as described below.

—*Journal of Magnetic Resonance Imaging* 13:967-975, 2001.

Advanced Imaging Technique Helps Predict Risk for Alzheimer's Disease. Each year Alzheimer's disease (AD) and other dementias cast a shadow over a growing number of lives. An estimated 4 million Americans now suffer from AD, while countless others are impaired by related dementia disorders. Early detection of AD is difficult because preclinical symptoms such as mild memory loss may be overlooked as a common and expected condition among the elderly. Improved diagnostic techniques are needed, since existing tools have limited ability to predict which individuals with mild memory loss will progress to AD. Investigators at the NCRR-supported Neuroimaging Analysis Center at Brigham and Women's Hospital used magnetic resonance imaging (MRI) to determine whether persons in the preclinical phase of AD could be accurately identified before they developed clinically diagnosed dementia. The MRI scans of various brain regions showed significant differences between normal individuals and those who later developed AD and predicted which patients with memory impairment would develop AD.

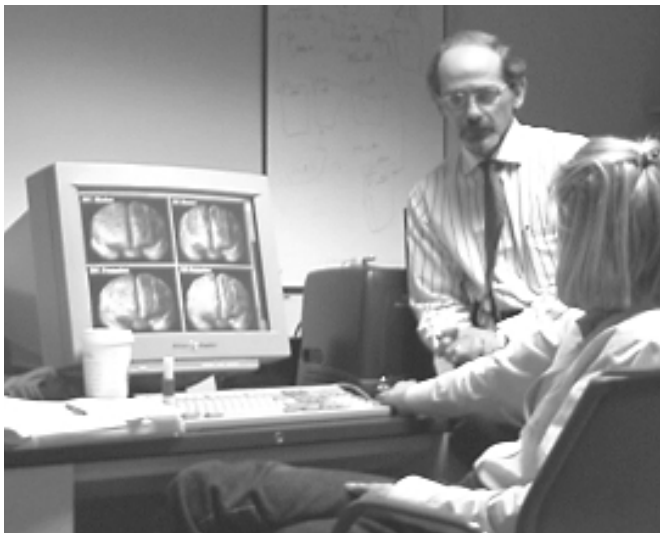
A second study conducted at the NCRR-supported Center for Advanced Magnetic Resonance Technology at Stanford University showed that magnetic resonance spectroscopy may be a suitable noninvasive tool for monitoring disease progression in patients with AD. Serial measurements of the brain chemical N-acetyl aspartate, which is a marker for living brain cells, showed significant reductions in patients with AD over a one-year period. This work is particularly important because it may enhance evaluation of the many new drugs currently being developed to treat AD.

—*New England Journal of Medicine* 343:450-455, 2000; *Annals of Neurology* 47:419-420 and 430-439, 2000; *Lancet* 355: 1696-7, 2000.

Imaging Technique Reveals Changes in Brain Structure. Both human development and degenerative disease processes are known to affect the volume of brain substructures. But detecting, tracking, and quantifying these structural changes have proven difficult, in part because observations must be made throughout the brain and must be made at different times. Researchers at the NCRR-funded Laboratory of Neuro Imaging at the University of California, Los Angeles, now have created detailed three-dimensional images that map growth patterns in the developing human brain over time. The researchers discovered that different parts of the brain grow at markedly different rates during child development. Between the ages of 3 and 6, peak growth rates were observed in an area of the brain responsible for mental vigilance and planning of new actions. Older children displayed fastest growth in a region of the brain related to spatial association and language function. This group of researchers also found that the areas of the brain that grow fastest in children also degenerate fastest during the early stages of Alzheimer's disease. The sensitivity of the new experimental protocol may help in tracking the effects of various treatments for Alzheimer's disease and other brain disorders.

—*Nature* 404:190-193, 2000.

Parkinson's Disease Treatment in Nonhuman Primate Model. Parkinson's disease (PD), which affects primarily the elderly, can be defined by stages. At the onset of clinical symptoms, tremor, limb stiffness, slowness of movement, and gait distur-



Neuroimaging tools developed by Dr. Arthur Toga and his colleagues disclose how brain structures change and grow during childhood. *Photo courtesy of Dr. Toga, University of California, Los Angeles*

Interdisciplinary research conducted by Dr. Gilberto Gonzalez and his colleagues at Massachusetts General Hospital enabled creation of imaging software that generates "risk maps" of the human brain.
Photo courtesy of New England Regional Primate Center

bances appear but do not interfere with daily life. Advanced stages are characterized by sufficient disability to require assisted care. At present, drug therapies are largely designed to replace the essential brain chemical dopamine, which is produced in insufficient quantities in PD patients. Scientists at the NCRR-supported New England Regional Primate Research Center are testing and systematically evaluating promising drug candidates that enhance dopamine activity in a monkey model of PD. The ability to identify and objectively assess drug efficacy in an animal model of both early and late stages of the disease will expedite the development of new, effective therapeutics.

—*Journal of Pharmacology and Experimental Therapeutics* 292:714-724, 2000.

Improved Prediction of Tissue Damage in Stroke Patients. Efforts to limit tissue death in acute stroke patients may be improved significantly by identifying tissue that is receiving reduced blood flow but remains viable. Novel technologies, known as diffusion-weighted and perfusion-weighted magnetic resonance imaging (MRI), have been developed that are highly sensitive and specific in diagnosing acute diminished blood flow to particular areas of the brain. Based on earlier studies of rhesus monkeys at the NCRR-supported New England Regional Primate Research Center, scientists at the Massachusetts Institute of Technology and the NCRR-funded neuroimaging resource at Massachusetts General Hospital designed and analyzed statistical formulas to evaluate the risk of damage for each unit of tissue assessed by MRI. These advanced computer-based technologies rapidly combined different types of MRI data into a single "risk map" of

the brain. Because it is essential to provide rapid treatment to stroke patients, this type of improved diagnostic procedure may one day help stroke patients survive without debilitating effects.

—*Stroke* 32:933-942, 2001.

Neuroimaging Technique Reveals Mechanism of Migraine Aura. Migraine headache is often preceded by a visual hallucination or illusion known as an aura. Typically, the aura is a serrated arc of scintillating, shining, crenelated shapes beginning close to central vision and then gradually expanding peripherally, followed by headache. The scintillations are followed temporarily by a blind region. Earlier studies have suggested a relationship between migraine aura and a phenomenon called cortical spreading depression (CSD), which is a wave of electrical charge changes in brain cells followed by long-lasting suppression of neural activity, but it has been difficult to test this hypothesis in the human brain. Now, using functional magnetic resonance imaging (fMRI), researchers at the NCRR-supported Center for Functional Neuroimaging Technologies at Harvard Medical School have shown that several characteristics of CSD correspond to progression of the aura.

The investigators studied three male patients who had migraine aura and recorded continuously the MRI changes that were related to blood oxygenation levels in their brains during five episodes. The MRI changes indicated an abnormal blood flow that progressed slowly over the brain cortex, corresponding to progression of the migraine aura. The researchers conclude that the migraine aura is probably evoked by aberrant electrical activity of neurons and related cells characteristic of CSD, and that blood flow changes develop due to fluctuations in neuronal activity during the visual aura. They plan to do additional studies to clarify the relationship between CSD and onset of headache.

—*Proceedings of the National Academy of Sciences USA* 98:4687-4692, 2001.


NEW BRUNSWICK SCIENTIFIC

New Approaches to Pathogenesis

THE FIRST STEP TO EFFECTIVELY COMBATING disease is to understand how it originates and develops in the body. In recent years, interdisciplinary investigations and new research tools and technologies have greatly expanded our knowledge of pathogenesis—the precise mechanisms by which disease develops. Uncovering details of the molecular, cellular, and progressive nature of disease can lead to novel and more effective strategies for prevention and treatment.

A researcher in Dr. Fred Blattner's laboratory at the University of Wisconsin, Madison, selects bacteria for use in DNA sequencing experiments. *Photo by Jeff Miller, University of Wisconsin, Madison*

Understanding E. coli *Pathogenicity.* A strain of the bacterium *Escherichia coli (E. coli)* known as O157:H7 causes an estimated 75,000 illnesses a year in the United States, according to the Centers for Disease Control and Prevention, and can be deadly to children, the elderly, and people with weakened immune systems. The food-borne pathogen is now considered a major threat to public health. Supported by NCRR Shared Instrumentation Grants, researchers at the University of Wisconsin, Madison, sequenced all the 5,450 genes of the O157:H7 strain to seek clues to what makes the organism so dangerous. Compared to the harmless *E. coli,* the O157:H7 strain had dramatically increased the size of its genome and had acquired 1,300 genes not found in the harmless strain. Some of them were very similar to those of the bacterium *Salmonella,* the plague-causing organism *Yersinia,* and the dysentery-causing microorganism *Shigella*. Now that the genes unique to this pathogenic strain have been uncovered, scientists may be able to develop better vaccines and drugs as well as improved diagnostic tools for early identification of this deadly pathogen.

—*Nature* 409:529-533, 2001.

Mechanisms of Chromosome Missegregation in Cancer Cells. When a normal, healthy cell begins to divide, its chromosomes line up along the center of a structure called a spindle. As the cell divides, thread-like structures called microtubules guide the chromosomes to form two new cells. In cancer cells this delicate process becomes faulty, resulting in a large number of chromosome deletions and structural abnormalities. Such abnormalities are among key features used by pathologists to diagnose cancer.

Using advanced cell-imaging systems purchased via an NCRR Shared Instrumentation Grant, researchers at the University of Pittsburgh have provided the first graphic illustration of how faulty chromosome segregation can lead to genetic defects such as abnormal or missing chromosomes. Fluorescence microscopy revealed the mechanisms by which chromosomes are distributed unevenly when oral cancer cells divide. This is the first study to show why cancer cells contain too few or too many chromosomes. Using this information, investigators may be able to screen individuals at risk for cancer, as well as develop and apply better prevention and treatment strategies.

—*Proceedings of the National Academy of Sciences USA* 97:303-308, 2000.

Phospholamban Affects Contractility of the Heart. It is well known that heart muscle contractions increase in response to increased frequency of specific stimuli, but the underlying mechanism is not understood. In this study, phospholamban, a specific regulator of the calcium transport mechanism in the heart muscle, was evaluated for its involvement in cardiac contractility. Heart muscle tissue from mice with genetically deleted phospholamban failed to respond in the expected manner, while heart tissue from wild-type mice responded as predicted. Based on this finding, the researchers at the NCRR-supported Sarcoplasmic

Dr. Evangelia Kranias and her colleagues developed mutant mice that lack normal levels of the protein phospholamban, which regulates calcium levels in the heart. Studies of these animals shed light on the mechanisms of heart muscle contraction. *Photo courtesy of the University of Cincinnati College of Medicine*

Reticulum Mutant Mouse Resource concluded that phospholamban is a major determinant of the cardiac force-frequency relationship. The resource, located at the University of Cincinnati College of Medicine, offers the scientific community access to specialized animals that produce insufficient levels of phospholamban. Studies of these mutant mice can aid understanding of calcium's role in normal heart function.

—*American Journal of Physiology. Heart Circulatory Physiology* 278:H249-H255, 2000.

Elevated Autoantibody Levels in Coronary Artery Disease. Autoantibodies are antibodies produced by the body's immune system against specific parts of its own body. Autoantibodies against actin and myosin (proteins that may be exposed in damaged heart muscle) and autoantibodies against troponin (a complex protein involved with heart muscle contraction) were found to be elevated in patients who had had a recent acute heart attack. Investigators at the NCRR-supported General Clinical Research Center at Mt. Sinai School of Medicine found that in 33 patients, followed for three months after acute heart attack, all three autoantibodies were elevated. In patients with higher levels of these three autoantibodies, there was a higher risk of a later myocardial infarct or heart attack. The data also suggest that elevated levels of these autoantibodies may represent markers of earlier or ongoing heart tissue damage due to insufficient blood supply or inflammation, such as atherosclerosis. Such information about a patient's previous heart attack or the likelihood of another attack can enable implementation of preventive measures.

—*American Journal of Cardiology* 85:870-872, 2000.

Novel Virus Isolated from New World Monkeys. Cancer-causing viruses related to Epstein-Barr virus (EBV), which is implicated in development of B-cell lymphomas and carcinomas in humans, were believed to be endemic only in Old World primates such as macaque monkeys. This notion has now been disproved by investigators at the NCRR-supported Wisconsin Regional Primate Research Center, collaborating with researchers at Harvard University. For more than 30 years, scientists have studied

By genetically analyzing tumors that develop naturally in the common marmoset, scientists found traces of DNA from Epstein-Barr-like viruses, which also cause cancers in humans. Studies of the virus in this animal model may enhance discovery of pathogenic processes and potential therapies. *Photo by Rich Block, Santa Barbara Zoological Gardens*

a New World monkey known as the common marmoset *(Callithrix jacchus),* which develops spontaneous B-cell lymphomas like those caused by EBV in Old World monkeys. However, researchers were unable to confirm that the marmoset tumors were caused by an EBV-like virus. Nevertheless, the researchers showed that the marmoset genome contained DNA segments that were related to EBV gene sequences. Using a cell line established from a B-cell lymphoma biopsy, the scientists have now succeeded in isolating an EBV-related virus. The identification of both Old World and New World EBV-related viruses provides an important animal model system for studying the different pathogenic pathways for EBV-induced lymphomas in humans.

—*Proceedings of the National Academy of Sciences USA* 98:1224-1229. 2001.

Type 2 Diabetes Detection in High-Risk Individuals. The most common form of diabetes—non-insulin-dependent, or type 2 diabetes—affects approximately 15 million individuals in the United States, according to the American Diabetes Association. To improve early detection of diabetes, the level of blood glucose that is now considered acceptable in fasting patients has been lowered, but reports indicate that many people who have acceptable levels still are diagnosed with diabetes on the basis of a more accurate 2-hour oral glucose tolerance test (OGTT). Investigators at the NCRR-supported General Clinical Research Center at Indiana University studied 244 individuals who were at high risk of developing diabetes. They found that between 29 percent and 48 percent of the study participants who had fasting blood glucose levels below the new cut-off value were diagnosed with diabetes according to the

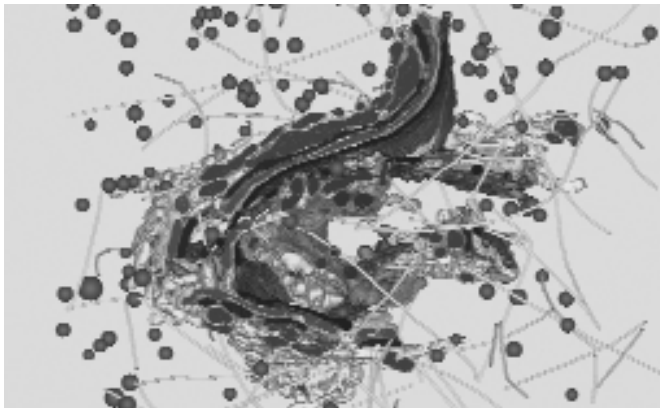
OGTT. A test called HbA1c provided better results, but 39 percent of the participants diagnosed with diabetes still were considered normal by the HbA1c test. The scientists recommend that for people at risk, the fasting blood glucose test should be supplemented with the HbA1c test to improve diagnostic accuracy. Early detection permits appropriate treatment and will have a significant impact on American public health.

—*Diabetes Care* 24:465-471, 2001.

Electron Microscopy Used To Model the Fine Structure of Insulin-Secreting Cells. The beta cells of the pancreas are the sole source of insulin secretion in humans. Death of the beta cells, or their failure to secrete adequate amounts of insulin, leads to severe forms of diabetes. Scientists used electron microscopy to image the Golgi apparatus—a cellular component that is essential for insulin secretion in beta cells—to study its fine structure and function, and to gain a fundamental understanding of insulin secretion. Electron microscopy data were collected at two NCRR-supported Biomedical Technology Resource Centers—the Resource for Visualization of Biological Complexity in Albany, New York, and the Boulder Laboratory for Three-Dimensional Fine Structure in Colorado. Each of these two research resources houses one of the few intermediate voltage cryoelectron microscopes for biology in the United States.

Understanding the function of the Golgi apparatus is not only important for defining the mechanism of insulin secretion. If the Golgi apparatus is defective, it will affect the proper secretion of many other proteins and may lead to metabolic and immunological disorders.

—*Proceedings of the National Academy of Sciences USA* 98:2399-2406, 2001; *Biochemical Society Transactions* 29:461-467, 2001.



Using advanced microscopy and imaging resources, scientists created this detailed three-dimensional reconstruction of the Golgi apparatus, a subcellular structure that plays a critical role in insulin secretion. *Image courtesy of Dr. David Mastronarde, Boulder Laboratory for 3-D Fine Structure*


LARGE EGGS
GRADE A
FRESH EGGS
SUPER
VALLEY

New Preventive Strategies Against Disease

HEALTHY DIETS, VACCINES, AND EARLY diagnosis and treatment of health problems are among the many strategies for dramatically reducing the incidence of disease and enhancing the quality and longevity of life. Research in prevention involves investigating the outbreak of emerging infections and examining the behavioral, genetic, and environmental aspects of health and disease.

A diet that combines low salt intake with an abundance of fruit, vegetables, and low-fat dairy products can quickly and significantly reduce blood pressure, a recent clinical study found. *Photo courtesy of Brigham and Women's Hospital*

Low Dietary Sodium Enhances DASH Diet's Blood Pressure-Lowering Effect. The diet, Dietary Approaches to Stop Hypertension (DASH), which emphasizes fruits, vegetables, and low-fat dairy products, has been shown to lower blood pressure substantially both in people with hypertension and those with normal blood pressure, compared with a typical American diet. Now a multicenter study involving two NCRR-supported General Clinical Research Centers has shown that a further blood pressure reduction could be achieved by combining the DASH diet with a sodium intake that is lower than the current recommendation of 2,400 milligrams per day.

The researchers randomly assigned 412 participants to eat either a control diet typical for the United States or the DASH diet. Within the assigned diet, participants ate foods with high, intermediate, or low levels of sodium for 30 consecutive days in random order. At the end of each 30-day period, the participants' systolic and diastolic blood pressure was measured. At each sodium level, the DASH diet was associated with a significantly lower systolic blood pressure than the typical American diet. Compared with the control diet with the high sodium level, the low-sodium DASH diet reduced blood pressure by about 7.5 mm Hg in

nonhypertensive participants, and by about 11.5 mm Hg in patients with high blood pressure. The scientists emphasize that the long-term benefits depend on people's ability to make profound changes in their diets.

—*New England Journal of Medicine* 344:3-10, 2001.

Prevention of Drug-induced Depression. Patients treated with interferon alfa-2b, which has antiviral as well as anticancer properties, often have severe depression that even may result in suicide. Researchers at the NCRR-supported General Clinical Research Center at Emory University in Atlanta, Georgia, now report that administration of an antidepression drug to interferon-treated patients can prevent this debilitating depression.

In a double-blind study of 40 patients with malignant melanoma, the investigators randomly assigned 20 patients to receive the antidepressant drug paroxetine and 20 to receive a placebo. All the patients received high doses of interferon alfa-2b. During the first 12 weeks of interferon therapy, two of 18 patients (11 percent) in the paroxetine group and nine of 20 patients (45 percent) in the placebo group developed major depression. The researchers note that the mechanism by which interferon causes depression and neurotoxic effects and the mechanism by which paroxetine alleviates these effects are not known.

—*New England Journal of Medicine* 344:961-966, 2001.

Advances in Development of an AIDS Vaccine. One of the major challenges to controlling the AIDS epidemic is development of an effective vaccine. The retrovirus that causes an AIDS-like condition in macaque monkeys is an important tool in understanding the factors that contribute to disease induction and progression both in monkeys and humans. Scientists at the Vaccine Research Center and the NCRR-supported Yerkes Regional Primate Research Center at Emory University, collaborating with researchers at other institutions, have developed a vaccine that stimulates an immune response against several viral proteins. Macaque monkeys were immunized twice with DNA segments that encode a number of simian immunodeficiency virus (SIV) and human immunodeficiency virus (HIV-1) proteins. Twenty-four weeks after the initial immunization, the animals received a booster shot with an engineered animal poxvirus that does not replicate in human or animal cells. Although the immunizations did not prevent viral infection, the vaccinated animals only had low levels of virus in their blood and did not become ill. In contrast, three of four nonvaccinated control animals had died of AIDS by 23 weeks after virus administration. This vaccine combination has the potential for providing a relatively simple vaccine to help control AIDS in humans.

—*Science* 292:69-74, 2001.

Dr. Harriet Robinson and her colleagues showed that an experimental vaccine prevented the development of AIDS in monkeys, despite exposure to high levels of the simian immunodeficiency virus. *Photo courtesy of the Yerkes Regional Primate Research Center*

New Device for Cancer Diagnosis. Barrett's esophagus is a condition that develops in people with chronic heartburn. In this disease, chronic inflammation causes the normally pink tissue lining the esophagus to be replaced with reddish, colon-like tissue. Over time, this tissue can turn into a pre-cancerous condition known as dysplasia, and then to a type of cancer known as adenocarcinoma. Virtually all adenocarcinomas of the lower esophagus occur in patients with Barrett's esophagus.

The prognosis for patients who are diagnosed with adenocarcinoma of the lower esophagus is quite poor, but the chances of successful treatment improve significantly if the disease is detected at either the Barrett's esophagus or the later pre-cancerous stage. Detection of pre-cancer in Barrett's esophagus is clinically challenging, because Barrett's dysplasia is invisible to the eye.

With support from NCRR, a research group at the Massachusetts Institute of Technology has developed a noninvasive device to detect and diagnose Barrett's esophagus. This device uses three optical techniques in combination: fluorescence, reflectance, and light scattering. This novel tool has also been utilized to detect and diagnose pre-cancerous tissue in the oral cavity, the cervix, the colon, and the urinary bladder.

—*Gastroenterology* 120:1620-1629, 2001.

Chickenpox Vaccine Proved Effective. Chickenpox vaccine consisting of live, weakened virus was approved for use in the United States in 1995 and is recommended for persons 12 months or older. Because many questions have been raised about the use and effectiveness of the vaccine, researchers supported by the NCRR-funded Children's General Clinical Research Center at Yale University in New Haven, Connecticut, in collaboration with investigators at Columbia University in New York City, conducted a study of the vaccine as it is used in clinical practice.

More than 300 children with potential cases of chickenpox were identified in pediatric practices in the New Haven area and were assessed by research assistants within a week after diagnosis. Of the 243 children with confirmed cases of the disease, 56 had previously received the chickenpox vaccine, but about 86 percent of these children developed only mild forms of the disease. In contrast, less than half of the 187 unvaccinated children developed only a mild case of chickenpox, and more than half developed a moderate or severe case of the disease. Of 56 vaccinated children with chickenpox, 86 percent had mild disease, whereas only 48 percent of 187 unvaccinated children with chickenpox had mild disease. The investigators concluded that the chickenpox vaccine, as it is used in clinical practice, is highly effective.

—*New England Journal of Medicine* 344:955-960, 2001.

Dr. Michael Feld (left) demonstrates a noninvasive device that uses light to identify cancer cells. Assisting him (left to right) are visiting scientist Markus Mueller, Dr. Kamran Badizadegan of Children's Hopsital in Boston, and Dr. Irene Georgakoudi of MIT. *Photo by Les Cuneo*

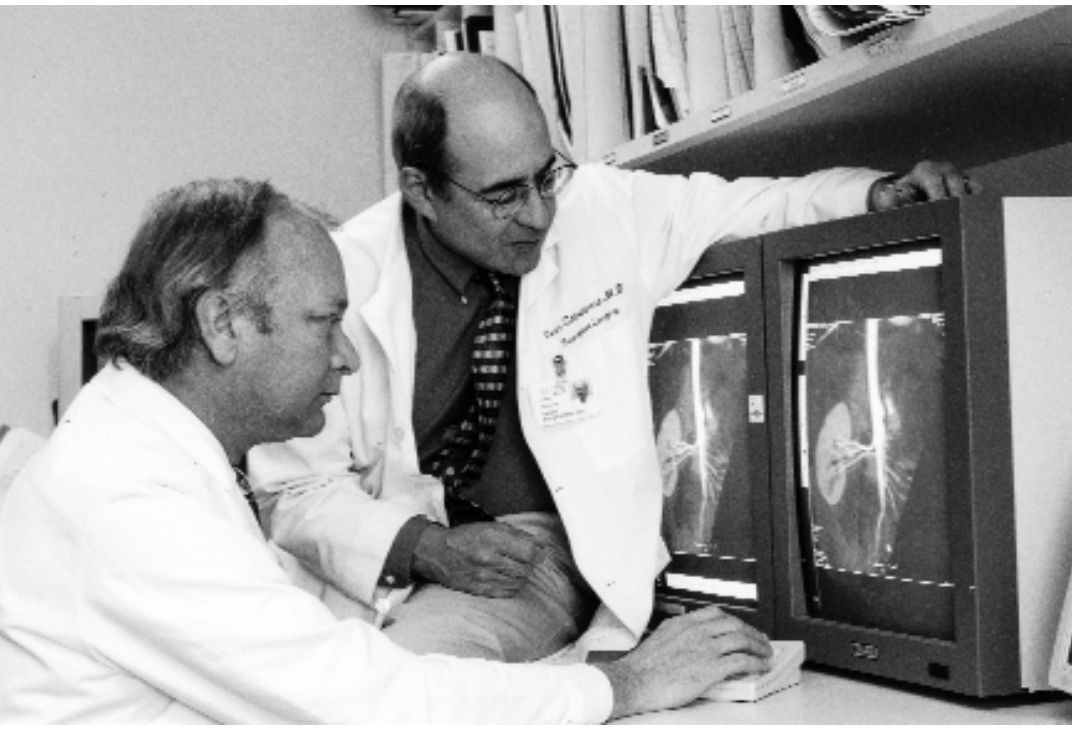
New Avenues for Development of Therapeutics

THE PURSUIT OF NEW THERAPIES depends in part on advances in bioengineering, structural biology, and genome-related sciences, as well as access to appropriate environments for conducting clinical investigations. Knowledge of the three-dimensional structure of a particular disease-related enzyme or cellular receptor can accelerate the discovery and lead to enhanced effectiveness of drugs and other therapies. Studies of animal models can offer clues to the effectiveness of potential therapies or reveal the biological underpinnings of therapeutic approaches. And patient-oriented research is the ultimate proving ground for potential new therapies.

Dr. L. Lyndon Key evaluates the coordination skills of a young patient who has osteopetrosis. Dr. Key and his colleagues developed the first FDA-approved therapy for this life-threatening condition. *Photo by Jeff Dodge*

By providing the scientific tools, non-human models, and infrastructure essential to performing cutting-edge research, NCRR enhances all aspects of the development of new therapeutics.

Therapy Approved for Rare Bone Disorder. Bones in healthy individuals are continuously built up and broken down, with no net change in bone quantity. But patients who inherit a rare disease known as osteopetrosis have defective bone-dismantling mechanisms, leading to excessive bone formation and heavy, brittle bones that can crowd out bone marrow. Because marrow spaces are production sites for oxygen-carrying red blood cells and infection-fighting white blood cells, patients with osteopetrosis often also develop severe anemia and infections. Accumulating bone can also encroach on optic and auditory nerves, leading to loss of sight and hearing. Patients with the most severe form of osteopetrosis have few treatment options



Drs. Oscar Salvatierra (right) and Robert Herfkens examine images of a transplanted kidney. A therapeutic regimen developed by Dr. Salvatierra and his colleagues improves the outcome for pediatric patients who received kidney transplants. *Photo by Steve Gladfelter, Stanford University*

and often die within the first decade of life. But an NCRR-supported clinical investigator at the Medical University of South Carolina has developed and tested the first successful osteopetrosis therapy, which received FDA approval in February 2000. Studies conducted for more than a decade at the General Clinical Research Center confirm that regular administration of interferon-gamma-1b can slow progression of the disease by reducing the activity of bone-forming cells and by improving immune function. Research on osteopetrosis is also shedding light on the basic cellular and molecular mechanisms that underlie bone formation, which could contribute to greater understanding of more common bone disorders, such as osteoporosis.

—*Journal of Interferon and Cytokine Research* 20:645-652, 2000.

Steroid-free Immunosuppression for Kidney Transplantation in Children. Corticosteroids, which belong to a family of compounds that form the backbones of several hormones and cholesterol, are normally produced by the outer layer of the kidney called the cortex. Corticosteroids affect a variety of essential metabolic processes and have been a cornerstone of immunosuppressive therapy for 40 years despite a host of adverse side effects. Investigators at the Stanford University General Clinical Research Center now have developed a regimen consisting of three non-steroidal drugs to suppress the immune system of 10 children through their pre- and post-transplant periods. These agents, daclizumab, tacrolimus, and mycophenolate mofetil, resulted in a 100 percent survival rate for both patients and their kidney transplants. Furthermore, side effects such as high blood pressure, high cholesterol, and facial and body

disfigurement, commonly seen in patients who are immunosuppressed by steroids, were not observed with this new treatment. Since this protocol began two years ago, these children are showing significant growth advantage over children with steroid-based immunosuppression protocols.

—*Transplantation* 72:13-21, 2001.

Mechanism of Oocyte Maturation Unraveled in Nematode. Oocytes in the nematode *Caenorhabditis elegans,* like those of most animals, are present in an immature form until they encounter sperm, which causes them to mature. Researchers have now, for the first time, identified the component of sperm that causes these profound changes.

The scientists—using animals supplied by the NCRR-supported Caenorhabditis Genetics Center—fractionated sperm by high-performance liquid chromatography, injected the fractions into the reproductive tract of spermless female nematodes, and monitored which fractions mimicked the presence of intact sperm. The investigators showed that the major sperm cytoskeletal protein (MSP) provides both the oocyte maturation signal and ovulation initiation signal. Each of those functions is associated with a separate end of the molecule. MSP constitutes about 15 percent of the nematode sperm; it also plays a role in sperm locomotion, which enables sperm to crawl along a solid substrate like an amoeba. MSP is present in other nematodes, and similar proteins have been found in yeast, plants, and animals. The researchers suggest that it might be a good target for drugs against parasitic worms, which constitute major health problems in many countries.

—*Science* 291:2144-2147, 2001.

Coagulation Factor VIII Gene Transfer in Severe Hemophilia A. Hemophilia is an inherited bleeding disorder resulting from low or absent levels of any of a number of blood clotting factors. In the severe form of hemophilia due to factor VIII deficiency, bleeding into joints, soft tissues, and vital organs can occur spontaneously. The primary treatment has been periodic infusions of factor VIII, which is concentrated from human blood products or genetically engineered.

Moving toward this goal, researchers assisted by the NCRR-supported General Clinical Research Center at

Drs. Michael Miller (left) and David Greenstein identified a protein that plays a critical role in nematode reproduction. The molecule may serve as a target for experimental therapies that combat parasitic worms. *Photo by Dana Johnson, Vanderbilt Medical Center*

Dr. David Roth and his colleagues evaluated a gene therapy protocol that safely reduced bleeding episodes in patients with severe hemophilia. *Photo courtesy of Transkaryotic Therapies*

Beth Israel Deaconess Medical Center in Boston evaluated a novel gene therapy protocol that transformed patients' own cells into factor VIII-producing factories. The procedure first involved introducing factor VIII genes into cultures of patient-derived skin cells, which were then injected into the patient's abdominal cavity. In four of the six patients receiving this therapy, factor VIII levels increased over baseline, and this increase correlated with improvements in clinical measures of bleeding and need for additional administered factor. Also, there were no serious adverse events and no development of inhibitors against the clotting factor, even after two years of follow-up. In one patient, the beneficial effects lasted 10 months. The implications of this study are far-reaching because this approach may be applicable to treatment of hemophiliacs with deficiencies in other clotting factors.

—*New England Journal of Medicine* 344:1735-1742, 2001.

Treatment of Anxiety Disorders in Children and Adolescents. Anxiety disorders are the most common psychiatric illnesses in children, but many children with these disorders do not receive treatment. The illnesses can range from separation anxiety, in which the child is afraid of being separated from a parent, to generalized anxiety disorder that can interfere with academic and social functioning. Studies have shown that childhood anxiety disorders can foreshadow psychiatric illnesses later in life that can lead to major depression and suicide attempts. In a multicenter study that depended in part on the resources of the NCRR-funded General Clinical Research Center at Johns Hopkins University in Baltimore, investigators studied 128 children with various anxiety disorders who had received psychological treatment for three weeks without improvement. The children were randomly assigned to receive a drug named fluvoxamine or placebo for eight weeks and then evaluated to assess the degree of anxiety and impairment.

Children in the fluvoxamine group had a mean decrease of almost 10 points in symptoms of anxiety, but children in the placebo group showed only a three-point decrease. Among children in the fluvoxamine group 48 of 63 children (76 percent) responded to the treatment, compared with 19 of 65 children (29 percent) in the placebo group.

The researchers concluded that fluvoxamine is an effective treatment for children and adolescents with anxiety disorders.

—*New England Journal of Medicine* 344:1279-1285, 2001.

Structural Insight into Improving Cholesterol-Reducing Medicines. Elevated cholesterol levels are a primary risk factor for coronary artery disease, which is a major problem in developed countries and currently affects 13 to 14 million adults in the United States alone, according to investigators. But cholesterol is also an essential component of the body's biochemical inventory because it is the starting material for the synthesis of many hormones. The enzyme known as HMGR, which performs a key step in cholesterol biosynthesis, can be blocked with drugs called statins that bind very tightly to the enzyme, prevent its activity, and effectively lower blood cholesterol levels. These inhibitors are widely prescribed medicines in the treatment of high blood cholesterol. The three-dimensional molecular structures of the active portion of human HMGR complexed with six different statins were determined using X-ray crystallography. Part of the data collection for this project was done using the brilliant X-ray beam produced at the NCRR-supported Macromolecular Diffraction Facility at the Cornell High Energy Synchrotron Source (CHESS). The results show that the statins bind to the enzyme at the same location as the natural substrate. The statins thus occupy the active site and prevent binding of the natural cholesterol precursor substrate and render the enzyme inactive. Visualization of statins bound to HMGR will assist chemists in their attempts to develop even better medicines to lower cholesterol levels.

—*Science* 292:1160-1164, 2001.

Enzyme Replacement Therapy for Treatment of Fabry's Disease. Fabry's disease, an inherited metabolic disorder, is marked by a buildup of fatty material in the kidneys, heart, skin, and brain because of a deficiency of an enzyme called alpha-galactosidase A (α–gal-A). Lacking the enzyme, most patients with Fabry's disease cannot break down and clear these fatty substances from cells and tissues. Because there is no effective treatment that reduces the fatty accumulation, patients have extreme pain and

Dr. Christine Eng and her colleagues evaluated a successful enzyme replacement therapy for Fabry's disease, an inherited condition that often causes death by age 40. *Photo courtesy of Baylor College of Medicine*

often die in early adulthood from kidney failure or cardiovascular complications. Researchers at the Mount Sinai School of Medicine and a number of collaborating centers report that enzyme replacement therapy offers the first hope for treating the disease. In a multicenter study, partly conducted in the NCRR-supported General Clinical Research Centers at Mount Sinai and the Cedars-Sinai Medical Center, 58 patients received genetically engineered (recombinant) human α–gal-A, which cleared the fatty substance globotriaosylceramide (GL-3) from the circulation and reduced GL-3 levels in liver, kidney, and heart tissues. This study demonstrates the efficacy of recombinant α–gal-A in the treatment of the clinical symptoms of Fabry's disease with minimal side effects.

—*New England Journal of Medicine* 345:9-16, 2001.

Candidate Drug for Treatment of Lupus. The disease systemic lupus erythematosus (SLE) is marked by an imbalance in certain types of T lymphocytes, which leads to increased production of a cell surface-associated compound known as CD154 and overproduction of an immunoregulatory substance called interleukin-10. At the same time, production of the important compound interferon-gamma, a basic component of the immune system, is inadequate. These abnormalities of the immune system lead to the production of autoantibodies—antibodies that harm the body in which they are produced—and the irreversible organ failure associated with SLE.

In a study assisted by the NCRR-supported General Clinical Research Center at Wake Forest University, researchers studied how the drug trichostatin A affects the lymphocytes of lupus patients. Trichostatin A, which inhibits an enzyme involved in modification of proteins called histones, significantly reduced the expression of CD154 and IL-10 and increased the expression of IFN-gamma in the lupus T cells. This pharmacologic agent may be a candidate for the treatment of this autoimmune disease.

—*Proceedings of the National Academy of Sciences USA* 98:2628-2633, 2001.

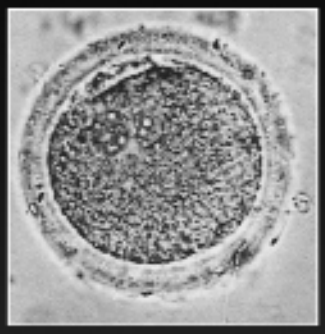
Women Are at Risk of Developing Drug-Associated Heart Problems During Menstrual Cycle. Women's hearts recharge, or repolarize, more slowly after a beat than do men's hearts. Women are therefore more prone than men to develop dangerous cardiac arrhythmias after taking drugs that prolong cardiac repolarization. Researchers at the NCRR-supported General Clinical Research Center at Georgetown University Medical Center, Washington, DC, have now shown that this drug-associated risk is even higher during the menstrual and ovulation phases of the menstrual cycle.

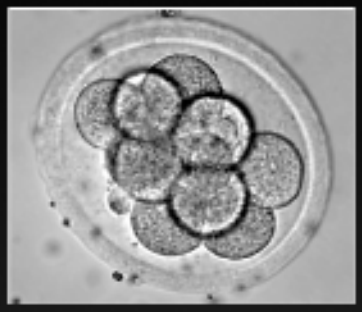
To see if sex hormones can influence a potentially dangerous drug's adverse effects (as has been shown in animal studies), the investigators evaluated 58 healthy adults (38 men and 20 women) aged 21 to 40 years. The participants received a low intravenous dose of the drug ibutilide, which is used to stop a heart arrhythmia called atrial fibrillation by slowing down the repolarization, and they were subsequently monitored for two hours. Women received the drug on three separate occasions corresponding to menstrual cycle phases (menses, ovulation, and luteal).

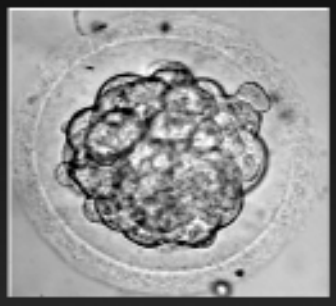
Measuring a property of the electrocardiogram called the QT interval, which indicates the repolarization time, the investigators found that after ibutilide infusion the QT interval was increased significantly more in women during menses and ovulation than in women during the luteal phase and compared with men. The researchers note that according to the Centers for Disease Control and Prevention sudden cardiac death rose about 30 percent in young women during the past decade. Although the investigators cannot be sure that the rise in sudden death is related to drug-induced heart problems, it is a possibility, they say.

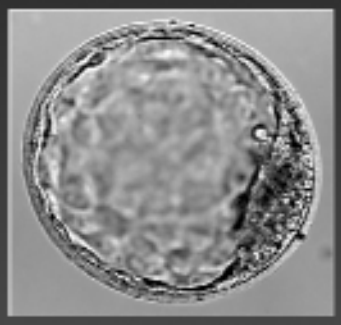
—*Journal of the American Medical Association* 285:1322-1326, 2001.

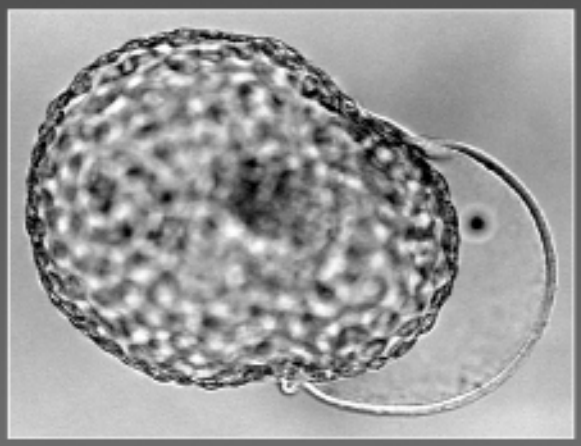
Dr. Michael Kilborn and his collegues have discovered that women are more susceptible to drug-induced heart problems during certain phases of the menstrual cycle. *Photo by Beth Porter, Georgetown University Medical Center*












Fetal
Maternal

Genetic Medicine

THE SEQUENCE OF THE HUMAN GENOME, as well as the genomes of several other organisms, holds enormous promise for biomedicine and public health. Gene-related investigations have enhanced our ability to identify inherited mutations that contribute to cancer risk, developmental abnormalities, and other disorders and have led to improved strategies for treating and preventing disease. Comparative analyses between the genomes of different species have revealed the functions of once-poorly understood proteins in complex organisms, such as humans. And the high-throughput technologies developed for genome-related studies are now being applied to other types of biomedical investigations, greatly speeding the pace of discovery.

Creation of transgenic embryos proceeds (clockwise from upper left) from a fertilized egg to a multicelled embryo; formation of primitive outer placenta; blastocyst embryo, which is injected with a foreign gene; later blastocyst; cross-section of placenta; and successful outcome of pregnancy. *Montage by Bob Becker, courtesy of Wisconsin RPRC*

Transgenic Expression in Rhesus Monkey Placental Tissues. In recent years immense progress has been made in understanding the function of individual genes through the production of mice in which genes have been added or removed. The situation is much more difficult with other species, and production of transgenic monkeys poses unique problems. Among several alternative strategies for introducing novel genes, self-inactivating (SIN) viral vectors to deliver the gene without continuing further replication is particularly promising. Using this approach, scientists at the Wisconsin Regional Primate Research Center (RPRC), the University of Wisconsin, and the Holland Laboratory of the American Red Cross have demonstrated successful gene transfer into rhesus monkey embryos, two of which resulted in live births and expression of the transferred gene in the animals' placentas.

These studies demonstrate the successful integration of a gene into the products of conception in a nonhuman primate model. Further studies that have great relevance to human health may now be possible.

—*Proceedings of the National Academy of Sciences USA* 98:10728-10732, 2001.

Structure of a Gene Expression Machine. The multisubunit enzyme RNA polymerase II (Pol II) is the central engine of gene expression in higher organisms. It reads the sequence of one strand of the DNA double helix, and in so doing creates an RNA message through a process called transcription. The RNA message is then translated into protein, the class of molecules responsible for cellular activities and communications. This transcription enzyme, Pol II, is a molecular machine, regulated by the activities of a number of proteins. If this regulation goes awry, it can affect cellular metabolism and normal development, and in some cases cause cancer. The atomic structure of Pol II from yeast was determined using X-ray crystallography on two different crystal forms. X-ray crystallographic data for these studies were collected at the NCRR-supported Synchrotron Radiation Structural Biology Resource at Stanford University. Not only do these crystal structures give cell biologists their first clear view of yeast Pol II in action, but they also open the door to seeing exactly how the enzyme interacts with the many other protein factors that regulate its activity. This may ultimately have implications for therapeutics developed for cancer, and will lead to a greater understanding of the process of normal development.

—*Science* 292:1863-1876 and 1876-1882, 2001.

Genome-Wide Screening of Protein Interactions. The recent deciphering of the human genome will gain medical significance only when scientists can determine how these genes function in the human body. The genes and their protein products orchestrate the complex activities within each cell. Understanding this intricate web of protein interactions requires new large-scale approaches. In collaboration with a biotechnology company, NCRR-supported researchers at the University of Washington have developed an automated system for genome-wide screening of thousands of protein interactions that might occur within a cell. This new technology was initially tested in baker's yeast *(Saccharomyces cerevisiae),* which serves as a model organism for understanding human biology and disease. Using a technique known as the two-hybrid assay, high-throughput technology, and a database system that identifies novel protein interactions, the researchers detected nearly 1,000 putative protein-protein associations, many of which involved poorly characterized yeast proteins that can now be studied in new contexts. This information will be valuable for determining the correlation between specific human genes and complex diseases such as metabolic disorders, cancer, and autoimmune diseases.

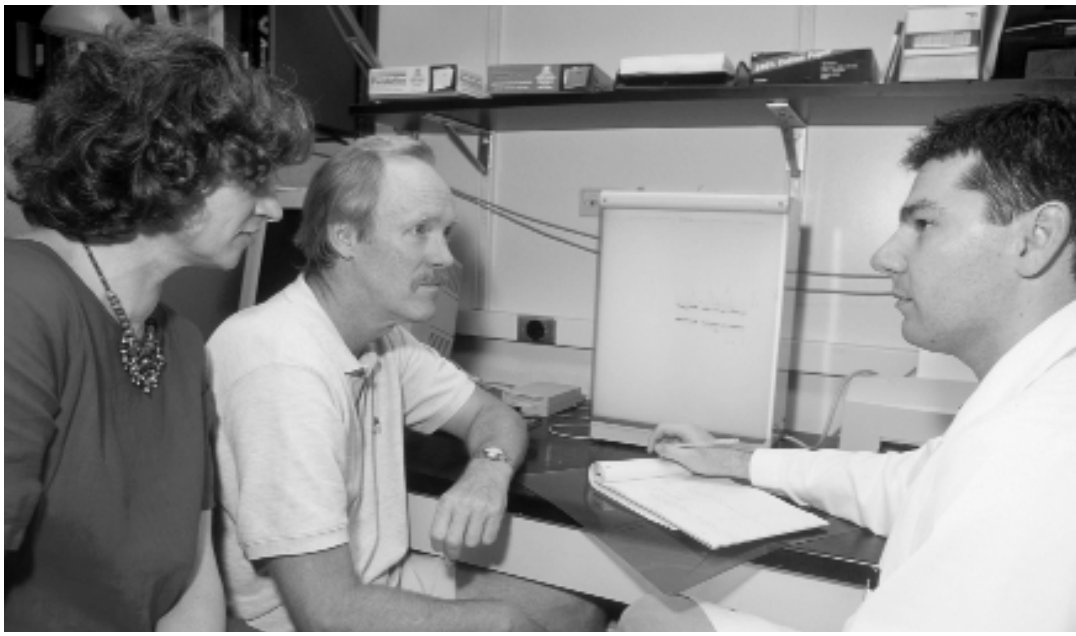
—*Nature* 47:623-627, 2000.

Detection of Mutations in Transgenic Fish. Fish may be used to assess health hazards associated with exposure to chemicals in aquatic environments and to provide alternative nonmammalian animal models in mutagenesis and carcinogenesis studies. Increasingly, fish have been seen as valuable animal models in genetics, developmental biology, and toxicology. Recent advances in fish transgenesis have made it possible to enhance the utility of fish by generating new animal models. NCRR-supported investigators at the University of Georgia developed a transgenic fish called medaka *(Oryzia latipes)* that carries a specific gene for quantitation of spontaneous and induced mutations. In this new animal model for in vivo mutation

detection, the transgenic fish carries a gene *(cII)* derived from a bacterial virus known as bacteriophage lambda that easily mutates when exposed to a variety of environmental pollutants. These investigations showed that many of the fundamental features of mutation found in transgenic rodents are shared by the transgenic fish. Its small size, sensitivity, well-characterized histopathology, short generation time, and cost-effective husbandry contribute to the utility of this transgenic fish species in routine testing of a wide variety of compounds.

—*Proceedings of the National Academy of Sciences USA* 97:12655-12660, 2000.

University of Hawaii Identifies First Gene Mutations in Elastic Tissue Disease. While relatively rare, occurring in about 1 in 25,000 live births, pseudoxanthoma elasticum (PXE) can have devastating consequences. In PXE, elastin fibers between cells of the skin, retina, and arteries become calcified and lose their resilience. Skin can show premature aging, bleeding in the retina can cause blindness, and premature arteriosclerosis can necessitate heart bypass surgery in patients still in their twenties. By comparing DNA from 17 unrelated PXE patients and normal individuals, an international research team was able to distinguish the disease-causing gene and identify mutations. The study received partial support from the NCRR-funded Research Centers in Minority Institutions Program at the University of Hawaii. The PXE gene codes for production of a transport protein that shuttles proteins across cell membranes. The gene has been associated with drug resistance that occurs when drug compounds are not carried across the cell membrane into the cell. Discovery of the gene responsible for PXE makes



Drs. Katalin Csiszar, Charles Boyd, and Oliver Le Saux (left to right) identified genetic mutations that lead to the blood vessel disease known as PXE. *Photo by Bob Chinn, University of Hawaii*

Scientists have created a genetic linkage map for the baboon, the first nonhuman primate genome to be mapped. *Photo courtesy of the Washington Regional Primate Research Center*

it possible to screen for the disorder and implement dietary interventions to lessen the impact of the disease. Studies of this gene and its protein product also may lead to better understanding of how drugs and other compounds can gain access to cells.

—*Nature Genetics* 25: 223-227, 2000.

A Genetic Linkage Map of the Baboon Genome. Nonhuman primates are valuable animal models for the study of human diseases. Their close evolutionary relationship to humans presents opportunities for comparative analyses of genome structure and gene function, known as genomics. In many cases, however, scientists have not yet determined which genes are located on each of the chromosomes in nonhuman primates. This placement of specific genes or gene functions at particular sites in the genome is known as genetic linkage mapping. The development of genetic linkage maps for nonhuman primates would provide new opportunities for diverse lines of research and comparative studies in human genetics and gene function. Scientists at the NCRR-funded Southwest Regional Primate Research Center and their collaborators have developed a genetic linkage map for the baboon. The baboon linkage map is the first reported for any nonhuman primate species.

—*Genomics* 67: 237-247, 2000.

Mutations Within a Skeletal Muscle Gene Cause Muscle Disease. Myotonia congenita (MC) is a genetic disease associated with abnormalities in the chloride channel of skeletal muscle, which is involved in controlling muscle movement. The disease is characterized by intermittent and progressive weakness. To date, more than 35 mutations, or variants, of the chloride channel gene (CLCN1), located on chromosome 7q35, have been identified. Patients afflicted with MC have clinical symptoms of varying severity. Investigators at the NCRR-funded General Clinical Research Center at the University of Utah have characterized the physiological effects of five such mutant genes by isolating them and then introducing them into cells growing in culture. Studies on these cells documented the altered ability of chloride ions to pass through each of these uniquely modified channels, thereby simulating characteristics of the disease variants. Pharma-

ceutical researchers can now design drugs that are specific for each disease variant.

—*Neurology* 54:937-942, 2000.

Lifespan Research in Worm May Benefit Human Research. It seems far-fetched to suggest that genes involved in controlling the lifespan of yeast and a lowly worm would have any bearing on the lifespan of higher animals, or even humans. Nevertheless, scientists studying the nematode *Caenorhabditis elegans*—supplied by the NCRR-supported Caenorhabditis Genetics Center—have discovered a gene, *sir-2.1*, that is closely related to the yeast gene *SIR2*, which is involved in controlling yeast lifespan. Introducing an extra copy of *sir-2.1* extends the lifespan of *C. elegans* by up to 50 percent through production of a protein named Sir2, and extra copies of *SIR2* similarly extend the lifespan of yeast cells. In nature, both of these mechanisms are associated with decreased availability of nutrients. A limited food intake also has been shown to prolong youth-associated characteristics in monkeys and other higher animals, suggesting that similar mechanisms may extend across species.

—*Nature* 410:227-230, 2001.


Luminex100

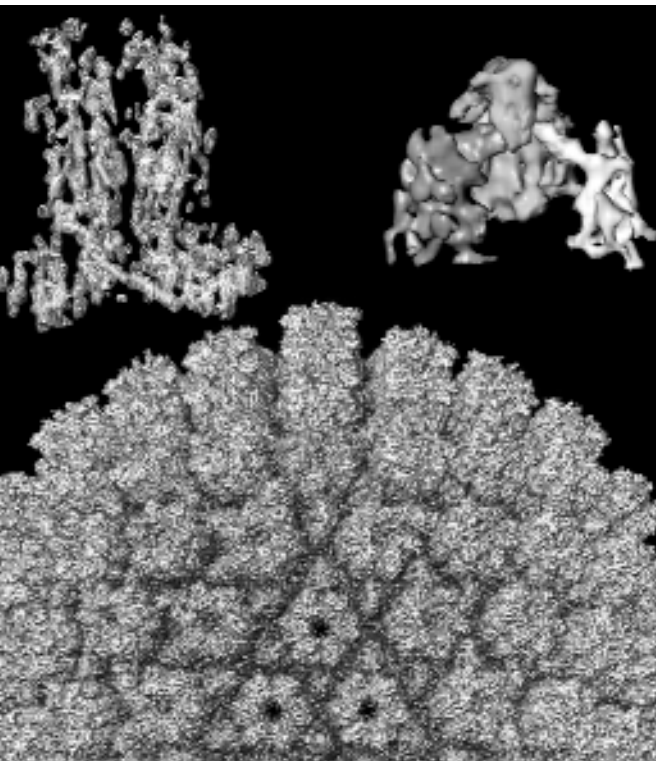
Bioengineering, Computers, and Advanced Instrumentation

PROGRESS IN BIOMEDICAL SCIENCE AND PATIENT care is closely linked to the development of new technologies, research instruments, and computer hardware and software. Bioengineering integrates physical, chemical, and mathematical sciences as well as engineering principles with the study of medicine, yielding innovative processes, devices, and biomaterials. Computers and advanced instrumentation enhance the early detection of disease and reveal the inner workings of the living body in health and in disease states.

Dr. John Nolan and his colleagues developed a rapid technique based on flow cytometry that inexpensively obtains genetic "fingerprints" of bacteria and other cells. *Photo by LeRoy N. Sanchez, Los Alamos National Laboratory, New Mexico*

NCRR supports the development of a variety of cutting-edge technologies and instruments and ensures that these tools are made accessible to the biomedical research community. Access to this critical infrastructure provides a wealth of knowledge for preventing, diagnosing, and treating disease.

Fingerprinting Bacteria. Identification of pathogenic bacteria is important for medical diagnosis and food and water safety. Rapid identification of bacteria would allow physicians to administer early, specific therapies to their patients. Scientists at the NCRR-supported Flow Cytometry Resource Center, Los Alamos National Laboratory, have developed a new technique for bacterial identification that lowers the cost and speeds the analysis of DNA samples extracted from bacteria. The technique provides greater precision and a wider range of applications than current methods. DNA extracted from as few as 1,000 bacteria are treated with specific enzymes that cleave the DNA into fragments, the lengths of which are unique



Using advanced microscopy and imaging technologies, scientists acquired this detailed three-dimensional likeness of the outer coat of a human herpesvirus, which reveals potential targets for new drug development. *Image courtesy of Dr. Z. Hong Zhou, University of Texas–Houston Medical School*

to particular bacteria. This mixture of DNA fragments is passed through a flow cytometer, and within 10 minutes the DNA "fingerprint" of the organism is known. Using this method it is possible to distinguish between harmless strains of *E. coli* and the toxic strains that cause food poisoning. The scientists are designing an inexpensive portable version of their laboratory equipment that will be usable in hospitals and in the field.

—*Cytometry* 41:203-208, 2000.

Shining a Light Through the Brain. Using a thin, flexible headband that contains optical fibers, scientists at the NCRR-funded General Clinical Research Center at Stanford University can safely and noninvasively image changes in brain oxygen levels in adults and critically ill newborns. The headband fibers both emit and detect low-intensity light that travels through brain tissues. Because red and near-infrared light is absorbed by blood, and because changes in blood oxygen levels alter the amount of absorption, the headband technology is able to pinpoint brain regions with fluctuating oxygen levels. Coupled with real-time computer analysis, the imaging technique holds promise as a bedside device for generating continuous, noninvasive brain images that enable diagnosis or monitoring of disease.

—*Journal of Cerebral Blood Flow and Metabolism* 20:469-477, 2000.

Visualization of the Herpesvirus Capsid. Human herpesviruses are large and structurally complex viruses that infect more than half the population of the United States and cause a variety of medical problems ranging from cold sores to blindness to cancer. When a herpesvirus invades a cell, it disassembles and releases a large protein structure, called a capsid, that encloses the viral genetic material. The capsid then delivers its DNA content into the nucleus of the cell, where the viral DNA is incorporated into the cellular DNA, causing the host cell to create more viruses. The three-dimensional structure of the 20-sided polyhedron-shaped capsid of herpes simplex virus type 1 was elucidated at the NCRR-supported National Center for Macromolecular Imaging (NCMI). The technique uses electron cryomicroscopy, in which the virus capsid particles were frozen and imaged in three dimensions by bombardment

with electrons. NCMI has developed software to visualize and animate the three-dimensional image of this extremely complex virus using computer graphics. Knowledge of the structure of the herpesvirus may facilitate development of more effective antiviral therapies.

—*Science* 288:877-880, 2000.

New Approaches to Integrated Protein Separations and Mass Spectrometry. Technical developments in mass spectrometry and knowledge about complete collections of genes, called genomes, present previously unimaginable opportunities for sophisticated experiments in biochemistry. Leading goals are to improve understanding of diseases and to identify new protein and gene targets for development of therapies. To facilitate these experiments, new techniques for separating, quantifying, and identifying proteins are constantly evolving. NCRR-supported investigators designed novel approaches for separating the thousands of proteins found in complex biological samples. These new systems, which use combinations of sensitive mass spectrometry and advanced protein separation methods, can detect up to 100,000 proteins in a single experiment. These sophisticated analysis technologies will make it possible to associate minute protein abnormalities with particular diseases and open the door to significant improvements in diagnosis and therapy.

—*Nature Biotechnology* 19:242-247, 2001; *Analytical Chemistry* 73: 1707-1720, 2001; *Electrophoresis* 22:1652-1668, 2001.

New Methods for Analysis of Protein Phosphorylation. Protein phosphorylation, in which phosphate is attached enzymatically to protein molecules, is both ubiquitous and critically important in living systems. The presence of phosphate at specific sites on a protein may enhance or abolish the protein's activity. Mass spectrometric methods have been developed previously to identify and quantify in an isolated protein the specific amino acids that are phosphorylated. However, in the analysis of complex mixtures of proteins, identification of specific sites of phosphorylation, or even of phosphorylated proteins, is highly problematic. Two NCRR-supported laboratories—located at Rockefeller University in New York City and the University of Washington in Seattle—have approached this problem in parallel. By attaching a chemical tag only to phosphorylation sites in a mixture of protein fragments or whole proteins, the new analytical tools can examine protein phosphorylation on a system-wide basis. A complete inventory of a cell's proteins and their functions will help scientists understand how healthy and diseased cells function.

—*Nature Biotechnology* 19:375-378 and 379-382, 2001.

Identifying the Functions of Proteins. The human genome sequencing projects have revealed that one-third to one-half of the identified genes are unique, meaning they have no homology, or sequence similarity, to previously identified genes. Determining sequence homology is often a useful starting point for elucidating the function of a gene. For genes with no sequence homology, it is necessary to develop a new technology to identify their function. With assistance from the NCRR-funded mass spectrometry resource at Rockefeller University, scientists used a combination of conventional separation methods, mass spectrometry, conventional light microscopy, and electron microscopy to identify 40 unique proteins that formed a

Dr. Peter Seeberger (right), along with graduate student Emma Palmacci (left) and Dr. Obadiah Plante, developed an automated instrument that rapidly synthesizes complex sugars known as oligosaccharides. *Photo by Donna Coveney, Massachusetts Institute of Technology*

pore between the cell nucleus and the cytoplasm of yeast cells. This pore allows large molecules to get into and out of the cell nucleus. These detailed studies will allow researchers to draw conclusions about similar functions in human cells and provide targets for development of drugs for diseases involving nuclear transport defects.

—*Journal of Cell Biology* 148: 635-51, 2000.

Automated Synthesis of Complex Sugars. The important molecules in any living organism can be broken down into four groups: nucleic acids, proteins, sugars, and others. Major advances in our understanding of the structure and function of both nucleic acids and proteins would have been impossible without automated techniques to synthesize these molecules. With the advent of automated technologies, researchers were able to create large quantities of these molecules, which enhanced their investigations. A similar automated process for synthesizing complex sugars has been difficult to develop, but has recently been solved. Supported by an NCRR Shared Instrumentation Grant, researchers at the Massachusetts Institute of Technology have developed an automated instrument that can accomplish this complicated task. The automated synthesizer promises to deliver large quantities of normal and abnormal sugars for study. Changes in the metabolism and structure of sugars have been implicated in many diseases such as infectious diseases, disorders of the immune system, and genetic disorders. Once these molecules are in the hands of researchers, a much deeper and complete understanding of sugar-related diseases is expected.

—*Science* 291:1523-1527, 2001.

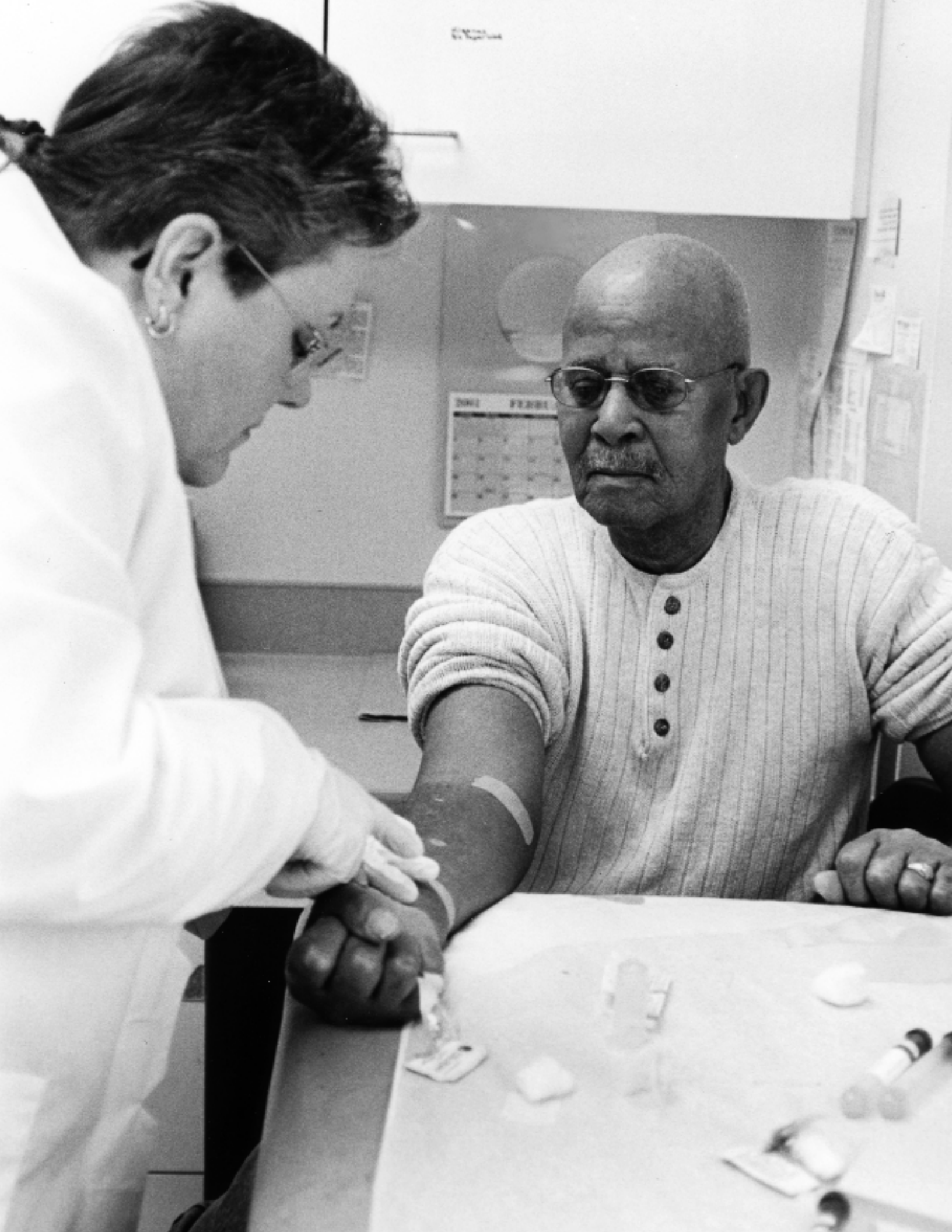
Going Through the Motions. Images of proteins in textbooks and scientific journals generally make these molecules appear static and immobile. But in fact biophysical studies have established that proteins are in constant motion that can range from tiny vibrations to large-scale reorientation of domains and unfolding of major parts of the molecule. Now scientists at the NCRR-supported National Magnetic Resonance Facility at the University of Wisconsin-Madison have used nuclear magnetic resonance and biochemical studies to correlate the structural states of a protein and the dynamics of its interconversion directly with its biochemical activity. They have thereby succeeded in developing a model for the regulation of nitrogen regulatory protein C (NtrC), which is an important signal molecule that controls gene expression in bacteria. NtrC belongs to a family of proteins that, in addition to controlling gene expression, also are involved in chemotaxis, antibiotic resistance, and many other processes.

The investigators found that the protein constantly alternates between two conformations, or shapes, like an on–off switch. One conformation, associated with an active form of NtrC, is attained when the protein is phosphorylated; if the protein loses its phosphate, it becomes inactive and changes its conformation. The researchers suggest that such stabilization of preexisting conformations may be a fundamental property of protein activation.

—*Science* 291:2429-2433, 2001.

Mechanism of Potassium Channel Function Revealed. The flow of ions through channels that cross the cell membrane regulates the electrical currents and potentials essential for the proper function of many types of cells, such as heart and nerve cells. Although it has been known for many years that the channels open and close to regulate the ion flow, the detailed mechanism was not known until now. Investigators at Rockefeller University, using the NCRR-supported resource Macromolecular Crystallography at the National Synchrotron Light Source at Brookhaven National Laboratory, have shown in molecular detail how the flow of potassium ions through a membrane channel can be blocked. Structural studies conducted during the pastthree years had shown that the potassium channel consists of four identical subunits that fit together to form a cone-shaped pore that spans the cell membrane. Four "windows" in the side of the channel provide access to the inside of the channel. The Rockefeller researchers' structural studies show that groups of amino acids at the ends of the long amino acid chains of the four subunits form ball-and-chain-like structures, one of which can pass through one of the "windows" and plug the channel to stop the ion flow. These findings explain why drugs that effectively block potassium channels have structures that are similar to the channel's own plug and why certain antibiotics with similar structures can cause irregular heartbeats.

—*Nature* 411:657-661, 2001.



Health Disparities

WHEN IT COMES TO HEALTH AND DISEASE rates in the United States, not all populations are affected equally. Although minority groups represent less than one-fourth of the total U.S. population, they bear a disproportionate burden of the country's disease-related mortality rates. In the United States, infant mortality, diabetes, hypertension, AIDS, kidney disease, and a variety of cancers claim a disproportionate toll on minority populations, particularly African Americans.

A clinical scientist at Washington University in St. Louis draws blood from a volunteer participant in a study of prostate cancer genetics. *Photo by Cissy Lacks for the Urological Research Foundation, St. Louis, Missouri*

NCRR recognizes the urgent need to close the health gaps between minorities and other populations and to develop minority health and training programs at biomedical research institutions. Through programs that enhance research infrastructure at minority institutions and promote career development of minorities, NCRR helps to strengthen the representation of minority groups in the scientific workforce. NCRR also supports several single- and multi-center clinical studies that examine the incidence and potential interventions for health-related problems that disproportionately affect minority Americans.

Prostate Cancer Susceptibility. Prostate cancer is the second leading cause of cancer mortality among men in the United States and is particularly prevalent in African Americans. Although studies on the lifestyle of patients point to the importance of environmental factors, many scientists believe that genetic factors also play a major role. Scientists at an NCRR-supported genetic analysis resource at Case Western Reserve University collaborated with clinical researchers at Washington University in St. Louis to conduct a genome-wide scan of 504 brothers with prostate cancer. The investigators succeeded in identifying five regions linked to prostate cancer susceptibility, with the strongest of these located on chromosome 16q, which also is suspected of containing a tumor suppressor gene.

Dr. Jay Vadgama and his colleagues are examining the genetic and molecular factors that contribute to breast cancer in African American and Hispanic women.
Photo courtesy of Dr. Vadgama, Charles R. Drew University

A more detailed analysis was then done on subgroups defined by family history of prostate cancer, age, and family history of breast cancer. This analysis revealed additional potential susceptibility regions for prostate cancer. Detecting such genes may provide avenues for future screening and therapy, as well as help to clarify the biological basis of prostate cancer.

—*American Journal of Human Genetics* 66:933-944, 2000.

Cancer Gene Mutations in African American Women. Breast cancer is a leading cancer in American women, but according to data from Surveillance, Epidemiology, and End Results—a 1973 through 1993 review—the incidence of breast cancer is lower in African American women than in white women. However, the mortality in African Americans is much higher than in whites. Mutations in the breast cancer susceptibility gene *BRCA1* and *BRCA2* confer increased risk of breast cancer in the white population, but few studies on minorities have been reported. To investigate if African Americans might carry ethnically specific mutations, scientists supported by NCRR's Research Centers in Minority Institutions Program at Charles R. Drew University of Medicine and Science in Los Angeles screened 54 African American women with breast cancer for mutations in regions of the *BRCA1* gene where a number of mutations already had been found. The scientists detected four novel *BRCA1* mutations in the 54 women, but one of the mutations was present in three of the women, suggesting that African Americans may carry unique mutations in that gene.

—*Journal of the National Medical Association* 92:29-35, 2000.

Ethnic Differences in Cyclosporine Pharmacokinetics. The metabolism and elimination—known as pharmacokinetics—of many drugs are affected by ingestion of grapefruit juice, which contains a component that interacts with particular liver enzymes. This effect may inadvertently cause a patient to receive more or less than the intended drug dose. For a drug like cyclosporine, which prevents rejection of an organ transplant by the recipient's body, the grapefruit juice effect is especially critical. Investigators have shown earlier that grapefruit juice causes cyclosporine to be

Dr. Janice Douglas heads the steering committee for the African American Study of Kidney Disease and Hypertension (AASK). The multicenter study compared the effectiveness of three common blood pressure drugs and identified one that was comparatively less effective in slowing progression of kidney disease. *Photo by Mike Sands, Case Western Reserve University*

eliminated more slowly than normal in white and Asian people, but no studies have been carried out on African Americans until now. Researchers at the College of Pharmacy and the NCRR-supported General Clinical Research Center at the University of Iowa administered cyclosporine orally in water or grapefruit juice to 11 African Americans and 11 Caucasians and then measured the concentrations in blood during the subsequent time period. Compared to cyclosporine ingested in water, grapefruit juice increased the peak blood concentration in Caucasians by 8 percent but by 39 percent in African Americans and prolonged the elimination time more in African Americans than in Caucasians. African Americans receiving cyclosporine are therefore at a particularly high risk of being overdosed with the drug, which can have serious consequences.

—*Journal of Clinical Pharmacology* 41:317-329, 2001.

Advances in Treating African Americans With Kidney Disease Due to High Blood Pressure. Mortality in the United States from disease of the blood vessels due to hypertension has declined progressively over the past two decades, in part because of improved treatment of high blood pressure. However, during the same period, the incidence of kidney failure due to hypertension has increased steadily, particularly among African Americans. In certain age groups, the risk of hypertensive kidney failure is 20 times greater for African Americans than for Caucasians. The African American Study of Kidney Disease and Hypertension (AASK) was designed to evaluate the impact on progression of hypertensive kidney disease

of three drugs belonging to different antihypertensive drug classes: metoprolol, amlodipine, or ramipril. NCRR-supported investigators from the Morehouse School of Medicine and Charles R. Drew University found that among participants with protein in their urine, the ramipril group had a 38 percent reduced risk of decreased kidney function and a slower disease progression than those in the amlodipine group.

—*JAMA* 285:2719-2728, 2001.

Prevention of Heart Attacks by Lowering Blood Pressure. High blood pressure, or hypertension, which is a major risk of heart attack and cardiovascular disease, affects minorities disproportionately. A large number of blood pressure-lowering drugs are available, but they often reduce the blood pressure through different mechanisms, and in many cases their relative efficacies have not been carefully compared. In a multicenter trial—sponsored by the National Heart, Lung, and Blood Institute with participation of the NCRR-supported Research Centers in Minority Institutions Program at Morehouse School of Medicine and four General Clinical Research Centers—investigators compared the two drugs doxazosin and chlorthalidone. A total of more than 24,000 patients participated in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which took place at 625 centers across the country. The patients, about 50 percent of whom were minorities, were 55 years or older, had high blood pressure, and had at least one other risk factor for coronary heart disease.

Dr. Thomas Redlinger and his colleagues found that blood folate levels dropped significantly among postpartum Hispanic women, many of whom had stopped taking vitamins after childbirth. This folate insufficiency may contribute to the disproportionately high rate of neural tube defects among offspring of Hispanic women.
Photo by Adriana Galindo, University of Texas, El Paso

The investigators found after three years' follow-up that the antidiuretic drug chlorthalidone, compared with doxazosin, significantly reduced the risk of cardiovascular disease, particularly congestive heart failure, in high-risk hypertensive patients. Evaluating drug efficacy in large multiethnic trials will result in better treatment for all patients.

—*Journal of the American Medical Association* 283:1967-1975, 2000.

Declining Folate Levels in Postpartum Hispanic Women. A number of studies have shown that women who receive the vitamin folic acid during pregnancy are at less risk of giving birth to children with neural tube defects, such as anencephaly and spina bifida, which are associated with high mortality and severe physical and mental handicaps. According to several studies, the prevalence of neural tube defects is two to three times higher among children of Hispanic women than among those of Caucasian women, a difference that may be associated with lack of folic acid. Hispanic women give birth more frequently and have more children than women of many other ethnic groups. Because they are likely to become pregnant relatively soon after giving birth, they are at risk of becoming deficient in specific, essential nutrients such as folic acid. Investigators supported by the NCRR Research Centers in Minority Institutions Program at the University of Texas, El Paso, monitored the folic acid content in red blood cells in 188 low-income Hispanic women 1 to 12 months after they had given birth. During the first four months, the mean folate level in the women's red blood cells decreased 23 percent, from more than 1,300 mg/ml to 1,017 mg/ml. Only 35 percent of the mothers used vitamin supplements beyond one month postpartum. The results suggest that these mothers are at risk of giving birth to babies with neural tube defects.

—*Journal of Women's Health & Gender-Based Medicine* 9: 397-403, 2000.

Funding Activities

NCRR Funding Activities, Fiscal Year 2000

RESEARCH AREAS	FUNDING*	MAJOR SUPPORT
Clinical Research	$ 212,235,000	■ 78 General Clinical Research Centers (GCRC) ■ 88 Clinical Associate Physician (CAP) Awards ■ 42 Mentored Patient-Oriented Research Career Development Awards ■ 9 Mentored Medical Student Awards ■ 5 Minority Clinical Associate Physician (MCAP) Awards ■ 2 Agency Agreements for K30 Support ■ 2 Conferences ■ 1 National Gene Vector Laboratory ■ 1 National Disease Research Interchange
Biomedical Technology	$ 137,931,000	■ 66 Biomedical Technology Resource Centers ■ 48 Research Projects ■ 36 Exploratory/Developmental Research Projects ■ 156 Shared Instrumentation Grants (SIG) ■ 2 Conferences ■ 1 Research Training Fellowship ■ 1 Research Contract
Comparative Medicine	$ 120,091,000	■ 8 Regional Primate Research Centers (RPRC) ■ 22 Animal Models/Animal and Biological Materials Resources ■ 1 Research Program Project ■ 54 Research Projects ■ 31 Resource-Related Research Projects ■ 7 Exploratory/Developmental Research Projects ■ 2 FIRST Awards ■ 1 Conference ■ 18 Special Emphasis Research Career Awards (Laboratory Animal Sciences) ■ 13 Institutional National Research Service Awards (NRSA) ■ 6 NRSA—Student Short-Term Research Training ■ 2 NRSA—Individual Postdoctoral Fellowship ■ 15 Cooperative Agreements ■ 4 Research Contracts ■ 2 Mid-Career Investigator Awards
Research Infrastructure	$ 173,034,000	■ 18 Research Centers in Minority Institutions (RCMI) ■ 5 RCMI—Clinical Research Infrastructure Initiative (RCRII) ■ 3 Centers of Clinical Research Excellence (CCRE) at RCMI-eligible institutions ■ 8 Specialized Neuroscience Research Centers (cofunded) ■ 19 Centers of Biomedical Research Excellence at IDeA Institutions ■ 7 Research Infrastructure in Minority Institutions (RIMI) (funded by the NIH Office of Research on Minority Health) ■ 46 Research Projects at IDeA Institutions (cofunded) ■ 1 Specialized-Comprehensive Center at IDeA Institutions (cofunded) ■ 57 Science Education Partnership Awards (SEPA) ■ 11 K-12 Program Awards ■ 44 Research Facilities Improvement Construction Awards ■ 19 Animal Facilities Improvement Awards ■ 4 Research Contracts
Small Business Innovation Research and Small Business Technology Transfer	$ 14,363,000	■ 57 Small Business Innovation Research Grants ■ 6 Small Business Technology Transfer Grants ■ 1 Small Business Innovation Research Contract
Total	$ 657,654,000	

** In addition, $2,608,000 of reimbursable authority from other Federal agencies was obligated by NCRR in FY 2000.*

NCRR Funding Activities, Fiscal Year 2001

RESEARCH AREAS	FUNDING*	MAJOR SUPPORT
Clinical Research	$ 240,706,000	■ 79 General Clinical Research Centers (GCRC) ■ 59 Clinical Associate Physician (CAP) Awards ■ 63 Mentored Patient-Oriented Research Career Development Awards ■ 3 Minority Clinical Associate Physician (MCAP) Awards ■ 1 Agency Agreement ■ 2 Conferences ■ 5 National Gene Vector Laboratories ■ 1 National Disease Research Interchange ■ Partial support for 15 K30 awards (curriculum development) ■ Partial support for 3 research ethics training grants
Biomedical Technology	$ 157,679,000	■ 64 Biomedical Technology Resource Centers ■ 45 Research Projects ■ 30 Exploratory/Developmental Research Projects ■ 152 Shared Instrumentation Grants (SIG) ■ 4 Conferences ■ 1 Research Training Fellowship ■ 5 Research Contracts
Comparative Medicine	$ 136,433,000	■ 8 Regional Primate Research Centers (RPRC) ■ 25 Animal Models/Animal and Biological Materials Resources ■ 1 Research Program Project ■ 52 Research Projects ■ 34 Resource-Related Research Projects ■ 7 Exploratory/Developmental Research Projects ■ 2 FIRST Awards ■ 6 Conferences ■ 20 Special Emphasis Research Career Awards (Laboratory Animal Sciences) ■ 13 Institutional National Research Service Awards (NRSA) ■ 7 NRSA—Student Short-Term Research Training ■ 2 NRSA—Individual Postdoctoral Fellowship ■ 17 Cooperative Agreements ■ 6 Research Contracts ■ 6 Mid-Career Investigator Awards
Research Infrastructure	$ 241,803,000	■ 18 Research Centers in Minority Institutions (RCMI) ■ 5 RCMI—Clinical Research Infrastructure Initiative (RCRII) ■ 3 Centers of Clinical Research Excellence (CCRE) at RCMI-eligible institutions ■ 8 Specialized Neuroscience Research Centers (cofunded) ■ 29 Centers of Biomedical Research Excellence at IDeA Institutions ■ 24 Biomedical Research Infrastructure Networks (in IDeA states) ■ 7 Research Infrastructure in Minority Institutions (RIMI) (funded by the NIH Office of Research on Minority Health) ■ 57 Science Education Partnership Awards (SEPA) ■ 43 Research Facilities Improvement Program Awards ■ 20 Animal Facilities Improvement Program Awards ■ 3 Research Contracts
Small Business Innovation Research and Small Business Technology Transfer	$ 18,365,000	■ 65 Small Business Innovation Research Grants ■ 5 Small Business Technology Transfer Grants
Total	$ 794,986,000	

** In addition, $3,415,000 of reimbursable authority from other Federal agencies was obligated by NCRR in FY 2001.*

Discrimination Prohibited Under provisions of applicable public law enacted by Congress since 1964, no person in the United States shall, on grounds of race, color, national origin, handicap, or age, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity (or, on the basis of sex, with respect to any education program or activity) receiving Federal financial assistance. In addition, Executive Order 11141 prohibits discrimination on the basis of age by contractors and subcontractors in the performance of federal contracts, and Executive Order 11246 states that no federally funded contract may discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. Therefore, all programs of the National Center for Research Resources are operated in compliance with these laws and Executive Orders.

National Center for Research Resources (NCRR)

National Institutes of Health

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Publication Order Form

QTY: Research Resource Directories

_____ *Biomedical Technology Resources* Directory (2001)

_____ *Clinical Research Resources* Directory (2001)

_____ *Comparative Medicine Resources* Directory (2001)

QTY: Fact Sheets: NCRR Grant Programs

_____ *Animal Models, Genetic Stocks, Biological Materials, and Information Resources*

_____ *Biomedical Technology Resource Centers*

_____ *General Clinical Research Centers*

_____ *Institutional Development Awards*

_____ *National Gene Vector Laboratories*

_____ *Regional Primate Research Centers*

_____ *Research and Animal Facilities Improvement Programs*

_____ *Research Centers in Minority Institutions and RCMI Clinical Research Centers*

_____ *Science Education Partnership Awards*

_____ *Shared Instrumentation Grants*

_____ *Research Career Development and Training Opportunities*

QTY: General

_____ *NCRR Reporter* (quarterly magazine)

_____ *NCRR: A Catalyst for Discovery* brochure

_____ *NCRR Highlights: 2000–2001*

_____ *Strategic Plan for the National Center for Research Resources: 1998–2003*

The National Center for Research Resources ensures that essential tools and research resources are readily available to NIH-supported investigators nationwide. NCRR-supported resources—a comprehensive range of human, animal, technological, and more—enable biomedical research advances.

Grants Information On-Line

NCRR Funding Opportunities
http://www.ncrr.nih.gov

Clinical Research
http://www.ncrr.nih.gov/clinical.htm

Comparative Medicine
http://www.ncrr.nih.gov/compmed.htm

Biomedical Technology
http://www.ncrr.nih.gov/biotech.htm

Research Infrastructure
http://www.ncrr.nih.gov/resinfra.htm

Shared Instrumentation Grants
http://www.ncrr.nih.gov/biotech/btshrgr.htm

Small Business Innovation Research Grants
http://grants.nih.gov/grants/funding/sbir.htm

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National Institutes of Health
National Center for Research Resources

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