National Center for Research Resources

NCRR Reporter

*NCRR: Catalyst for Discovery*

**U.S. Department of Health and Human Services**
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# 40 Years

## *Providing Research Resources That Enable Biomedical Discovery*

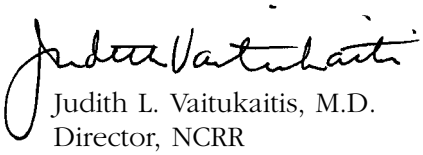
# From the Director

This year marks the 40th anniversary of the National Center for Research Resources (NCRR). While the organization has had several transformations and slight name changes, the sustaining goal has remained the same—keeping pace with the biomedical community's changing needs for research tools and infrastructure.

The research resources needed for scientific investigations change dramatically over time as more complex research queries are posed and, in turn, require new technologies, biomaterials, and expertise. Many research tools unheard of just a decade ago—including functional MRI and "knockout" animals—are now considered critical to understanding the cause of disease and protecting the health of Americans. But these critical resources did not develop spontaneously; they required sustained support over long periods of time—sometimes for decades—before they reached their full potential. And the true beauty of this evolutionary process is that, with the inquisitive spirit of investigators and continued research support, many of these essential tools and resources will have applications we never could have anticipated.

With the advent of NCRR's anniversary, we have taken the opportunity to look back at how sustained support has contributed to some of the research advances that have taken place over the past 40 years. This issue of the *NCRR Reporter* highlights the importance of infrastructure support to critical studies of hypertension; success with organ transplants; improvements in imaging tools and computers; advancements in mass spectrometry and structural biology; and the identification of an AIDS-like virus in nonhuman primates. While this look back is certainly not all-encompassing, it illustrates the diversity and magnitude of NCRR's commitment to provide research resources that underpin all areas of scientific inquiry supported by NIH.

Throughout the years, NCRR has worked in alliance with its NIH partners and the biomedical community to anticipate and provide the requisite tools for their scientific needs. From supporting the prototype of the first minicomputers in 1962 to the cloning of the world's first "knockout" pig this year, NCRR has remained flexible and responsive to the ever-changing resource needs of biomedical researchers. And our goal remains the same today—providing the research resources that will allow scientists to achieve the biomedical breakthroughs of the next 40 years and beyond.



Judith L. Vaitukaitis, M.D.
Director, NCRR


NCRR Reporter

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The "**News from NCRR**" section, which normally appears in the back of the *NCRR Reporter,* can be accessed online at **www.ncrr.nih.gov/whatsnew.asp**.

# NCRR at 40

## *Providing Research Tools That Enable Biomedical Discovery*

For four decades and counting, the National Center for Research Resources has operated by the guiding principle that access to proper tools—or research resources—opens the door to scientific creativity and enables health-related discoveries. When it was founded in 1962, the Division of Research Facilities and Resources (as NCRR was then known) consisted of a patchwork of newly established programs that provided diverse services and technologies to NIH-funded investigators. Then as now, support was provided for biomedical technology and instruments, renovation and construction of research facilities, General Clinical Research Centers (a nationwide network of specialized sites for conducting patient-oriented research), and primate centers (which enhance scientific access to these important animal models).

Over the years, these original programs have expanded and flourished, and NCRR has sought additional opportunities for meeting researchers' needs. Today NCRR supports several programs that enhance minority participation in biomedical science. Other programs provide career opportunities and professional training in clinical research, veterinary science, and a variety of technologies. The biological models supported by NCRR now range from single cells and simple organisms to nonhuman primates. And the GCRCs are embracing new technologies—including bioinformatics, advanced imaging tools, wireless communications, and genome-related sciences—to enhance patient care.

This special edition of the *NCRR Reporter* features a 40-year timeline of significant achievements, as well as seven "Stories of Discovery" that demonstrate the important contributions research resources have made to health-related science. With ready access to critical research tools and infrastructure, scientists can seize unexpected opportunities as they arise, and emerging health concerns can be addressed. Having the right tools has made all the difference.

# NCRR Milestones: 40 Years of Research Resources

## 1962

John F. Cook, MIT

**June 15.** Established the National Center for Research Resources, then known as the Division of Research Facilities and Resources (DRFR).

Provided seed money for creation of prototype **minicomputers**, known as LINCs.

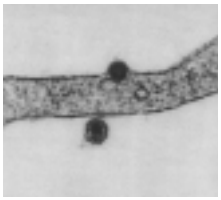
## 1963

Supported Dr. Thomas Starzl's groundbreaking success in human **liver transplantation**.

## 1964

Launched an ongoing collaboration with the Institute of Laboratory Animal Resources (ILAR) to develop national guidelines for the **care and use of laboratory animals.**

## 1984



Enabled identification of **simian retrovirus-1** as the cause of an AIDS-like disease.

## 1985

Established the Research Centers in Minority Institutions **(RCMI) Program**.

## 1986

Funded the first national laboratory dedicated to biomedical applications of **fluorescence** at the University of Illinois.

## 1987

Supported the first extramural **supercomputing resource** dedicated to biomedical research at the Pittsburgh Supercomputer Center.

## 1988

Established the **Research Facilities Improvement** Program.

Supported research that led to the birth of the world's first **rhesus macaque created via in vitro fertilization**, embryo cryopreservation, and embryo transfer.

## 1990

Merged with other NIH components to become the National Center for Research Resources (**NCRR**).

Supported the first annual RCMI International **AIDS symposium**.

Enabled isolation and cloning of the simian immunodeficiency virus (**SIV**), which causes AIDS in monkeys.

## 1991

Supported the world's first **functional MRI** studies of the human brain.

Established the **Science Education Partnership** Awards, designed to improve literacy in the life sciences.

## 1992

Enabled development of an **improved fMRI** technique that depends on deoxygenated blood to identify activated brain regions.

## 1993

Demonstrated the feasibility of **"collaboratories"** when scientists in Chicago operated a sophisticated electron microscope in California, at a research resource headed by Dr. Mark Ellisman, above.

## 1994

Developed NCRR's first comprehensive **strategic plan** with assistance from the biomedical research community.

## 1995

## 1966

Funded the first national centers for biomedical **mass spectrometry and NMR spectroscopy**.

## 1969

Changed name to the Division of Research Resources (**DRR**).

## 1971

Began to support **outpatient studies** at the General Clinical Research Centers (GCRCs).

## 1972

Began to fund early development of **CLINFO**, a user-friendly computer system that is still used for clinical investigations.

Initiated a biomedical research and training program to increase **minority participation** in biomedical research.

## 1973

Established a GCRC-based training program to launch **young physicians** on a career in clinical research.

## 1977

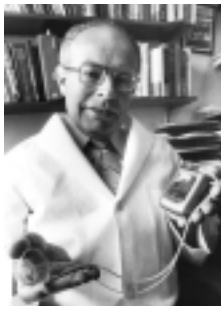
Published introductory issue of the ***NCRR Reporter,*** then known as the *Research Resources Reporter.*

Supported clinical trials of the first successful systemic antiviral agent (vidarabine), paving the way for more contemporary **antiviral therapies**. Drs. Richard Whitley, above left, and Charles Alford, right, led the studies.

## 1979

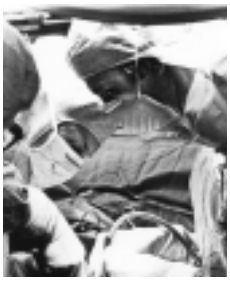
Funded the first **synchrotron** resource devoted to biomedical investigations.

## 1980



Enabled clinical studies of the first automatic implantable defibrillator, which has since saved hundreds of thousands of lives. Invented by Dr. Michel Mirowski, left, the device uses a mild electric shock to **correct irregular heartbeats**.

## 1982



Created the **Shared Instrumentation Grant** Program to help biomedical scientists purchase expensive state-of-the-art equipment.

Supported the first successful combined **heart-lung transplantation** in the United States.

Supported the first isolation and culturing of **embryonic stem cells** from a primate.

Established the **National Gene Vector Laboratories**, in collaboration with other NIH components, to enable clinical study of potential gene therapies.

Launched the **RCMI Clinical Research Infrastructure** Initiative to enhance clinical research at minority institutions.

## 1999

Using the high-speed communications network Internet2, initiated **eight "collaboratory" projects**, allowing scientists to access research resources at remote sites.

## 2000

Supported creation of the first **genetically engineered monkey**.

## 2001

Established a network of 10 **Islet Cell Resource Centers** to enable studies of promising therapies for type 1 diabetes.

## 2002

Supported cloning of the world's first **"knockout" pigs**, which lack one copy of a specific gene.

# 2002


Hospital of Chard
J. T. Wright, Jr.

# Stories of Discovery

## The Computer Revolution in Biomedical Science

Back in the 1950s, computers were like castles on the hill—large, expensive, and very mysterious. Since most biomedical scientists could not afford their own computers, they often shared a central computer and sometimes waited a day or so to get the results. Today, of course, small computers are found in practically every laboratory in the country, where they have revolutionized biomedical science. Researchers now routinely use computers to analyze experimental results and to perform such esoteric functions as viewing three-dimensional (3-D) models of complex molecules and "touching" chromosomes and viruses in virtual reality. Early NCRR support proved instrumental in transforming computers into a useful tool for the biomedical scientist.

***In 1980, Drs. Robert Langridge (standing) and Thomas Ferrin at the University of California, San Francisco, added color to 3-D computer graphics displays of molecules.*** *(Photo by Richard Brooks)*

It all started in 1961 when Wesley Clark, an electrical engineer at Lincoln Laboratory at the Massachusetts Institute of Technology (MIT), designed a small computer for a brain researcher at MIT. Clark wanted his computer to be easy to program, easy to communicate with while it was operating, and able to process biological signals directly. At the time, no computer came close to fulfilling these criteria. Clark also wanted his machine to be short enough to see over and affordable enough for the typical university laboratory.

In 1962, Clark and his colleague, Dr. Charles Molnar, built a working model of the computer, using existing electronic modules rather than building new circuits. They dubbed

***Collage, clockwise from upper left: Surgeons at a Minnesota GCRC began to explore pancreas transplants as a treatment for diabetes in the late 1970s (pages 9-11). In 1984 Drs. Robert Collins and Arthur Toga depended on shared instruments; Dr. Toga now heads an NCRR-supported imaging resource (pages 11-14). Synchrotron studies enabled this detailed visualization of a ribosome subunit (pages 21-23). Dr. Jackson Wright, Jr. is a lead researcher in a multi-site study of kidney disease and hypertension in African Americans (pages 14-16). Dr. Ronald Desrosiers evaluates experimental AIDS vaccines in nonhuman primates (pages 19-21).***

their creation LINC, partly as a bow to Lincoln Laboratory and partly as a pun alluding to how the user could link closely to the machine. LINC was about the size of a refrigerator and used recording tapes that were small enough to fit in a jacket pocket, another revolutionary concept for the time.

With $400,000 in seed money from NCRR—and similar sums contributed by the National Institute of Mental Health and NASA—Clark and Molnar launched a plan to offer free LINCs to biomedical scientists. In exchange, researchers had to spend a summer building their own computers in a learning workshop and then evaluating them in their laboratories. Eventually 12 LINCs were built at the workshop, and users quickly discovered that the computers enabled more rapid and efficient execution of experiments. Also, LINC allowed users to fine-tune ongoing experiments, reformulating hypotheses "on the fly" as data accumulated. The LINC development team eventually relocated to Washington University in St. Louis, where, with Dr. Jerome Cox, Jr., they established the Resource for Biomedical Computing, funded by NCRR from 1964 to 1997.

***The nanoManipulator allows users to see 3-D images of microscopic biological objects and manipulate these objects using a stylus. Here graduate student Scott Paulson prods a tobacco mosaic virus particle.*** *(Photo by Todd Gaul, courtesy of the Department of Computer Science, University of North Carolina-Chapel Hill)*

*The small laboratory computer may never have been developed without government support, including crucial start-up funds from NCRR.*

At Washington University, derivatives of LINC were used to plan radiation treatments for cancer and to monitor cardiac rhythm abnormalities in a hospital. In addition, an early molecular modeling system was developed using LINC as its foundation. This system displayed 3-D stick figures of molecules, which the user could manipulate. Today computer modeling of molecules has largely replaced the cumbersome ball-and-stick models of molecules that were hard to manipulate.

NCRR-supported computer resources—particularly at the University of North Carolina (UNC) at Chapel Hill and the University of California, San Francisco (UCSF)—soon developed additional molecular modeling programs. At UNC, Dr. Frederick Brooks, Jr. and his students created GRIP-75 (Graphics for Interacting Proteins), which helped to solve the 3-D structures of numerous proteins and other molecules, including transfer RNA, which plays an essential role in protein biosynthesis.

The UCSF resource, established by Dr. Robert Langridge in 1970, developed a suite of molecular modeling software programs that are now widely used to identify potential drugs. These programs sort through a database of about 250,000 chemicals to identify those with 3-D structures that seem to fit snugly into the active site of a target molecule, such as a disease-related enzyme. Researchers then use a molecular graphics program to view detailed images of how the selected chemicals might bind with the target molecule. If the computer-based results look promising, the researchers obtain the actual chemicals and conduct laboratory studies to see if the chemicals act in real life as they do on the computer screen.

Using these software programs, the UCSF computer graphics resource helped to identify a potential therapy for Chagas' disease, which affects an estimated 16 to 18 million people in Latin America, according to the World Health Organization. The promising drug, now in clinical trials, blocks a key enzyme in the disease-causing parasite. The system also has enabled researchers to identify another compound that shows promise in animal studies as a possible treatment for Alzheimer's disease.

At the UNC resource, a system called the nanoManipulator allows users to not only see molecules and larger structures, such as chromosomes and viruses, but also "touch" and manipulate them. The nanoManipulator is linked to a scanning probe microscope, which examines a specimen by moving an ultrafine probe over it, much like a stylus moves over a phonograph record. Scientists control probe movements with a joystick device called a force-feedback stylus. The forces generated where the probe meets the specimen are magnified nearly a millionfold and used to produce both 3-D images of the specimen that can be seen through virtual reality goggles and sensations that can be felt through the stylus.

With the stylus, the user can push against these objects and feel resistance. With a bit more pressure, the user can move these objects around and even bend or rupture them. In this way, the nanoManipulator affords scientists real-life experiences with the physical characteristics of molecules and viruses that previously had to be estimated through mathematical calculations. To develop systems such as the nanoManipulator requires high-performance computers, which operate faster than usual laboratory computers. NCRR currently supports four high-performance computing centers around the country that are engaged in projects such as creating computer models of the nervous system and classifying gene and protein superfamilies.

To make the most of rare and expensive instrumentation, NCRR also funds "collaboratory" projects that enable scientists in one part of the country to link up to a resource in another part via the high-speed communications network Internet2. Researchers across the country can now view specimens under a high-voltage electron microscope at the University of California at San Diego or use the nanoManipulator at the University of North Carolina without having to leave their home laboratories.

Although computers today are indispensable to biomedical science, the small laboratory computer may never have been developed without government support, including crucial start-up funds from NCRR. Because scientific laboratories constitute a limited market, and designing a new type of computer is an expensive undertaking, industry in the 1960s may never have considered a minicomputer such as LINC profitable enough to be worth developing. But once Clark and Molnar got their computer off the ground with Federal seed money, industry recognized the potential for profit and developed the computer further, eventually transforming it into a widely used tool in biomedical laboratories.

*—Steven Stocker*

## Life-Saving Advances in Organ Transplantation

For centuries, health practitioners have recognized the potential of replacing injured or diseased organs and tissues with healthy ones, but only in recent decades has transplantation saved the lives of thousands of people who otherwise had no hope of survival. According to the United Network for Organ Sharing, an estimated 20,000 critically ill Americans receive organ transplants each year, and most can expect to survive for at least three years after the operation. Advances in transplantation illustrate how interdisciplinary efforts—among molecular biologists, geneticists, animal researchers, and clinical investigators—lay a solid foundation for improving human health.

When the first successful kidney transplantation was performed between identical twins half a century ago, scientists had little understanding of the molecular basis of graft acceptance or rejection. Trial-and-error studies in animals and humans had shown that transplants from one individual to another resulted in aggressive inflammation and organ rejection, whereas transplants within the same individual (such as skin grafts in a burn victim) often succeeded. The chief impediment, researchers eventually learned, was the immunologic barrier—the body's determination to reject and destroy any substance that it viewed as foreign, whether a disease-causing microbe or a life-saving kidney.

A key to understanding the immunologic barrier came not from clinical research but from a series of experiments in mice that could never

have been performed in humans. Beginning in the 1930s, researchers at the Jackson Laboratory in Bar Harbor, Maine, repeatedly mated sibling and other closely related mice until the offspring were genetically alike. By transferring cells and tissues from one mouse to another, scientists eventually discovered that transplant success depended on the similarity of cell-surface structures, or antigens, between donor and recipient. The Jackson Laboratory researchers then identified a single genetic region on a specific chromosome that encoded these mouse transplantation antigens. By the 1960s similar molecules—termed human leukocyte antigens (HLA)—had been identified on one of the human chromosomes. Today these molecules serve as the basis for human tissue-typing techniques that match compatible transplant recipients and donors, thus greatly enhancing the recipients' chances of survival.

While basic scientists pieced together the functions of the HLA complex, clinical investigators were achieving unparalleled success in transplanting organs between unrelated individuals through use of drugs that suppress the recipient's immune response. Early immunosuppressants, such as azathioprine and prednisone, enabled successful transplantation of the human heart, liver, lungs, pancreas, and kidneys. NCRR's General Clinical Research Centers (GCRCs) provided critical research infrastructure for many of these pioneering investigations. Of the first 200 kidney transplantations performed in this country, 75 percent were evaluated in the GCRCs. Likewise, Dr. Thomas Starzl depended on GCRC support when he performed the world's first successful liver transplantation at the University of Colorado in 1963. These procedures not only extended the lives of transplant recipients but also expanded the knowledge of surgeons throughout the world, giving them the impetus to continue these daring operations.

*Islet cell transplants may help free diabetic patients from the need for insulin injections.*

***Dr. Thomas Starzl, shown in 1977, pioneered successful procedures for transplanting human livers.*** *(Photo courtesy of the University of Colorado Medical Center)*

The introduction of the immunosuppressant cyclosporin in the early 1980s further revolutionized the field by dramatically improving graft survival: between 1980 and 1995, one-year survival rates for most types of organ transplants climbed from 60 percent or less to between 75 and 98 percent. The scientific team that performed the first successful combined heart-lung transplantation in the United States, with support from the GCRC at Stanford University, attributed their success to the use of cyclosporin as well as their previous experience performing heart-lung transplantations in nonhuman primates—another critical animal model that NCRR makes available to the biomedical research community.

Today the focus of transplantation research is not so much to prevent organ rejection—the primary concern a half-century ago—but rather to meet an urgent and increasing need for appropriate donor organs. About 80,000 U.S. citizens now await compatible organs, according to United Network for Organ Sharing, and each year more than 6,000 Americans die while waiting. Organ shortage is an especially acute problem for minority populations, who are often most in need of transplants. End-stage renal disease, a primary reason for kidney transplantation, occurs four times more often among African Americans than Caucasians, principally because

blacks have higher rates of hypertension and autoimmune disease.

To help narrow the gap between organ need and availability, some researchers are exploring the potential of generating artificial organs and tissues, transplanting partially encapsulated organs or cell suspensions, or developing "bridge" technologies to keep patients alive while awaiting compatible transplants.

Another option under consideration is xenotransplantation, or transplantation from animals to humans, although organ rejection is one of the main obstacles to this approach. Many researchers consider pig organs to be a reasonable alternative to human organs for transplantation, since they're similar in size. But pig cells display a sugar molecule on their surface that is quickly recognized and attacked by the human immune system, leading to transplant failure.

In January 2002, NCRR-supported scientists at the University of Missouri-Columbia and at a small bioengineering firm in Massachusetts took a significant step forward when they announced that they had cloned the world's first knockout pigs that lack one copy of a gene needed to produce this notorious sugar. Dr. Randall Prather and his colleagues took fetal pig cells; knocked out, or disabled, the gene; performed nuclear transfer to create the modified embryos; and implanted the embryos into surrogate sows. The resulting four piglets that survived all lacked one copy of this gene, yet they still had a second working copy, since most genes come in pairs. The researchers now hope to breed these pigs to produce offspring that lack the gene entirely.

Beyond organ transplantation, NCRR has also enabled advances in transplantation of tissues and cells, including life-saving bone marrow transplants. More recently, NCRR collaborated with the Juvenile Diabetes Research Foundation International to establish a nationwide network of Human Pancreatic Islet Cell Resource Centers. These regional centers will isolate, characterize, and distribute insulin-producing islet cells for transplantation into patients with Type 1 diabetes. Recent studies suggest that these transplants may help free diabetic patients from the need for insulin injections.

***The world's first knockout pigs, shown here three weeks after birth, lack one copy of a gene that causes the human immune system to swiftly reject pig transplants.*** *(Photo by Jim Curley, University of Missouri Office of Extension and Agricultural Information)*

Thanks to the sharing of ideas between disparate disciplines, and the hundreds of courageous transplant recipients who participated in clinical studies, transplantation has moved beyond its experimental phase to the point where it is often the treatment of choice for chronic failure of the kidneys, heart, liver, or lungs. The tools and techniques developed over the past decades have greatly enhanced understanding of the genetic and molecular basis of the normal immune response. These findings hold promise not only for those patients awaiting transplants but also for anyone who is at risk for diseases—such as AIDS, multiple sclerosis, and even the flu—that trigger an immune response.

*—Victoria L. Contie*

## MRI: "X-Ray Vision" without the X-Rays

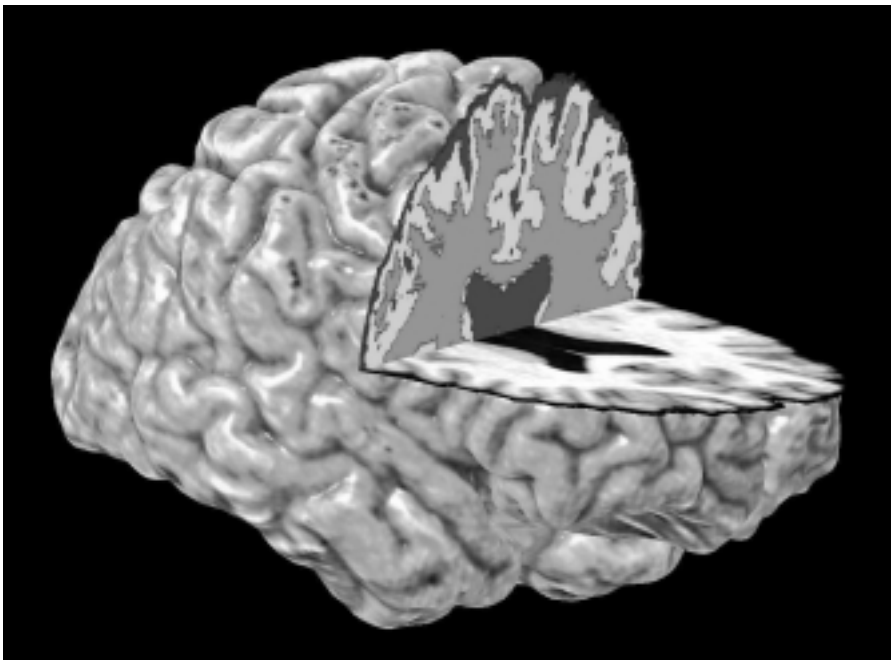
Ever since the discovery of X-rays in 1895, scientists have been developing techniques to see inside the body without using surgery. One of today's most ubiquitous imaging tools is magnetic resonance imaging (MRI), which provides clear pictures of the body's interior—including tissues, organs, and blood vessels—without the use of hazardous radiation. Through its support of advanced technologies and instruments, NCRR helped to usher MRI from its obscure beginnings nearly three decades ago into the widely used diagnostic tool now found in hospitals and research centers nationwide.

MRI is based on a phenomenon known as nuclear magnetic resonance (NMR), first observed more than 50 years ago. When placed in strong magnetic fields, the nuclei of certain atoms resonate—that is, absorb specific radiofrequencies beamed at them and then emit their own radiofrequency signals. Because

these signals are influenced by the chemical environment surrounding the resonating nuclei, scientists can identify a sample's constituent chemicals by their NMR frequencies. In the early 1970s NCRR established some of the first national NMR centers devoted to biomedical research.

A critical breakthrough came in the mid-1970s, when Dr. Paul Lauterbur showed that NMR frequencies could be used to produce two-dimensional (2-D) images of samples, ranging from vials of water to a pecan nut to a live clam, as long as the samples contained resonating nuclei, such as hydrogen. The basic principles behind these early MRI scans underlie even today's most sophisticated MRI instruments. Dr. Lauterbur's investigations of MRI and NMR tools and technologies, from the late 1970s through the 1990s, depended in part on the technology-based infrastructure that NCRR funding provided.

Since its debut, MRI has become the primary imaging technique for analyzing internal structures to diagnose disorders of the brain and spinal cord, major blood vessels, and other organs and systems. With 2-D or 3-D MRI, clinicians can detect structural abnormalities caused by tumors, trauma, or tissue degeneration, possibly even before symptoms appear. A recent MRI study conducted in part at the NCRR-supported Neuroimaging Analysis Center at Brigham and Women's Hospital found that individuals in the early stages of Alzheimer's disease show distinctive changes in three brain regions.



***With MRI, researchers can visualize both the surface of the brain and its underlying structures.*** *(Photo courtesy of Dr. Arthur W. Toga, Laboratory of Neuro Imaging)*

*With MRI, clinicians can detect structural abnormalities, possibly even before symptoms appear.*

Other researchers at the NCRR-supported Laboratory of Neuro Imaging (LONI) Resource at the University of California, Los Angeles, observed a wave of nerve cell loss that spread through the brains of schizophrenic patients in their late teens or early 20s, as the disease progressed. These same researchers, headed by LONI Director Dr. Arthur Toga, have identified periods of rapid growth of certain brain regions in normal children. Brain systems involved in learning languages grow swiftly between the age of 6 and puberty, a period in which children most easily grasp new languages.

Besides studying structure, MRI also can be used to study the physiology of the body through techniques such as functional MRI (fMRI), which was pioneered with NCRR support. Using fMRI, researchers can determine which parts of the brain are functioning during various activities.

The first published fMRI studies were conducted by separate teams of NCRR-supported investigators. With equipment purchased through NCRR Shared Instrumentation Grants, Dr. Bruce Rosen and his colleagues in 1991 used fMRI to see increased activity in a brain region associated with visual perception when people watched flashing visual patterns. The technique involved infusing a volunteer's bloodstream with a chemical contrast agent, which enabled imaging of increased blood flow to activated brain regions. Today, Dr. Rosen heads the NCRR-supported Center for Functional Neuroimaging Technologies at Massachusetts General Hospital.

Then in 1992, three scientific teams reported an additional break-

through—the ability to acquire fMRI images without the use of a contrast agent. Instead, the new method relied on the increased radiofrequency signal produced by oxygen-rich blood in the vicinity of active brain regions. Being completely noninvasive, this technique soon became the standard for fMRI. The three research teams, who published their findings within one month of each other, were headed by Dr. Kamil Ugurbil, director of the NCRR-supported NMR Imaging and Localized Spectroscopy resource at the University of Minnesota; Dr. James Hyde, then-director of an NCRR-supported Paramagnetic Resonance Resource at the Medical College of Wisconsin; and Dr. Rosen at Massachusetts General Hospital.

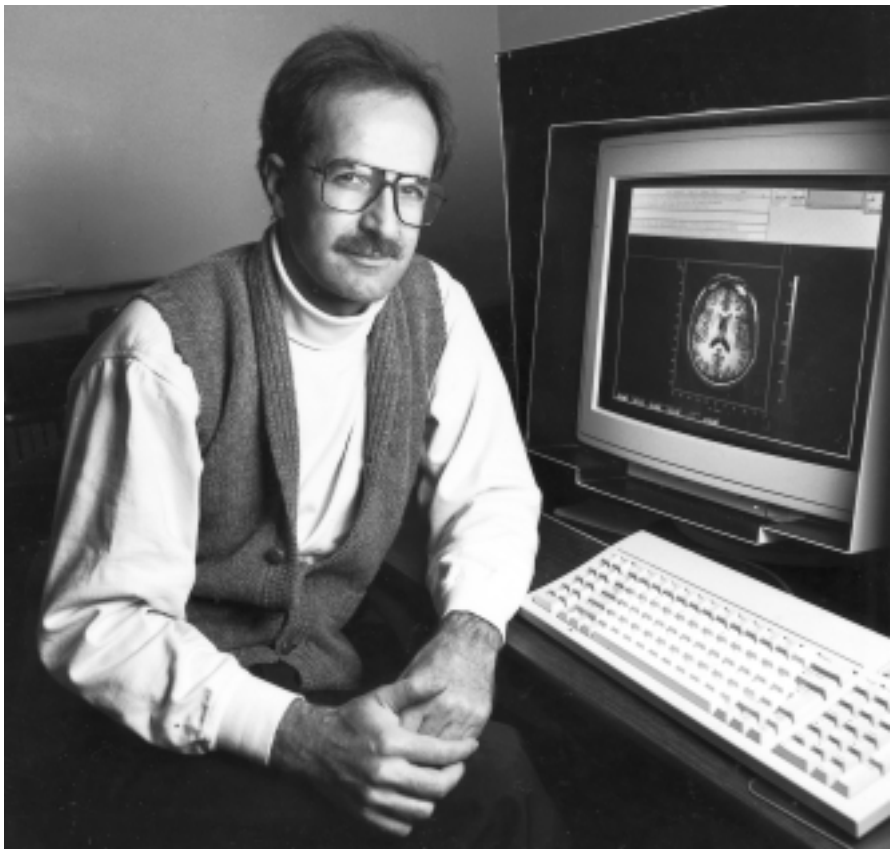
*Patterns of brain activity indicate whether an experience will be remembered well, remembered poorly, or totally forgotten.*

More recent fMRI studies, conducted with NCRR support, have identified brain regions involved in responding to a visual cue with appropriate movements and the regions involved in recognizing human faces or common objects. This technique also facilitates the study of mental processes such as memory formation. NCRR-supported scientists have identified patterns of brain activity associated with transforming short-term memories into long-term memories and other patterns that indicate whether an experience will be remembered well, remembered poorly, or totally forgotten.

The standard MRI scanner used in human studies contains a 1.5 tesla magnet. However, researchers are finding that higher magnetic power provides higher levels of resolution. In structural MRI, stronger magnets make the images more distinct, and in fMRI they allow researchers to observe brain responses to rapid events. Several NCRR-funded biomedical technology resource centers are conducting clinical MRI studies with magnets that range from 2.0 to 4.1 tesla.

Besides functional imaging, other physiology-based MRI techniques include MR angiography, which produces images of blood flow, and MR spectroscopy, which reveals the biochemistry of specific organs or tissues. Recently, Dr. Warren Manning and his colleagues at Beth Israel Deaconess Medical Center in Boston showed that MR angiography could detect impaired blood flow to the heart muscle, which could lead to a heart attack.

In operating rooms, surgeons are beginning to use another type of MRI technology known as interventional MRI, in which they watch 3-D images in real time to observe details of tissues during surgery. Dr. Ron Kikinis, director of the



***Dr. Kamil Ugurbil headed one of three research teams that developed a completely noninvasive method for acquiring fMRI images of brain activity.*** *(Photo courtesy of University of Minnesota)*

Neuroimaging Analysis Center, and his colleagues developed rapid computational methods that combine structural MRI, fMRI, and MR angiography into a single image. This technique has allowed neurosurgeons to determine the exact boundaries of brain tumors and their proximity to vital brain regions and major blood vessels.

Interventional MRI, with its integration of three different types of MR images, exemplifies the increasing sophistication of both MRI instruments and computers. These integrated technologies now allow scientists to conduct entirely new types of studies. For example, 3-D brain images of many patients with a disease (such as Alzheimer's disease or schizophrenia) can now be integrated into a composite image of a "typical" brain of someone with that disease. However, to produce these composite images requires thousands of patients and trillions of bytes of computer memory, both of which are beyond the capacities of the average laboratory. To address this problem, NCRR is funding the new Biomedical Informatics Research Network (BIRN), a high-performance computer network that allows laboratories around the country to share data. The network also connects various computers around the country into one large supercomputer, which can rapidly analyze the shared data. Through BIRN, researchers in different disciplines will be able to collaborate on projects and make discoveries that previously would have been impossible. BIRN is just one example of how NCRR serves as a "catalyst for discovery," by creating and providing critical research technologies and shared resources.

*—Steven Stocker*

# Too Much Pressure: Relieving the Burden of Hypertension

***Dr. Patricia Gabow (right) and her colleagues at the University of Colorado compared classes of antihypertensive drugs in treating patients who have both hypertension and autosomal dominant polycystic kidney disease.*** *(Photo by Stephen Stremsterfer, Public Relations and Marketing Office, Denver Health)*

Chances are that you know someone with hypertension, or you may have the condition yourself. According to the National Center for Health Statistics, 24 percent of people in the United States between the ages of 20 and 74 have hypertension, or high blood pressure. For men 75 years or older, the number rises to 64 percent, and for women, 77 percent. Because prolonged hypertension often leads to stroke, heart disease, kidney damage, or blindness, the prevalence of high blood pressure constitutes a major public health problem.

An NCRR-supported network of General Clinical Research Centers (GCRCs), established 40 years ago, has enabled critical discoveries into the causes of and cures for hypertension. In the early 1960s, clinical investigations at one of the original GCRCs, at Vanderbilt University in Tennessee, helped lay the groundwork for more recent findings about hypertension mechanisms. Dr. Grant Liddle, a physician at the center, identified a family with a rare form of hypertension, now known as Liddle's syndrome. Other researchers later found that in this disorder the kidneys reabsorb too much sodium and water from the blood, leading to an expansion of blood volume and therefore an increase in blood pressure. Dr. Liddle determined that the syndrome had a dominant form of inheritance, meaning that individuals who inherited at least one gene for Liddle's syndrome developed the disease. He speculated that the gene produced an abnormality in the kidneys. But for the next three decades, researchers were unable to locate enough Liddle's syndrome patients to explore that possibility.

A break came in 1989, when the original patient diagnosed with Liddle's syndrome in the 1960s was evaluated at another GCRC—this time at the University of Alabama at Birmingham, where she received a kidney transplant. Once the new kidney was in place and functioning, the clinical indicators of Liddle's syndrome—including the severe hypertension—disappeared, thus confirming Dr. Liddle's original theory that a kidney abnormality must underlie the syndrome.

*Research on rare disorders can shed light unexpectedly on more common disorders.*

In the mid-1990s, Dr. Richard Lifton and his colleagues at Yale University took this finding to a new level of specificity, when they uncovered the genetic and molecular underpinnings of Liddle's syndrome. Assisted by the resources of the Yale GCRC, Dr. Lifton and colleagues found that the syndrome arises from mutations that produce abnormal sodium channels in the cell membrane. These misshapen channels, in turn, promote the flow of sodium from the kidney filtrate back into the blood. Water from the filtrate follows the sodium, leading to increased blood volume and pressure. Scientists now suspect that similar, but less severe, mutations are responsible for more common forms of hypertension, thus demonstrating that research on rare disorders can shed light unexpectedly on more common disorders.

GCRCs also played an important role in the development of a class of antihypertensive drugs known as angiotensin-converting enzyme (ACE) inhibitors. These drugs block the production of angiotensin II, a hormone that raises blood pressure. ACE inhibitors are especially useful in the treatment of hypertension caused by kidney disease or blockage of the arteries leading to the kidneys. They also are a favored treatment for mild, uncomplicated hypertension because they produce fewer side effects than many other antihypertensive drugs.

Clinical trials of the first ACE inhibitor, captopril, were conducted at several GCRCs in the late 1970s. Early studies showed that captopril was effective in patients with severe hypertension and with hypertension associated with kidney disease, while later studies showed that ACE inhibitors could lower blood pressure in most cases of hypertension, regardless of the cause.

Besides reducing blood pressure, ACE inhibitors also can slow the advancement of kidney disease in hypertensive patients. In a recent study, Dr. Patricia Gabow and her colleagues at the University of Colorado GCRC compared two classes of antihypertensive drugs—diuretics and ACE inhibitors—in treating patients who have both hypertension and autosomal dominant polycystic kidney disease. The latter condition results from a genetic defect that gives rise to numerous cysts in the kidneys, and eventually leads to kidney failure. About half of those with polycystic kidney disease also develop hypertension. Although the two drugs proved comparable in controlling blood pressure, ACE inhibitors preserved renal function longer than did the diuretics.

Similarly, a nationwide study that compared three popular types of blood pressure drugs identified two—ACE inhibitors and beta-blockers—that had the added benefit of significantly slowing progression of kidney disease in African American patients with hypertension. The third drug

***Dr. Keith Norris (standing), director of the RCMI Clinical Research Infrastructure Initiative at Charles R. Drew University of Medicine and Science, is an investigator in the African American Study of Kidney Disease and Hypertension.*** *(Photo by Emma Taylor)*

type, a calcium channel blocker, is the most commonly used antihypertensive drug among African Americans. The findings are significant because African Americans tend to develop hypertension earlier in life and have more severe hypertension at all ages than Caucasians, and as a result, have a fivefold greater rate of kidney failure, according to the American Heart Association. Of the 21 sites participating in this ongoing trial, known as the African American Study of Kidney Disease and Hypertension, more than half depend on NCRR-supported clinical research infrastructure. These critical resources include at least eight GCRCs and three sites funded by the Clinical Research Infrastructure Initiative of NCRR's Research Centers in Minority Institutions Program.

Perhaps the most heartening news about hypertension is the recent finding that changing one's diet can be as effective as antihypertensive drugs in reducing blood pressure. Evidence for this comes from the Dietary Approaches to Stop Hypertension (DASH) studies, which rely on GCRC participation. An early study looked at the effects on blood pressure of three diets: a control diet similar to the average American diet (low in fruits and vegetables and high in fat); a diet high in fruits and vegetables but containing the same amount of fat as the control diet; and the DASH diet that was high in fruits and vegetables and low in fat. Results showed that, after eight weeks, the DASH diet reduced blood pressure more than the fruits-and-vegetables plus high-fat diet, which in turn reduced blood pressure more than the control diet. Blood pressure reductions were greater in participants with hypertension than in those without.

Last year further investigation showed that the DASH diet, coupled with low sodium intake, could reduce blood pressure even more than the DASH diet alone. In this study, participants ate either the DASH diet or a typical American diet for three months. In addition, both groups consumed three different levels of sodium for one month each in random order. The sodium levels were 3,500 milligrams a day (the average level consumed by Americans), 2,300 milligrams a day (the upper limit currently recommended by the National High Blood Pressure Education Program), and 1,200 milligrams a day. Results showed that the largest blood pressure reductions were achieved by those on the DASH diet with a daily sodium intake of 1,200 milligrams.

*Changing one's diet can be as effective as antihypertensive drugs in reducing blood pressure.*

All of these advances—from the molecular mechanisms of hypertension to effective therapies and prevention—depended on the critical research infrastructure that NCRR supports. Through the GCRCs and other NCRR programs, clinical investigators have access to the essential research tools that enable scientific advances.

—***Steven Stocker***

## Mass Spectrometers Weigh the Evidence for Health and Disease

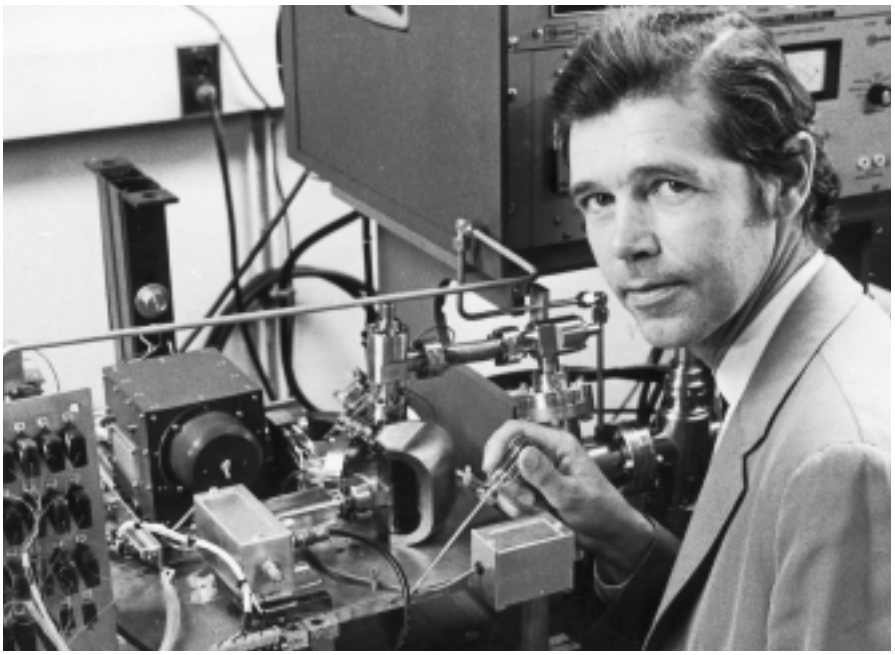
Preoccupation with weight is widespread in America. Everyone knows that the body's mass affects the way one feels, functions, and interacts with others, and physicians use weight as a quick indicator of an individual's health, activities, and endurance. What's less well-known is that mass is similarly informative at the molecular level. Scientists have long recognized that atoms and molecules have distinctive weights, but only recently have they discovered that molecular mass also offers insight into the functions, interactions, composition, and overall shape of complex biological molecules like proteins and DNA. These discoveries were made possible by technological advances to molecular weighing machines known as mass spectrometers.

Over the past four decades, NCRR-supported scientists have incrementally enhanced the sensitivity and flexibility of mass spectrometry to address some of the most pressing problems related to human health. Clinicians now use the technique to identify toxic compounds in blood or urine, screen newborns for inherited disorders, and detect illegal use of steroids by athletes. Today's high-throughput mass spectrometers can identify and characterize hundreds of complex proteins at near-instantaneous speeds. This makes mass spectrometry a star player in the emerging new discipline known as proteomics, which seeks to detect and evaluate the thousands of pro-

teins expressed by the genome and then understand how these molecules work in concert to maintain life.

The first mass spectrometer was created nearly a century ago by Nobel Prize-winning physicist J. J. Thomson, discoverer of the electron. Initially the province of physicists, early mass spectrometers were massive, arcane instruments capable of analyzing only small, stable, volatile compounds. Although these original machines bear little resemblance to today's sophisticated models, the underlying principles are remarkably similar and simple. Then as now, molecules must be vaporized into the vacuum of the mass spectrometer and then converted into charged ions. The ions, which may be broken into even smaller pieces called fragment ions, can be steered and focused by the magnetic, electrostatic, and radiofrequency fields used as lenses within the mass analyzer. The ionized molecule's mass and charge together determine its trajectory.

The mass spectrum itself is akin to the colorful spectrum produced when sunlight passes through a prism. But whereas a prism separates light into a continuum of distinctive colors of varying wavelengths, a mass spectrometer splits molecules into distinctive ions and focuses them along a continuum of varying masses. Because mass spectrometers also measure the relative abundance of each ion, scientists can determine the overall mass of a molecule, the mass of each ion piece, and the relative abundance of each piece, all of which provide clues to the composition and structure of compounds under study.



***Dr. Klaus Biemann (shown in 1975) headed the first national mass spectrometry resource funded by NCRR. His laboratory pioneered biomedical applications and computer databases associated with mass spectrometry.*** *(Photo by Calvin Campbell, Massachusetts Institute of Technology)*

Some of the first breakthroughs on the biological front occurred in the late 1960s at the Massachusetts Institute of Technology (MIT), where Dr. Klaus Biemann and his colleagues paired mass spectrometry (MS) with gas chromatography (GC), a technique that separates different types of molecules in a mixture. With NCRR support, the MIT lab pioneered the clinical application of GC/MS by providing Boston-area hospitals with analyses of blood and urine from unconscious patients and children with suspected metabolic disorders. More sensitive than other techniques, GC/MS could rapidly identify even small amounts of toxic substances or abnormal metabolites in body fluids, allowing physicians to select appropriate, sometimes life-saving, therapies. Dr. Cathy Costello—then a postdoctoral trainee at MIT, and now director of the NCRR-supported mass spectrometry resource at Boston University School of Medicine—headed the GC/MS clinical service for several years. Demand for these analyses expanded so rapidly in the 1970s that commercial laboratories eventually began to offer GC/MS services to hospitals nationwide.

*Clinicians use mass spectrometry to identify toxic compounds in blood or urine.*

Dr. Biemann's laboratory also devised innovative computer systems for acquiring, storing, and processing GC/MS spectra. The resulting searchable databases could quickly identify unknown compounds by comparing them to known spectra.

Today expanded versions of these digital libraries are a mainstay of clinical diagnostics and research.

Mass spectrometry took another leap ahead in the 1980s when improved techniques for ionizing molecules revolutionized the study of large fragile compounds such as proteins. Earlier ionization protocols were so harsh that proteins were often destroyed before they could be effectively ionized. Proteins amenable to ionization with the old techniques often splintered into fragments that were either too small and numerous for successful analysis or too large and unmanageable to focus into a detectable spectrum.

But the so-called "soft" ionization techniques known as matrix-assisted laser desorption ionization (MALDI) and electrospray ionization (ESI) were gentle enough to vaporize and ionize large proteins without destroying them. These ion sources can be coupled with exquisitely sensitive, high-resolution mass spectrometers to systematically study the detailed structures of enormous proteins. These new capabilities fundamentally altered the role of biomedical mass spectrometry, from a limited contributor to an indispensable core technique.

***Dr. Alma Burlingame has headed the NCRR-supported mass spectrometry resource at the University of California, San Francisco, since its founding in 1978.*** *(Photo by Paul Fusco, University of California, San Francisco)*

*The mass spectrum is akin to the colorful spectrum produced when sunlight passes through a prism.*

These and other advances have opened a new world of opportunities for biomedical scientists. Two NCRR-supported mass spectrometry resources—headed by Dr. Alma Burlingame at the University of California, San Francisco, and by Dr. Brian Chait at Rockefeller University in New York—helped to uncover the detailed three-dimensional structure of the prion protein, responsible for mad cow disease and devastating human brain disorders. Other research teams, assisted by the NCRR-supported Resource Center for Biomedical Complex Carbohydrates at the University of Georgia, used mass spectrometry to examine complex sugar-studded proteins on the surface of the human AIDS virus, suggesting that these molecules help to camouflage HIV and evade the body's immune system. And several teams of scientists have depended on NCRR-supported mass spectrometry resources to compare very small quantities of proteins in both tumor and normal cells, with the ultimate goal of identifying potential drug targets.

By coupling mass spectrometry with today's powerful computers, NCRR-supported investigators have also developed high-throughput techniques that are a cornerstone in today's proteomics investigations. These sophisticated systems can obtain mass spectra at record rates exceeding 100 acquisitions per second, and then make intelligent decisions about which ions in a spectrum should be selected for further analysis. Using these integrated technologies, scientists have systematically analyzed proteins expressed in various cells or tissues, and have identified multiple protein components of critical cellular structures such as the ribosome or nuclear pore complex. These detailed inves-

tigations offer exciting possibilities for development of highly targeted, highly effective new therapies.

From its humble beginnings 100 years ago, mass spectrometry has matured into a sophisticated, sensitive, and indispensable tool with surprising versatility. It raises the threshold for what can be discovered and accomplished in biomedical science, and it contributes to a broad and detailed picture of the complex underpinnings of life. The landmark discoveries achieved with J. J. Thomson's primitive instrument could not have been even imagined in his lifetime. Scientists today expect that mass spectrometry will continue to grow and expand in unforeseen ways, and offer significant opportunities for enhancing human health.

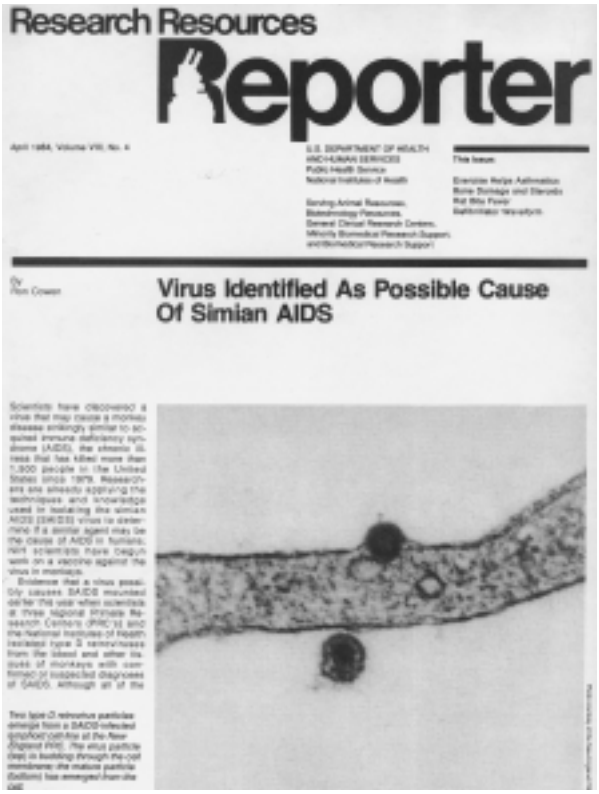
*—Victoria L. Contie*

## Monkey Viruses and Human AIDS

More than 20 years ago—as concerns about a mysterious and deadly new disease known as acquired immunodeficiency syndrome (AIDS) began to sweep the nation—scientists at the California Regional Primate Research Center (RPRC) were puzzling over an outbreak of infections that were decimating their monkey colonies. Inexplicably, dozens of animals became dangerously thin and weak, and many developed malignant tumors, severe herpesvirus or bacterial infections, anemia, or inflammation of brain tissues. Most affected animals were dead in a matter of months. Meanwhile, on the other side of the country, researchers at the New England RPRC near Boston noticed a similarly disturbing trend among their macaque monkeys. As investigators launched a search for the disease-causing agent, they little suspected the enormous impact their efforts would later have on understanding AIDS virus infections in humans and developing methods for its treatment, control, and prevention.

The more researchers learned about the monkey syndrome, the more obvious it became that the human and simian disorders were strikingly similar. Both diseases were marked by a weakened immune system that laid the body vulnerable to a variety of infections that normally did not cause disease. Scientists on both coasts began to suspect that studies of this monkey immunodeficiency disorder, or simian AIDS, could provide otherwise-unobtainable insights into the progression of human AIDS.

Back in 1980 no one knew what caused AIDS. Suspects ranged from a variety of viruses to a recreational drug known as poppers. Without knowing the causative agent, it was impossible to study or diagnose the earliest stages of human infection. A critical lead came in 1983, when two teams of scientists independently isolated a new human retrovirus—with a genome consisting of RNA rather than DNA—from the tissues of AIDS patients. Skeptics questioned whether this virus, now known as the human immunodeficiency virus (HIV), could produce the severe immunodeficiency characteristic of AIDS. Only two other retroviruses were known to infect humans, and both of these caused cancer. Crucial support for a retroviral basis of AIDS in primates came when RPRC investigators isolated and identified a new virus, which they dubbed simian retrovirus-1 (SRV-1), from the tissues of AIDS-affected animals in 1984. When the isolated virus was injected into healthy monkeys, the animals developed an AIDS-like disorder within a month. Studies of simian AIDS offered the first


Research Resources Reporter

Virus Identified As Possible Cause Of Simian AIDS

***In 1984 scientists at the Regional Primate Research Centers isolated the deadly virus that had swept through their animal colonies, causing an AIDS-like disease.***

opportunity to track the immune system's initial response to this highly contagious retrovirus.

Although SRV-1 triggers an AIDS-like disease, researchers were disappointed to learn that the simian virus was unexpectedly different—structurally and genetically—from HIV. Therefore, scientists at the New England RPRC decided to systematically search for HIV-like viruses (lentiviruses) in their primate colonies. They eventually isolated the virus now known as the simian immunodeficiency virus (SIV) from several species.

As the closest known relative of HIV, SIV not only looks similar to the human virus under the microscope, but also has similar genes, biological properties, and effects on the immune system. Like its human counterpart, the simian virus particularly infects and destroys white blood cells known as T-helper (or CD4) cells. Because these cells are required for the body to mount an effective immune response against disease-causing agents, their destruction explains the profound immunodeficiency seen in humans and monkeys with AIDS.

SIV infection of macaques is now widely considered the best animal model for human AIDS and is used by hundreds of AIDS researchers worldwide. In many cases, SIV infection progresses to AIDS rapidly—in a matter of months rather than the decade typically seen in HIV-infected humans—which makes the animal model suitable for timely investigation of the disease process. The model has proven especially useful for evaluating potential AIDS vaccines. Monkey studies allow scientists to challenge vaccinated animals with potent strains of virus to determine if the vaccine is protective.

Some SIV vaccines completely protect animals from even the most deadly variants of SIV. These vaccines are made of live but weakened (or attenuated) strains of SIV, in which one or more viral genes are deleted. Vaccinated animals have remained virus-free and healthy for years after complete viral challenge. Since even a weakened virus may cause disease when used as a vaccine, live attenuated AIDS vaccines may be deemed too risky for human use. Yet the monkey studies offered proof of principle that an AIDS vaccine can prevent infection. Researchers are now scrutinizing the immune responses of vaccinated monkeys to identify the factors that keep SIV infection at bay.

***Monkeys, like humans, are naturally susceptible to viruses that cause immunodeficiency.*** *(Photo by Vince Warren, Oregon Regional Primate Research Center)*

Many experiments suggest that antibodies alone are incapable of thwarting an SIV attack, and that protection against the AIDS virus will also depend on activation of white blood cells known as killer (or cytotoxic) T-cells. These cells take advantage of the fact that SIV- and HIV-infected CD4 cells display several viral proteins on their surfaces, and so can be easily identified and destroyed. In fact, RPRC-supported investigations have shown that a powerful army of killer T-cells can nearly eliminate all traces of SIV from the body in the first weeks of infection by homing in on a viral protein known as tat. Although tat is displayed on all SIV- and HIV-infected CD4 cells, a few viruses have mutant versions of tat, which allow them to escape the killer T-cell assault. Eventually, these mutant viruses are able to repopulate the animal's bloodstream and cause full-blown infection. Identification of specific tat mutations may assist the design of effective AIDS vaccines that stimulate a broader killer T-cell response.

*SIV infection of macaques is now widely considered the best animal model for human AIDS.*

Scientists have also identified portions of additional viral proteins that are displayed on infected cells and might be used to further enhance potential AIDS vaccines.

Studies of SIV in macaques have also shed light on the factors that affect transmission of the AIDS virus from one individual to another. In humans, HIV is most often transmitted when mucosal surfaces are exposed to infected fluids, usually during sex or birth. Monkey studies allowed scientists to identify the mucosal cells in females that are initially infected during heterosexual transmission of the virus. The SIV model also confirmed that the virus could be transmitted to newborns that swallow amniotic fluids or breast milk from infected mothers. These discoveries open new opportunities for blocking HIV transmission with drugs, vaccines, or other precautions.

Knowledge gained from SIV research demonstrates the importance of studying diseases that arise spontaneously in animals. Because scientists were alert to changes in the health of their nonhuman primate colonies, and because they had access to unique scientific resources and expertise at the RPRCs, they were able to develop an animal model that continues to provide critical insights into the understanding and treatment of human AIDS.

*—Victoria L. Contie*

*Monkey studies offered proof of principle that an AIDS vaccine can prevent infection.*

## Synchrotrons Illuminate Atomic Architecture of Life

The principle "form follows function" is espoused by designers and architects who believe that the shapes of objects should suit their intended use. This principle also holds true in biology. In fact, form is so critical to the function of biological molecules that even the slightest alteration in a protein's three-dimensional (3-D) structure can produce life-threatening disorders such as sickle cell anemia or Lou Gehrig's disease. By studying the minute details of molecular shape and its impact on the human body, structural biologists have gained a deeper understanding of the molecular bases of disease and have used this knowledge to devise improved therapies for disorders ranging from AIDS to the flu. Many of these discoveries depended on the use of a very bright and versatile type of light known as synchrotron radiation. NCRR support over the past two decades has been critical to enhancing the usefulness of synchrotron technologies to the biomedical community.

Synchrotron radiation is generated in large ring-shaped buildings, up to a mile in circumference, that house a vacuum pipe around their entire length. When electrons or other subatomic particles accelerate through the pipe, they radiate a wide spectrum of light, including intense and brilliant X-rays. Because synchrotron facilities were originally built for the study of subatomic particles, physicists generally regarded the radiation as an unwanted energy leak. By the early 1970s, however, a handful of researchers recognized that the intense light emitted by synchrotrons could be harnessed to probe the structures of matter—including biological molecules—through X-ray diffraction. By shining X-rays through crystallized molecules from many different angles and then capturing the patterns produced by diffracted X-rays, scientists can calculate how the X-rays had been deflected, and from this mathematically deduce the 3-D structures of the molecules. Until recently, such studies took years—sometimes decades—to complete.

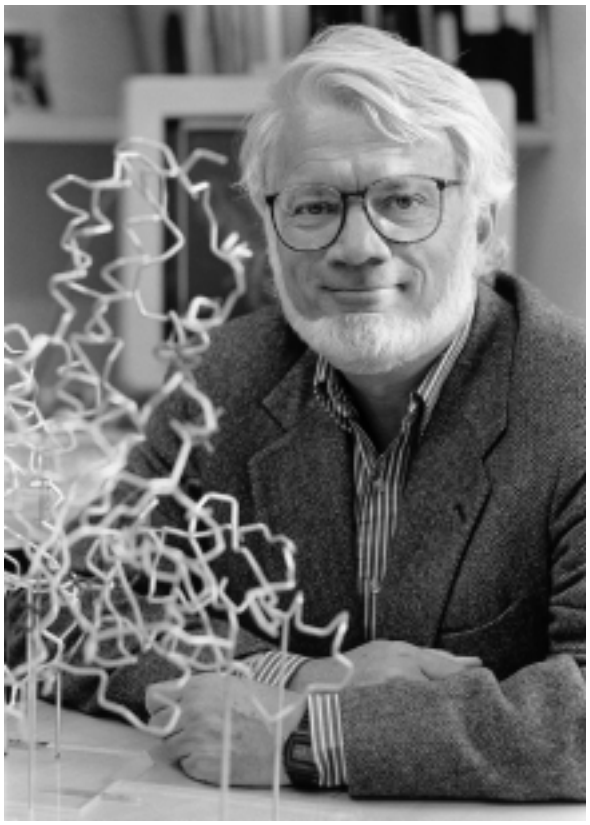
Biologists quickly discovered that synchrotron radiation offered many advantages over X-rays produced by conventional laboratory devices. Because synchrotron radiation is at least 1,000 times brighter, vast quantities of diffraction data could be collected more rapidly from smaller crystals. And because synchrotron radiation is also tunable, researchers could select specific wavelengths for their studies. Specialized laboratories were built along the circumference of synchrotron facilities to siphon off the X-rays and focus them into narrow beamlines, thereby tapping this otherwise-wasted resource.

Despite the advantages offered by synchrotron radiation, X-ray crystallography remained a tedious and frustrating procedure, in part because available instruments, computers, and techniques lacked the desired sensitivity and speed.

NCRR provided a critical boost to the emerging field in 1980, when it funded one of the nation's first synchrotron laboratories dedicated solely to biomedical research. Located at Stanford University, the Synchrotron Radiation Biotechnology Resource pioneered new X-ray methods for determining the 3-D structures of proteins and other biologically important compounds.

Today NCRR supports 25 X-ray beamlines at four of the five major synchrotron facilities in the United States. Technological advances made at these resources—combined with enormous improvements to computers and genome-related technologies—have transformed X-ray crystallography from a laborious technique to a powerful research tool for molecular biology. In 1970, fewer than a dozen protein structures had been solved at atomic resolution; today that number surpasses 2,000, with solvable structures becoming increasingly large and complex.

With a detailed understanding of molecular shape, scientists can develop highly targeted drugs that snugly latch onto and deactivate disease-related molecules. Potential and proven therapies against several notoriously stubborn viruses—including those that cause the flu, AIDS, and even the common cold—have been identified with assistance from NCRR-supported synchrotron resources. For instance, Dr. Michael Rossmann's groundbreaking 1985 study—the first to describe a human virus in atomic detail—depended on access to synchrotron radiation at the MacCHESS resource at Cornell University. The study revealed details of a previously undetected crevice on the surface of human rhinovirus 14, a primary cause of the common cold. Additional research confirmed that the crevice—which is similarly shaped in most strains of rhinovirus—snaps onto the surface of human cells as a first step in the infection process. In ongoing synchrotron-based studies, Dr. Rossmann and his colleagues identified several candidate drugs that settle into the viral crevice and thereby block attachment to cells. One of these compounds, known as pleconaril, has shown success in phase 3 clinical testing conducted at 200 sites and is now undergoing FDA review.



***Using synchrotron X-rays, Dr. Thomas Steitz and his colleagues determined the 3-D structure of part of a bacterial ribosome, shown here as a model. In both bacteria and higher organisms, ribosomes play the role of the cellular "factories" in which proteins are synthesized.*** *(Photo by Michael Marsland, Yale University)*

While pleconaril blocks viral entry to cells, other structure-based antivirals were designed to thwart viral activities after a cell has been invaded. Once inside the cell, many viruses depend on enzymes known as proteases, which trim large viral proteins into smaller functional proteins essential to their survival. More than a decade ago, the MacCHESS and Stanford synchrotron resources enabled some of the earliest atomic-scale analyses of the HIV protease, alone and in combination with candidate drugs that appeared to block its active site. This work contributed to the development of a new generation of HIV protease inhibitors, several of which are now in clinical use.

High-resolution structural studies have also identified compounds that block viral escape from the cell, thereby halting its spread. Scientists have long known that the human influenza virus depends on the enzyme neuraminidase to free itself from the surface of infected cells, but it wasn't until the mid-1980s that the enzyme's 3-D structure was determined by an Australian research team, who relied on access to U.S. synchrotron beamlines. Since then, NCRR-supported synchrotron resources have enhanced analyses of compounds that plug the active site of neuraminidase and limit the spread of infection. Two of these neuraminidase inhibitors—known as zanamivir (Relenza) and oseltamivir (TamiFlu)—received FDA approval in 1999 for treatment of influenza A and B infections.

With advances in synchrotron technologies, scientists can now scrutinize the structures of large

molecular complexes, such as ribosomes, which are critical to the normal functioning of cells. The ribosome is an enormous cellular component, typically containing three RNA molecules and more than 50 proteins. As the protein-making machines of the cell, ribosomes have long been scrutinized via microscopy and other techniques that have offered only coarse representations of their contours. Once again, it took synchrotron-based analyses to acquire unprecedented details of the ribosome's 3-D configuration. In 1999 three research teams depended on NCRR-supported resources for their X-ray diffraction studies of ribosome crystals from bacteria. Their investigations not only pinpointed regions critical to protein manufacture but also identified how antibiotics may bind to and disrupt the activities of bacterial ribosomes.

*Therapies against notoriously stubborn viruses have been identified with assistance from synchrotron resources.*

Today new crystallization approaches and robotics are speeding the pace at which crystals can be generated, and improved cryopreservation methods help preserve samples that are exposed to hot and brilliant synchrotron beams. Beam focusing has been enhanced to allow data collection from smaller crystals, and methods for processing and analyzing data have become more efficient. NCRR has supported developments in all these areas. Because the demand for structural analyses is expected to skyrocket in the coming years, NCRR will continue to explore new strategies for enhancing access to and the usefulness of synchrotron radiation for biomedical studies.

*—Victoria L. Contie*

***The National Synchrotron Light Source at Brookhaven National Laboratory on Long Island, New York, produces brilliant X-rays, or synchrotron radiation, that can be used to determine the 3-D structure of complex proteins.*** *(Photo courtesy of Brookhaven National Laboratory)*

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