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# NCRR Reporter

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CRITICAL RESOURCES FOR YOUR RESEARCH


## Obesity Sheds Its Mysteries

Exploring the causes and consequences of excess weight

## FROM THE DIRECTOR

# Clinical Research and Public Trust

THE NCRR-FUNDED General Clinical Research Centers (GCRCs) have a long history of supporting critical research related to a wide range of diseases and conditions, from AIDS and cancer to heart disease and hypertension. This issue of the *NCRR Reporter* examines three GCRCs that are using specialized staff, laboratories, and equipment to focus on obesity, one of this nation's greatest health concerns. The need to understand the causes and prevent the harmful effects of obesity is central to prevention and therapy; in FY 2004, more than 280 obesity-related research projects were conducted on the GCRCs.

For obesity research and many other clinical studies to remain viable, it is essential to build trust and communicate research findings and outcomes to the participants in clinical trials, remembering that patients and other volunteers are our partners in research. It is vital that we engage, enhance, and maintain the public's trust throughout clinical trials and beyond. Major efforts are under way at the National Institutes of Health (NIH) to effectively reach this goal. Last month, for instance, the Director's Council of Public Representatives released the "Report and Recommendations on Public Trust in Clinical Research for the NIH Director," which sets out recommendations for building trust in the NIH and scientific research. Complementary efforts include the NIH Public Trust Initiative and the NIH Roadmap for Medical Research.

Within the GCRCs, NCRR launched a successful effort to build public trust several years ago with the creation of a new staff position, the Research Subject Advocate (RSA). Established in early 2001, RSAs assist GCRC investigators in the safe and ethical conduct of clinical studies. For instance, the RSAs help to develop the data and safety monitoring plans required for all NIH-funded clinical studies. These plans stipulate the individuals responsible for adverse event tracking, the procedures for safety monitoring performance, and agency reporting requirements. At the same time, RSAs interact with potential participants and enrolled clinical research volunteers to enhance their understanding of clinical research and the vital role played by volunteer research subjects.

By facilitating the conduct of safe, ethical, and respectful clinical research, NCRR hopes to enhance the public's participation and trust in the clinical research enterprise. Robust participation, in turn, will strengthen clinical research efforts nationwide and move us toward our ultimate goal of improving the nation's health.

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### CRITICAL RESOURCES



### SCIENCE ADVANCES



NCRR Reporter

This quarterly publication of the National Center for Research Resources fosters communication, collaboration, and resource sharing in areas of current interest to scientists and the public.

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**On the Cover:** With a growing portion of the U.S. population tipping the scales with excess body weight, researchers are using NCRR-supported clinical resources to take a close look at the complex roles of hormones and metabolism in obesity, and at the health risks that obese children face. The findings offer no quick fixes, but they do unmask some popular myths.
PHOTO BY LAWRENCE MANNING/CORBIS

# QUICK TAKES

New tools and updates from NCRR Resources

## Software Probes the Proteome

An online computer program to identify proteins and their genes is being upgraded from a limited experimental tool to a powerful, easily accessible, and free Web-based resource. Financed by an NCRR grant of more than $1 million over three years, the upgrade will enhance the Genome Fingerprint Scanning (GFS) program, developed and managed by Morgan Giddings and colleagues at the University of North Carolina at Chapel Hill School of Medicine. The GFS program uses mass spectrometry data on protein fragments, called peptides, to identify proteins and their genes. The software will greatly enhance the burgeoning field of proteomics, which seeks to determine how proteins function and interact.

Using only raw, unannotated DNA sequences, the GFS program pinpoints genes and their protein products by determining which sequences would likely produce particular peptide masses. The software therefore does not rely on gene or protein databases. Already the GFS program has identified novel proteins and genes in viruses and single-celled organisms. Upgrades planned for the GFS software include browsable peptide maps overlain on genome data, expanded lists of searchable genomes, and the ability to search multiple genomes simultaneously. Researchers can access the GFS software and learn about the latest upgrades at http://gfs.unc.edu.

**The GFS software has found new proteins and genes in the single-celled organism *Tetrahymena thermophila*.**

## Resource Tackles Atrial Fibrillation

A competition offered via the Web has generated software that one day may aid patients with fibrillating hearts. The 2004 PhysioNet/Computers in Cardiology Challenge asked researchers to develop computer algorithms that use electrocardiogram (ECG) data to predict when transient episodes of atrial fibrillation, called paroxysmal atrial fibrillation (PAF), would end. Winners of the competition produced computer programs that correctly predicted PAF termination in 90 percent or more of cases. Knowledge of the ECG patterns that signal the end of a PAF episode could help clinicians treat or even prevent more dangerous cases of sustained atrial fibrillation.

PhysioNet (www.physionet.org), a Web-based component of the NCRR-supported Research Resource for Complex Physiologic Signals, offers online access to extensive physiological signal data, such as ECG recordings, gathered daily in health-care settings. In addition to open-access software like that generated by the competition, the resource provides online signal-data archives, publications, tutorials, and discussion forums.

## Pediatric Web Site Helps Parents

**Pediatric clinical trials may be less perplexing to parents, thanks to a new online guide.**

Parents who are considering enrolling a child in a clinical trial will benefit from the new Parents' Guide to Medical Research (www.researchchildren.org). Created by Children's Hospital Boston, the online guide describes the medical research process, addresses common misunderstandings about clinical research, explains parents' rights and responsibilities, and offers advice on evaluating a study. Information is provided both in text form and through a series of video clips. The site also contains a section that helps parents to create customized questions to ask the study investigators.

The online guide was funded through the NIH Human Subjects Research Enhancements Program. This program, managed by NCRR, is designed to increase protections for individuals participating in clinical studies, and supports programs to educate patients and their families about clinical trials.

IMAGE COURTESY OF JACEK GAERTIG, UNIVERSITY OF GEORGIA (ABOVE), PHOTO BY JAVIER AMADOR-PENA, CHILDREN'S HOSPITAL BOSTON (ABOVE RIGHT)

Peromyscine mice are helping scientists to study rodent-borne diseases like Lyme disease and Hantavirus pulmonary syndrome.

# The Mouse With Boots

*Laboratory mouse's wild cousin sheds new light on disease and adaptation.*

**BY WILLIAM OLDENDORF**

RANGING FROM ALASKA to Central America, the deer mouse is one of the most common North American mammals. But in biomedical research, the deer mouse (*Peromyscus maniculatus*) has traditionally taken a back seat to its domesticated distant cousin, the laboratory mouse (*Mus domesticus* or *M. musculus*), which shared common ancestors 25 million years ago. In recent decades, however, the deer mouse and related *Peromyscus* species have played a steadily expanding role in scientific laboratories, in part because peromycines, as the major rodent species in North America, serve as reservoirs for significant human pathogens, like those that cause Lyme disease, Hantavirus pulmonary syndrome, and even bubonic plague.

"Whenever there's a newly emerging infectious disease, *Peromyscus* is immediately suspect," says Michael J. Dewey, associate professor of biological sciences and head of the *Peromyscus* Genetic Stock Center at the University of South Carolina, Columbia. The rising popularity of peromyscines also is partly attributable to their genetic diversity and physiological robustness. Unlike laboratory mice, which have been inbred for genetic homogeneity, the genetically diverse peromyscines are better models for studies in toxicology, infectious diseases, and the physiology of habitat adaptation and behavior.

The *Peromyscus* Genetic Stock Center—founded in 1985 and now cofunded by NCRR and the National Science Foundation—plays a central role in supporting research on *Peromyscus*—or the "mouse with boots," referring to the animal's white feet. The center supplies 9 wild-type species and 26 mutant and genetically distinct substrains of *Peromyscus*. Because pathogens carried by wild mice pose a potential risk to both personnel and laboratory animals, researchers are reluctant to trap wild animals for their own use; therefore, animals supplied by the stock center are guaranteed to be free of specific pathogens. Over the past five years, the center has shipped an average of about 1,000 animals per year to 110 labs.

"If someone is considering using *Peromyscus*, we tell them everything they need to know," says Dewey. The center also publishes a quarterly newsletter; maintains a reprint archive, the PeroBase online database; and provides onsite research facilities for visiting scientists.

The deer mouse *P. maniculatus* attracted national attention in the early 1990s when it was implicated in the outbreak of Hantavirus pulmonary syndrome in the Four Corners region of the Southwestern United States. Another species, *P. leucopus* ("white-footed mouse"), is a major reservoir for Lyme disease in the Northeast. "These two species are far and away the most abundant in nature and are used for many different studies," says Dewey.

Peromyscines are essential to another area of public health

PHOTO BY CLINT COOK

research—understanding how mammals metabolize xenobiotics, or substances foreign to the body. Compared to peromyscines, traditional laboratory mice are generally less healthy and are physiologically challenged because they are heavily inbred. In contrast, Dewey says, "peromyscines can show how normal, ordinarily adapted organisms respond to xenobiotics." Substances studied to date include ethanol, insecticides, polychoryl biphenyls (PCBs), ammonium perchlorate (an industrial byproduct), and trinitrotoluene (TNT).

Because the animals live in a wide range of North American habitats—from wetlands and beaches to deserts, mountains, and forests—peromyscines offer an ideal model for examining the biology of adaptation. "By studying how the physiology of these animals differ, we get some idea of what allows them to adapt," says Dewey. For instance, the stock center supplies strains of *P. maniculatus* adapted to sea level and 10,000-foot elevations, as well as strains of *P. polionotus*, a native of the Southeast, with coat colorations adapted to different habitats such as the forest or beach. Research using these strains has clarified the role of hemoglobin in high-altitude adaptation and also suggested that coat coloration and patterning is controlled by five or six genes.

One of the most intriguing peromyscine studies focuses on social behavior. Like other rodents, most peromyscines are polygamous. However, the West Coast species *P. californicus* is monogamous. This behavior appears tied to levels of the hormones oxytosin and vasopressin in the mouse's blood. "There's a very strong correlation between behavior and the hormonal profile of an animal," Dewey observes. Although other mammals exhibit distinctive adaptive traits and behaviors, peromyscines are easier to study because they readily adapt to laboratory colony conditions.

A major focus of the center is developing new tools for genetic research. "Because we are now in the genomic era, the degree to which *Peromyscus* can be studied genetically will determine its usefulness to the scientific community," says Dewey. In studies of adaptive physiology and behavior, Dewey notes, "we have defined some of the hormones, but the genes underlying these hormones are not yet well understood."

*Peromyscus* researchers are fortunate that the genome of the

## HOW THE RESOURCE HELPED MY RESEARCH

**Durland Fish**, professor of epidemiology at the Yale University School of Medicine, has been using *Peromyscus leucopus* supplied by the *Peromyscus* Genetic Stock Center for the past 10 years. "We do transmission studies for tick-borne pathogens that use *Peromyscus* as a natural reservoir," says Fish. "We transmit these pathogens continuously between natural hosts and natural vectors in the lab." Diseases studied include Lyme disease; human anaplasmosis (often a co-infection with Lyme disease); and babesiosis, a malaria-like ailment found in some parts of the Northeast.

DURLAND FISH

In a recently concluded study, Fish's group examined whether vaccinating *P. leucopus* in the wild against Lyme disease reduces infection rates in the deer tick, which carries the infectious agent to humans. The center provided essential support by allowing the researchers to evaluate vaccine effectiveness in the laboratory prior to use in the field. "To do studies that parallel what we see in the field, we have to work with the natural reservoir species," comments Fish. If his experimental approach proves successful, an oral Lyme disease vaccine could be incorporated into mouse feed and distributed throughout the natural habitat of *P. leucopus*, thereby inoculating them against Lyme disease in the same way that oral vaccines are now used successfully to inoculate raccoons against rabies.

PHOTO COURTESY YALE SCHOOL OF MEDICINE

Because they live in a wide range of habitats—from wetlands and beaches to deserts and mountains—peromyscines offer an ideal model for examining the biology of adaptation.

**Stock center director Michael Dewey and colony manager Janet Crossland examine a specimen of *Peromyscus aztecus*.**

traditional laboratory mouse has been fully sequenced and mapped. "We can use this background work in mice as a Rosetta stone for defining the principal genetic features of *Peromyscus*," says Dewey. "By determining the location of a relatively small number of *Peromyscus* molecular markers and comparing them to the genome of the laboratory mouse, we can infer the location of thousands of *Peromyscus* genes." The resulting map will not only aid research in habitat adaptation and behavior but also shed light on host-parasite interactions and speciation.

The center also houses reprints of more than 3,000 *Peromyscus*-related publications, some dating back 100 years. Dewey believes these sometimes-obscure publications are valuable because they contain observations and avenues of investigations that could not be adequately pursued in the past but can now be addressed with modern techniques. For instance, researchers in the 1960s found that cross-breeding two species—*P. maniculatus* and *P. polionotus*—leads to offspring that are either over- or undersized, depending on which species is the male and which is the female. The size differences result from disruption of a process known as genomic imprinting, says Paul Vrana, assistant professor of biological chemistry at the University of California, Irvine. In this process, sets of genes that regulate growth are normally switched on or off according to whether they were inherited from the mother or father. In humans, disrupted genomic imprinting is associated with several genetic disorders as well as some cancers. "Several imprinted genes are perturbed in cancers because they are powerful growth factors," says Vrana, who uses *Peromyscus* supplied by the center for his research on genomic imprinting.

Vrana also collaborates with the center on genome mapping. "Imprinted genes are found in clusters around the genome," says Vrana. "We're curious to analyze the *Peromyscus*-imprinted regions in order to understand what defines these domains, since we know key regulatory domains in imprinted regions are very different between species." Unlocking the secrets of imprinted genes, he says, could provide basic insights into other aspects of growth. "Growth seems to vary tremendously among different species of mammals, from shrews to blue whales. A lot of this is set within the womb, where many of these imprinted genes act," says Vrana. "Although scientific use of *Peromyscus* will not soon overtake the laboratory mouse, clearly the more species we study, the broader picture of biology we will get."

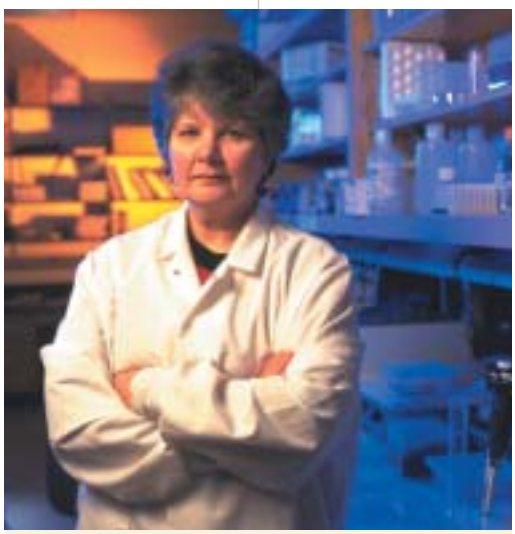
**TO GAIN ACCESS:** To obtain animals, information, or other assistance from the *Peromyscus* Genetic Stock Center at the University of South Carolina, qualified scientists should contact Janet Crossland, the colony manager, by calling 803-777-3107 or e-mailing at maicrosslan@stkctr.biol.sc.edu, or you may visit the center's Web site at http://stkctr.biol.sc.edu. For information about other comparative medicine resources, visit NCRR's online directory at www.ncrr.nih.gov/ncrrprog/cmpdir/cmdirectory.asp.

PHOTO BY CLINT COOK

# B-Virus Resource Provides Life-Saving Diagnoses

THE CALL CAME, as many do, in the middle of the night. This time it was the U.S. armed forces. During the Persian Gulf War, a group of macaques had escaped from a zoo in Kuwait, and one had bitten an American serviceman, possibly exposing him to a potentially fatal case of herpes B-virus infection. Could the laboratory help by conducting some diagnostic tests?

While the circumstances of that particular call were unusual, staff members at the National B-Virus Resource Center take such requests in stride. "I'm available 24/7, 365 days a year," says Julia Hilliard, principal investigator of the resource center, housed at the Viral Immunology Center at Georgia State University in Atlanta. The NCRR-supported resource center provides rapid diagnostics and related services that are not readily available anywhere else in America. Regarding the serviceman in Kuwait in the early 1990s, the tests provided good news, and the soldier returned to his duties.



**Julia Hilliard directs the nation's premier B-virus laboratory, providing testing and other services for medical researchers who may have been exposed to the herpes B-virus through their work with primates.**

The B-virus, *Herpesvirus simiae*, is common among macaque populations, causing only a mild infection and few symptoms in nonhuman primates. But the virus can be surprisingly deadly when passed on to a human. Because the B-virus spreads by exposure to contaminated saliva or other body fluids, typically through a bite or scratch, medical researchers who work with macaques are at risk of contracting the virus, as are veterinarians, pet owners, and zoo workers. Often, initial injuries are so mild that people believe they are not at risk. Lesions may appear at a wound site, followed by flu-like symptoms about three weeks after the initial injury.

"When a patient is symptomatic, it's critical to move quickly," Hilliard says. If untreated, a B-virus infection can produce paralysis in the lower limbs. The paralysis then can ascend through the body, eventually affecting the respiratory system, resulting in death. Five Americans have died of exposure to the B-virus in the last 14 years; the most recent was in 1997. Fortunately, physicians can treat early-stage infections with acyclovir, the antiviral drug also used to treat patients infected with the herpes simplex virus.

Scientists have long known that the B-virus is related to the herpesviruses typically found in humans. But recent DNA sequencing of the B-virus genome, completed last year by resource scientist Ludmila Perelygina, led to the unexpected discovery that the B-virus has only one gene that is not found in the human herpes simplex viruses. Researchers now hope to learn how that single gene might make a nonlethal human virus turn deadly.

Hilliard also is intrigued by the fact that some people have a degree of immunity to the B-virus. In parts of Asia where wild macaques are common, many people scratched or bitten by infected animals do not get sick from the exposure. After collecting blood samples from people in Indonesia, Hilliard and her colleagues were surprised to find that individuals who had been exposed to the B-virus did not have antibodies to the virus and did not develop symptoms.

While scientists at the National B-Virus Resource continue to study the virus, much of the day-to-day work involves diagnostic testing of blood and other samples. The center tests from 20,000 to 35,000 samples yearly. About half of those are from research centers that are trying to establish and preserve seropositive-free macaque populations. The rest come from various sources, mostly involving possible exposures by workers at research facilities, zoos, wildlife sanctuaries, or veterinary offices. The center also develops and implements diagnostic assays that may aid management of clinical disease, and an educational outreach program informs people about the dangers of the B-virus and what can be done to prevent infection. Overall, the National B-Virus Resource provides a unique suite of services beneficial to both the public health and the research community. **—PHILIP BULMAN**

**TO GAIN ACCESS:** The National B-Virus Resource Center (www.gsu.edu/bvirus) at Georgia State University provides rapid virological and serological analyses to identify B-virus infections in humans and nonhuman primates, especially macaques. Work is done in a specialized biocontainment laboratory (BCL-4). Cost reimbursement is requested for laboratory procedures to identify potential B-virus infections. For information about additional NCRR-supported comparative medicine resources, visit NCRR's online directory at www.ncrr.nih.gov/ncrrprog/cmpdir/cmdirectory.asp.

PHOTO BY BILLY HOWARD

# Providing Tools of the Trade

*Shared instrumentation grants get results.*

JUST A FEW YEARS AGO, Gerald Hart faced a turning point. Advances in genomics had spawned the new field of proteomics to investigate the countless proteins encoded by DNA. As the newly appointed director of the department of biological chemistry at Johns Hopkins University in Baltimore, Hart wanted his university to be a key contributor to proteomics research. But in the late 1990s, researchers at Johns Hopkins lacked ready access to the sophisticated types of mass spectrometers needed for proteomics work.

"I decided that, as department chair, it was important for me to make available to people at Johns Hopkins a state-of-the-art mass spectrometry facility for proteomics," Hart recalls.

Fortunately, Hart knew just where to go: NCRR's Shared Instrumentation Grant (SIG) Program. Since 1982, the SIG Program has provided NIH-funded researchers with state-of-the-art biomedical instruments costing between $100,000 and $500,000—a price range beyond the reach of most investigators. Because several investigators must share SIG-funded equipment, the program maximizes the benefits gained from federal money spent.

"The SIG Program is the only competitive program at NIH for providing instrumentation in that price range to a broad group of NIH grantees on a shared-use basis," explains Marjorie Tingle, who oversees the SIG Program for NCRR's Division for Biomedical Technology Research and Research Resources. Tingle estimates the SIG Program has granted more than 2,000 awards, with each funded instrument benefiting an average of six to eight major users. "The program has had a broad impact on a large number of NIH grantees," she says.

Hart applied for a SIG grant in 2000 and received nearly half a million dollars to purchase new mass spectrometry equipment. A mass spectrometer measures the masses of proteins or protein fragments to reveal which proteins are present in a biological sample, and in what proportions. Hart used the SIG award to substantially upgrade an existing matrix-assisted laser desorption ionization (MALDI) time-of-flight mass spectrometer and to purchase a quadrupole electrospray ionization time-of-flight mass spectrometer called a QSTAR, a more advanced instrument that greatly enhances proteomics research. More than 300 people from at least 100 labs at Johns Hopkins have so far been trained to use the new MALDI spectrometer, which is more sturdy than the QSTAR and therefore does not have to be run by a technician.

***Gerald Hart (above, at right) and colleague Robert Cole work with SIG-funded mass spectrometry equipment at Johns Hopkins University. John Hutton (opposite) used SIG grants to purchase a new DNA sequencer (shown) and flow cytometer for the University of Colorado.***

Vern Carruthers, associate professor of molecular microbiology and immunology at the Johns Hopkins University Bloomberg School of Public Health, is one NIH-funded proteomics researcher who has made good use of both of the new instruments. "These mass spectrometers give you really nice, clean, definitive data," he says. "They add credibility to your studies."

Carruthers used the new instruments to study certain proteins of the single-celled parasite *Toxoplasma gondii,* a human pathogen that causes toxoplasmosis. The mass spectrometers identified sites where enzymes called proteases cleave these proteins, thereby facilitating parasite invasion of host cells. The cleavage sites give clues to the types of proteases involved and how they operate. Carruthers and other researchers are now investigating how drugs could target these proteases and provide better treatments for toxoplasmosis.

Researchers at the University of Colorado Health Sciences

PHOTO COURTESY OF GERALD HART

Center in Denver also are benefiting from two new SIG-funded instruments, awarded to the university's Barbara Davis Center for Childhood Diabetes in 2000 and 2002. The Barbara Davis Center investigates type 1 diabetes, in which the immune system attacks and destroys pancreatic cells that produce insulin. The center also treats patients with the disease, which typically appears during childhood.

Because of the SIG awards, NIH-funded researchers at the

Barbara Davis Center and elsewhere at the university now have access to a new FACSCalibur flow cytometer. This instrument uses lasers to read fluorescent tags placed on different types of cells, allowing researchers to sort, quantify, and analyze cell populations. Investigators also have a new Prism 3100 Genetic Analyzer DNA sequencer to aid genetic analyses, including screening children for genetic susceptibility to type 1 diabetes. The cost for each instrument was in the range of $120,000 to $150,000.

"These are essential tools for the sort of research we do," says John Hutton, director of research at the Barbara Davis Center and principal investigator for the two SIG grants. "Being without them would be like taking off your right arm.

The number of researchers using the instruments has grown steadily since the grants were received, Hutton says, with 17 scientists now relying heavily on the cytometer and 61 investigators using the DNA sequencer. Technicians must run the sequencer, but researchers can operate the cytometer themselves once they have been trained.

Ronald Gill, a Barbara Davis Center researcher and director of the university's Transplant Immunology Program, says the new cytometer has enhanced his research. "Compared to older machines we had, the FACSCalibur is far easier to use, and it's far more powerful," he says. "We're also doing more types of analysis, things we simply couldn't do before."

Gill is studying organ transplants in animals to uncover possible techniques for preventing rejection of pancreatic tissue transplants in patients with type 1 diabetes. In a study of heart transplants in mice, Gill and his colleagues used the new cytometer to clarify how immune-system T cells interact with other cell populations to trigger transplant rejection. Gill is now using the cytometer to analyze what happens to T cells when the immune response is blocked by drugs to prevent rejection.

The new DNA sequencer also surpasses the machine it replaced, with sharper resolution and the ability to read longer stretches of DNA, says George Eisenbarth, executive director of the Barbara Davis Center. Eisenbarth uses the new sequencer to screen children for genotypes that increase their risk for developing type 1 diabetes. In a second screening, also aided by the DNA sequencer, children with susceptible genotypes are then assessed for the presence of autoantibodies directed against their pancreatic tissue, an early warning sign of type 1 diabetes. To detect the autoantibodies, scientists use a radioactive protein tag synthesized from DNA. The sequencer ensures that the DNA has the correct sequence to produce the tag.

"Every year we screen serum from tens of thousands of children from all over the world for risk of diabetes," says Eisenbarth, who notes that his laboratory is the core facility for autoantibody screening for several international and NIH diabetes programs.

Shared instrumentation grants also pay off in ways that go beyond the value of the instruments themselves. Hutton notes that the new SIG-funded instruments help the Barbara Davis Center stay competitive as one of twelve NIH-funded Diabetes and Endocrinology Research Centers. Hart says his SIG funding helped Johns Hopkins University land a Proteomics Center grant from NIH worth $18 million over seven years. "We basically went from almost zero proteomics to becoming a major player as a direct result of this instrumentation funding," he says. **—SCOTT J. BROWN**

**APPLY FOR FUNDING:** SIG grantees receive a single award to cover the cost of the new instrument. Grantees must pay all costs required to set up, maintain, and operate the instrument. Grants are available to all domestic public and nonprofit institutions, including universities, hospitals, health departments, and research organizations. To be eligible for funding, applicants must identify three or more NIH-funded investigators who will use the instrument, although the principal investigator of the grant does not have to be funded by NIH. Potential applicants are strongly encouraged to contact NCRR SIG Program staff. Additional information about SIG grants is available at http://www.ncrr.nih.gov/biotech/btshrinstr.asp.

To receive funds for more expensive instruments, costing from $750,000 to $2 million, researchers may apply to NCRR's High-End Instrumentation (HEI) Program. More information on HEI grants is available at http://www.ncrr.nih.gov/biotech/btheinstr.asp.

PHOTO COURTESY OF JOHN HUTTON

# Obesity Sheds Its Mysteries

*Clinical researchers explore the causes and consequences of excess weight.*

**BY TINA ADLER**

In just 25 years, the percentage of obese individuals in the United States has doubled, from about 15 percent to 30 percent of the adult population. In response to this unhealthy trend, drug companies are expanding research on obesity drugs, and public health officials are waging campaigns to get people to move more and eat less. Meanwhile, federally funded scientists are advancing our understanding of the possible causes and cures for obesity, from the molecular level on up. Some of the nation's most sophisticated clinical research is taking place at the NCRR-supported General Clinical Research Centers (GCRCs), which provide an ideal research environment for complex clinical studies. Particularly valuable for obesity studies is a staff of highly trained bionutritionists who use the state-of-the-art equipment at GCRCs to analyze metabolism and track consumption of all foods, down to the level of micronutrients.

Equally important, the GCRCs undertake studies that pharmaceutical companies avoid because the research is unlikely to be profitable, notes Julio Licinio, a pharmacologist and professor of psychiatry and medicine at the University of California, Los Angeles (UCLA).

## HORMONES' COMPLEX ROLE

Scientists are uncovering multiple, complex connections between hormones, appetite, weight, and sexual maturity. In a recent study conducted at the GCRC at UCLA, Licinio and colleagues documented the dramatic results of administering the hormone leptin to three obese adults with a rare genetic mutation that deprived them of the hormone. Leptin, a multifunctional hormone, plays a key role in appetite regulation, sexual maturation, and immune system function. Indeed, children who lack the hormone succumb to routine illnesses early in life.

Participants in Licinio's study—all members of the same extended family—lived in the GCRC for 6 months and then returned daily for another 12 months. Periodically during the study, for a week at a time, the GCRC staff measured the participants' total food intake. "Using the metabolic kitchen, we could calculate every thing they ate, including nutrients like magnesium," Licinio says. "That was invaluable. I couldn't have gotten that kind of help anywhere else."

Soon after receiving leptin, the participants ate much less—for a while, about 50 percent less—and they started to lose weight. They also became more active and eventually reached a healthy weight, primarily through the loss of fat. "An advantage of leptin treatment might be that patients lose primarily fat, not muscle," notes Licinio. The participants told Licinio that their obesity originated during childhood, when they ate excessively. But by the time they joined the study, participants were eating close to a normal number of calories. Being sedentary apparently helped maintain their excess weight.

**Julio Licinio found that leptin led to weight loss in patients who lacked the hormone.**

Earlier studies have demonstrated that leptin replacement not only leads to dramatic weight loss in leptin-deficient children but also normalizes sexual maturation. However, researchers had not yet studied the hormone's effects on adults who had been obese since childhood and had failed to develop normally. "It wasn't known if leptin could rescue adults who had missed going through puberty as youngsters," says Licinio.

Participants in the UCLA study experienced dra-

**Kong Chen (left) and Mac Buchowski found that few overweight patients can blame excess weight on slow metabolism.**

matic changes in their endocrine system and metabolism soon after beginning leptin therapy. The male participant, at age 27, went through puberty for the first time, and the two women began ovulating. Their personalities changed as well, transforming within two weeks from infantile and passive to energetic and adult, Licinio says.

Most obese people have high levels of leptin but are insensitive to the hormone, so administering leptin would not help these individuals lose weight. However, 10 to 15 percent of the obese population has low levels of leptin, and it's not yet clear how leptin treatments might help them, says Licinio.

## TAKING THE MYTH OUT OF METABOLISM

At Vanderbilt University's GCRC, researchers are using high-tech equipment to debunk patients' old-fashioned excuses for weight gain. "Overweight patients think they must have a slow metabolism," says Mac Buchowski, director of bionutrition at the GCRC and an adjunct professor of medicine. But only the GCRC's whole-room calorimeter, also known as a metabolic chamber, knows for sure. In the room, which is about the size of an average bedroom, the patient's rate of oxygen uptake and carbon dioxide production during rest and activities is monitored. The researchers use that data to calculate energy expenditure, which, even for overweight patients, is usually in the normal range. The room replaces metabolic carts that require the patients to sit still and breathe into a mask. Only eight metabolic chambers are currently operating in the United States. Vanderbilt's is particularly sophisticated, as it measures oxygen and carbon dioxide every minute. In addition, it has floor sensors that measure activity.

The Vanderbilt research team recently used the whole-room calorimeter to measure walking and stepping efficiency among 60 men and 85 women of various weights. When walking at a normal speed, the heavier participants burned more calories than the normal-weight participants did. Generally, the heavier people are, the more calories they use, the team's studies show. "Every movement takes more effort, especially if you are not familiar with the movement," says Kong Chen, director of the energy balance laboratory and lead author of the study.

Which brings up the practice effect. When obese men walked slowly, they burned fewer calories than their healthy-weight companions did, the team reports. The heavy men normally walk slowly, so they are very efficient at it, explains Chen. The practice effect crosses body-type boundaries. For example, aerobics teachers burn fewer calories doing the same moves as their less-practiced aerobics students, Buchowski and his colleagues have shown.

A new use for the chamber will be to validate activity-monitoring devices—sophisticated motion sensors that study participants can wear on their belts or wrists to measure their activity levels every minute. "In addition to determining metabolism, a metabolic chamber is a really unique tool for using as a gold standard to develop, calibrate, and validate the tools we send people out in the community with," says Chen.

## OBESE KIDS AT RISK

When it comes to obesity, being a little obese is indeed less risky than being severely obese. The latter group faces double the risk of premature death than the former, studies of adults have demonstrated. The same principle holds true for obese children, according to recent research by pediatrician Sonia Caprio of Yale University and her colleagues.

In a study done at Yale's GCRC, the researchers assessed 439 children and adolescents of different racial backgrounds for metabolic syndrome, a constellation of disorders, including dia-

PHOTO BY ANNE RAYNER, VANDERBILT UNIVERSITY

**Sonia Caprio has shown that overweight children are at risk for diabetes, hypertension, and heart disease.**

betes and hypertension, that greatly increases the risk for heart disease. The participants underwent glucose tolerance testing, as well as measurements of their blood pressure, blood lipids, C-reactive protein, and adiponectin, a hormone that influences appetite and appears to help prevent plaque from accumulating in arteries.

Half of the severely obese children had metabolic syndrome, and its prevalence increased directly with the severity of obesity. In a relatively short follow-up period, eight of the participants with metabolic syndrome developed type 2 diabetes. Previous investigations of metabolic syndrome were slightly less alarming. Between 1988 and 1994, only about 7 percent of overweight adolescents had metabolic syndrome, as did almost 30 percent of the obese teens, the team notes. It's been well documented that obese adolescents face an increased risk of type 2 diabetes. However, Caprio and her colleagues note that diabetes may be part of a much larger problem, as evidenced by the strong link between metabolic syndrome and obesity in all age groups.

The prevalence and problems of obesity worldwide have finally hit the front pages, and supersize is now a bad word. The nation's girth has yet to start shrinking from this increased scrutiny, but with support from the GCRCs, researchers' efforts to understand obesity may mean a leaner, healthier population in the long run.

*The research described in this article is supported in part by the NCRR Division for Clinical Research Resources. For information about other NCRR-funded resources for clinical research, visit www.ncrr.nih.gov/ncrrprog/clindir/crdirectory.asp.*

## ADDITIONAL READING


- Licinio, J., Caglayan, S., Ozata, M., et al. Phenotypic effects of leptin replacement on morbid obesity, diabetes mellitus, hypogonadism, and behavior in leptin-deficient adults. *Proceedings of the National Academy of Sciences USA* 101:4531-4536, 2004.
- Yildiz, B. O., Suchard, M. A., Wong, M. -L., et al. Alterations in the dynamics of circulating ghrelin, adiponectin, and leptin in human obesity. *Proceedings of the National Academy of Sciences USA* 101:10434-10439, 2004.
- Weiss, R., Dziura, J., Burgert, T., et al. Obesity and the metabolic syndrome in children and adolescents. *New England Journal of Medicine* 350:2362-2374, 2004.





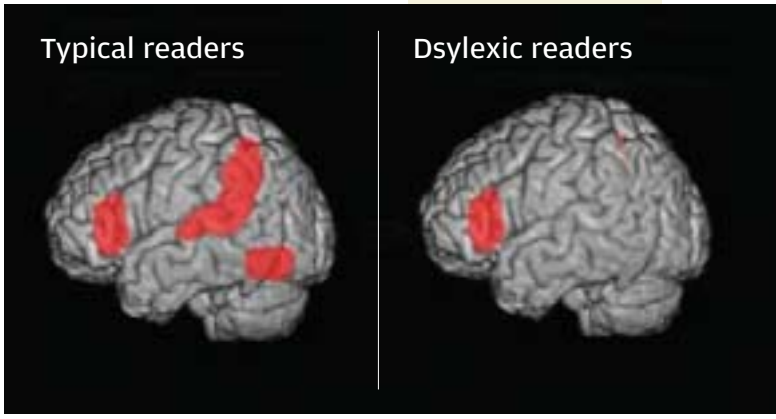

# Brain Scans Shed Light on Adult Dyslexia

The brains of middle-aged adults can be surprisingly nimble as they learn new skills, according to a recent study of adults with dyslexia. Using a technique known as functional magnetic resonance imaging (fMRI), researchers found that special training to improve reading skills can lead to detectable changes to the brain's reading centers.

A team led by pediatrician Guinevere Eden of the NCRR-funded General Clinical Research Center at Georgetown University Medical Center in Washington, D.C., used fMRI to scan the brains of 38 adults, half of whom had dyslexia. While being imaged, participants performed tasks that required the ability to interpret the sounds, or the phonics, of language.

Following the imaging, half of the dyslexic group participated in eight weeks of daily phonics training, which improved reading accuracy. Previous studies have shown phonics to be a problem area for dyslexics. Compared both to their initial fMRIs and to images from the untrained dyslexic participants, the trained participants' fMRIs revealed increased brain activity in the left hemisphere—the area active in typical readers who do not have dyslexia. However, activity in the right hemisphere increased as well, which may be the brain's way of compensating for possible deficiencies in regions that would typically be activated in normal readers. The finding reveals an important difference between adults and children, as children with dyslexia are not known both to compensate for a weakness and to improve in a particular area of the brain.

Understanding dyslexia at the biological level is key to developing useful training methods, Eden says. For example, findings from this new study




**Brain images obtained while subjects are reading reveal different regions of activation (red) in people with and without dyslexia.**

PHOTO BY GALE ZUCKER (ABOVE LEFT), IMAGE COURTESY OF SOCIETY FOR NEUROSCIENCE AND GUINEVERE EDEN (ABOVE)

suggest that approaches used for children may not necessarily work for adults. Nevertheless, the brain is much more malleable during adulthood than was once thought, Eden says. "Researchers had believed that all structural changes had to happen early on, but now we know that you can see substantial changes in how an adult brain handles reading," Eden notes. Whether these changes result from a rewiring of the brain or a simple activation of different areas is a key question that researchers now face as they seek better approaches for treating dyslexia. (*Neuron* 44:411-422, 2004)

**—TINA ADLER**

**NCRR RESOURCES:** The General Clinical Research Center (GCRC) at Georgetown University Medical Center supports clinical researchers from Georgetown and other District of Columbia hospitals. The center is one of more than 80 NCRR-supported GCRCs nationwide. Information about the Georgetown GCRC can be found at http://gcrc.georgetown.edu. To learn more about the GCRC program, visit www.ncrr.nih. gov/clinical/cr_gcrc.asp.

# Aging Neurons on the Move

As part of the normal aging process, brain cells that once lined up neatly one above the other in so-called microcolumns fall out of place. This disorganization may contribute to normal, age-related cognitive decline, a new study of rhesus monkeys is showing. A team of biologists and physicists analyzed microcolumns from the prefrontal cortex of young and elderly monkeys from the NCRR-funded Yerkes National Primate Research Center at Emory University in Atlanta. The researchers then compared the condition of the microcolumns to the animals' performance on memory tests.

"We found that very slight movements in the position of neurons are correlated with the animals' declining cognitive performance," says Luis Cruz, a physicist at the Center for Polymer Studies at Boston University. Displacement of neurons by one neuronal diameter was enough to completely disrupt the neurons' vertical organization, they report. Because the relationship between the test scores and neuronal changes are only correlational, the neuronal changes may not be the actual cause of declining memory. Instead, the changes may be a marker for age-related cognitive decline. The neuronal changes may be caused by other normal changes occurring at the same time in the aging brain, including atrophy of synapses and dendrites in the prefrontal cortex, which impair cognition.

To detect the tiny changes in the microcolumns, the team mapped out the position of the neurons, then overlapped individual maps, and eventually derived a mathematical picture of the average neuron and its environment. "Our method, which is unique, lets us see very small changes in neurons and characteristics in the microcolumns that previously went undetected," says Cruz.

"It presented a challenge when we ruled out neuronal loss as one of the mechanisms of aging," says Cruz.

Nonhuman primates are ideal subjects for this type of study, notes principal investigator Douglas Rosene, who is affiliated with both Boston University School of Medicine and Yerkes. Unlike humans, the monkeys at Yerkes have uniform environmental exposures, including similar living conditions, diet, and health care. Moreover, Yerkes and other National Primate Research Centers are among the nation's only sources of aged monkeys for scientific studies. "Without the centers, there would be no elderly monkeys available to researchers," Rosene says.

The new investigation is part of a long-term National Institutes of Health-funded study on the neural basis of age-related cognitive decline, which Rosene has led since the late 1980s. Earlier study results debunked the idea that a reduction in the number of neurons in the elderly brain led to a drop in brain power. "It presented a challenge when we ruled out neuronal loss as one of the mechanisms of aging," says Cruz. Only when scientists noticed a relationship between microcolumn disorganization and Alzheimer's disease did they decide to investigate whether a similar disorganization occurs during the normal aging process. Cruz, Rosene, and their colleagues plan to continue their studies by examining microcolumns in middle-aged animals. By better understanding both normal and abnormal structural changes that occur in the brain, the researchers hope to better diagnose and ultimately treat age-associated disorders. (*Proc Natl Acad Sci USA* 101:15846-15851, 2004)

**—TINA ADLER**

**NCRR RESOURCES:** The Yerkes National Primate Research Center at Emory University is one of eight NCRR-funded National Primate Research Centers. Each center has experienced research and support staff to facilitate the development of nonhuman primate models of human health and disease for biomedical investigations. The centers are affiliated with academic institutions and accessible to biomedical and behavioral investigators who have research project grants from the National Institutes of Health and other sources. For more information about the National Primate Research Centers, visit www.ncrr.nih.gov/compmed/cm_nprc.asp.

## NCRR Names Associate Director of Comparative Medicine

**Franziska Grieder** has been appointed associate director of NCRR's Division of Comparative Medicine (DCM), which supports programs and resources for advancing biomedical research through the use of nonhuman models. DCM-funded resources include the eight National Primate Research Centers and


FRANZISKA GRIEDER

five Mutant Mouse Regional Resource Centers (MMRRCs). Since 2000, Grieder has managed DCM's Laboratory Animal Sciences Program, where she created the MMRRC Program and also supervised grants related to mammalian models for human illness, diseases of laboratory animals, and training in comparative medicine. With a doctorate in veterinary medicine from the University of Zurich and a Ph.D. in viral pathogenesis from the University of Wisconsin-Madison, Grieder is an expert on the Venezuelan equine encephalitis (VEE) virus, a potential biowarfare agent. Since 1993, Grieder has been on the faculty at the Medical School of the Uniformed Services University of the Health Sciences. ■

## New Center Examines DNA Variation

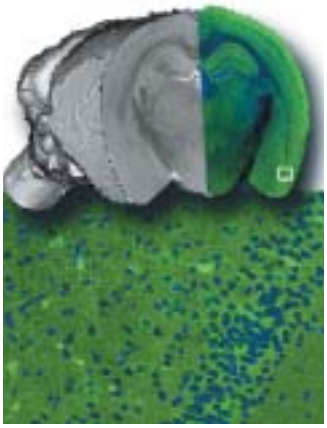
As the list of genetic variations associated with human disease grows, researchers need ever-faster methods to identify and study those variations. NCRR has stepped forward to meet that challenge by funding the first national center for high-throughput analysis of the most common type of variation in the human genome—single nucleotide polymorphisms, or SNPs (pronounced "snips"). A SNP consists of variant forms of a single base molecule at a particular position in the genome.

The new High-Throughput Genotyping Center will be located at the Eli and Edythe L. Broad Institute of the Massachusetts Institute of Technology and Harvard University in Cambridge, Massachusetts. The center will be headed by **Dr. Stacey Gabriel**, who currently oversees SNP-related work at the Broad Institute. With a five-year grant totaling more than $14 million from NCRR's Division for Clinical Research Resources and Division of Comparative Medicine, the new center will provide tools to affordably identify SNPs associated with diseases such as diabetes and hypertension and to screen individuals for the presence of those SNPs, a process known as genotyping. The center also will help identify SNPs in animals that may correlate with genetic variations that contribute to human disease.

The center will have the capacity to process billions of genotypes per year, at a cost of mere pennies per genotype. The first genotyping studies are expected to begin at the new center in early 2005. ■

## Informatics Network Gets Boost

An infusion of additional funding from NCRR will enhance the innovative Biomedical Informatics Research Network (BIRN). Funded by NCRR's Division for Biomedical Technology Research and Research Resources and Division for Clinical Research Resources, this collaborative



**In this BIRN image of a mouse brain (top), and in the magnified close-up beneath, pathological cellular bodies are labeled in blue and an associated protein in green, to aid study of neurodegenerative disease.**

network of 22 research centers will receive an additional $32.8 million over the next five years. BIRN was established in 2001 to advance medical research by developing information technologies to ease data sharing between geographically separated research groups. The network's initial focus has been on computer infrastructure, particularly unified databases, needed for multi-institutional studies of neurological disorders.

The largest share of the new funding, $18.8 million, will go to the University of California San Diego Medical School, which serves as the coordinating center for BIRN and also participates in all three of BIRN's initial test bed projects on neurological disorders. The remainder, nearly $14 million, will be granted to Massachusetts

General Hospital, which is involved in the two test bed projects that focus on imaging the human brain. One of these projects examines brain structure; the other studies brain function. The third BIRN project performs imaging studies on mouse brains to shed light on human neurological disorders.

Through its test bed projects, BIRN will develop data-sharing tools that will be applicable to other areas of biomedical research. For more information about BIRN, visit www.nbirn.net, or see the *NCRR Reporter*, Fall 2003, pages 5-7. ■

## NCRR Funds New Clinical Center

A new General Clinical Research Center (GCRC) has been established at the Sacramento Veterans Affairs Medical Center in California. With an award of $5.5 million over five years from NCRR's Division for Clinical Research Resources, the new center will conduct clinical studies of AIDS, cancer, vascular biology, bone metabolism, and neuroscience—scientific strengths of the University of California, Davis, and the Veterans Affairs Northern California Healthcare System (VANCHCS) in Sacramento, which are jointly operating the new GCRC.

Like the 80 other GCRCs across the country, the new 7,500-square-foot center provides an optimal setting for medical researchers to conduct safe, controlled, state-of-the-art, patient-oriented studies to find better ways to prevent and treat disease. The center is available to all UC Davis and VANCHCS investigators funded by NIH or other peer-reviewed sources. Clinical trials proposed for the new GCRC include research into a newly identified neurodegenerative disease affecting men, studies to aid the development of an AIDS vaccine, and tests of a soy extract thought to protect the bones of postmenopausal women. ■

## New IOM Members Depended on Research Resources

Among the 65 new members elected to the Institute of Medicine (IOM) in October are 11, listed below, whose research relied on NCRR-funded resources.

**Ernest Beutler**, principal

[CONTINUED ON BACK COVER ➤]

*IN MEMORIAM*

## Dr. Leo A. Whitehair

With great sadness, we report that Dr. Leo A. Whitehair, who served for 10 years as director of NCRR's Division of Comparative Medicine, died on November 2, 2004, after a long battle with cancer.

Dr. Whitehair retired from NCRR in 1999, after more than three decades of service. He joined the Division of Research Resources, NCRR's predecessor, in 1968 as a health scientist administrator in the Animal Resources Program, which later became NCRR's Division of Comparative Medicine (DCM). He headed NCRR's National Primate Research Centers Program from 1975 until 1989, when he was promoted to DCM director. As head of DCM, Dr. Whitehair oversaw grants, training programs, and publication efforts crucial to advancing research related to human and animal diseases. During his long career, he helped researchers capitalize on many breakthroughs in animal research, including the development of a nonhuman primate model for AIDS.

Colleagues recall the joy and satisfaction he found in his work, which he passed on to others.

"Dr. Whitehair made invaluable contributions to comparative medicine research," says Dr. Judith Vaitukaitis, director of NCRR. "Equally important, he was a gifted administrator who inspired teamwork and camaraderie among his colleagues. He will be remembered for his helpfulness, honesty, warmth, and sense of humor."

Dr. Whitehair received a doctorate in veterinary medicine from Kansas State University and also held a doctoral degree in food science from the University of Wisconsin. His many professional honors include NCRR's Outstanding Performance Award, and he was the first recipient of the Distinguished Service Award of the American Society of Primatologists. Before coming to NIH, Dr. Whitehair served for 13 years as a veterinary officer in the U.S. Air Force, with positions at the Aerospace Medical Laboratory at Wright-Patterson Air Force Base, the Armed Forces Food Institute, and the Atomic Energy Commission.

[ CONTINUED FROM PAGE 15 ]

investigator of the NCRR-supported General Clinical Research Center (GCRC) at The Scripps Research Institute. He relies on the GCRC to study the genetic underpinnings of metabolic disorders.

**Diana D. Cardenas**, University of Washington Medical Center. Cardenas used the university's GCRC in her studies of patients with spinal cord injuries.

**Fred E. Cohen**, University of California, San Francisco (UCSF). Cohen has relied on the NCRR-supported Resource for Biocomputing, Visualization, and Informatics at UCSF to develop computer models of protein structure.

**Sheldon Cohen**, Carnegie Mellon University and University of Pittsburgh Medical School. The GCRC aids his studies of how stress increases the risk of infectious disease and how personality traits and behaviors influence that risk.

**Mahlon R. DeLong**, Emory University School of Medicine. Emory's GCRC helped DeLong to evaluate surgical techniques for treating Parkinson's disease.

**Robert J. Desnick**, Mount Sinai School of Medicine. He uses the school's GCRC to study inherited disorders. Desnick's research laid the groundwork for routine use of enzyme replacement therapy for Fabry's disease.

**James G. Fox**, Massachusetts Institute of Technology (MIT). With NCRR funds, Fox established a diagnostic laboratory for animal research at MIT and administers a program to train veterinary scientists in biomedical research.

**Robert Freedman**, University of Colorado Health Sciences Center. Freedman used the university's GCRC to study how and why the nervous systems of schizophrenic patients respond abnormally to repeated sensory stimuli.

**Apostolos Georgopoulos**, University of Minnesota. He used the NCRR-supported NMR Imaging and Localized Spectroscopy Resource at the University of Minnesota to study brain activity during memory and mental imagery tasks.

**Alan E. Guttmacher**, deputy director of the National Human Genome Research Institute. In his previous position at the University of Vermont College of Medicine, Guttmacher relied on the university's GCRC to help conduct an international survey of hereditary hemorrhagic telangiectasia patients.

**Stephen T. Warren**, Emory University School of Medicine. With NCRR support, Warren created a repository of patient DNA samples at Emory's GCRC and has used it to study X-linked genetic disorders such as fragile X mental retardation. ■

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