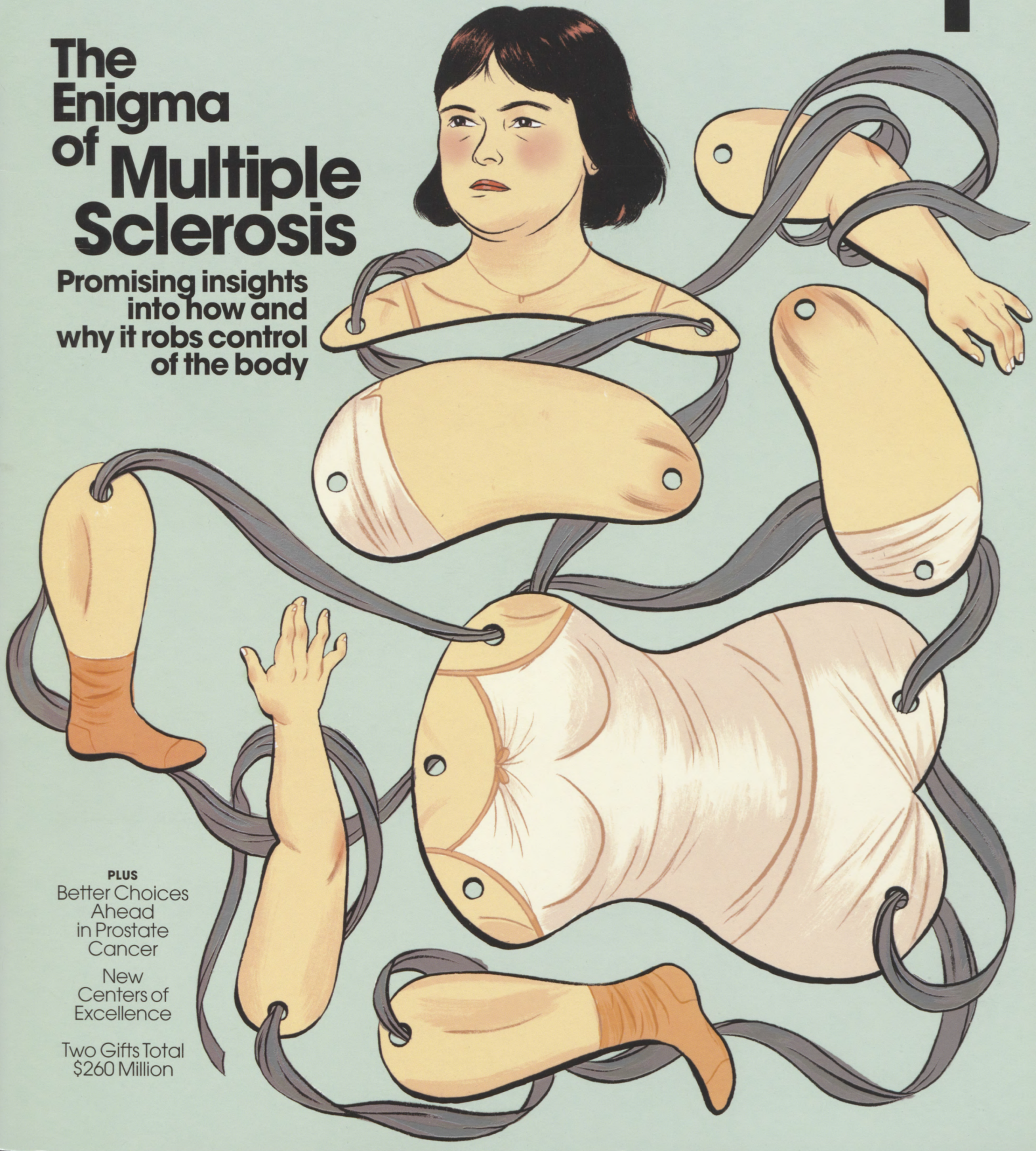
# NYU PHYSICIAN

THE MAGAZINE OF NEW YORK UNIVERSITY SCHOOL OF MEDICINE

WINTER 2008–09
VOLUME 60 • NO. 1

## The Enigma of Multiple Sclerosis

**Promising insights into how and why it robs control of the body**



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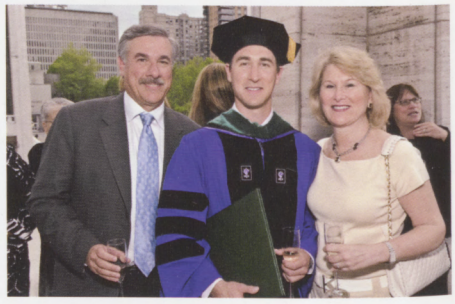

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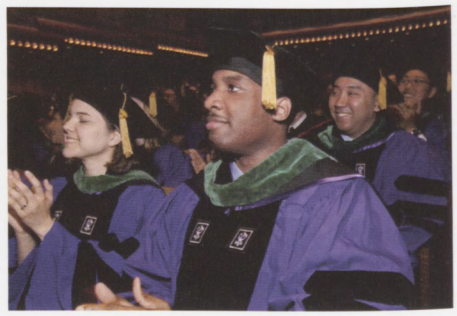

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# NYU PHYSICIAN



ON THE COVER:
Illustration by:
Jillian Tamaki


**"A lot of people, when something like this happens to them, they automatically shut down...."**
Ronald Thompson, diagnosed with MS in 2002

## Cover Stories

## The Enigma of Multiple Sclerosis

Advances in basic research, medical imaging, and clinical care are helping to unravel the mystery of MS, a brain disease that strikes young people.



## Departments

### From the Dean



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# Our Journey

*A KEY PART OF OUR MISSION AS AN ACADEMIC* medical center is to foster the search for new knowledge. In this regard, we have made truly remarkable headway.

The establishment of our first six new Centers of Excellence (*see page 6*) is an inspiring example of what we can achieve. These centers reflect some of our institution's greatest strengths. They are focused on many important health problems in the U.S. and around the world—addiction, Alzheimer's disease and related disorders, multiple sclerosis, skin diseases, and musculoskeletal diseases. And they have mobilized more than 260 outstanding scientists and clinical researchers to come together to work in highly collaborative, multidisciplinary groups. • The goal is to translate advances more swiftly into new and better ways of diagnosing and treating patients and preventing disease. I am deeply gratified by the enthusiastic response of our faculty to these new Centers of Excellence, which would not have been possible without their extraordinary expertise and commitment. Hundreds of clinicians and researchers from the Medical Center—and throughout the University—seized the opportunity to participate. • One of the most gratifying things we are experiencing this year is the phenomenally enthusiastic support that our donors have demonstrated for efforts like these. Not only have the centers received generous funding from trustees who share our vision, but, as you know, we have enjoyed a true outpouring of support, marked by several gifts of $100 million or more (*see story on facing page*) from members of our board. • These gifts are a powerful endorsement of our efforts—and our talented team of physicians, scientists, nurses, faculty, and staff. •

Robert I. Grossman

**DEAN & CEO** ROBERT I. GROSSMAN, M.D.



PHOTOGRAPH BY
**BUD GLICK**

# NYU Receives Two New Gifts Totaling $260 Million

## Donations from longtime benefactors will support a new Kimmel Pavilion and rebuild Tisch Hospital.

Mrs. Helen L. Kimmel at Dean's Honors Day ceremonies.

NYU LANGONE MEDICAL CENTER took a giant step toward its goal of reshaping itself as a world-class academic medical facility with the announcement that two longtime benefactors have donated $260 million for construction of a new medical pavilion and the refurbishment of Tisch Hospital.

Together, the two connected facilities will form the centerpiece of an integrated, state-of-the-art medical center for the 21st century.

Dean Robert I. Grossman, M.D., announced the gifts at the conclusion of Dean's Honors Day 2008, sending a wave of excitement through the audience gathered in Farkas Auditorium. The first gift was a $150 million dollar donation from Helen L. Kimmel, designated for the new Helen L. and Martin S. Kimmel Pavilion, which will be built adjacent to Tisch Hospital.

"The new Kimmel Pavilion will pioneer 24/7 operations," said Dr. Grossman, "partnering with our teams of physicians across the entire continuum of care with the most advanced technologies. Helen Kimmel is championing our quest to bring clinical care to a new level in a facility that is both esthetically and ecologically state-of-the-art." As he spoke, an architect's rendering of the pavilion was flashed onto the wall behind the stage.

After the applause quieted, Mrs. Kimmel addressed the group. "I want to thank you all," she said. "I must say, it was because my husband Marty and I became so excited at the way Bob Grossman is leading this medical center that we decided to do this. With Bob's leadership, we're going to be tops in the country!"

The Dean then announced a second gift of $110 million from an unnamed family who are longtime benefactors of the Medical Center. "This is a gift to refurbish Tisch Hospital," he said, "to secure its future and transform the face of patient-centered care throughout our Medical Center." Another series of architectural slides lit up the stage, showing what the renovated space will look like and how the refurbished Tisch Hospital will link to the new Kimmel Pavilion.

### An Extraordinary Record of Giving

The pair of gifts take on even more weight when viewed in the context of NYU Langone's other recent development efforts. With the addition of this $260 million, NYU Langone has now raised a total of $506 million from some 17,000 donors in 2008—an amount believed to be the largest ever raised by any academic medical center in a single year.

**HELEN L. AND MARTIN S. KIMMEL PAVILION**
(Artist's Rendering, East River View)

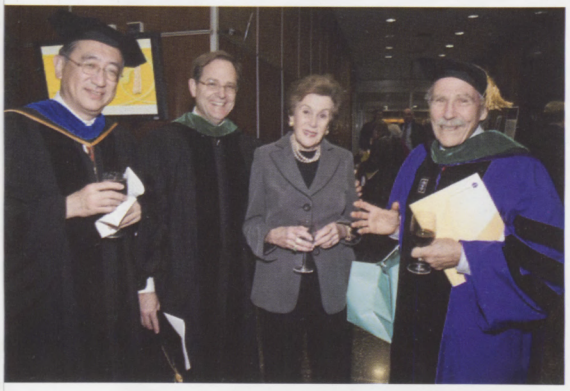

**TISCH HOSPITAL REFURBISHMENT**
(Artist's Rendering, First Avenue View)


PHOTOGRAPH: RENÉ PEREZ

For Mrs. Kimmel, who received a B.A. in mathematics from Barnard and has been a Medical Center trustee since 1984, her gift caps a long record of extraordinary support for the Medical Center on the part of herself and her late husband Martin, also a Medical Center trustee, who passed away earlier this year. Their past contributions include $10 million to establish the Helen L. and Martin S. Kimmel Center for Stem Cell Biology in 2005, followed a year later by an additional gift of $15 million to establish the Helen L. and Martin S. Kimmel Center for Biology and Medicine at the Skirball Institute for Biomolecular Medicine. In addition, immediately following the announcement of her gift for the Kimmel Pavilion, it was announced that Mrs. Kimmel will be making a $4 million contribution to the Medical Center to establish the Helen L. and Martin S. Kimmel Wound Healing Center.

The Kimmels have also endowed two basic science professorships, in molecular immunology and pharmacology, as well as a new professorship in advanced cardiac therapeutics, and have supported Medical Center programs in cancer, epilepsy research, rehabilitation, urology, and vascular research. Their contributions also enabled the construction of the Helen L. and Martin S. Kimmel Center for University Life at the Washington Square campus.

"Given Mrs. Kimmel's passion for science, and her amazing track record as an enabler of discovery," noted Dr. Grossman, "Mrs. Kimmel's decision to support a new clinical facility has special meaning: the new facility will have the space and capability that will allow us to translate research at an unprecedented level." ●



Mrs. Kimmel with faculty members (from left) Dr. Tung-Tien (Henry) Sun, Dr. Herbert Lepor, and Dr. Richard P. Novick at Dean's Honors Day reception.

Dean Grossman and Mrs. Kimmel at Valentine Mott Founder's Day dinner.

## Highlights of the new Kimmel Pavilion and Tisch Hospital Refurbishment

### The New Kimmel Pavilion

Construction on the Helen L. and Martin S. Kimmel Pavilion will start in 2012 and is expected to be completed by 2016. Plans call for a 500,000-square-foot pavilion featuring a number of state-of-the-art elements:

- The pavilion's upper floors will contain all private patient rooms, including VIP amenities and space for family members.
- The lower floors will contain multi-purpose procedure and surgical rooms dedicated to cancer, cardiovascular, neurological, and pediatric procedures. High ceilings will be incorporated to accommodate the most advanced medical technology.
- In addition, the pavilion will incorporate cutting-edge work flow and IT systems, so that physicians can see real-time images and vital statistics of patients during surgery, and researchers can track and compare patient data.
- The pavilion's design will also include a "green" infrastructure for maximum energy efficiency.

### The Tisch Refurbishment

The Kimmel Pavilion will be connected on two floors to Tisch Hospital, which itself is slated for an extensive makeover. The $110 million gift announced by Dr. Grossman will go toward phase one of the Tisch renovation. This initial five-year phase will include:

- Creation of an expansive new Family Resource Center just off the Tisch Lobby (in the area now used for medical records, which will be digitized and stored electronically), featuring physician consult rooms, a business area with phones and Internet access, a children's play area, and areas for meditation and relaxation.
- Renovation of the Tisch Lobby to improve patient flow and create new space for a permanent café.
- Construction of a new elevator bank on the exterior of the hospital.
- Upgrading of the laboratory facilities on the third and fourth floors, including consolidation and expansion of the clinical and anatomical labs.
- Relocation of the hospital's in-patient pharmacy to an expanded, state-of-the-art space on the third floor—a move that will also free up 4,500 square feet of additional space on the ground floor for use by the Emergency Department.

This initial phase will lay the foundation for the later phases of the renovation plan, which call for completely renovating the upper floors in Tisch Hospital, and refurbishing Tisch's exterior. ●

PHOTOGRAPHY (LOWER LEFT) RENÉ PEREZ; (UPPER RIGHT) JULIANA THOMAS

By Elizabeth Cohen

# Shaping the Future of Surgery

## Carol Scott-Conner, M.D. ('76), Ph.D., M.B.A.

LIKE SO MANY MOMS IN THE 1950S, Dr. Carol Scott-Conner's mother taught her to sew. Unlike most mothers, however, she also gave her daughter the heart whenever she prepared a turkey. "I would dissect it," recalls the woman who went on to become the second female to chair a department of surgery in the United States.

"I was interested in what was inside, and how it worked. From the earliest age, I was curious about the sciences; I wanted to know the names of all the animals and stars. I wanted to understand everything."

Although many thought science a closed door for women in the 1960s, her father, a physicist, encouraged her to believe she could walk right through that door. Being shy and soft-spoken "complicated things," she says. But intellectual curiosity and the self-confidence she developed because of her father's faith in her helped, and she decided to pursue her dream of a career in medicine.

To prepare herself, she studied electrical engineering at MIT because she thought this would be good preparation for surgery. Her father had pointed out that technology was increasingly important in medicine. "Doctors," he told her, "don't understand machinery well enough."

In 1976 she graduated from NYU School of Medicine. By then, Dr. Scott-Conner says, "I had realized I probably wasn't going to find a cure for cancer, but still I wanted to make a real difference." She came to the realization that she loved surgery, which she calls the "fixing of people," and she stayed on at NYU to do her residency. She was chief surgical resident. A legendary teacher, Dr. Frank Spencer, M.D., then chairman of the Department of Surgery (and now in charge of the New Clinical Facility Initiative), inspired her to set her sights even higher. "I got the sense from him that to head a department of surgery was the most important thing you could do in the whole world," she says. "Not only could you help patients and pass on knowledge to your students, but you could be active at a national level, shaping the future of surgery."

First, she needed more education and experience as a surgeon. In 1988 she earned a Ph.D. in anatomy and cell biology at the University of Kentucky. Beyond that, "I knew I would need to demonstrate I had administrative skills," she says. So, in 1995, while she was chief of staff at University Hospital in Jackson, Mississippi, and a full professor on the University of Mississippi School of Medicine faculty, she went to night school at Millsaps College to get an M.B.A. "She is indefatigable," says H. Leon Pachter, M.D., an NYU colleague who has known her since 1975 and today is the George David Stewart Professor of Surgery and chairman of the Department of Surgery. "A first-rate intellect and 100 percent devoted to the job at hand."

She was ready, and she knew it. But, she adds, "I also knew the field of surgery had been dominated by men for a long time. I could tell the people interviewing me were thinking, 'You are a woman and our department is mostly men. What makes you think you can lead them successfully?'" The members of the Department of Surgery at the University of Iowa Carver College of Medicine had the insight to see that she would be a great leader; in 1995 she accepted their chairmanship.

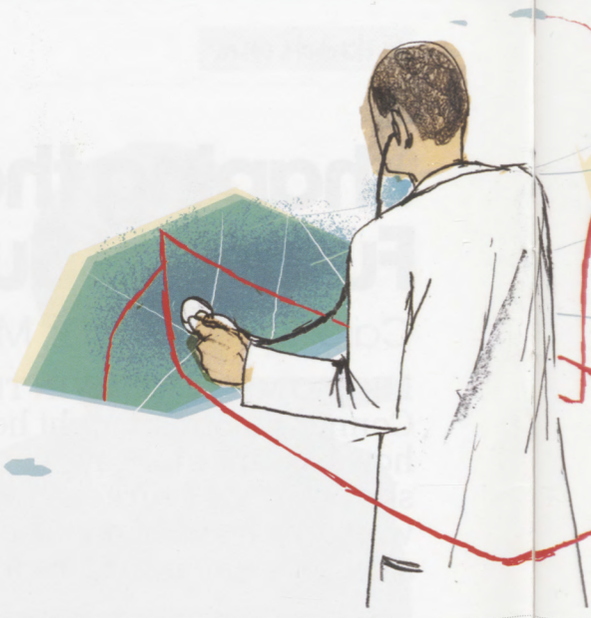
For nine years Dr. Scott-Conner led the department. Once she was in the job, she felt her authority was respected by colleagues and patients. The achievement she is proudest of is establishing the University of Iowa as a Level I Trauma Center. She also worked hard to increase the percentage of surgical residents who were women. And, while she was chairwoman, she continued writing and published *Minimal Access Surgical Anatomy*. She has five textbooks to her credit, including *Operative Anatomy*, a text that has become a standard. Nor did she stint on her research: She is author or coauthor of more than 125 articles.

"I finally retired in 2004," Dr. Scott-Conner says, "when I realized I was ready to spend my time focusing on patients again. I am an old-fashioned surgeon at heart." Today she is professor of surgery in the Division of Surgical Oncology at the University of Iowa Carver College of Medicine. "Surgery, like cabinetry or sculpture, is all about doing something with your hands," she says. "Then this amazing thing happens. In the weeks and months that follow, the patient comes back again, and because of what you did with your hands they are healed."

Jean Arndt, breast center care coordinator at the University of Iowa Carver College of Medicine, knows first-hand how much Dr. Scott-Conner's patients value her kindness as well as her expertise. "Many times, when I'm taking patients into exam rooms," Arndt says, "they tell me how good they felt in the operating room because she held their hands while they went to sleep." ●

▸ Dr. Scott-Conner (right) with Dr. Kristine Orion, a surgery resident at the University of Iowa Carver College of Medicine.

PHOTOGRAPH: SUSAN MCCLELLEN



# Centers of Excellence Created to Speed Medical Breakthroughs

WHEN IT COMES TO TRANSLATIONAL MEDICINE—converting discoveries in the research laboratory into effective therapies for patients—working collaboratively is the coin of the realm. NYU Langone Medical Center aims to take synergy to a new level with its recent designation of six new Centers of Excellence.

These centers without walls, comprising more than 260 scientists, will speed the development of new treatments, diagnostics, and disease-prevention strategies by bringing together integrated teams of experts from different fields to focus on selected groups of diseases.

The six centers—addiction, brain aging and dementia, multiple sclerosis, musculoskeletal diseases, skin cancer, and urological disease—address pressing health challenges and are fields where NYU claims leadership. "We're recognizing that these are areas of real strength that we want to continue to support and grow," explains Vivian Lee, M.D., Ph.D., M.B.A., vice dean for science and chief scientific officer.

"Each center has an impressive research component and a strong clinical track record," notes Dr. Lee. "And with this new designation," she adds, "our patients and their families will be further assured that they are receiving world-class care enhanced by the latest advances in science."

The announcement culminates a yearlong effort. In the fall of 2007, Dr. Lee, together with Robert I. Grossman, M.D., Dean and CEO, invited physicians and researchers throughout the NYU community to submit proposals outlining potential centers. "A number of groups came together around different themes, such as diseases or areas of science," says Dr. Lee. This early stage of the selection process was extremely productive in and of itself, she points out. "The gatherings that resulted gave many people an opportunity to meet for the first time. For example, several retreats each drew nearly a hundred scientists and physicians, many of whom hadn't met before. In some cases, they even led to ideas for new grant proposals."

Seventy-six groups submitted letters of intent to the Science Strategy Committee, and 18 were asked to draft formal proposals. Of these, the six centers were ultimately selected by the committee.

The centers will receive additional financial support to fill key positions and add technical capabilities. Fifteen million dollars in new funding (made possible by gifts from, among others, NYU Langone board members Tom Murphy and Fiona Druckenmiller) will be available to the program. Another $15 million is slated for new core facilities and shared resources for the medical center, such as a mouse behavioral lab, a bioinformatics center, a biostatistical consultation center, a universal tissue biorepository, and a recently established high throughput sequencing facility.

"While some of these facilities have been specifically requested by one of the new centers, all of them will be utilized by many members of our faculty, to the benefit of the broader medical center," says Dr. Lee. "The Centers of Excellence process has been a tremendous success, and is just one of many initiatives under way to advance science and discovery at NYU Langone. These new shared resources will be an important part of that effort, as will ongoing efforts to develop and enhance the research environment and infrastructure."

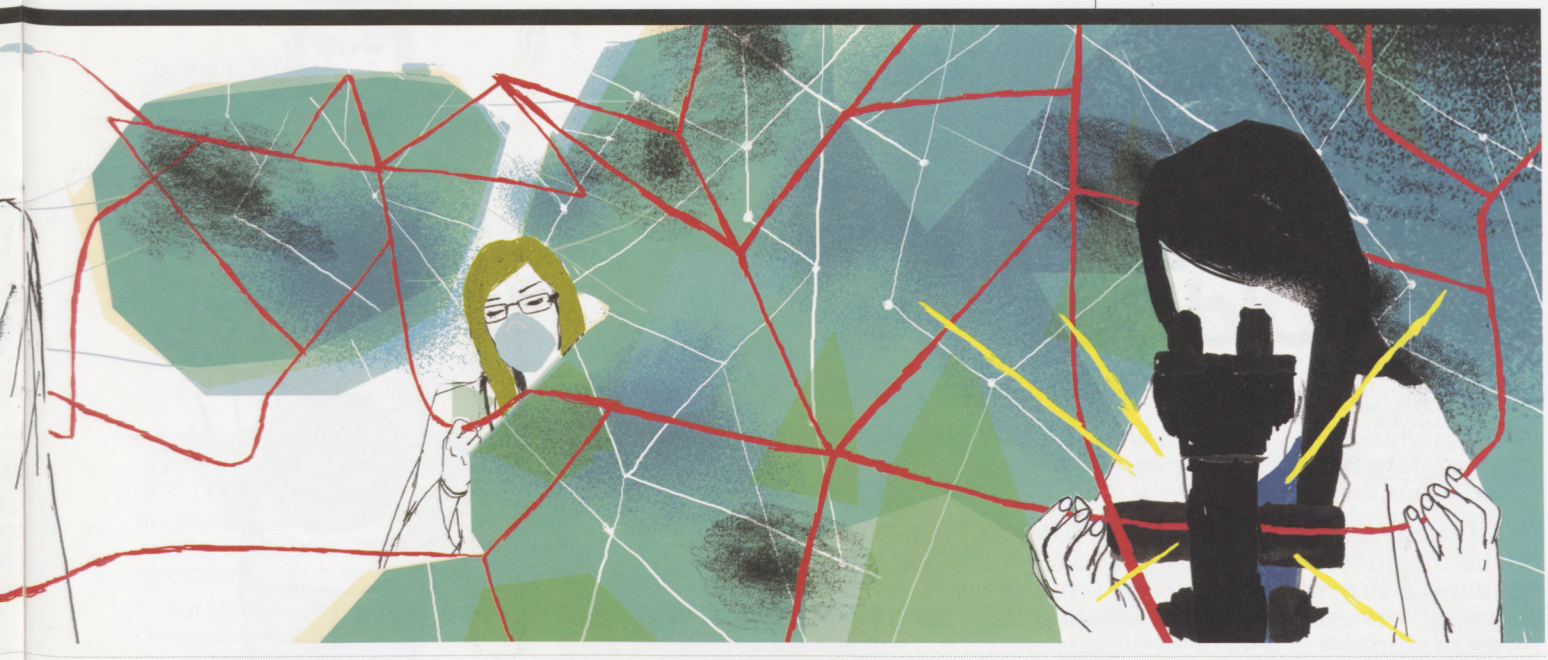
She expects to see more centers designated in the years ahead. "The plan," she says, "is to review the Centers of Excellence in three years. The centers' leaders have set high expectations, and we look forward to celebrating their successes. At that time, we also will open up the process again and hope to designate new centers."

## The Six Centers of Excellence

### 1 Addiction

**DIRECTOR:** John Rotrosen, M.D., professor of psychiatry / VA New York Harbor Healthcare System **GOAL:** To improve prevention, diagnosis, and treatment of all types of addictions, from drugs, alcohol, and tobacco to gambling, eating disorders, and sexual risk-taking. Clinicians will draw on the center's research in basic neuroscience, population health, genetics, imaging, social science, behavioral science, and other fields. Initial translational projects will focus on impulsivity, cognitive control, and addictive behaviors; physical exercise strategies; medication therapy; new forms of intervention in healthcare settings; and prevention and early intervention in children and adolescents.

ILLUSTRATION BY JON HAN



## 2 Brain Aging and Dementia

**DIRECTOR:** Ralph Nixon, M.D., Ph.D., professor of psychiatry and cell biology / vice chairman of research, Department of Psychiatry / director of Silberstein Institute for Aging and Dementia

**GOAL:** To provide one-stop multidisciplinary evaluation and cutting-edge care in the diagnosis, treatment, and prevention of Alzheimer's disease, Parkinson's disease, and other neurodegenerative disorders. The center will bring together specialists in neurology, psychiatry, medicine, psychology, and clinical social work. Scientists and clinicians will use animal models and humans to study the fundamental disease process of brain disorders, enabling the center to move new therapies quickly from drug discovery to early clinical trials.

## 3 Cancers of the Skin

**DIRECTOR:** Seth Orlow, M.D., Ph.D., the Samuel Weinberg Professor of Pediatric Dermatology and chairman of the Department of Dermatology, professor of cell biology and pediatrics **GOAL:** To develop new ways to prevent, diagnose, and treat skin cancers. Building on the existing Interdisciplinary Melanoma Cooperative Group—comprising some 40 researchers from more than a dozen disciplines—the center will offer patients unprecedented scientific focus on specific conditions. These include specialized clinics for organ transplant patients with skin cancer, as well as unique therapeutic protocols developed at NYU. Extensive patient tissue databases will also yield new clinical insights.

**"Each center has an impressive research component and a strong clinical track record."**

## 4 Multiple Sclerosis

**CO-DIRECTORS:** Joseph Herbert, M.D., associate professor, neurology (neurorehabilitation/MS); James Salzer, M.D., PhD., professor of cell biology and neurology

**GOAL:** To pursue cures for multiple sclerosis (MS) by integrating various disciplines. The center's neuroscientists will use established mouse models to explore the disease's causes, in order to prevent damage to myelin and nerves and to enhance generation of new myelin. Clinicians will offer multidisciplinary clinical and rehabilitative care, including access to drug trials and new therapeutic strategies. The center's neuroimaging experts will interface with basic scientists and clinicians, and advance their pioneering work in MR spectroscopy, diffusion tensor imaging, diffusion/perfusion, and sodium imaging, in order to improve detection of MS lesions, explore the disease's pathogenesis, and monitor new therapies.

## 5 Musculoskeletal Disease

**CO-DIRECTORS:** Steven B. Abramson, M.D., professor of medicine and pathology, director, Division of Rheumatology; Joseph D. Zuckerman, M.D., Walter A.L. Thompson Professor and chairman of Orthopaedic Surgery **GOAL:** Build on expertise at NYU School of Medicine and NYU Hospital for Joint Diseases, to focus on advancing understanding and treatments of arthritis, autoimmunity, and the repair/regeneration of musculoskeletal tissues. Key areas of concentration are the molecular mechanisms of osteoarthritis, joint degeneration, and tissue repair; development of tissue biorepositories for genomic, pharmacogenetic, and toxico-genetic analysis; research on clinical trials and health outcomes; lupus and autoimmune diseases, including rheumatoid arthritis; and bioengineering more effective bone and cartilage implants.

## 6 Urologic Disease

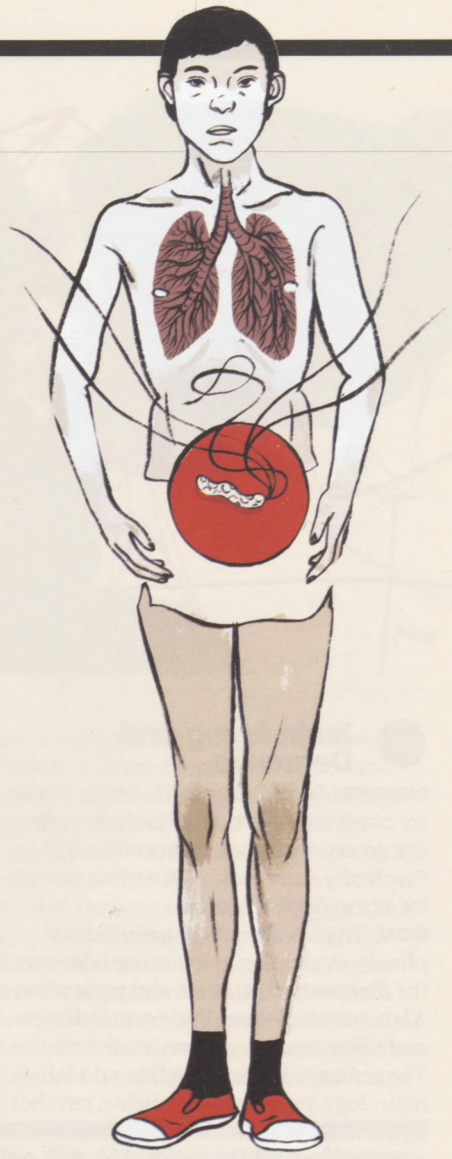
**CO-DIRECTORS:** Herbert Lepor, M.D. the Martin Spatz Chairman of the Department of Urology, professor of pharmacology; Tung-Tien (Henry) Sun, Ph.D., professor of cell biology, Rudolph L. Baer professor of dermatology, professor of pharmacology and urology; Xue-Ru Wu, M.D., professor of urology and pathology

**GOAL:** To develop innovative treatments for urological disorders, including prostate and bladder cancer, urinary tract infection, and kidney stones. The center includes 34 basic scientists and clinicians from 12 academic departments. Areas of focus include improving detection of low-risk prostate cancers that can be treated with minimally invasive therapies; how bladder-specific cancer markers discovered at NYU can be used to assess effectiveness of bladder cancer treatments; and investigating an NYU-engineered virus that attacks tumor cells in the prostate and bladder while sparing normal cells. ●

By Anastasia Toufexis

# New View of an Old Bug

## Yes, *Helicobacter pylori* may lead to ulcers and stomach cancer, but it may also protect against asthma and obesity.



**OVER THE PAST HALF-CENTURY, ASTHMA IN CHILDREN HAS BEEN** ratcheting up steadily in the U.S. and other developed countries. As many as 15 percent of American children now suffer from the coughing, wheezing, and chest tightness that characterize the disease. A recent study by School of Medicine researchers suggests one explanation for this increase: the absence of the common stomach bacterium *Helicobacter pylori*.

Martin J. Blaser, M.D., the Frederick H. King Professor of Internal Medicine and chairman of the Department of Medicine, along with Yu Chen, Ph.D., assistant professor of epidemiology, examined the health records of some 3,300 Americans under age 20, compiled in 1999 and 2000 as part of the National Health and Nutrition Examination Survey (NHANES), a research program conducted by the Centers for Disease Control and Prevention (CDC). The result: Among teens and children, carriers of the *H. pylori* bacterium were 25 percent less likely to have asthma, according to the findings published in the *Journal of Infectious Diseases*. Among those aged three to 13, this protective effect reached 59 percent. "Carriers were also 40 percent less likely to have hay fever, eczema and other allergic skin conditions," says Dr. Blaser.

The new study extends earlier findings by Drs. Chen and Blaser, showing that adults with *H. pylori* were less likely to have developed asthma as children. "These data suggest *H. pylori* may play a role in the development of childhood asthma," says Dr. Chen.

These and other studies are painting a much more complex picture of a bacterium that until recently was seen primarily as a pathogen linked to peptic ulcers and stomach cancer. Ironically, this more nuanced view is emerging at a time when *H. pylori* is rapidly vanishing. "This has been the dominant organism in our stomach for at least 60,000 years," says Dr. Blaser, who has studied the bacterium for over two decades. "A century ago, almost everyone had it. Today maybe less than 6 percent of U.S. children under age 10 carry it."

Dr. Blaser attributes the decline to widespread use of antibiotics. "Parents and doctors use them like water," he says. "We're creating a cleaner world that makes it harder to pass along the bacterium."

Drs. Chen and Blaser believe the bacterium protects by fostering a more finely tuned immune response. The immune systems of children with asthma or hay fever are hypersensitive. *H. pylori*, the doctors theorize, promotes growth in the stomach lining of regulatory T-cells, which dampen reaction to allergens.

"Our hypothesis is that if you have *H. pylori* in your stomach, you have a greater population of regulatory T-cells that are setting a higher threshold for sensitization," says Dr. Blaser. "If a child doesn't have *H. pylori* and has contact with a few cockroaches, he may get sensitized to them. But with *H. pylori*, even if a child has contact with many cockroaches, he may not get sensitized because his immune system is more tolerant." This more relaxed immune response may lower the risk of developing asthma, hay fever, or eczema.

**"*H. pylori* has been the dominant organism in our stomach for at least 60,000 years," says Dr. Blaser. "A century ago, almost everyone had it. Today maybe less than 6 percent of U.S. children under age 10 carry it."**

The disappearance of *H. pylori* may also be playing a prominent role in the steep rise of esophageal cancer, diabetes, and obesity. "These are three of the fastest growing conditions in the developed world," says Dr. Blaser. "Evidence indicates the bacterium protects against gastric reflux disease, which, if unchecked, can lead to esophageal cancer. As for diabetes and obesity, the stomach makes hormones that affect appetite and energy homeostasis. *H. pylori* regulates these hormones."

The researchers stress that there is still a long way to go before anyone should consider inoculating children or themselves with *H. pylori*. "More studies are needed to confirm the associations and uncover the mechanisms by which *H. pylori* may reduce risk of childhood asthma and related disease," says Dr. Chen.

Still, Dr. Blaser can envision a tantalizing future of innovative treatments. "Maybe we'll find or engineer a milder form of *H. pylori* that we can give to kids to get its benefits without the risk of ulcers and stomach cancer," he says. "Alternatively, we may discover ways to introduce the microbe in childhood, then eradicate it in adulthood."

The biggest lesson so far, he adds, is that, "We shouldn't expect we can wipe out without consequences an organism that's been with us for tens of thousands of years." ●



ILLUSTRATIONS BY
JILLIAN TAMAKI

By Royce Flippin

# A "Neglected" Malaria Gets Its Due

## Led by an NYU researcher, a team cracks the genome of *P. vivax*.

**WHEN PEOPLE TALK ABOUT MALARIA,** they usually mean *Plasmodium falciparum*—the species endemic to Africa, where it kills more than 800,000 people a year, most of them children under five. The other major malaria species, *Plasmodium vivax*, accounts for 40 percent of the world's malaria cases and is the most prevalent species outside Africa, predominating in Central and South America and Asia.

But although *P. vivax* triggers debilitating flu-like symptoms, including fever, headache, and vomiting, and can cause permanent learning disabilities in children, it is rarely fatal. This, plus the fact that it can't be cultured in a lab, has led *P. vivax* to be largely neglected by researchers, with most funding going to study *P. falciparum* instead.

*P. vivax* is emerging from the shadows, however, following the recent announcement that a team led by NYU's Jane Carlton, Ph.D., has fully sequenced the *P. vivax* genome. "Until now, *vivax* malaria could be studied only by infecting monkeys with it, which raises ethical issues and can be extremely expensive," says Dr. Carlton. "Mapping its genome provides our first real glimpse into the parasite's biology."

The announcement coincided with the publication of a cover article by Dr. Carlton's group in the October 9, 2008, issue of *Nature*, detailing their research to date. The issue also included a report from other investigators on the sequencing of *P. knowlesi*, a malaria in monkeys now thought to be infecting humans as well.

While the decoding of *P. vivax* made headlines, the sequencing itself was completed in 2006. Since then, Dr. Carlton and her fellow investigators have been analyzing the genome's structure for clues about how the parasite might be attacked with drugs or a vaccine. "We've been comparing *P. vivax* to three other malaria species' genomes—*P. falciparum*, *P. knowlesi*, and a rodent parasite," says Dr. Carlton.

They've already made some intriguing discoveries, including the fact that, unlike the *P. falciparum* genome, which is constituted almost exclusively of AT-rich DNA, *P. vivax* has many more regions of GC-rich DNA—a finding with potential therapeutic implications. The investigators have also been doing evolutionary analysis of genes common to *P. vivax*—which is believed to have started as a monkey parasite before jumping to humans—and *P. knowlesi*.

In another discovery that holds more immediate promise, the Carlton team has uncovered significant metabolic similarities between *P. vivax* and *P. falciparum*—including an organelle called the apicoplast, which contains several metabolic pathways vulnerable to therapeutic targeting. "This is very interesting," Dr. Carlton observes, "because anti-falciparum drugs designed to disrupt these pathways are already under development. We hope they'll be effective against *P. vivax* as well."

The investigators have also found that *P. vivax* shares a number of vaccine-candidate genes with *P. falciparum*. Two of these antigens are currently under study in vaccine trials.

As always with *vivax* malaria, funding for such investigations is scarce. In fact, the sequencing of *P. vivax* nearly didn't happen after the genome project ran out of money in 2003. Additional funding from the Burroughs Wellcome Fund and NIH allowed the project to be restarted a year later.

The Carlton group's recent breakthroughs come at a time when *vivax* malaria is getting new attention from the world health community—in part because of evidence that a more severe form of *P. vivax*, apparently fatal in some cases, is emerging. Experts are also realizing that *P. vivax* poses a major challenge to the global eradication of malaria since, unlike *P. falciparum*, it can hibernate in the human liver for up to five years before reemerging to cause symptoms—making detection and treatment difficult. As Dr. Carlton points out, "There's only one drug that attacks *P. vivax* in its dormant stage, and it can't be used by pregnant women or people with a blood disorder called G6PD, which is common in areas where *P. vivax* is endemic. We need to find other drugs that can attack this dormant stage."

Another goal is to learn more about the mechanisms involved in the parasite's resistance to existing drugs—an increasing problem with both *vivax* and *falciparum* malaria. "We've used homology modeling to compare proteins in *P. vivax* and *P. falciparum* that are known to mutate and cause resistance in *falciparum*," says Dr. Carlton. "One prediction from this modeling is that *vivax* should be less likely to develop resistance to artemisinin, a very potent anti-malarial drug, which is good news. It also appears that, like *P. falciparum*, *P. vivax* is likely to develop resistance to atovaquone, a drug used in combination with other antimalarials—not great news, but at least it alerts us to monitor patients for this drug resistance in the future." ●

ILLUSTRATION BY NICK LU

By Elizabeth Dougherty

# A Question of Balance

## Researchers uncover a key factor in the overproduction of inflammatory cells.

A HEALTHY IMMUNE SYSTEM is a balancing act between two opposing yet intimately connected forces, one calming and the other inflammatory. Sometimes called the yin and yang of adaptive immunity, pro-inflammatory cells (the "yang") dominate when the body needs protection, and regulatory cells (the "yin") soothe the immune system when it doesn't.

When this balance is disrupted and there is an overload of fiery yang cells, inflammatory disease results. In recent years scientists have linked a striking number of autoimmune disorders to excess pro-inflammatory cells, including psoriasis, inflammatory bowel disease, and multiple sclerosis. "The number of inflammatory diseases known to involve T helper 17 (Th17) cells"—those pro-inflammatory yang cells—"seems to be growing every week," says Dan R. Littman, M.D., Ph.D., the Helen L. and Martin S. Kimmel Professor of Molecular Immunology, and professor of pathology and microbiology.

For this reason, Dr. Littman has been on a quest to understand the molecular pathways that stimulate the production of these cells. He has uncovered a complex regulatory network, including one particularly promising potential therapeutic target that may help ameliorate diseases associated with overproduction of Th17 cells.

Scientists first discovered the role of Th17 cells in disease several years ago, using a mouse model considered the best current model of multiple sclerosis (MS). Scientists can induce an MS-like disease called experimental autoimmune encephalomyelitis (EAE) in these mice by triggering their immune systems to attack the myelin sheaths that protect nerve cells. In 2005, scientists found that if they destroyed a mouse's ability to create new Th17 cells, they were no longer able to induce EAE in the mouse.

Following that finding, researchers led by Dr. Littman, using the same EAE mouse model, discovered that the protein known as retinoic acid-related nuclear orphan receptor (ROR)-gamma-t plays a pivotal role in the production of Th17 cells. Dr. Littman's team showed that when incoming signals trigger a naive, or unspecialized, T-cell to make ROR-gamma-t, the cell differentiates, or specializes, into an inflammatory Th17 cell. When different signals trigger the same cells to additionally make another factor, Foxp3, this inactivates ROR-gamma-t and directs the cell to differentiate into a calming regulatory T-cell instead (*see story on facing page*).

Based on their breakthrough study, which appeared in the September 22, 2006, issue of *Cell*, the researchers theorize that if a drug can be found that blocks ROR-gamma-t activity, this may reduce the number of Th17 cells and help treat inflammatory diseases. "We think it's a real therapeutic opportunity," says Dr. Littman. "We're not sure if it will be effective in MS, but we expect it to be effective in at least some autoimmune diseases."

Juan J. Lafaille, Ph.D., associate professor of pathology and medicine and a collaborator on Dr. Littman's studies, strikes a similarly cautious note. While both Th17 cells and ROR-gamma-t play a proven role in the development of EAE in mice, notes Dr. Lafaille, "It isn't clear yet that regulating Th17 cells through ROR-gamma-t will help cure MS."

Then again, it wasn't clear until recently whether ROR-gamma-t mattered in any human inflammatory disease. In fact, several recent studies had suggested otherwise. But Dr. Littman published a study in *Nature Immunology* last March showing that mouse and human Th17 cell differentiation are indeed very similar.

These findings hinged on the source Dr. Littman used for human immune cells. To study the intricacies of T-cell differentiation, scientists need immune cells that aren't yet cued for specialization. In laboratory mice raised in pathogen-free conditions, like those used for EAE studies, says postdoctoral fellow Nicholas Manel, Ph.D., "All cells are naive." But the studies that threw into question the role of ROR-gamma-t in humans used human blood donated by adults who likely were exposed to many pathogens. "You know their cells have been cued," says Dr. Manel.

To avoid this, Drs. Littman and Manel studied Th17 cell differentiation using human cord blood from the placenta. Unexposed to pathogens, this blood mimics the unspecialized blood of laboratory mice. By confirming that both human and mouse Th17 cell differentiation involve homologous molecular pathways, these findings "validate the significance of ROR-gamma-t in the human system," says Dr. Littman.

The Littman lab is now identifying candidate drugs for regulating Th17 production by screening for small molecules that block the action of ROR-gamma-t, a step that could lead, says Littman, to "therapeutic medications for a variety of inflammatory diseases." ●

ILLUSTRATIONS BY JILLIAN TAMAKI

By Barbara LaVage

# Calming a Misguided Immune System

## New findings link custom-made cells to allergic reactions.

WHEN IT COMES TO ALLERGIES, the problem and the solution both lie within us. Our immune systems respond to foreign proteins with an arsenal of cells, some of them programmed to recognize and attack harmful invaders they have encountered in the past. Normally, any protein previously identified as harmless is allowed to pass, but sometimes the immune response goes awry and attacks in the absence of a real threat, triggering an allergic reaction.

Now, in hopes of finding a way to prevent these misguided responses, researchers at the School of Medicine have zeroed in on another class of immune cells that block allergic reactions. These regulatory T (Treg) cells are custom-made every time we eat or inhale an unknown protein for the first time—ensuring that the next time we encounter the substance, the body won't mount an allergic response. Defects in the ability to make these cells, which are manufactured according to instructions from a gene called Foxp3, leave a person highly susceptible to becoming allergic.

"Every time we don't have an allergic reaction to something, it's not because nothing is happening," says Maria A. Curotto de Lafaille, Ph.D., research assistant professor of pathology, who led the research. "In fact, something very important is happening: We're making regulatory T-cells that recognize a specific allergen we've eaten or inhaled."

While most T-cells originate in the thymus, the researchers have found that Foxp3-directed Treg cells arise in mucosal tissue, which lines the respiratory and digestive tracts and serves as a barrier against allergens. Dr. de Lafaille and her colleagues in the Program of Molecular Pathogenesis at the Helen L. and Martin S. Kimmel Center for Biology and Medicine at the Skirball Institute for Biomolecular Medicine described their investigations in a recent issue of the journal *Immunity*.

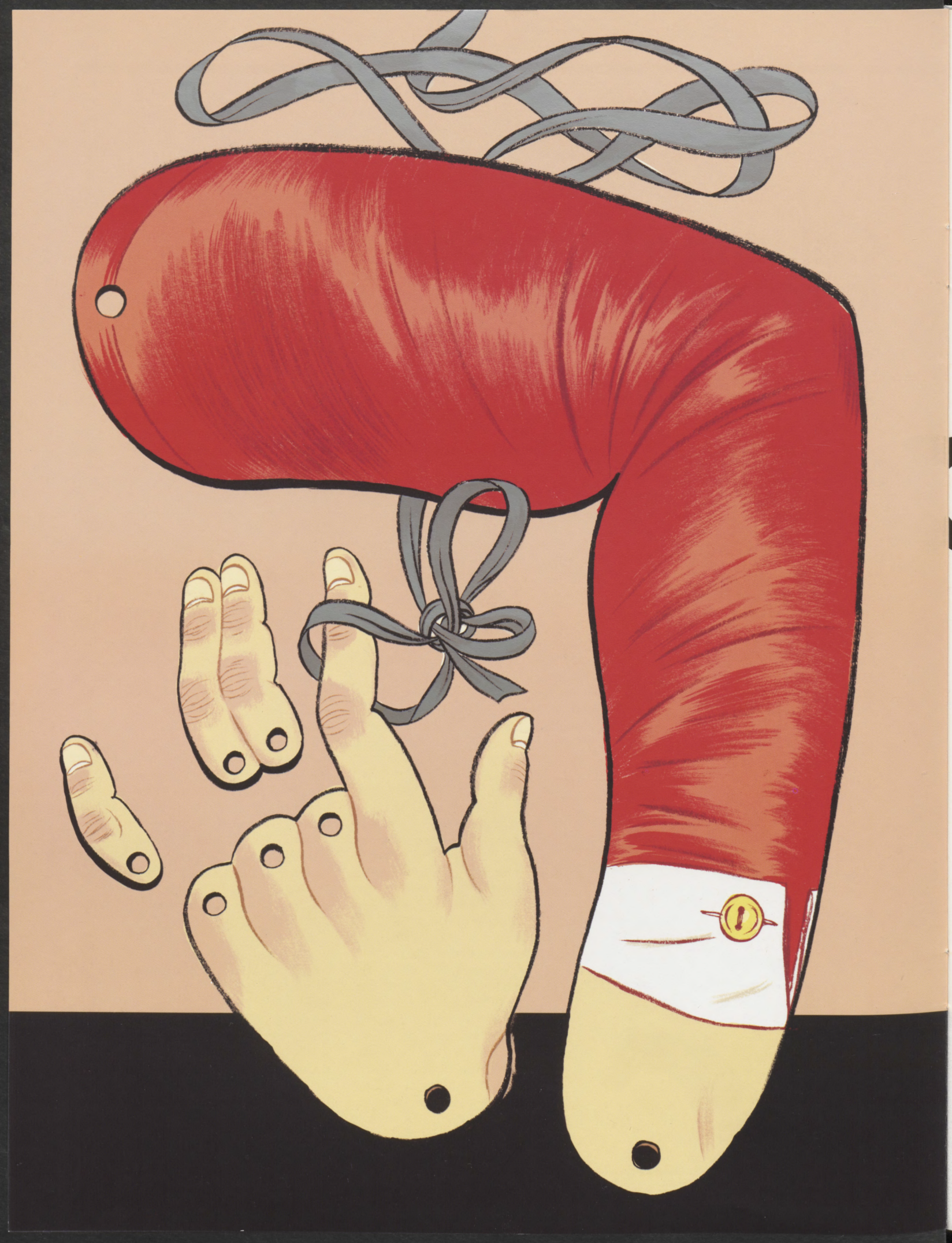
One of their findings may hold the key to understanding a serious consequence of asthma: permanent lung damage due to chronic inflammation. When the researchers induced allergic asthma in mice with and without Foxp3 defects, they found high concentrations of protective Treg cells in the inflamed lung tissue of those without the defect. Although the cells didn't prevent inflammation, they kept it under control and stopped it from spreading to other areas of the body.

"We think that, over time, these regulatory T-cells end up completely shutting off the inflammation," Dr. de Lafaille explains. If a way could be found to increase the number of Treg cells in the lungs, long-term inflammation might be prevented.

Dr. de Lafaille and her colleagues in Dr. Juan J. Lafaille's laboratory are currently investigating ways to grow allergen-specific Treg cells in the lab. "The big challenge," she says, "is how to isolate the cells that recognize the specific allergens an individual is allergic to." If they succeed in doing this, it may be possible someday to inject Treg cells into people who can't make their own. The group published a paper in *Nature Medicine* last February, with Yi Ding as the lead investigator, describing one method of making the Treg cells. Another promising area of research involves stimulating the body itself to manufacture the cells.

Their work represents an important step in understanding the genetic and cellular mechanisms underlying allergies. This may lead to more-effective therapies that prevent allergic responses from occurring, rather than just suppressing symptoms and reducing inflammation after an allergic reaction has already occurred, as current treatments do. And since Treg cells are produced in response to all potential allergens, the findings are applicable to a broad range of allergic reactions and autoimmune diseases.

The study published in *Immunity* identifying the role of Foxp3-positive Treg cells in blocking allergies and controlling inflammation was supported by grants from the National Institutes of Health, the National Multiple Sclerosis Society, and the Sandler Foundation. Co-authors of the study were Maria A. Curotto de Lafaille; two former postdoctoral students in pathology, Nino Kutchukhidze and Shiqian Shen; Yi Ding, a recent Ph.D. in pathology; Herman Yee, M.D., Ph.D., associate professor of pathology; and Juan J. Lafaille, Ph.D., senior investigator and associate professor of pathology and medicine. Co-authors of the paper published in *Nature Medicine* were Yi Ding; Shiqian Shen; Andreia C. Lino, a graduate student; Maria A. Curotto de Lafaille; and Juan J. Lafaille. ●



# OUT OF CONTROL

Basic research in immunology and molecular neurobiology is revealing why the immune system goes into attack mode in MS patients.

*By* LOIS WINGERSON

*Illustration By* JILLIAN TAMAKI

**In 1860, Margaret Gatty,** a popular children's author and nature writer, finally saw a doctor in London about the weakness and trembling in her right hand, which had been getting worse for 12 years. When he could find nothing wrong with her, she sought out Dr. Thomas King Chambers, who later described her case in *The Lancet*. Gatty's muscle fibers were degenerating from overuse, he theorized, because she spent her leisure time "furiously digging in her garden with a masculine spade" and mowing her lawn with a scythe.

Gatty visited numerous other doctors as her disabilities increased. They disagreed, and ridiculed one another's opinions. "Still," she wrote in her diary, "one must believe that the Drs. know something." They didn't. She continued to deteriorate, eventually dying of a respiratory infection.

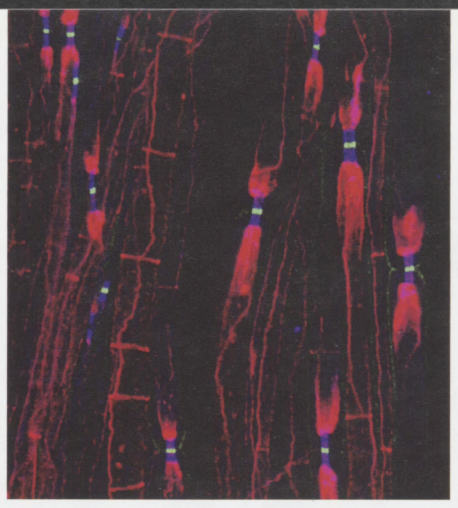
Six years after her first doctor's visit, the legendary French neurologist Jean-Martin Charcot gave the first definitive description of what probably affected Gatty. He described patients who had progressive movement and vision disorders, and plaques disseminated throughout their nervous systems at autopsy. He called the disorder *sclerose en plaque disseminée* (disseminated sclerotic plaques).

Thanks in part to Charcot's groundbreaking work, multiple sclerosis soon gained worldwide recognition as a distinct disease. But for more than a century afterward, even as researchers worked to unravel its biology, MS patients had little to rely on other than the hope that "the Drs. know something."

Fortunately, that has changed in recent decades. Doctors now know, for instance, that if Margaret Gatty did indeed have MS, it was her immune system's T lymphocytes, or T-cells, (not gardening) that damaged the nerves in her brain and spinal cord by chewing away at their sheath of myelin, the fatty substance that coats and insulates the body's nerve fibers, much like the insulation around a lamp cord. This loss of myelin ruins the ability of nerves to send impulses, resulting in a wide range of debilitating symptoms.

Scientists have also developed a handful of medications that slow the progress of MS somewhat. Still, these medications are far from a cure. "The available therapies are not satisfactory. Every physician will tell you that," observes Juan J. Lafaille, Ph.D., associate professor of pathology and medicine. "There's big room for immunologists to come up with something."

One key question is what sets off this immune system attack, and how to prevent it. But that isn't the whole story: MS also involves the failure of two protective factors—cells that should restrain the immune system (but don't), and another group of cells that could replace myelin and rebuild nerve fibers (but don't).



Myelinated nerve fibers stained in different colors. Information flow along myelinated nerves depends on molecular pores, called sodium channels (green), that are concentrated at specific sites along the fiber. When myelin is lost in MS, this site-specific localization is also lost.

These failures are the mysteries that captivate Dr. Lafaille and neurologist James L. Salzer, M.D., Ph.D., professor of cell biology and neurology, who together founded the Collaborative MS Research Center at NYU with support from the National Multiple Sclerosis Society. Their recent discoveries about the interactions of nerve cells and immune cells could lead to a whole new group of MS therapies.

**A CLEAN SLATE** For Dr. Lafaille, the quest to understand how the immune system misfires began with a Ph.D. in Brazil, and continued at the Massachusetts Institute of Technology in the laboratory of geneticist Susumu Tonegawa, who won the Nobel Prize for his research on the immune system. Dr. Tonegawa was also one of the first to study the immune and nervous systems using the knockout mouse—a term referring not to pugilistic rodents, but rather mice that have had individual genes eliminated through genetic engineering. This technique lets researchers define a gene's normal function by observing what happens when that gene is missing.

In Dr. Tonegawa's lab, Dr. Lafaille started by asking why we don't *all* develop multiple sclerosis. He focused on the immune system's T-cells that recognize and attack the molecule myelin basic protein (MBP), known to be a target of immune attack in MS. All normal animals have some T-cells that recognize MBP, but, it was hypothesized, not enough of them to damage myelin. To his surprise, however, when Dr. Lafaille bred mice supercharged with T-cells that can attack myelin, the mice remained completely normal.

Puzzled, Dr. Lafaille decided to clean the slate by creating mice that had only T-cells primed to attack myelin, and no other T-cells at all. These knockout mice invariably developed a condition similar to MS, known as experimental autoimmune encephalitis (EAE). Clearly, they lacked something that had protected the first set of mice from developing autoimmune nerve damage, despite their abundance of anti-myelin T cells.

Dr. Lafaille called these protective factors, which work to suppress the body's immune response, regulatory T-cells. Today, hundreds of laboratories are studying the effects of different types of regulatory T-cells on allergies, autoimmune diseases, inflammation, and other disorders. Dr. Lafaille's team is focusing on their interactions with other immune cells and with nerve cells, using the new live imaging technique intravital microscopy (see sidebar) to watch what happens when mice are injected with the regulatory T-cell that blocks demyelination of nerve fibers.

"So far, we've found that injecting regulatory T-cells prevents EAE in mice—and, even more important, ameliorates its symptoms in mice who already have EAE," says Dr. Lafaille. "We can't say that yet

## REVOLUTION IN MICROSCOPY

FOR DRS. JUAN Lafaille and James Salzer, the prospect of actually seeing the cellular actors in the very complicated drama of MS is now a reality, thanks to intravital microscopy, a breakthrough technology advanced at NYU by two Skirball Institute investigators, Wen-Biao Gan, Ph.D., associate professor of physiology and neuroscience and Michael Dustin, Ph.D., the Irene Diamond Professor of Immunology and professor of pathology.

Until recently, even the most sophisticated neural imaging has been able to capture only single moments in time. This extraordinary new approach lets doctors see live, moving pictures of cellular events inside the nervous system. The difference is profound. "Journals publish countless still images of interactions between immune cells and nerve cells, made using tissue slices and microscopes," explains Dr. Dustin. "It's difficult to figure out from these 'snapshots' just what's happening over time." The action is much clearer in the movies he is making with intravital microscopy. "There have been lots of ideas about the dynamics of those interactions between lymphocytes and glial cells," adds Dr. Dustin. "Now we may be able to deduce or even examine what's happening."

Working together, teams led by Dr. Dustin and Dr. Gan have been perfecting this technology, which involves tagging neurons with a green fluorescent protein, then using a sophisticated optical technique called two-photon microscopy to safely penetrate biological tissue and capture these cells in action.

Researchers are currently imaging cellular events both in tissue culture and in the brains and spinal cords of live, anesthetized mice, by peeking through a surgically created, ultrathin window about 0.2 millimeters in diameter (roughly the width of a human hair) in the mouse's skull. The method is safe enough to continue studying the same mouse for up to two years (its normal lifespan), notes Dr. Gan.

He has begun imaging nerve cells as they interact with microglia, the first cells to react to a brain infection. Dr. Dustin is imaging immune cells in the spinal cords of mice with EAE. Drs. Lafaille and Salzer will be watching the footage to see if it sheds new light on what they have already learned. ●

PHOTOMICROGRAPH COURTESY OF JOSE RIOS AND JAMES SALZER


Neurologist James L. Salzer, M.D., Ph.D., (left) and immunologist Juan J. Lafaille, Ph.D.

about MS, because it hasn't been tested yet in patients. We hope someone will be inspired to try it." In the long term, adds Dr. Lafaille, their research could lead to immunosuppressive medications that target only the part of the immune system that affects myelin, a key step toward curing MS.

**WRONG SIGNALS** Dr. Lafaille's colleague, Dr. Salzer, is studying another part of the demyelination puzzle—why it is that nerves damaged by MS fail to grow new myelin coats. The *plaques disseminees* that Dr. Charcot observed are not merely evidence of a destructive process. They are scars from the body's repeated, futile attempts to repair the damage from the disease's attacks on myelin.

"In MS, the damaged nerves don't remyelinate completely," says Dr. Salzer, "and some never remyelinate at all." Precursors to glia, the cells that normally nourish nerve fibers and wrap them in myelin, have been seen lining the edge of MS plaques, but they don't make the repair.

"The cells exist in the brain, but they're not effective," says Dr. Salzer. Understanding them, and ideally finding ways to make them effective, is his next agenda.

As a graduate student, Dr. Salzer developed a method of growing nerve cells and glia in tissue culture. He learned that nerve cells emit a signal that stimulates glia to begin the myelin-wrapping process. Rather than focus solely on discovering the source of this signal, however, he decided to learn firsthand what happens when this process fails by becoming a clinical neurologist. During his residency at New York Hospital and later as an attending neurologist at Bellevue Medical Center, Dr. Salzer treated many patients with MS, while also continuing his research.

"We knew almost nothing about the signals that drove glial cells to make myelin, or how myelin itself formed," he recalls. "I thought that understanding those questions would help in developing therapies for myelin repair."

In 2005, Dr. Salzer finally identified the molecule that signals glia in the peripheral nervous system (known as Schwann cells) to begin the myelination process. It turned out to be a subtype of a molecular signal prominent in the nervous system, called neuregulin. Like Dr. Lafaille, Dr. Salzer made his discovery with the help of knockout mice—engineered, in this case, to eliminate certain subtypes of neuregulin. Working with cell cultures, he and his team found that while Schwann cells normally myelinate certain nerve cells, they fail to myelinate nerve fibers taken from mice lacking a specific subtype of neuregulin 1.

Next, Dr. Salzer's team found that when they turned *on* production of neuregulin 1 in nerve cells, using a genetically modified virus to drive the process, they not only induced Schwann cells to initiate myelination around nerves taken from their knockout mice, but even stimulated myelin growth around nerves that normally are *never* myelinated.

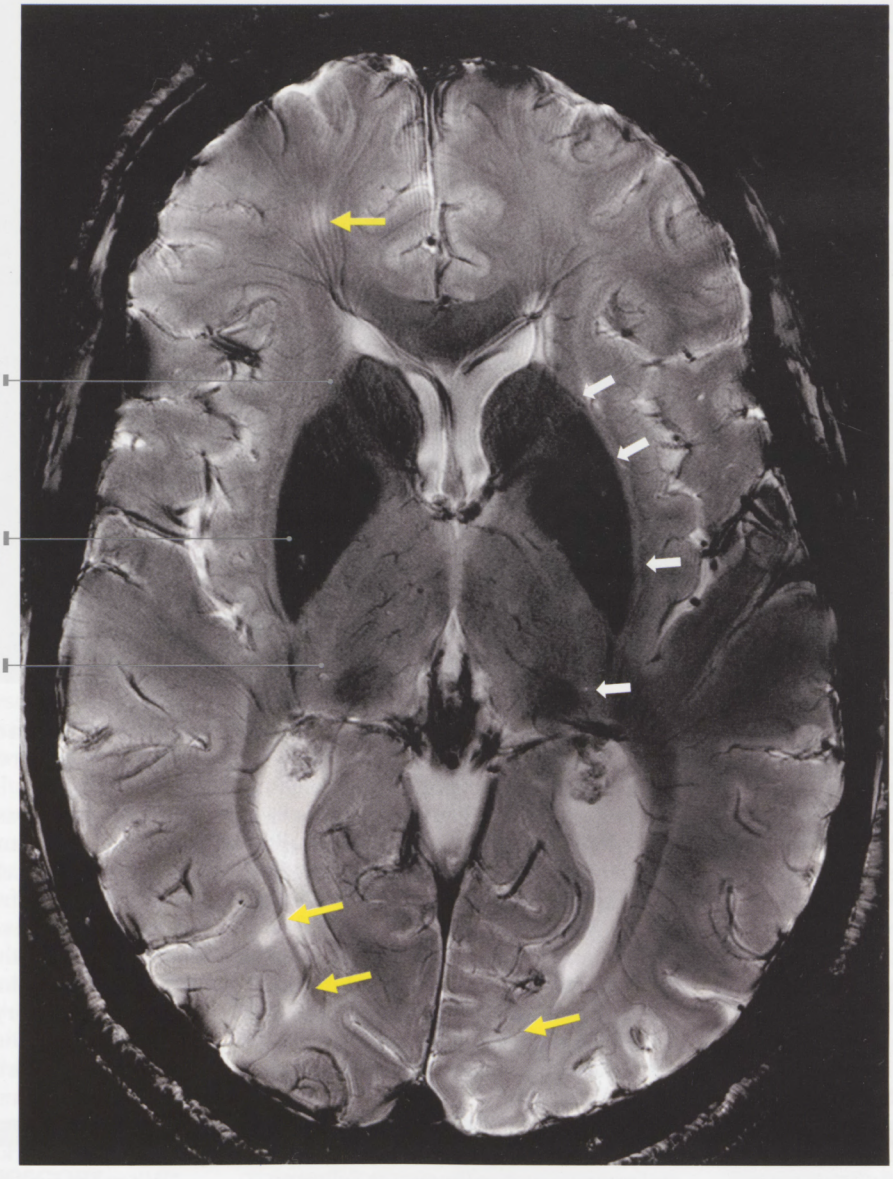
The discovery was significant. Whether it will lead to a treatment for MS remains to be seen. Schwann cells don't exist naturally in the brain and spinal cord. Although neuregulin 1 does have some effect on oligodendrocytes—the glia that myelinate nerve cells in the brain and spinal cord—they require other signals to carry out the process. When myelin is damaged in the brain, it's as if oligodendrocytes are waiting for an order to do their job, but never get the paperwork. Scientists have yet to discover the molecular identity of that work order.

"When an oligodendrocyte meets up with an axon during normal development, it's almost preprogrammed to make a myelin sheath," says Dr. Salzer. "However, in MS that's not the case. There are a surprising number of oligodendrocyte precursors scattered around the brain. Why aren't these cells able to migrate in and remyelinate nerve fibers damaged by MS?"

Dr. Salzer and his team are currently focused on identifying other molecules that may potentially be involved in triggering—or inhibiting—myelin formation in the brain. "To learn why remyelination doesn't happen well in MS, we're first trying to understand how remyelination occurs in a normal brain," he explains.

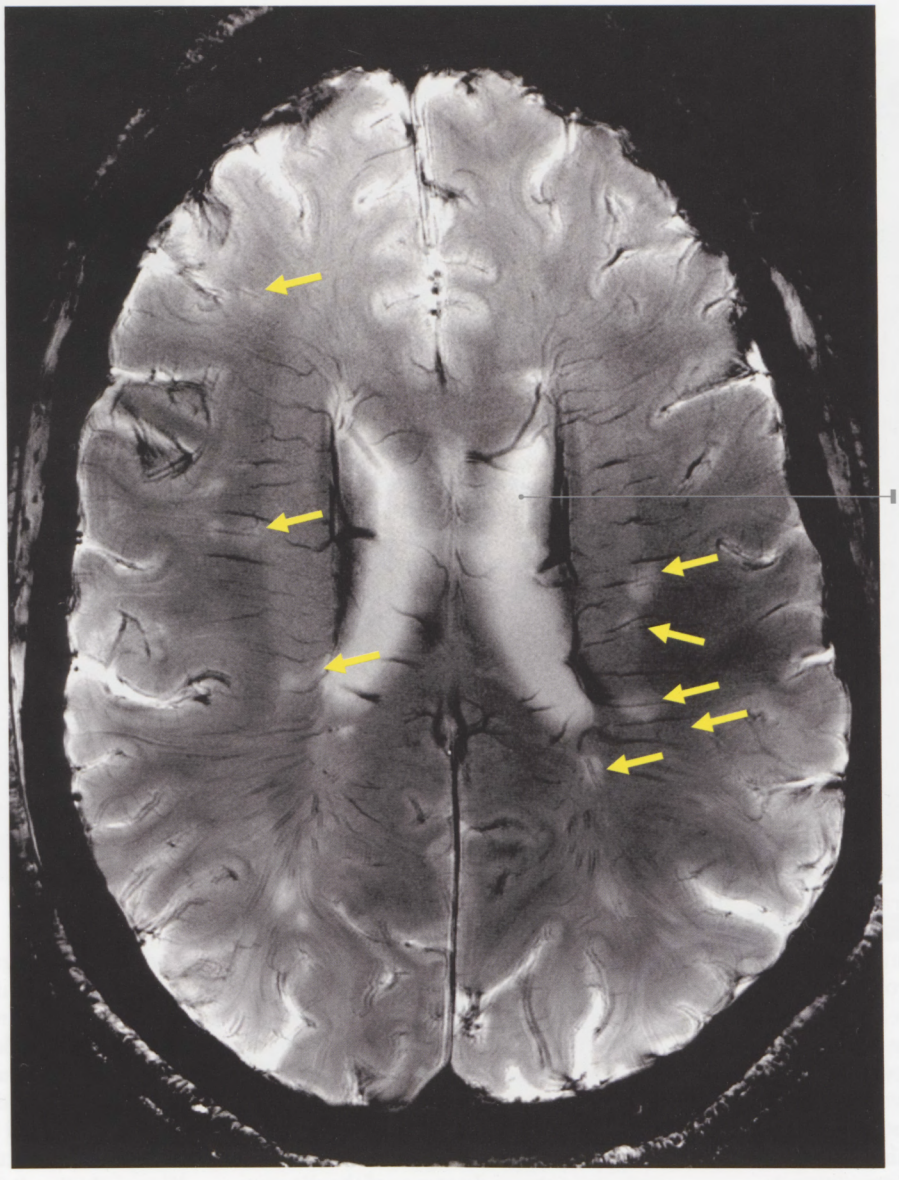
If Dr. Salzer can answer this riddle, "the Drs." will know a great deal more. ●

PHOTOGRAPH BY ETHAN HILL




A — ▲ SCAN
Brain images obtained with the ultra-high-field 7-tesla MRI scanner at NYU Langone Medical Center reveal subtle abnormalities that cannot be seen with conventional MRI. Images A and B are from a patient with multiple sclerosis and show subtle vascular abnormalities in very early lesions. Yellow arrows show inflammation surrounding venous blood vessels in these lesions, suggesting that blood vessel abnormalities are linked to the development of early lesions in MS patients.

**The 7-tesla magnet is 140,000 times stronger than the earth's magnetic pull. The Medical Center's 7-tesla MRI is one of a handful available for basic and clinical research in the U.S.**




B ▲ SCAN
Lesions are more abundant in image B, which was obtained from the periventricular region of the brain, where MS lesions are often found. White arrows in image A point to abnormal iron deposits, which can be detected on 7-tesla MRI, indicating early neuronal degeneration in deep gray matter (i.e., lentiform nucleus, head of caudate, and thalamus).

# Predicting the Course of MS

Powerful tools are enabling researchers to search for markers that may help predict when, and how fast, the disease will progress.

BY GINA SHAW

# What happens next?

➡ That's the question that confronts patients, clinicians, and researchers when a diagnosis of MS is made.

To patients, it's an especially agonizing question because they are usually young when MS strikes—the average age of onset is 27. Will they have a limp? Will they need a wheelchair? Will it affect their mind? Or will they have few if any symptoms?

To clinicians and researchers, it's frustrating that they simply don't know.

Multiple sclerosis confounds scientists, explains Oded Gonen, Ph.D., professor of radiology, and physiology and neuroscience, because they are unable to predict the course of this disease. Conventional imaging techniques offer confusing information. The number of lesions identified does not always correlate with the degree of disability. Moreover, these techniques fail to identify some lesions that influence the severity of the disease.

Dr. Gonen and his colleagues at NYU's Center for Biomedical Imaging are addressing these problems by bringing to bear an arsenal of the world's most powerful and sophisticated imaging techniques to find markers in the brain that will signal how severe the disease will become.

It is a mission he first undertook at the suggestion of Robert I. Grossman, M.D., Dean and CEO, when both were at the University of Pennsylvania. Dr. Grossman has devoted the past 20 years to the development of novel radiologic methods to unveil and understand the hidden signs of MS and to assess patients' response to treatment. This endeavor has earned Dr. Grossman an international reputation as a preeminent researcher in this field. He became chairman of radiology at NYU in 2001, and again recruited Dr. Gonen to join him.

Dr. Gonen is applying spectroscopy to the study of MS. "We're looking for imaging holy grails that will tell us accurately, specifically, and early if there are changes to the brain of MS patients, and whether those are good or bad changes," says Dr. Gonen.

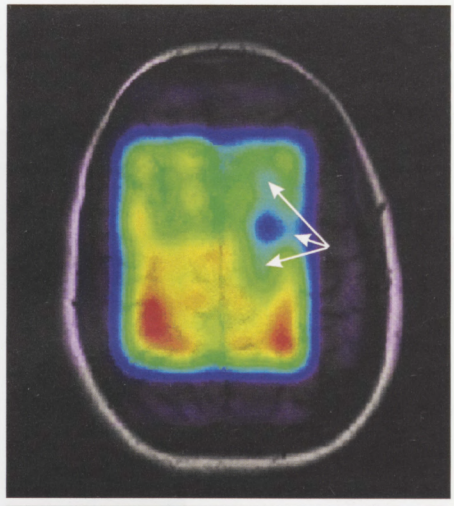
Dr. Gonen's studies are part of a decade-long collaboration with Dr. Grossman. Other researchers working in this area include Yulin Ge, M.D., associate professor of radiology, and Matilde Inglese, M.D., Ph.D., associate professor of radiology and neurology. All of their studies are supported in part by the National Institutes of Health.

Dr. Gonen is using MR spectroscopy to study four major brain metabolites that may prove to be useful biomarkers of MS: n-acetyl aspartate (NAA), an amino acid found only in the neurons and axons of the brain and a key marker of neuronal health and integrity; choline, a marker of membrane construction and breakdown; and creatine and myo-inositol, which in combination are markers of energy and proliferation of glial cells." (Glial cells help to form myelin, and they also transmit signals in the nervous system.)

"What I'm trying to do is determine whether those markers predict what is going to happen clinically before it happens," Dr. Gonen says. "Growing deficits of NAA will probably be reflected in cognitive dysfunction, for example, and an increase in regional choline levels may indicate that a lesion is about to appear there that may or may not also cause a relapse."

Dr. Gonen's study is tracking 25 MS patients in the early stages of the disease, and 25 age- and gender-matched controls, for five years. Three years into the research, his findings indicate that early on in the disease, there is little detectable difference in NAA levels—the essential marker of neuronal death—between MS patients and normal controls. Since patients at this stage of the disease usually have little cognitive dysfunction, this result jibes with his theories about NAA levels. He has found elevated levels of choline—the marker for the inflammatory stage of the disease, in which the myelin sheaths that shield the brain's axons are slowly destroyed.

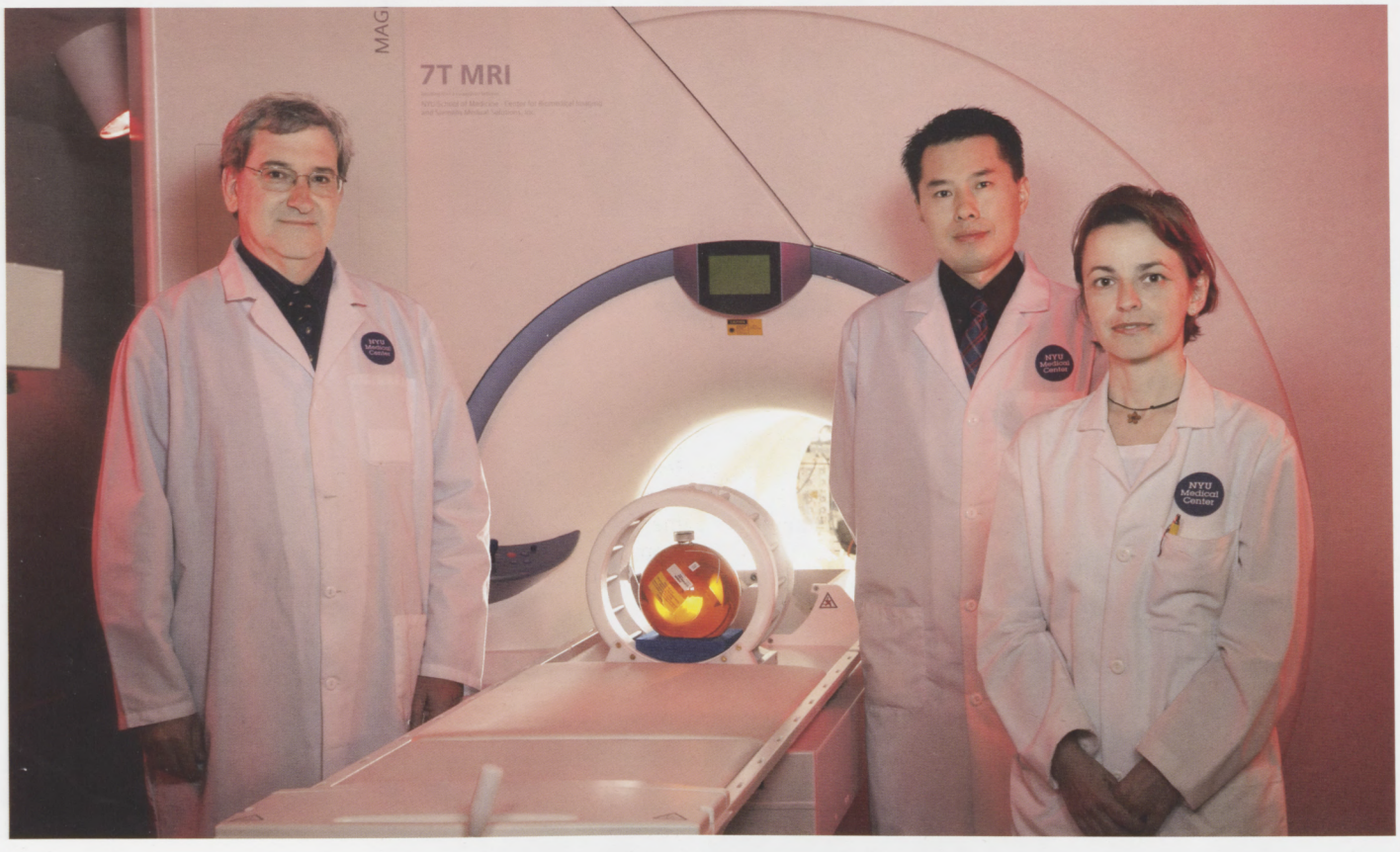
"The first thing that happens in the disease, that's what I think you should develop drugs to stop. My findings indicate that with MS, it's not neuronal damage, but inflammation or maybe even an earlier process," Dr. Gonen says. "That suggests to me that if you're a drug developer, you should focus on an anti-inflammatory treatment for the early stages, and the brain will take care of neuronal preservation."



Brain metabolites such as n-acetyl aspartate (NAA) may prove to be useful biomarkers for MS. Seen here is an MRI of the brain of a female MS patient, overlaid with the metabolic distribution of NAA, obtained with proton MR-spectroscopy (MRS) displayed in the format of a heat map for enhanced color contrast. Such images allow anatomic locations in the brain (from the underlying MRI) to be associated with metabolic activities (from the overlaid MRS). The white arrows point to a metabolic "hole," or deficit, over the visible lesion in the white-matter region of the brain as well as to a "halo" of NAA deficit surrounding it, which is not seen on the MRI.

**"We're looking for imaging holy grails that will tell us accurately, specifically, and early if there are changes to the brain of MS patients, and whether those are good or bad changes," says Dr. Gonen.**

BRAIN SCAN COURTESY OF ODED GONEN, M.D. PREVIOUS PAGES: 7-TESLA IMAGES COURTESY OF YULIN GE, M.D.




Oded Gonen, Ph.D., (left) with Yulin Ge, M.D., and Matilde Inglese, M.D., Ph D., in front of the 7-tesla MRI machine at NYU Langone Medical Center. The glowing orange and yellow globe in the center of the 7-T head coil contains pure oil, which is used for calibrating the system.

PHOTOGRAPH: ZACHARY ZSLAVIC

Neuroradiologist Dr. Inglese focuses on the clinical application of advanced MRI techniques in people with MS. She notes that imaging in common use today cannot detect prelesional injury, nor can it differentiate between lesions where there is merely inflammation and those that involve the death of axons. An axon is a critical part of a neuron because it transmits signals to other neurons. This is a critical distinction for the clinical picture because lesions where there is axonal loss are the only ones that lead to loss of function, such as a limp or cognitive problem.

"That's why there's this disconnect, this poor correlation between the number of lesions on the brain and the scores on rating scales used to measure disability," says Dr. Inglese.

Neuroradiologist Dr. Yulin Ge is focusing on inflammation. NYU is one of only a few major research centers in the country that have a 7-tesla MRI unit; most researchers are working with 3-tesla. (A tesla is a measure of MRI field strength—the higher the number, the more detailed the image.) Using 7-T, Dr. Ge has been able to detect differences among lesions that appear identical on conventional MRI. "What we're finding," says Dr. Ge, "is that the *number* of lesions is less important, because most lesions are found in white matter. The gray matter damage—neuronal damage—plays more of a role in neurological dysfunction and disability. Using quantitative MRI, we are developing methods to analyze the total lesion load so that we can better understand brain atrophy and the effect of treatment on that atrophy."

Dr. Ge is also using 7-T MRI to detect minuscule changes signaling that a lesion is about to develop. "We recently scanned MS patients and found that there are lots of subtle vascular abnormalities which had never been seen before in such detail," he says. "This vascular inflammation event is critical in the evolution of MS lesions. These findings not only highlight early lesion development, they will also be very important for monitoring treatment that might stop damage before it starts."

It will take time, though, before these techniques are available outside the research setting. Dr. Gonen wishes he and his colleagues could speed up the process: "I would like to know the future now. It's disheartening when your doctor puts you on a medication, five years elapse and you get worse, and the doctor says that it might have been the wrong medication all along. I don't want patients to have to hear that."●

# Life With Multiple Sclerosis

**There is no cure, but a holistic approach helps MS patients cope with an array of physical and cognitive symptoms.**

By Kyla Dunn
Photographs By Ethan Hill


PATIENT:
**RONALD THOMPSON**

Ronald was diagnosed with MS in 2002. Determined to enjoy life and always a night person, he still enjoys an active social life.

# Andrea and Ronald

**Thompson—a mother and son—share an apartment, half their genetic code, and a diagnosis of multiple sclerosis. Their experience of the disease, however, could not be more different.**

"Like day and night," Andrea, 55, says. "It's mind-boggling," agrees Ron, 30. Diagnosed almost a decade ago, Andrea still finds her symptoms manageable: some cramping in her legs, some numbness and pins-and-needles sensations in her hands, and a little vertigo. She walks everywhere from their home in Manhattan, including across the Brooklyn Bridge to work and a hundred blocks north to Harlem to visit her parents. Ron, on the other hand, was confined to a wheelchair within three years of his diagnosis at age 24. Andrea's type of MS is known as "relapsing-remitting," characterized by flare-ups of symptoms that subside within a few months. Ron's MS is "relapsing-progressive," with each exacerbation moving him another notch toward disability.

This bewildering variation is typical of MS, a chronic autoimmune disease that gives each patient an unpredictable cluster of symptoms. As many as 400,000 Americans have the disease, according to the National MS Society, and an estimated 10,000 new cases are diagnosed each year. At the MS Comprehensive Care Center, part of the NYU Hospital for Joint Diseases, a team directed by Joseph Herbert, M.D., helps patients cope with the wide range of deficits that can result. The center takes a holistic approach, bringing together neurologists, nurses, psychologists, social workers, occupational and physical therapists all in one place. In addition to classes in Fall Prevention and Strength and Balance, it offers an innovative Cognitive Rehabilitation program, even Clutter Management for those who have lost the ability to organize and plan effectively. At its Open Clinic seminars, patients learn about the latest MS research, as well as potential treatments, and the center is involved in clinical trials of new drugs.

Each MS symptom stems from an inflammatory lesion in the brain or spinal cord—areas where the patient's own immune cells mistakenly attack nerve cells responsible for sensation, movement, or thought. The attack strips away portions of myelin, the protective sheath that normally surrounds each nerve fiber and thereby allows it to conduct electrical signals smoothly. "The way the doctors explain it to me is this," says Andrea. "You have a wire—" She picks up an electrical cord from her living room floor and taps its plastic coating. "This is your myelin sheath. Underneath you have the copper. That's your nerve cell. What's happening with MS is that the outside of the cord gets frayed." MS is typically disabling rather than fatal, although in severe cases life-threatening complications such as breathing difficulties or aspiration pneumonia can occur. At the moment, there is no cure—only drugs that may slow the appearance of new lesions.

Inflammation of Andrea's optic nerves led to her diagnosis in 1999. At the time, she was the head teller at a bank and kept track of its cash. "This particular morning I looked at the ledger, and I couldn't see the numbers. All the numbers were doubled," she says. She had lost her depth perception, and was seeing spots. "I started crying," she recalls. "I said, I've got to go to the doctor because something's wrong." Treatment with IV steroids reduced the inflammation and restored some of her vision within weeks, yet continuing problems with her eyesight kept Andrea from returning to work for a year.

Then in August of 2002, Ron was diagnosed. "I used to be a skateboarder, snowboarder, rollerblader, mountain biker," he says. He had begun to trip unexpectedly, over nothing, and Andrea had noticed a change in his gait. "If you didn't know my son and you saw him walking in the street, you would have thought he was drunk," she says. When Ron's legs were too weak and uncoordinated to let him rollerblade, and his feet could no longer sense the cracks in the sidewalk, they started going to doctors. A year later, Ron was still "furniture walking" at home—leaning heavily on a couch or table to get from place to place. "Then he kept having exacerbations," Andrea says, "and it just progressed to the point where he couldn't walk." African Americans, like the Thompsons, are more likely to have a genetic variant that puts them at risk for severe MS. "They tend to be diagnosed a few years earlier, and the disease is more aggressive," Dr. Herbert explains. In response, the center is currently developing more-aggressive treatment approaches.

Ron is determined to make the best of it. "A lot of people, when something like this happens to them, they automatically shut down—like, oh, just because I can't walk I can't go anywhere. People are going to look at me," he says. "So what? Let them look at you!" Always a night person, he still goes out to bars and clubs. "I tease him, and his friends tease him," Andrea says. "They tell me Ron is like a babe magnet with this wheelchair. Girls are always jumping on his lap." Ron laughs. "Yeah, that's true. They feel bad for me, but at the same time they want to dance. And if I'm at the club, I'm going to get down and dance!"

There's no denying the logistical inconveniences, however. Ron's wheelchair won't fit through their apartment's bathroom door. "We got an estimate for how much it would cost to widen the doors and to do everything that has to be done," Andrea says. "It was a little under $25,000." It is difficult to juggle her part-time work as a secretary, multiple doctors' appointments, and caring for Ron. After a 14-hour double shift, she says, "I'm tired." Yet she still needs to help Ron transfer from one place to the other—to go to the bathroom, to get dressed, to get into bed. "I have to tell myself: Don't get angry; we don't have a home health aide at midnight."

Frequent injections are another unpleasant reality of MS. Before settling on his current MS drug, Tysabri, Ron tried almost every one of the ABCR drugs (Avonex, Betaseron, Copaxone, and Rebif) in use since the 1990s. Each modulates the immune system, in the hope of making

◂ **JOSEPH HERBERT, M.D.** Dr. Herbert directs the MS Comprehensive Care Center at the NYU Hospital for Joint Diseases.

MS flare-ups less frequent and less severe, and is injected somewhere between once a week and every day. The weekly Avonex injection needs to be given into a muscle, through a needle that is one and a quarter inches long. "I had to sit there and psyche myself up, ice my leg for 20 minutes or half an hour," Ron says. "Both me and my mother hate needles." Andrea hates them enough, in fact, to stretch her injections out to once every two or even three weeks, against doctor's orders. Avonex also produces a day of debilitating flu-like symptoms: fever, chills, sweating, muscle aches, and fatigue.

Despite the downside, says Lisa Laing, B.S.N., a certified MS nurse, certified rehab nurse, and the center's clinical coordinator, the injectable drugs were a major advance. Prior to the 1990s, there were no drugs available to slow progression of the disease. "Twenty, thirty years ago, if a patient was diagnosed with MS, there was this saying that a lot of doctors used: 'diagnose and adios,'" she says. "Those medications slowed down the disease progression by approximately 30 to 35 percent." Introduction of once-a-month Tysabri in 2004 was another major milestone. "It's really almost twice as effective as any of those injectable medications," she says. "It reduces the number of flare-ups by 67 percent compared to placebo." The medications do not work for every patient. But with Tysabri, Ron seems to have found a better treatment.

"There are a lot of other things that can go wrong, but so far we're holding our own," Andrea says, pausing to knock on wood. "It's been two years since Ron's had an exacerbation."

**Not all symptoms of MS** involve movement and sensation. Approximately half of patients experience cognitive symptoms. "My memory is horrible," says Evelyn Lebrón, 35, who was diagnosed in 1996. "You tell me something now, then ask me in two minutes—" She swipes a hand in front of her forehead as if cleaning a slate. "No recollection whatsoever."

Late in 2007, things reached crisis proportions at her job with a process server. "I would be billing the wrong attorneys and sending the wrong papers to the wrong courts," she recalls. One day, she had to ask her boss to explain something to her four separate times—even though she took notes (which she could not decipher later) and listened attentively. Evelyn went on disability for almost two months at the beginning of this year, during which she entered the MS Care Center's six-week cognitive training program, which is designed by staff psychologist Joshua Bacon, Ph.D., adjunct associate professor of neurology, and Tamar Fromm, who is the center's director of rehab services/senior clinical research coordinator, and a licensed occupational therapist and

certified clinical research coordinator. The program is intended to strengthen memory, problem solving, and concentration. "I did see an improvement," Evelyn says. "My memory still acts up, but I've learned to jot everything down. I have Post-it notes all over. I've cut down a lot on my mistakes."

People with MS are generally comfortable asking for this type of help, yet other symptoms of MS are so sensitive that patients hesitate to talk about them. "Sexual dysfunction is a common early symptom," explains Dr. Herbert, associate professor of neurology. This can involve decreased libido, erectile dysfunction in men, and genital numbness or lack of sensitivity in women. The list of uncomfortable topics doesn't end there.

"My biggest problem," Evelyn begins, then pauses for a long time, "is not having control of when I need to go to the ladies room." She finds bladder control fairly manageable; she simply goes every 45 minutes as a precaution. "But with the bowel," she says, "sometimes I have no control."

The embarrassment caused by these accidents can be profound. "I remember that happened when I first started dating my husband five years ago," she recalls. "All of a sudden I kind of shut down, and he was wondering what happened." She later mustered the courage to explain by phone: "I figured, if he wants to get the hell out, hey, it's better now than down the road." A lot of men had shied away once they learned about her illness. James was different. He told her there was nothing to be embarrassed about, and even invented a code word so she could let him know, discreetly, when an accident occurred. "Everyone has their guardian angel," she says. "He's definitely mine."

Social isolation can become a real problem for people with MS, says Fromm, who directs the occupational therapy program at the MS Care Center. "Some people retreat in their homes as their symptoms worsen," she explains. Depression is also common and may be a direct biological consequence of the disease. "We try to break the psychological paralysis and get them back out, enjoying what the city has to offer." Part of the center's holistic approach, these opportunities include trips to the Metropolitan Museum, Broadway shows, and "wellness" days of massage, yoga, and makeovers. Evelyn knows how valuable it can be to meet other people with MS. She met one dear friend through a telephone support group. "It's cool because I'm not embarrassed to talk to her about anything," she says. "Like, 'Are you having problems with your sex drive?'"

For Evelyn, the MS Care Center has been a "godsend." She says, "They have a very nurturing hand, Dr. Herbert has seen me when I've been at my wits' end, crying hysterically and in pain. You have to find a doctor who is willing to listen to you and do something to comfort you." She adds, "I now tell everyone: MS Care Center. You have to go there. Don't worry, they'll take care of you."

**While treatment may** be holistic, life for people with MS is often partitioned into two domains: one containing people who know about the diagnosis, and one containing people who don't. Outside of work, Alan Buckwalter, 44, is vocal about his MS and serves as a peer counselor. Yet he chooses to keep it quiet at the office. As a self-described Type A, working in the highly-competitive world of financial services, he says, "I don't want people to think I'm making excuses." He wears a red MS Society bracelet on one wrist under his business suit but says his colleagues don't have to know why.

**The fact that many of Alan's** symptoms are invisible does afford a certain amount of privacy. "I'm sort of the poster child, if you will," he says. "You'd never know if you saw me walking down the street that I had this horrible, horrible disease." During one exacerbation he lost feeling in the entire left side of his body, from the neck down, and still has no sensation in his left arm from fingertips to elbow. "You know when you sleep on your arm—and wake up with no feeling? Mine is like that 24 hours a day." He once ran his thumb over his moving table saw, and had to get ten stitches. "The nurses in the ER were wondering why I wasn't screaming," he says. There's also the profound fatigue that often comes with MS. "I don't want it to slow me down, but it does," Alan, a father of two, admits. "My sons hate it. They always want to play more."

Some exacerbations can be disconcertingly visible. For a couple of months, Alan had facial myokymia—a rapid pulsing of the muscles in his cheek. "Too much caffeine this morning" he would joke to people who stared. Part of MS is learning to live with uncertainty, since such exacerbations can occur at any time. Reacting promptly is key, Alan explains. "You have to get the inflammation down" in order to reduce long-term nerve damage.

Most effective is to prevent exacerbations from happening at all, and Alan has had enormous success with drug therapy. Diagnosed with relapsing-remitting MS in 1995, at age 31, he first began treatment with Avonex. But when a promising new drug, now called Tysabri, entered Phase III clinical trials in 2002, Alan signed up through the MS Care Center. "Somebody did the Avonex trial for me," he reasoned, "so I'm going to do this one." During the subsequent three years, while he was on Tysabri—a monoclonal antibody that blocks immune cells from entering the brain—not a single new lesion appeared on his MRIs. "I was in remission the entire time. No exacerbations," he says. And Tysabri is typically administered by IV just once a month.

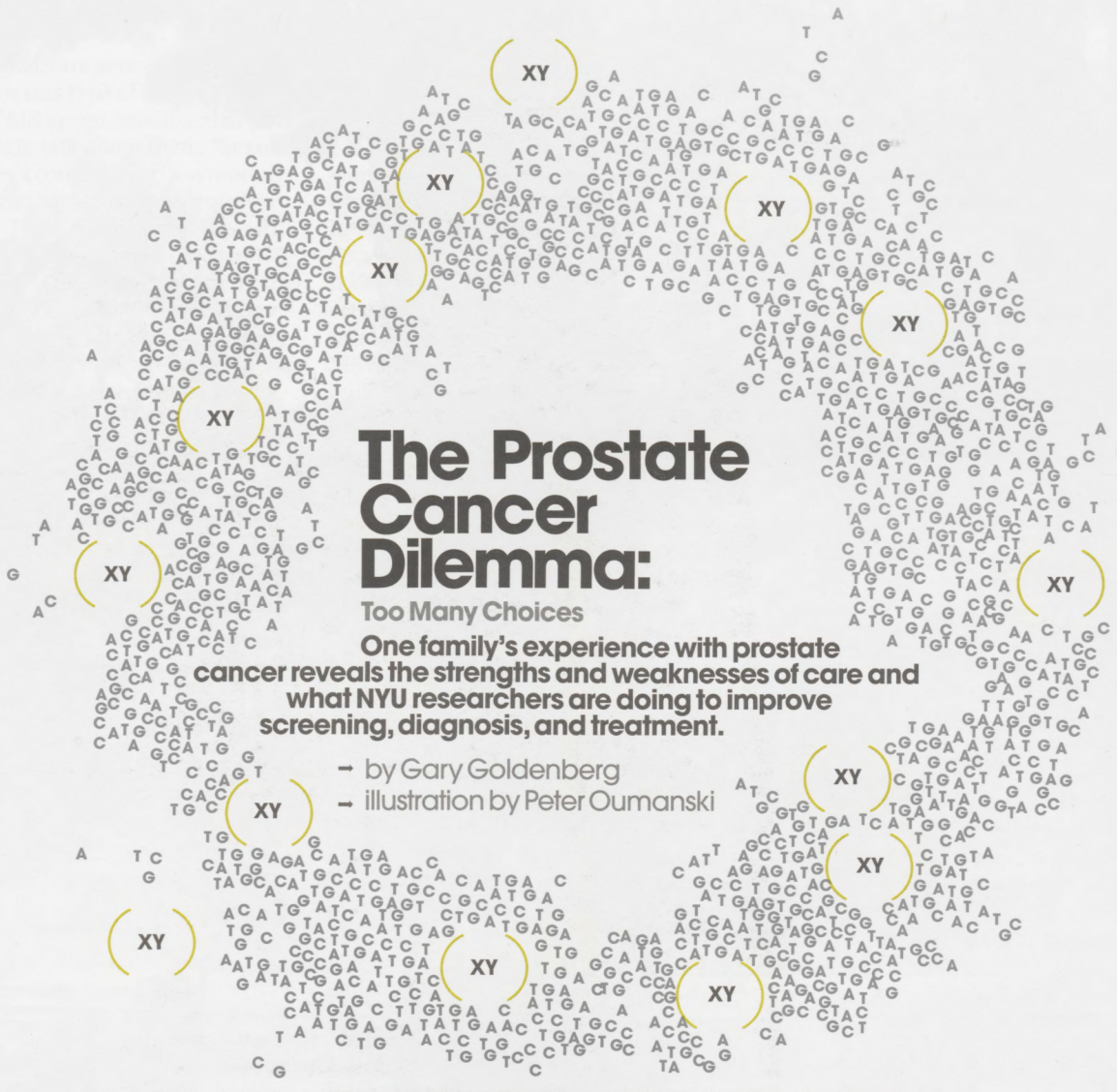
Alan realized how well the drug had worked for him in 2005 when the FDA abruptly pulled it from the market after two patients in a clinical trial died of a rare brain infection. After four months without Tysabri, Alan suffered two exacerbations back-to-back, each involving severe vertigo. "I had a hard time standing. I went to my older son's birthday party looking like I was drunk," he recalls. The FDA has put Tysabri back on the market—with a black box warning and restricted distribution—in response to the outcry from MS patients and their doctors. Alan has had no exacerbations and no new lesions since resuming treatment. Recurring pneumonia, though, has been a dangerous side effect, leaving Alan with permanent damage to his right lung. "Knowing the signs and symptoms," he says, "we can now catch it early." In July 2008 the drug's manufacturers reported two new cases of brain infection. For Alan, these are risks worth taking to keep his MS under control. "Knock wood. I say it every day: I'm such a lucky person," he says. For all MS patients, Dr. Herbert sees ample reason for hope: "There are some real blockbuster drugs coming down the pike," he says. Several oral drugs are currently being tested in clinical trials, as well as an IV infusion that is given just once a year.

Perhaps even Alan's drug hiatus was valuable in its own way: That summer, his seven-year-old son played bedside nurse, hooking up his father's IV steroids each day and going with him to appointments at the MS Care Center. "I don't want him to be afraid," Alan says. "I want him to understand Daddy's dealing with it." ●

**"We try to break the psychological paralysis and get patients back out, enjoying what the city has to offer,"** says occupational therapist Tamar Fromm.

PATIENT:
▸ **EVELYN LEBRÓN**

Evelyn was diagnosed with MS in 1996. A program at the MS Comprehensvie Care Center has helped her improve her memory and concentration.




# The Prostate Cancer Dilemma:

## Too Many Choices

**One family's experience with prostate cancer reveals the strengths and weaknesses of care and what NYU researchers are doing to improve screening, diagnosis, and treatment.**

→ by Gary Goldenberg
→ illustration by Peter Oumanski

→ **DONALD DENIHAN WAS JUST 38 WHEN HE LEARNED HE HAD LOCALIZED** prostate cancer, an unusually tender age for such a diagnosis. He suspected this day might come, but not nearly so soon. A few months earlier, his brother, ten years his senior, had been diagnosed with the disease. And 12 years before that, his octogenarian father had died of advanced prostate cancer, after suffering horribly with intractable bone pain for months.

Now, as if someone had mistakenly leaned on life's fast-forward button, Mr. Denihan had to face the tough decisions that come with prostate cancer, as well as his own mortality.

"A 38-year-old does not think about prostate cancer," says Mr. Denihan, a partner in Denihan Capital, a real estate investment company. "That's the furthest thing from your mind. You're thinking about raising your family, getting your business going."

The lifetime risk for prostate cancer for all men is about one in five, but the average age at diagnosis is 70. Apparently, Mr. Denihan's fate was written in his genes.

"Men with two or more first-degree relatives with prostate cancer have a fourfold increased risk for developing the disease," explains Harry Ostrer, M.D. professor of pediatrics, pathology, and medicine at NYU, and an expert in prostate cancer genetics.

In a sense, Mr. Denihan was lucky—not to have a hereditary disposition to cancer, of course, but to have fair warning. After his brother's diagnosis, Mr. Denihan went for a screening test, which revealed a PSA (prostate specific antigen) level of 3.9 ng/mL—just below the danger zone for the average senior, but a red flag for a 38-year-old, especially one with a checkered family history. PSA levels naturally rise with age; so a level that would be normal for an older man would be unusual for a younger man.

Following in his brother's footsteps, Mr. Denihan went to NYU Urology Associates for evaluation and advice. After a biopsy revealed he had localized cancer, he opted for a radical prostatectomy, the surgical removal of the prostate gland. Almost 10

years later, he remains cancer free, and his brother is doing well too.

"Early diagnosis probably saved his life," says Mr. Denihan's surgeon, Herbert Lepor, M.D., the Martin Spatz Chairman of the Department of Urology and professor of pharmacology at the School of Medicine and a pioneer in potency-preserving prostatectomy. "If he came to me in his fifties, I'd likely be telling him his disease was not curable and he would ultimately succumb to his cancer. Once prostate cancer spreads beyond the prostate, there's no cure."

## On the cusp of change

PERHAPS THE MOST UNUSUAL aspect of Mr. Denihan's case was that it was relatively clear what he should do every step of the way. His family history warranted early screening, and his age at diagnosis and his father's experience warranted aggressive treatment. For all too many men, however, figuring out how to deal with prostate cancer is a conundrum, starting with screening. PSA testing, the primary screening tool, is unreliable, leading to many false positives and needless biopsies and healthcare expenditures. As a result, medical societies disagree about the value of routine screening. The American Cancer Society supports it, but the American College of Physicians does not. Because 186,000 men will be diagnosed with prostate cancer this year, and 29,000 will die, the need for better screens and treatment is urgent.

Once prostate cancer is diagnosed, it's hard to predict which malignancies will linger harmlessly for years or even decades and which will quickly spiral out of control. Consequently, choosing an approach to care can be a roll of the dice. Patients are left to decide whether to watch and wait, and risk missing the window when the disease is localized and potentially curable, or to pursue aggressive surgical or radiation therapy, and risk serious quality-of-life side effects.

Researchers at NYU hope to answer some of these questions by developing personalized genetic screens, a better biopsy technique, a noninvasive focal ultrasound treatment, and novel approaches to advanced cancer.

## Personalized genetic testing

WHILE MR. DENIHAN had a good idea that prostate cancer was lurking in his genes, most other men haven't a clue. That may soon change.

In the 1990s geneticists were hot on the trail of a prostate cancer gene, buoyed by the discovery of individual genes for breast and colon cancer. "A whole bunch of candidate genes were identified, but all the studies had flaws," says Dr. Ostrer. "We don't know of any single gene that represents a high risk for developing prostate cancer. That whole line of inquiry has been put on the shelf for now."

Instead, researchers are looking for subtle genetic variations that distinguish which individuals are at greater risk for prostate cancer. Over the last year, 33 risk variants have been identified using DNA arrays, or gene chips, which have dramatically accelerated the analysis of gene expression across large swaths of the genome.

In a new study Dr. Ostrer and his colleagues are assessing the role of these risk variants in prostate cancer. To do so, they are tapping into a trove of tissue samples and clinical data collected from 1,800 of Dr. Lepor's patients since 2000, and correlating the expression of the variant genes with clinical outcomes.

"Because there are so many risk variants, every man is likely to have some," Dr. Ostrer says. "But we may be able to link certain combinations of these variants to different levels of risk." If so, this data could form the basis of a personalized genetic screening test, highlighting which men need to be especially vigilant about getting regular PSA tests and rectal exams.

DNA arrays might also prove valuable in characterizing the genetic signatures of cancers that are likely to progress, which would provide an invaluable guide to treatment.

In another project, a collaborative effort with Mount Sinai School of Medicine, Dr. Ostrer is studying whether genetic makeup can be used to predict the risk of incontinence, impotence, and other complications following brachytherapy, a popular alternative to prostatectomy in which radioactive seeds are implanted in the gland.

"We are at the very beginning of personalized genetic testing for prostate cancer," adds Dr. Ostrer. "We had 10 or 15 years of false starts looking for the single gene. But I imagine that in another 10 years, we will be using these risk variants all the time for making predictions and guiding therapy."

## Better biopsies

AFTER ALMOST A DECADE, Mr. Denihan still cringes at the thought of his prostate biopsy, which he remembers as "uncomfortable" at best. Certainly, there's nothing pleasant about having a biopsy gun inserted in your rectum, followed by the firing of a dozen or so tiny needles, one of several approaches for obtaining tissue samples. But at least the test worked as intended. Too often, biopsies miss malignant tissue, giving patients a false sense of security.

A new device called TargetScan may reduce this uncertainty. TargetScan employs a stationary rectal ultrasound probe and three-dimensional imaging to map the prostate. The system records exactly where biopsy samples are taken, ensuring accurate sampling of the entire gland, reports Samir Taneja, M.D., the James M. Neissa and Janet Riha Neissa Associate Professor of Urologic Oncology and director of the Division of Urologic Oncology, who is leading a nationwide trial of the device.

TargetScan may make "watchful waiting" (i.e., active surveillance) less of a gamble. "If I find a small, nonaggressive cancer in a 70-year-old man, I'm probably going to offer the patient the option to observe the cancer. With this device, I can go back a year later and biopsy exactly the same spot and determine whether the cancer is progressing," says Dr. Taneja, who also serves as a scientific adviser for TargetScan's manufacturer, Envisioneering Medical Technologies.

TargetScan's mapping capabilities could also allow for focal therapy, in which only the cancerous portion of the prostate is treated, potentially minimizing side effects.

## Focal therapy

WHEN IT CAME TIME to select a treatment, Mr. Denihan chose radical prostatectomy, even though it carries a small risk of urinary incontinence and a significant risk of impotence. "Seeing firsthand what my father experienced—the bleeding, the constant pain—I wanted the cancer out immediately, no matter what the consequences were," he says.

For Mr. Denihan, the consequences were relatively minor. His bladder control returned within days, and his potency within months. "It's not the same as it was before," he says, referring to his erectile function. "But I have nothing to complain about."

However, many other patients do, especially older men, who tend to have the most trouble with erectile dysfunction after prostatectomy. About four in 10 patients suffer this indignity, even with highly experienced surgeons like Dr. Lepor, who has performed the operation some 3,600 times. "That is where I have to do better," he says.

An alternative to surgery may be a new noninvasive therapy called high-intensity focused ultrasound (HIFU), which uses high-frequency sound waves to destroy prostate tissue. The sound waves, which are generated with a rectal probe, can be focused anywhere in the prostate within 3 mm of precision, an area slightly bigger than the head of a pin.

"With TargetScan information, we would be able to do focal treatment and remove only cancerous portions of the gland," says Dr. Lepor, who is heading the first nationwide study of HIFU, which will compare it to brachytherapy. Moreover, HIFU can be repeated if more cancerous tissue is detected at a later date, which is not true with either brachytherapy or external beam radiation.

Dr. Lepor suspects that HIFU will be

▲ Prostate cancer survivor **Donald Denihan** (second from right) places his arm around his surgeon, **Dr. Herbert Lepor**. From left to right: brother **Benjamin (Patrick),** cousin **Daniel** and brother **Laurence**.

PHOTOGRAPH BY WESLEY MANN

less effective than prostatectomy in curing the more aggressive cancers, but it will likely be associated with quicker recovery and better preservation of potency. "Today, radical prostatectomy is largely reserved for the treatment of men with low-risk cancers, and the survival of these men may not be compromised if they choose to undergo HIFU," he says. "If studies at NYU and other institutions confirm these predictions, some patients will find HIFU an attractive option. But HIFU won't be for everyone."

## Androgen deprivation alternative

LEFT UNCHECKED, prostate cancer usually proceeds slowly, and sometimes silently. Eventually, symptoms begin to appear—such as frequent urination, increased urination at night, difficulty starting and maintaining a steady stream of urine, and blood in the urine. Unfortunately, these are also the symptoms of benign prostatic hyperplasia, or BPH, the annoying but not dangerous enlargement of the gland common in men after age 50; distinguishing cancer from BPH can be difficult. When prostate cancer metastasizes, it typically spreads to the bones, lymph nodes, rectum, and bladder. At this point, the most common symptom is bone pain, often in the pelvis, ribs, or spine. Prostate cancer can also compress the spinal cord, leading to leg weakness and urinary and fecal incontinence.

By the time Mr. Denihan's father was diagnosed, the cancer had already spread far and wide. His main recourse was surgical castration to stem the flow of male hormones called androgens, which accelerate the growth of cancer cells. The therapy did little good for his cancer or his quality of life. Within two years, he was gone.

A quarter-century later, androgen deprivation remains the standard therapy for advanced cancer, though it is now accomplished by the administration of hormones. "We've been using the same basic approach for 65 years," says Anna Ferrari, M.D., associate professor of medicine (oncology). "We need better therapies."

Androgen deprivation does work for a time, yet it ultimately fails as the surviving cancer cells develop resistance. To make matters worse, patients invariably suffer from hot flashes, fatigue, or sexual dysfunction, as well as other serious side effects. The elder Mr. Denihan was no exception.

An alternative approach, being developed by Dr. Ferrari and her colleagues at NYU, is to block the function of the androgen receptor, rather than depriving the body of androgen. Blocking the activity of this key molecule seems to debilitate prostate cancer cells more than other androgen-dependent cells in the body, thereby lessening side effects. To strengthen the therapy, the researchers are adding agents that disrupt the resistance pathways that tumor cells develop. Clinical trials in men with recurrent prostate cancer after primary therapy and in men who are no longer responding to hormone therapy will be launched within the year.

Dr. Ferrari is also experimenting with immunotherapies for men with different stages of prostate cancer, including at least three different vaccines. She is testing new chemotherapy regimens, some in combination with cancer vaccines, for men with metastatic disease.

## The next generation

THESE DAYS, MR. DENIHAN is back to thinking about raising his family and growing his business, not about prostate cancer. But as he inches into middle age there comes a new worry: Have his three young sons inherited the family predisposition for the disease? If so, will physicians be able to do anything to stop it? More than a few fathers have the same worry, and the same hope. ●

# Lori's Choice

**IF YOU KNEW YOU were going deaf, what price would you pay for a few extra weeks of listening to Mozart, the sound of your lover's voice, or the wind rustling through the trees?**

About a year ago, Long Islander Lori Davila faced such a terrible calculus. A benign tumor was pressing against her brainstem. The ever-enlarging growth had to be removed, even though it would mean certain deafness. But every day she waited increased the risk of neurological complications, or worse.

Lori, now 30, opted to have the surgery as soon as possible, rather than take the gamble. "But when I learned I would lose my hearing," she says, "I cried for about two months straight."

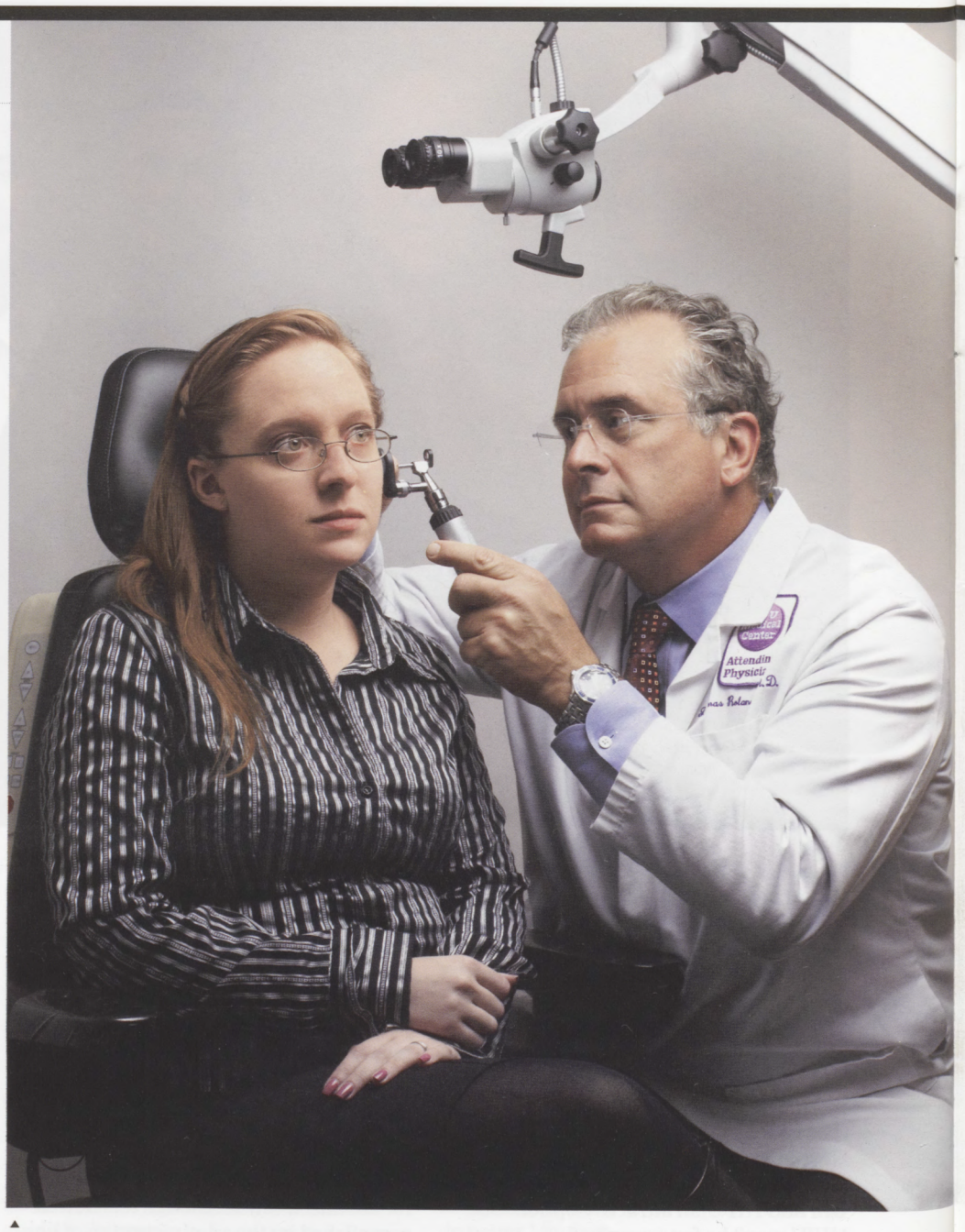
The operation also left her face partially paralyzed. Now, she faces multiple surgeries for new tumors in her brain and on her spine.

Such is the lot of patients with neurofibromatosis type 2 (NF2), a rare and incurable genetic disorder in which one tumor after another infiltrates the central nervous system. Typically, the auditory nerves are the first to be affected, starting in early adulthood. (In a more common sister disease, NF1, the growths primarily affect the peripheral nerves.)

Over the years, Lori has grappled with depression, yet she remains optimistic and good-humored, especially now that she's found a multidisciplinary team of specialists at NYU who are well acquainted with this "orphan" disease and can offer hope in the form of experimental therapies.

Like many other NF2 patients, Lori spent years searching for physicians who could provide any help. Most of the neurologists she visited hadn't even heard of the disease. "Anytime I saw a new doctor, I'd print out information on NF2 from Wikipedia for them to read before my visit," she says.

Lori's battle with NF2 started in college, when her vision began to fade. She was referred to a local neurologist, who discovered a tumor engulfing one of her auditory nerves. The tumor was removed, leaving her deaf in the affected ear, a common side effect of the surgery. Her recovery was complicated by a cerebral spinal fluid leak, necessitating a spinal tap and five extra days in the hospital. She struggled to complete the semester; dropping out meant losing her health insurance.



Lori Davila and J. Thomas Roland Jr., M.D.

Lori had no idea what to expect in the months and years ahead. "The doctors knew nothing about NF, other than I had it," she says. "I didn't know where to go for information. So I just tried to be normal and got regular MRIs to make sure nothing grew too big." But the disease progressed, eventually affecting her sense of balance, disrupting her sleep, and sapping her energy.

About two years ago, her face started tingling and she began losing hearing in her good ear. Through a friend, she learned about the NF2 team at NYU. The timing was fortunate. "Planning is critical for these patients," says J. Thomas Roland Jr., M.D., associate professor of otolaryngology and neurosurgery, who manages her care. "I've seen more than a few cases where surgery was delayed and removing the tumors caused substantial nerve damage, so much that remedies like ABIs or nerve grafts were no longer possible."

At NYU the tumor on her brainstem was discovered and removed. She has since undergone several other procedures at the Medical Center, including a nerve graft, reducing her facial paralysis, and an auditory brainstem implant (ABI), restoring partial hearing in one ear.

By default, Dr. Roland has become Lori's primary care provider. "No one else was

PHOTOGRAPH BY WESLEY MANN

overseeing her care," he says. "That's when I had this idea that we should have a center where patients like her can get comprehensive care, the latest information, and proper counseling, as well as access to clinical trials."

With a grant from the Children's Tumor Foundation, NYU is establishing a center for patients with NF1, NF2, and a related disease called schwannomatosis, bringing together specialists in neurosurgery, otolaryngology, ophthalmology, pain management, audiology, rehabilitation, and counseling. The center, the first of its kind in the metropolitan area, will also coordinate basic and clinical research into causes and treatment of NF.

"I am still struggling to get back to a normal life," says Lori, who stays in constant touch with friends and family and other NF2 patients via e-mail and instant messaging (which is how she was interviewed for this article). "It was very difficult to learn how to communicate. I lost my hearing months after getting married—as if married couples don't have a hard enough time communicating! I pushed everyone—my family, my closest friends, my husband—to learn to ASL (American Sign Language). I refuse to be that quiet person in the corner left out of all conversations. With lip reading and my ABI, I can understand what people say, and it's making it easier."

Easier, but not easy. "I can get away as passably normal to strangers, but once I start to talk or smile, it's impossible to miss," she explains. "A lot of people treat you differently when something looks physically wrong with you."

Although NF2 patients are living longer and longer these days, thanks to early and aggressive surgical intervention, the only effective treatment, Lori's future is uncertain. "I have been deeply worried because of the number of tumors I still have," she says. "I am hoping desperately I can get on some type of medication to prevent me from having to have more surgery."

Several promising anti-tumor drugs are now in the research pipeline, and NYU is preparing to launch several clinical trials.

In the meantime, Lori soldiers on, "enjoying the little things that I can do and do have." She looks forward to finding a job that can accommodate her disabilities and has started a small embroidery business to raise NF2 awareness and money for research.

"All these patients impress me overwhelmingly with their courage, fighting through this disease and grabbing the most out of life that they can," says Dr. Roland. ●



# The Music of the Night

## To cure sleep apnea, an ancient instrument may be best medicine of all.

PUFFY-CHEEKED AND RED-FACED, with beads of sweat across his forehead, Kazim Yildiz, 42, is steadily vibrating his lips, much like a baby blowing bubbles. He is playing a didgeridoo, believed to be the world's oldest wind instrument. Traditionally crafted from a branch of a eucalyptus tree, the cylindrical wooden tube is indigenous to Australia, where it's been used in traditional Aboriginal ceremonies for thousands of years.

Now, modern medicine has found a new use for this ancient artifact. With practice, the didgeridoo produces an eerie, reverberating bellow. But to those afflicted with sleep apnea—a potentially serious sleep disorder in which breathing repeatedly stops and starts—the sound is music to their ears.

"In people with sleep apnea, the airway intermittently collapses during sleep," explains Dennis Hwang, M.D., a researcher in the Division of Pulmonary and Sleep Medicine. "We believe that learning to play the instrument strengthens the muscles of the upper airway and reduces the airway collapsibility during sleep."

Yildiz, an information technology expert at Merrill Lynch, is part of a 10-person study being conducted at NYU to determine whether playing the didgeridoo regularly can help to cure their disorder. Sleep apnea (Greek for "without breath") affects as many as one in five middle-age adults, who literally stop breathing for moments while they are asleep. These stoppages cause the brain to wake up, which allows breathing to resume, but the pattern may leave him sleepy and irritable during the day. Loud snoring is a common symptom of sleep apnea, although not everyone who snores has the disorder.

"Lately, I started feeling very drowsy and tired during the day and waking up many, many times during the night," says Yildiz. "I couldn't stay awake, and I thought, something is wrong."

Recent studies suggest that sleep apnea increases the risk of high blood pressure, diabetes, heart attack, and stroke. Traditional therapy uses continuous positive airway pressure (CPAP), delivered through a cumbersome mask and tubing, to keep the airways open. But CPAP is not for everyone.

Playing the didgeridoo is likely to be a much more pleasant option.

In 2005, researchers in Switzerland reported in the *British Medical Journal* that playing the didgeridoo decreased daytime sleepiness, and the severity of sleep apnea, in people with the condition. In the NYU study, researchers will measure the patients' airway collapsibility before and after lessons to document how much the instrument strengthens the muscles. The key, says Dr. Hwang, is probably the peculiar "circular breathing" technique, which allows the player to sustain a note almost indefinitely without pausing to inhale.

Instructor Giten Tonkov of the Energy of Breath Institute has been playing the didgeridoo for eight years. He still remembers the first time he heard its distinctive sound. "It was mysterious and mystical," he says, "and the power of the vibration it gives out is very different. It struck a chord with me." ●

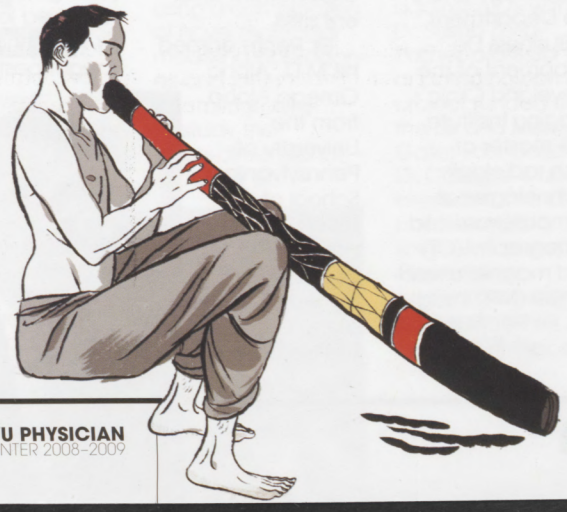


ILLUSTRATION BY JILLIAN TAMAKI

# Dr. Manno to Lead Pediatrics Department

CATHERINE SCOTT MANNO, M.D., has been appointed chairwoman of the Department of Pediatrics. Dr. Manno was previously at the University of Pennsylvania School of Medicine and the Children's Hospital of Philadelphia (CHOP), where she held the Elias Schwarz Endowed Chair in Pediatric Hematology and served as associate chairwoman of clinical activities in the Department of Pediatrics and senior physician in the Division of Hematology.

Dr. Manno has been the principal investigator of several clinical research studies in the area of hemophilia, most recently leading a Phase I study of gene transfer into the liver in subjects with hemophilia B. She has published widely on such topics as gene therapy for hemophilia, neonatal transfusion medicine, and bleeding disorders in children.

In addition, Dr. Manno served in various administrative roles at Penn and CHOP, including president of the executive committee of the medical staff, co-chair of the Clinical Translational Research Center Council, and medical director of the Hemostasis and Thrombosis Center and the Comprehensive Hemophilia Program. She was honored at both institutions with numerous awards for outstanding teaching.

At Hahnemann Medical College, where she earned her M.D., she was inducted into the Alpha Omega Alpha Medical Honor Society. Dr. Manno completed her residency in pediatrics at St. Christopher's Hospital for Children in Philadelphia and her fellowship in pediatric hematology-oncology at CHOP. She is a fellow of the American Academy of Pediatrics, a member of the American Pediatric Society, and a member of the medical and scientific advisory committee of the National Hemophilia Foundation. ●

## Dr. Pagano is HHMI Investigator

MICHELE PAGANO, M.D., the May Ellen and Gerald Ritter Professor of Oncology in the Department of Pathology, has been named an investigator at the Howard Hughes Medical Institute (HHMI). Investigators are selected for their creativity, innovative ideas, and productivity.

Dr. Pagano's research focuses on the protein components of the ubiquitin system, a key element of the cell's recycling function. His wide-ranging and productive investigations of these proteins, called F-box proteins, have shown that they play a powerful role in many cellular processes, including the control of cell proliferation.

Dr. Pagano received his M.D., with honors in molecular endocrinology, from the Federico II University in Naples, Italy, in 1989. A postdoctoral fellow at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, from 1990 to 1992, he was a principal investigator and scientific co-founder of Mitotix Inc. in Cambridge, MA, from 1992 to 1996. He joined the NYU faculty in 1996. ●

## Dr. Reinberg Receives HHMI Collaboration Award

DANNY REINBERG, PH.D., professor of biochemistry, received a new multi-million dollar award from the Howard Hughes Medical Institute to lead a collaborative project to study the genetics underlying differences in longevity, social behavior, and brain aging in ants. Dr. Reinberg, a cellular biologist who studies gene expression and an HHMI investigator since 1994, became interested in ants because they exhibit a wide range of behaviors, and have comparatively long lives.

Using ants as a model, his group will investigate how epigenetic changes, which are passed from one generation to the next but are not coded in genes, shape the behavioral adaptations in ant communities. "I truly believe that this project has opened the door for my next 20 years of science," says Dr. Reinberg. His group first plans to sequence the genomes of three ant species. The newly funded HHMI Collaborative Innovation Awards are intended to encourage scientists to undertake large, new projects that require a team of collaborators with a range of expertise. ●

PHOTOGRAPHY BY: BEN FERRARI (DR. MANNO AND DR. RECHT); PAUL SCHNECK (DR. PAGANO); RENÉ PEREZ (DR. REINBERG)

# Dr. Recht Named Radiology Chairman

MICHAEL P. RECHT, M.D., has been appointed chairman of the Department of Radiology. Dr. Recht comes to NYU from the Cleveland Clinic, where he was chairman of the Department of eRadiology and of the Department of Business Development of the Cleveland Clinic's Imaging Institute.

A master of such radiologic technologies as computer-assisted tomography (CT) and magnetic resonance (MR) imaging, Dr. Recht is also a leader in the field of "eRadiology." This relatively new discipline, engendered by the development of digital imaging in place of traditional films, has opened the way to remote diagnosis and collaborative interpretation by experts from different sites.

Dr. Recht earned his M.D., Alpha Omega Alpha, from the University of Pennsylvania School of Medicine. He completed his internship in medicine at the Graduate Hospital of Philadelphia and his residency in diagnostic radiology at the Hospital of the University of Pennsylvania, where he was chief resident.

A prolific author whose work appears regularly in prestigious peer-reviewed journals, Dr. Recht has also taught postgraduate courses around the globe. He has chaired the research committee of the Society of Skeletal Radiology, the musculoskeletal committee of the American College of Radiology Imaging Network, and the sponsorship committee of the International Skeletal Society. His honors include the Norman Glazer Resident Teaching Award at the Cleveland Clinic Foundation and the 2001 President's Award from the International Skeletal Society. ●

# Drs. Katz and Priori to Head New Cardiac Programs

STUART KATZ, M.D., has been named the first Helen L. and Martin S. Kimmel Professor of Advanced Cardiac Therapeutics and director of the new Heart Failure Program at NYU Langone Medical Center. Prior to joining the medical center earlier this year, he served as director of Yale University's Heart Failure/Transplantation Program.

A widely respected clinician and researcher, Dr. Katz has focused his career on patient-oriented clinical research, education, and care, and has made major contributions to our understanding of endothelial dysfunction in patients with heart failure. Most recently, he has been investigating the biological effects of iron stores in the body on vascular function, and evaluating the potential clinical applications of erythropoietin, a hormone that controls production of red blood cells, in patients with acute coronary syndromes. He has also devoted substantial effort to mentoring junior faculty pursuing clinical research careers.

Dr. Katz will work closely with cardiovascular experts at the medical center, both medical and surgical, to establish a multidisciplinary program devoted to innovative strategies for treating heart failure. He will also collaborate with basic and translational investigators to explore novel gene, cellular, and device-based therapies for patients with cardiovascular disease.

After receiving his M.D. from Downstate Medical Center and an M.S. degree in biostatistics from Columbia School of Public Health, Dr. Katz completed his internship in internal medicine at Baltimore City Hospital, and his residency in internal medicine at Francis Scott Key Medical Center, part of Johns Hopkins Medical Institutions. He went on to work with renowned cardiologist Edmund Sonnenblick, M.D., as a cardiology research fellow at Albert Einstein College of Medicine, becoming a faculty member there. He subsequently served on the faculty of Columbia College of Physicians and Surgeons before joining Yale University School of Medicine as an associate professor of medicine in 2001.

A recipient of the Henry L. Moses Clinical Research Award and numerous research grants from the American Heart Association and National Institutes of Health, Dr. Katz has published over 100 articles on heart failure and related topics. He is a section editor for the *Current Heart Failure Reports* journal, and he serves as an ad hoc reviewer for many other journals. ●

SILVIA G. PRIORI, M.D., PH.D., has been named professor of medicine and director of the new NYU Cardiovascular Genetics Program. A clinical cardiologist who is internationally recognized for her research on inherited cardiac arrhythmias, she previously was director of the Molecular Cardiology and Electrophysiology Laboratories at Fondazione Salvatore Maugeri in Pavia, Italy. There she established the world's largest genetic databank and clinic for patients with inherited cardiac ion channel disorders—the leading cause of cardiac death for people under 40.

Dr. Priori received her M.D. and her Ph.D. in cardiology pathophysiology from the University of Milan. At the Pavia clinic, Priori's group developed genetic testing for many of these inherited cardiac disorders, while also pursuing their molecular pathophysiology through the creation of mouse modeling as well as molecular, cellular, and biophysical studies.

Dr. Priori will now bring this multidisciplinary approach to NYU, where she will work closely with NYU Langone's cardiac electrophysiology team, directed by Dr. Larry Chinitz, to establish a clinical and molecular genetics program devoted to inherited cardiac diseases. The program is supported by gifts from the Beatrice Snyder Family Foundation and Mr. Harold Snyder, The Diane and Raphael Recanati Family Foundation, and the Leon H. Charney Foundation.

In addition to coordinating all of the advanced cardiovascular genetics and genomic studies being conducted at NYU, Dr. Priori will also oversee the creation of new clinical facilities to evaluate, counsel, and treat patients and families potentially at risk for life-threatening inherited heart rhythm disorders such as long-QT syndrome.

A major goal of the new program is to establish a joint clinical database including patients evaluated at NYU as well as those seen in Pavia, Italy. Dr. Priori will also establish a translational research program in the Joan and Joel Smilow Research Center, which will focus on furthering our understanding of the molecular basis for inherited arrhythmias and will also explore novel therapies for patients at risk of sudden cardiac death. ●

PHOTOGRAPHY BY ALESSANDRO VECCHI (DR. PRIORI)

# Dr. Cardozo Receives New Innovator Award

TIMOTHY CARDOZO, M.D., PH.D., assistant professor of pharmacology, was one of 31 scientists nationwide to receive the Director's New Innovator Award from the National Institutes of Health. The five-year award, established in 2007, supports exceptionally creative, promising investigators who propose innovative projects that have the potential for unusually high impact. Dr. Cardozo is working to establish new drug discovery and design methods using a combination of novel molecular modeling approaches and X-ray crystallography to study the three-dimensional structure of

molecules. He is developing a vaccine against AIDS with Dr. Susan Zolla-Pazner, professor of pathology, on a project funded by the Bill and Melinda Gates Foundation. Dr. Cardozo is also interested in finding novel ways to target the parasite *Plasmodium falciparum*, which causes malaria, among other pursuits. ●

# Dean's Honors Day Brings a Bounty of Awards and Recognition

TRADITIONS FORM THE FOUNDATION of an institution—a way of acknowledging where we have been and where we are heading, and a reminder of the common purpose that joins all of us. • For NYU Langone, Dean's Honors Day has come to exemplify this communal bond. Instituted in 2002 to salute newly appointed and promoted faculty members, this annual celebration took on an even deeper meaning in 2007 with the addition of two new awards: The Valentine Mott Founders Award, given to key supporters of the Medical Center, and the Master Awards, honoring selected faculty members for career excellence in the Medical Center's three mission areas.

The second presentation of these new honors on November 10, at the 2008 Dean's Honors Day, was a special moment, made even brighter by the surprise announcement of two major gifts.

### The Valentine Mott Founders Award

The Valentine Mott Founders Award, named after the world-renowned vascular surgeon who co-founded the NYU School of Medicine in 1841, is given to individuals who have made exceptional contributions to NYU Langone. Last year's inaugural award was presented to Medical Center trustee Joel Smilow, whose support of NYU has included an endowed professorship in cardiology as well as funding for the Department of Urology, the Cardiac Prevention and Rehabilitation Center, and, most recently, the Smilow Research Center.

The 2008 Mott Awards went to two other longtime benefactors of the Medical Center, Helen L. Kimmel and Wilma "Billie" Tisch.

Mrs. Kimmel, together with her late husband, Martin, has made numerous gifts to NYU Langone over the years. Dean Robert Grossman, M.D., used the occasion of her Mott Award presentation to announce that Mrs. Kimmel is donating $150 million toward the construction of NYU's new clinical-care facility, to be named the Kimmel Pavilion *(for more on Mrs. Kimmel and her gift, see see page 3).*

Mrs. Tisch, with her late husband and longtime Medical Center Trustee, Laurence, has been a supporter of the Medical Center and the University for decades. A joint gift of $30 million made in 1989 by Billie and Laurence Tisch along with Laurence's brother Preston Robert Tisch and his wife, Joan, led to the renaming of Tisch Hospital in their honor. The family's name also graces the Tisch School of the Arts on NYU's Washington Square Campus.

A trustee of Skidmore College, of which she is also an alumna, Mrs. Tisch is co-president of the Tisch Foundation. Her son, Thomas, and his wife, Alice, are also trustees of both the Medical Center and the NYU Child Study Center. In addition, Alice chairs KiDS of NYU.

"We have been indebted to the Tisch family for nearly 20 years," said Dr. Grossman, who cited Mrs. Tisch's "vision, boundless energy, and strong intellectual leadership."

"Like Dr. Mott," noted Dr. Grossman, "Helen Kimmel and Billie Tisch have committed themselves to improving the lives of others, and both have a form of greatness that goes beyond any one single act but indeed reflects their whole character."

**The second presentation of these Valentine Mott honors was a special moment.**

### The Master Awards

The Master Awards honor faculty members for career achievement in the Medical Center's three mission areas—education, clinical excellence, and research.

"The initial idea behind Dean's Honors Day was to recognize an individual's achievements, such as being promoted to professor or being granted tenure," said Steven Abramson, M.D., vice dean for Education, Faculty and Academic Affairs. "But we also realized there were certain professors among our distinguished faculty who have reached such a pinnacle of accomplishment in mission areas that they stand out as models for the rest of us. The Masters Awards are NYU's way of honoring this lifetime of achievement."

Although each Master is recognized for a specific mission area, noted Dr. Abramson, "In point of fact, these individuals were often among the very best in other mission areas, as well. They are giants in their fields and their reputations are transcendent. When a school has a faculty like this, they become pillars of your culture, and they have an impact every day on people who come through this institution."

The 2008 Masters Awards honorees are Anthony J. Grieco, M.D., F.A.C.P., Master Educator; Albert Goodgold, M.D., Master Clinician; and Richard P. Novick, M.D., Master Researcher.

Dr. Grieco, '63, professor of medicine and associate dean for alumni relations and academic events, has held a variety of key teaching positions in the Department of Medicine, and has played a lead role in developing the department's education standards. He has also served as medical director of Cooperative Care, which helps family members become care partners for patients. His teaching honors include

Dean's Honors Day honorees and participants included: Back row, from left: **Dr. Albert Goodgold**, **Dr. Anthony Grieco**, **Dr. Steven Abramson**, **NYU President John Sexton**, **Dean and CEO Robert I. Grossman**, **Benefactors Mrs. Helen L. Kimmel** and **Mrs. Wilma "Billie" Tisch**, **Medical Center Chairman Ken Langone**, **University Chairman Martin Lipton**, **Dr. Robert Berne**. Front row, from left: **Dr. David D. Sabatini**, **Dr. Susan Harlap**, **Dr. Martin Blaser**, **Dr. Felicia Axelrod**, **Dr. Richard P. Novick**, **Mrs. Kimmel** and **Mrs. Tisch**, **Dr. Rodolfo Llinas** and **Dr. Grossman**, **Dr. Benard Dreyer** and **President Sexton**.

multiple Distinguished Teacher Awards in Clinical Science, and the University-wide Great Teacher Award.

As a general internist, Dr. Grieco studied the mechanism of antidiuretic hormone and the role of homocysteine in vascular occlusion. His identification of azarabine as a cause of fatal homocystinuria led to the drug's withdrawal, potentially saving innumerable lives. "He is the ultimate role model because he himself is such a sensational physician," said Dr. Grossman in presenting Dr. Grieco his award. "More than anyone else I can think of, he has a genius for seeing the best in his students. They become outstanding doctors because that is what he *believes* they can be."

Dr. Goodgold, professor of neurology and radiology, is legendary for his ability to diagnose neurological conditions—an ability he credits largely to his sense of curiosity. A faculty member in the Department of Neurology since 1960, he has also had a lasting impact on the medical students, residents, and fellows who have trained with him over the years. The greatest compliment he has received from other doctors, Dr. Goodgold has said, is that he taught them how to think, and transmitted to them his enchantment with science. He continues to study science, history, politics, Italian, literature, music, and the theater.

"Dr. Goodgold is renowned for his ability to see what no one else can see," said Dr. Grossman. "His diagnostic acumen is matched by his scientific insights into the origins of neurological disease. But his greatest gift as a doctor is the support he gives his patients."

Dr. Novick, '59, professor of microbiology and medicine and an investigator at the Skirball Institute for Biomolecular Medicine, recently had the honor of being named to the National Academy of Sciences. His research has focused on *Staphylococcus aureus*, a common bacterium that is the leading cause of hospital-acquired infections, and that is also becoming increasingly drug-resistant. Dr. Novick is widely regarded for his seminal work in plasmid biology—the study of extra-chromosomal DNA molecules that can confer antibiotic resistance on host bacteria. More recently, his laboratory discovered a master gene that controls a signaling pathway responsible for the production and release of the *S. aureus*'s toxins and other disease-causing products.

An adjunct professor at NYU School of Medicine for many years, Dr. Novick was director of the Public Health Research Institute in New York from 1982 to 1992, and became a member of the NYU faculty in 1993. "Dr. Novick is, and I suspect will forever remain, at the very forefront of our understanding of infectious diseases," said Dr. Grossman, "in particular the mobile genetic elements that are the chief culprits in virtually all lethal bacterial toxins and in those most resistant to antibiotics."

The 2007 Masters Awards honorees, honored at last year's ceremony, are Martin S. Nachbar, M.D., Master Educator; Frank C. Spencer, M.D., Master Clinician; and Rodolfo R. Llinas, M.D., Ph.D., and David D. Sabatini, M.D., Ph.D., Master Researchers.

Dr. Nachbar, '62, associate professor

PHOTOGRAPHS BY JAY BRADY

of microbiology and medicine and director emeritus of the Division of Educational Information, is a national leader in patient-simulation programs for medical education. A gifted teacher, Dr. Nachbar was already well-known for his engaging classes in microbiology when he first began incorporating computers into medical school education over 20 years ago. His Surgical Interactive Multimedia Modules (SIMMs), which take students through an entire simulated surgical process, are now used by over two dozen medical schools around the world.

Dr. Nachbar began work on these simulations in 1987, when computer technology was much less sophisticated. "We were one of the first schools to try to teach with personal computers," he said. "The technology has finally caught up with our ideas."

Dr. Spencer, professor of surgery, was the Medical Center's chairman of surgery for 33 years before retiring in 1999. As a Marine Corps surgeon in the Korean War, he violated military policy—risking a court-martial in the process—by setting up a battlefield operating room to repair arteries of wounded soldiers who would otherwise have lost limbs to gangrene. At NYU, he helped pioneer coronary artery bypass grafting and other cardiac surgery techniques. Still, for all Dr. Spencer's innovative brilliance as a surgeon, many of his former residents and students remember him best as an unforgettable teacher who placed special importance on treating patients with empathy.

Dr. Llinas, the Thomas and Suzanne Murphy Professor of Neuroscience, has chaired the Department of Physiology and Neuroscience since 1976. One of five NYU Langone faculty members admitted to the National Academy of Sciences, he is considered one of the founders of modern neuroscience. Dr. Llinas is particularly known for pioneering magnetoencephalography—a highly sensitive, noninvasive technology for measuring the brain's electrical activity.

Dr. Sabatini, the Frederick L. Ehrman Professor of Cell Biology and an international leader in research on intracellular protein trafficking, has chaired the school's Department of Cell Biology since 1972. Dr. Sabatini, a native of Argentina, is also a member of the National Academy of Sciences. His investigations have focused largely on how newly synthesized proteins are distributed within cells and come to their intended destinations—a process vitally important to the health of cells. Defects in protein transportation have been linked to many diseases, including cystic fibrosis, Alzheimer's disease, and certain forms of hypercholesterolemia.

Dr. Sabatini's discoveries helped lead to the formation of the signal hypothesis, which postulated that specific sequences of amino acids enable proteins to pass through intracellular membranes and enter the secretory pathway. More recently, his lab elucidated key aspects of the mechanisms by which viral infections spread within the body and throughout a population. Dr. Sabatini credits NYU Medical Center with providing the perfect setting for his work. "It's a place that attracts very intelligent, independent-minded people who are very curious," he said. "There's also a great spirit of collaboration and camaraderie. NYU scientists like to share their enthusiasm about what others are doing." ●

# Dr. Veva Zimmerman

VEVA H. ZIMMERMAN, M.D., died at her home in Vermont on January 31, 2008, at the age of 70. In addition to her career as a psychiatrist, Dr. Zimmerman, who was one of the few African American women in her generation to attend medical school, took a lifelong interest in supporting and mentoring minority women in the medical profession.

Dr. Zimmerman was known for her personal warmth and compassion and for her generosity and dedication to helping others. Among her many achievements, she initiated the School of Medicine's Programs in Preparation for the Professions (PIP), an initiative that offered educational seminars and faculty mentoring to New York City teenage minority students. Dr. Zimmerman felt strongly that with the appropriate guidance and opportunity, more minority students would seek out careers in medicine. As part of this effort, she helped bring about the creation in 1995 of the Salk School of Science, a unique Manhattan middle school established as a collaboration between NYU School of Medicine and the New York City Department of Education. The school offers an enriched science education with a special emphasis on the medical and biological sciences, in hopes of encouraging its students, particularly girls and minority children, to pursue medical careers.

Dr. Zimmerman graduated from Tufts Medical School in 1962, completing her internship at Bronx Lebanon Hospital and her residency in General Psychiatry at Bellevue Hospital. She became the Special Advisor to the Dean on Minority Affairs at NYU School of Medicine in 1975, and in 1981 was appointed a tenured Associate Professor of Psychiatry and Associate Dean for Student Affairs—becoming the medical school's first female and first African-American dean. She also maintained a private clinical practice.

Dr. Zimmerman remained at NYU until her retirement as professor of psychiatry in 2002. Following her retirement, she continued in private practice in Vermont while helping to manage the operations of Blackside, Inc., the film production company founded by her late brother, documentary filmmaker Henry Hampton, whose work included the award-winning civil-rights documentary *Eyes on the Prize*. She is survived by her husband, David, her two sons, Jacob Zimmerman and Tobias Zimmerman, and two grandsons. ●

DR. STANLEY ALLAN ISENBERG SERVED AS AN ARMY PHYSICIAN IN EUROPE DURING WWII.

# The Gift *of a* Lifetime

AFTER GRADUATION, Stanley Allan Isenberg, M.D. ('43M), served as a physician in Europe during World War II, where he earned a Bronze Star, and, as an avid photographer, he captured a visual record of his experiences there. He later established a private practice in internal medicine and served on the School of Medicine faculty for 35 years. Dr. Isenberg and his wife, Hazel, a medical researcher, had a son, Douglas, who died in infancy from a heart ailment. This tragedy led Dr. Isenberg to leave a stunning legacy of $10,000,000 to the School of Medicine to support cardiology research to make a significant difference for others with heart conditions.

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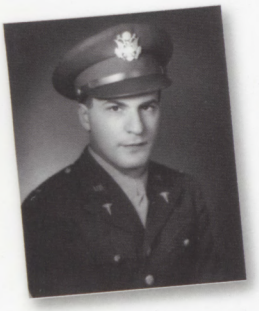

DR. STANLEY ALLAN ISENBERG

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