

A New Awakening

Deep Brain Stimulation is offering new hope to those in a minimally conscious state

It grabbed headlines worldwide in August: A research team spearheaded by Weill Cornell neuroscientists reported that a 38-year-old brain-injured man who was in a minimally conscious state (MCS) for seven years showed improvement in communication, complex movement and eating after deep brain stimulation surgery. The man, whose family has requested

anonymity, was largely unable to communicate or make purposeful movements after a 1999 assault left him severely brain-damaged.

That all began to change soon after doctors used thin probes to electrically stimulate a key area of his brain (see image above).

Before the procedure, “My son, as well as the entire family, had little hope of further recovery,” said the patient’s mother. “If it were not >>> page 4

A Possible Alternative to Embryonic Stem Cells

Easily accessed cells in testes can grow into multiple tissue types

PLENTIFUL, EASILY HARVESTED STEM CELLS IN the testes of male patients might someday provide them with a source of new tissue to treat their disease, suggests a breakthrough study in mice, led by Weill Cornell researchers and published in the Sept. 20 issue of *Nature*.

“Essentially, these spermatogonial stem cells (SPCs) do almost everything that embryonic stem cells can do—without the controversy,” said study senior author and director of the Medical College’s Ansary Center for Stem Cell Therapeutics, Dr. Shahin Rafii.

SPCs are found within the testes and typically generate germ cells, the precursors to sperm.

In their experiments in the lab, Dr. Rafii and colleagues concocted a specific biochemical environment for SPCs derived from the testes of adult mice. They then watched as these cells bypassed becoming germ cells and instead became multipotent adult >>> page 4

Dr. Andrew Schafer Appointed New Chairman of Medicine



LEADING HEMATOLOGIST

Dr. Andrew Schafer has been appointed chairman of the Department of Medicine and physician-in-chief at NewYork-Presbyterian Hospital/Weill Cornell Medical Center. Dr. Schafer has also >>> page 3

Gene Therapy Scores Against Parkinson's

First-ever clinical trial supports approach's safety, effectiveness

Motor function in patients with debilitating Parkinson's disease improved by up to 65 percent within three months of receiving a breakthrough gene therapy, reports a team led by Weill Cornell neuroscientists.

The small phase 1 clinical trial, reported this summer in *The Lancet*, is the first anywhere to test such a treatment for Parkinson's.

"It focused on the regimen's safety profile, which succeeded brilliantly—we saw no adverse events, toxicity or infection related to

motor function and other symptoms over a year of follow-up. "These remarkable results need to be replicated in a larger phase 2 effort, but success here may mark a milestone, not just for Parkinson's research, but for the treatment via gene therapy of other neurological illnesses," Dr. Kaplitt said.

He understands just how tough the road to this achievement has been.

Over the past two decades, Dr. Kaplitt's lab has pioneered the use of gene therapy against brain disease. More than 13 years ago, he

helped to develop a technique whereby surgeons deliver genes to tissue by enclosing it in a harmless adenovirus. In 2003, Dr. Kaplitt performed the world's first gene therapy surgery for Parkinson's, conducted at NewYork-Presbyterian/Weill Cornell. The treatment in the current trial involved inserting an adenovirus carrying the glutamic acid decarboxylase (GAD) gene into a key brain area.

"GAD produces a neurochemical called GABA, which can 'quiet' the excessive neuronal firing we see with Parkinson's," Dr. Kaplitt explained. "Parkinson's patients typically have low levels and activity of GABA, so we hoped intro-

ducing GAD could fix that."

So far the treatment seems to be a success. "With this small trial, we've shown that gene modification of the patient's brain cells can be done safely, with some effectiveness," Dr. Kaplitt said. "That could open the door to using gene therapy against a host of brain disorders." ■



Dr. Michael Kaplitt

treatment," said lead researcher Dr. Michael Kaplitt, associate professor of neurological surgery at Weill Cornell, and director of Movement Disorders Surgery at NewYork-Presbyterian/Weill Cornell.

The 12 patients included in the trial also charted steady, sustained improvements in

the Scope Weill Cornell

THE STEPHEN AND SUZANNE WEISS DEAN,
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Dr. Antonio M. Gotto Jr.

DEAN, WEILL CORNELL GRADUATE SCHOOL
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The Scope is a publication of Weill Cornell Medical College and Weill Cornell Graduate School of Medical Sciences. It is published ten times per year by the Office of Public Affairs, 525 East 68th Street, Box 144, New York, NY 10065; (212) 821-0560. scope@med.cornell.edu



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Weill Cornell Neuroscientists Hit the Mark—Twice

Studies on Ritalin and stroke highlighted in *Journal of Neuroscience*

Investigators at Weill Cornell landed a one-two punch this summer—academically speaking—with two “specially highlighted” papers appearing in July in the prestigious *Journal of Neuroscience*.

One study addressed a growing concern for American parents: the impact of long-term use of the ADHD stimulant Ritalin on the developing brain.

Researchers led by professor of neuroscience Dr. Teresa Milner fed newborn rat pups Ritalin (methylphenidate) for the first 35 days of life.

“We saw changes in the brains of treated rats, occurring in areas strongly linked to higher executive functioning, addiction and appetite, and social relationships and stress,” Dr. Milner said.

The good news: these alterations gradually resolved over time once Ritalin was discontinued.

And Dr. Milner said it's not clear whether these drug-linked neurological changes were for the better or worse. For example, treated

rat pups actually displayed less anxiety than their untreated peers. “It's still unclear, however, whether chronic Ritalin use over years might leave more lasting changes,” Dr. Milner said. “It's possible such changes might linger long into adulthood. We just don't know.”

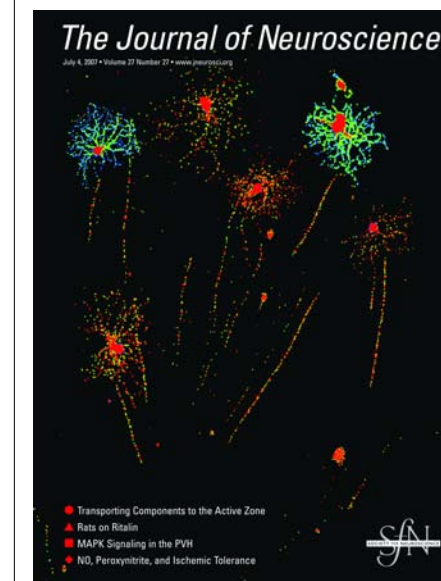
The findings of a second *Neuroscience* article echo an old adage: “What doesn't kill me makes me stronger.”

“We found that when we pre-conditioned brain tissue with some kind of noxious stimulus, it actually became 68 percent more resilient to any stroke occurring later on,” said Dr. Costantino Iadecola, director of neurobiology at Weill Cornell and an attending neurologist at NewYork-Presbyterian/Weill Cornell Medical Center.

In studies in mice, Dr. Iadecola discovered that “toughening up” brain tissue in this way relied on local, low-level production of a molecule called peroxynitrite.

“It's too dangerous to give humans peroxynitrite, but if we can learn more about how preconditioning works we might someday

be able to mimic the process to protect people at risk of stroke,” the researcher said. “What's great with this approach is that we are replicating something the brain already does naturally.” ■



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Dr. Andrew Schafer

been named the E. Hugh Luckey Distinguished Professor of Medicine.

Dr. Schafer joins Weill Cornell from the University of Pennsylvania, where he was the Frank Wister Thomas Professor and chairman of the department of medicine. Prior to that he was the Bob and Vivian Smith Professor and chairman of medicine at Baylor College of Medicine, and chief of the internal medicine service at

Methodist Hospital in Houston. “Dr. Schafer brings nearly 30 of years of outstanding experience in academic medicine,” said Dr. Antonio M. Gotto Jr., dean of Weill Cornell Medical College. “His research expertise, administrative skill, commitment to education and clinical acumen make him an ideal choice for chairman of the Department of Medicine.”

In his role, Dr. Schafer will have administrative responsibility for Weill Cornell's largest and most complex department, which includes 240 full-time fac-

ulty, 13 clinical divisions and two centers—the Iris Cantor Women's Health Center and Cornell Internal Medicine Associates.

An authority on coagulation, thrombosis, hemostasis, platelet function and vascular cell biology, Dr. Schafer has received numerous awards and published widely. He is president-elect of the American Society of Hematology and has been elected to membership in the American Society for Clinical Investigation and the Association of American Physicians, and to fellowship in

the American Association for the Advancement of Science. He has served on the Board of the Association of American Physicians and on the Board of Extramural Advisors of the National Heart, Lung and Blood Institute.

Dr. Schafer received his medical degree from the University of Pennsylvania, completed residency at the University of Chicago and a fellowship in hematology at the Peter Bent Brigham Hospital (now known as Brigham and Women's Hospital) and Harvard Medical School. ■

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A New Awakening Thanks to Deep Brain Stimulation



Dr. Joseph Fins (left) and Dr. Nicholas Schiff

for the deep brain stimulation surgery and rehabilitation, we would be no further along than we were in 1999. Now, my son can eat, express himself and let us know if he is in pain. He enjoys a quality of life we never

thought possible.”

The case is just the first in a pilot study that hopes to recruit 12 MCS patients. If the man’s unprecedented “awakening” is replicated in other individuals, it could revolutionize the

monitoring and care of the estimated 100,000 to 300,000 people currently in a minimally conscious state after brain trauma, experts say.

“This work challenges the approach to assessing and evaluating MCS patients,” says the study’s lead author, Dr. Nicholas D. Schiff, associate professor of neurology and neuroscience at Weill Cornell, and an associate attending neurologist at NewYork-Presbyterian Hospital/Weill Cornell Medical Center.

The minimally conscious state is distinct from a persistent vegetative state or coma, in that patients do show intermittent signs of awareness. They may even attempt to communicate using simple words or symbols. Unfortunately, these glimpses of con-

sciousness are usually fleeting.

Because recovery from MCS is exceedingly uncommon, most patients do not receive active rehabilitation and are cared for in long-term nursing facilities.

But the research team, who published their groundbreaking work in *Nature*, saw some reason for hope.

“We knew that some patients with MCS, including our subject, retain functioning brain networks above the baseline,” explains Dr. Schiff, who also directs the Laboratory for Neuromodulation at Weill Cornell.

The researchers were especially intrigued by cells in the brain’s central thalamus—cells that are thought to help the brain meet changing cognitive demands. “Our theory was that by

sending electrical impulses to this area, we could amplify the low level of activity that we believed was already there, thereby encouraging speech and movement,” Dr. Schiff explains.

The operation appears to have been a success. However, only time will tell if the patient builds on recent gains and continues to improve.

In the meantime, Dr. Schiff’s team is recruiting new MCS patients in hopes of replicating the achievement. If that happens, deep brain stimulation might someday revolutionize the care of these formerly “hopeless” cases, one expert says.

“It holds the potential for patients to recapture their lost personhood,” says Dr. Joseph J. Fins, the Weill Cornell physician-ethicist who helped guide the study’s design.

“Any intervention that can unlock the neurological potential of patients in MCS should have us reconsider how we care for these individuals,” says Dr. Fins, who is director of medical ethics at NewYork-Presbyterian/Weill Cornell. “It will force us to look at these therapeutically neglected patients in a new way—with an aim to real treatment.” ■



Tweet Insights Into Stuttering

THE MUCH-MALIGNED BIRD-BRAIN IS GIVING SCIENTISTS VITAL CLUES

to human stuttering, according to a Weill Cornell–led study in the June 19 *Proceedings of the National Academy of Sciences*. Long a model for research into human speech, the zebra finch has devoted parts of its brain to creating and interpreting birdsong. “We found crucial song-linked activity going on in the bird’s right brain—something that might give us a clue to human speech troubles, such as stuttering,” said lead author and Weill Cornell neuroscientist Dr. Santosh Helekar. ■

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A Possible Option for Embryonic Stem Cells

spermatogenic-derived stem cells (MASCs).

It was these MASCs that demonstrated “multipotency”—the ability to grow into a myriad of cell types, both in lab cultures and in living mouse tissue.

“We watched as MASCs became working blood vessel cells and connected up to form viable tissues. They also became functional ‘beating heart’ cardiac cells, brain cells, and a host of other cell types,” said Dr. Rafii, the Arthur Belfer Professor of Genetic Medicine.

“Other labs have achieved multipotency with adult stem cells before, but usually through some kind of complex genetic ‘tweaking’ that also raises cancer risk,” he added. “Our work is unique in that no such genetic manipu-

lation was required.”

The study—aided by scientists from Memorial Sloan-Kettering Cancer Center and the Howard Hughes Medical Institute—contained another research breakthrough.

“Up till now, it’s been difficult to distinguish SPCs from other cells in the testes. That has really stymied research,” Dr. Rafii said. “However, we discovered that only the SPC expresses a particular surface marker called GPR125. That’s a quantum leap forward in being able to identify, harvest and work with these cells.”

Hurdles remain, however. The scientists still don’t know how to prompt SPCs to become multipotent MASCs on demand. “We are looking for the bio-



Dr. Shahin Rafii

PHOTO BY CLARK JONES/© AP/HMMI

chemical and genetic ‘switch’ to do that,” Dr. Rafii said. “And of course we need to replicate these findings in humans.”

If both those efforts pan out, the implications for medicine could be enormous.

“For male patients, it would mean a readily available source of multipotent stem cells that don’t carry the ethical issues that plague embryonic stem cells,” Dr. Rafii said. Such stem cells could be used to grow tissues to repair or replace injured areas of the heart, brain and other organs.

“SPCs and MASCs also get around the issue of tissue-transplant rejection, since these stem cells come from the man’s own body,” the scientist noted.

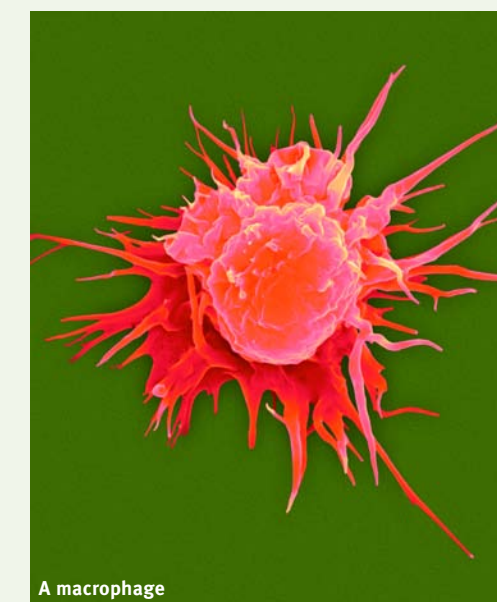
And for women? “The ovary also generates a large number of germ cells, and we would hope that similar techniques would work there as well. Right now that’s speculative, however,” Dr. Rafii said.

“Much remains to be done,” he continued, “but I think we’re at the beginning of something that’s really very exciting.” ■

Why Nature’s “Cholesterol Vacuum” Goes Wrong

LONG BEFORE LIPITOR, THE HUMAN BODY EVOLVED ITS OWN

cholesterol-clearing mechanism—cells called macrophages that eat up LDL plaques on vessel walls. Trouble is, this system doesn’t work very well and



A macrophage

can even exacerbate atherosclerosis over time. Now, a team led by Weill Cornell’s Dr. Lynda Pierini believes they know what goes awry. “Signaling mechanisms in the macrophage fail to tell it to leave the cell wall once it latches on to cholesterol,” said Dr. Pierini, whose team published their insights as a cover story in *Arteriosclerosis, Thrombosis, and Vascular Biology*. ■

Medical Mentors, Past and Future

Editor's Note: The following is an edited transcript of an address given by Dr. Joseph Fins, Chief, Division of Medical Ethics, at the annual White Coat ceremony, held on August 28 in Uris Auditorium.

As you put on your white coat for the very first time, I want to congratulate you on your accomplishments. But I also want to ask you to stop and think about all those people who made this wonderful occasion possible.

Of course you are most responsible for all the hard work and the long nights of study. The all-nighters, organic chemistry, perhaps a struggle through biochem, MCATs and all

If you were lucky you had multiple mentors. Maybe you just had one. But I doubt any one of you arrived here as a first-year student at Weill Cornell Medical College without one, even if you never thought of a professor, doctor or parent as a mentor.

Life is complicated and good mentors usually have some battle scars. They like to give advice, and more importantly, they know how to listen and bring out the best in you.

There is a rich tradition of mentoring in medicine but the word itself derives from Greek mythology at the time of the Trojan War. Mentor was a good friend of Odysseus and was charged by him to take care of his son Telemachus when Odysseus went off to

John L. Battenfeld. He had closed down his practice to become an E.R. doc at our community hospital and that is where I met him. He was very patient-centered before that phrase became part of our lexicon, and clinically very astute. In retrospect, he may have been the very best all-around doctor I have ever had the privilege of working with.

So what made him such a great mentor? Well, he was really good at what he did and was interested in passing it on to the next generation. He was kind and terrifically smart. And he packed a number of surprises. He was very broadly educated in the humanities thanks to the Jesuits who had taught him in college and Georgetown. I can vividly recall first learning about catgut, a kind of suture material, and Dante's "La Divina Comedia," at the same sitting. We were sitting in that old E.R. suturing up a little kid with a laceration. Between the sutures, he also explained who Dante was and why he was such an important poet.

It was this odd juxtaposition, so characteristic of Dr. Battenfeld, that made him a terrific mentor for me. Maybe not for you, but terrific for me. And that is another important lesson—you need to meet a lot of people in order to find a mentor who is a good fit. There were other docs in that E.R., with whom I had good relationships, but Dr. Battenfeld's experiences, temperament and interests were aligned enough with the person I was then and the doctor I might one day become.

The good news is that the richness of this place—and the depth and scope of our faculty—almost guarantees that there is a mentor here to be discovered and a relationship to be cultivated. Seek us out, find us, work in a clinic, find a spot in a lab. Ask questions, seek advice. We—my colleagues and I—would welcome that, and encourage you to do so.

So on this very happy day, let me wish you the best of success. As you don your new white coats, think of them as a symbol of all those mentoring relationships—past and future—that constitute the fabric of our community, a community of which you are now an important part. Welcome to Weill Cornell Medical College. ■



Dr. Paul Miskovitz (left) helps first-year student Norman Lee into his white coat while, at right, Dr. Joseph Fins assists Nii Koney.

those interviews. Yes, you were the ones who made it possible.

But there were others who made it possible for you to even try, and try to do your best. These were your parents, teachers, perhaps a doctor with whom you had the chance to work or volunteer. All these folks—mentors—have made a difference in your life. Remember them every time you proudly put on your white coat. Each of them will be symbolically there holding your coat open and adjusting its fit.

Troy. And Mentor lived up to this expectation, taking charge of young Telemachus' education and shepherding his development while Odysseus was away.

So what characterizes a good medical mentor and how do you find them? Let me tell you about one of mine who could serve as an example.

One medical mentor I had was a G.P. from my hometown of Rockville Centre, New York, with whom I worked as a volunteer while I was in high school. His name was Dr.

Dr. David Hajjar Appointed Senior Executive Vice Dean and Executive Vice Provost



DR. DAVID HAJJAR, dean of the Weill Cornell Graduate School of Medical Sciences, was appointed senior executive vice dean and executive vice provost of the Medical College. He was previously executive vice dean and vice provost.

"I am extremely proud of the faculty and students of Weill Cornell's Graduate School of Medical Sciences, whose dedi-

cation and insights continually advance biomedical research for the benefit of humanity," said Dr. Hajjar, who has served as the Graduate School's dean since 1997 and is currently its longest-serving dean. "I am also proud of what we have been able to accomplish to date in making the Medical College one of the premier institutions in the country."

A noted cardiovascular biologist, Dr. Hajjar is also the Frank H.T. Rhodes Distinguished Professor of Cardiovascular Biology and Genetics and professor of biochemistry and pathology and laboratory medicine.

Dr. Steven Gross Receives NIH MERIT Award

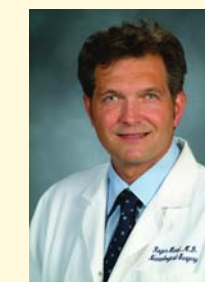


DR. STEVEN GROSS, professor of pharmacology and director of the mass spectrometry core facility, was awarded the prestigious Method to Extend Research in Time (MERIT) Award from the National Heart, Lung and Blood Institute of the NIH. Dr. Gross is a leading authority and pioneer in the pharmacology of the signaling molecule nitric oxide (NO). The \$2.5 million five-year grant will provide long-term support for continued research into this area, including further understanding of the NO-related trigger for vascular complications of diabetes, and the development of novel pharmaceutical approaches for treating the condition.

For nearly 20 years, Dr. Gross and his colleagues have worked on unlocking the mysteries of nitric oxide. In 2006, Dr. Gross reported the first-ever method of combing through the body's tens of thousands of proteins to inventory sites of S-nitrosylation (S-NO), a protein associated with NO. The state-of-the-art mass spectrometry method, called SNO Site Identification (SNOSID), represents a breakthrough for both basic science and drug research—a tool that may significantly accelerate understanding of NO signaling.

"I want to thank the NIH for their long-term support for our work," said Dr. Gross. "We hope to further elucidate the role of nitric oxide as it mediates peripheral blood flow, and uncover potential targets for therapies aimed at patients with diabetes."

Dr. Roger Hartl Named the First Harlan Clinical Scholar



Director of the spine program and assistant professor of neurological surgery, **DR. ROGER HARTL** has been named the first Leonard and Fleur Harlan Clinical Scholar. The award was made possible by a gift of \$1 million from Leonard and Fleur Harlan to support an outstanding junior faculty member in the field of neurological surgery.

Dr. Hartl is pursuing specific research on outcomes analysis in the treatment of complex spinal disorders. He has introduced new minimally invasive surgical techniques and stereotactic navigation for spinal surgery at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, for which he currently is collecting outcomes data.

Leonard and Fleur Harlan have been generous supporters of the Medical College since 1989. Mr. Harlan joined the Board of Overseers in 1998 and recently served as vice chair of the successful \$750 million capital campaign. He previously served as a member of the Weill Cornell Departmental Associates, an organization of lay people interested in supporting and following developments in medical research at the Medical College. ■

Cardiac Center Named for Weill Cornell Dean

Research and treatment center in Istanbul, Turkey, is dedicated to Dr. Antonio M. Gotto Jr.

DR. ANTONIO M. GOTTO JR., DEAN OF Weill Cornell Medical College, has been honored as the namesake of a new center for heart disease research and treatment in Istanbul, Turkey.

The Antonio M. Gotto Jr., M.D., Center for Cardiology and Cardiovascular Diseases will

triple the space dedicated to heart disease research at the Vehbi Koç Vakfi Foundation American Hospital in Istanbul. The facility is equipped with state-of-the-art technology and staffed by board-certified physicians and leading scientists.

"I am deeply honored and privileged,"

said Dr. Gotto, "to be associated with the Vehbi Koç Vakfi Foundation and one of Turkey's leading and most distinguished medical facilities. Establishing a Center such as this will enable the American Hospital to continue to provide the highest quality cardiac care to the >>> page 8

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Honoring the Dean in Istanbul



Dean Antonio M. Gotto Jr. (right) stands with Dr. David J. Skorton, president of Cornell University, at the dedication ceremony and portrait unveiling for the Antonio M. Gotto Jr., M.D., Center for Cardiology and Cardiovascular Diseases in Istanbul, Turkey.

region, as well as engage in the kind of significant research that will contribute to the health and well-being of the Turkish people and beyond.”

The American Hospital, which is affiliated with Weill Cornell Medical College, Columbia University College of Physicians and Surgeons and NewYork-Presbyterian Hospital, continues Weill Cornell’s commitment to global health initiatives and further cements its international medical presence. Weill Cornell has already established a presence in Tanzania, Haiti, Brazil, Austria and Qatar. In fact, with the Weill Cornell Medical College in Qatar, Weill Cornell became the first medical school in the U.S. to offer its M.D. degree overseas. ■



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Dr. Joseph Fins addresses first-year students at the annual White Coat ceremony, stressing the importance of medical mentors as guides for life.

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Weill Cornell researchers find that easily-harvested stem cells in the testes of male patients might someday provide them with a source of new tissue to treat their disease.

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