

**2 VASCULAR BIOLOGY**  
Helping good cells, and blocking bad ones.

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"Maurice R. and Corinne P. Greenberg Division of Cardiology"

# the **S**cope

Weill Cornell

News of the Joan and Sanford I. Weill Medical College and Graduate School of Medical Sciences of Cornell University May • June 2004

## Powerful Blood-Clot Inhibitor Created

**Insects' enzymes inspire re-engineering**

**W**eill Cornell researchers have determined the 3-dimensional structure of a human enzyme that is similar to one found in the

saliva of mosquitoes and other biting insects. In insects, enzymes of this family — called apyrases — are produced in the saliva and allow the pests to sip blood easily by keeping their meal free of blood clots.

Dr. Min Lu, associate professor of biochemistry, and colleagues used X-ray crystallography to work out the 3-D structure of apyrase in humans.

Normally, the human version of the enzyme does nothing to prevent blood clots. However, by re-engineering the human apyrase structure, the researchers were able to achieve a 100-fold boost in its ability to inhibit a blood-clot-promoting compound called adenosine diphosphate (ADP).

Any type of injury boosts ADP levels, including damage or blockage of blood vessels in the heart, brain, or elsewhere in the body. ADP causes platelets to morph from their normal disc-shape into spiky spheres that tend to stick together. The ADP boost is designed to keep bleeding under control, which would be a distinct disadvantage for thirsty bugs. >>> page 2



**RIBBON DIAGRAM** of the human apyrase propeller structure (green) with "sandwich" ring stacking between the substrate and the active site (red). The Ca<sup>2+</sup>-ion (blue sphere) is located in the middle of the central tunnel.

## Jay Monahan Center for Gastrointestinal Health Opens

**The** Jay Monahan Center for Gastrointestinal Health celebrated its official opening with a standing-room-only dedication and ribbon-cutting ceremony at the New York Weill Cornell Medical Center on March 30.

NBC "TODAY" co-anchor Katie Couric joined Dr. Antonio Gotto, dean of the Medical College; Dr. Herbert Pardes, president and CEO of New York-Presbyterian Hospital; Dr. Mark Pochapin, director of the Jay Monahan Center and associate professor of clinical medicine; and Lisa Paulsen, president and CEO of the Entertainment Industry Foundation, at a press

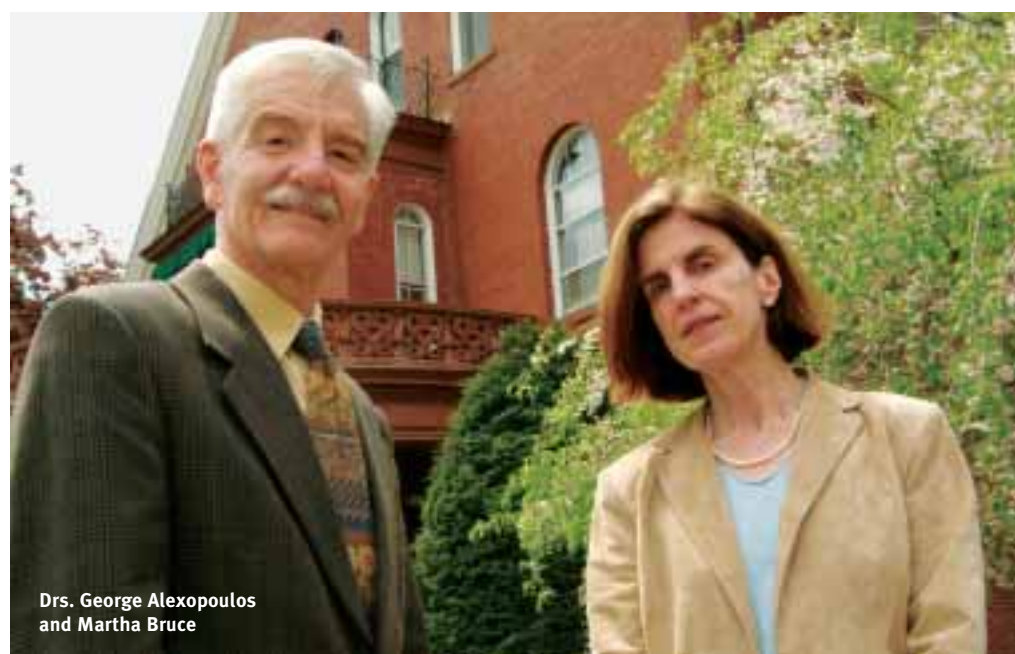
conference to announce the opening of the Monahan Center, named for Ms. Couric's late husband, who died of colon cancer at the age of 42.

Guests included New York State Health Commissioner Dr. Antonia Novello; local government leaders; members of the Medical Center's Community Advisory Board; Hospital trustees; patients; and Medical Center administrators, physicians, and staff.

"Studies show that more than 90 percent of lives could be saved through the early detection and treatment of colorectal cancer," noted Dr. Pochapin. It is our goal at the Monahan Center to encourage patients >>> page 2



**DR. ANTONIO GOTTO AND WIFE ANITA GOTTO (left); KATIE COURIC; AND DR. MARK POCHAPIN (far right), director of the Jay Monahan Center for Gastrointestinal Health, with his wife, Dr. Shari Midoneck, associate professor of clinical medicine.**



**Drs. George Alexopoulos and Martha Bruce**

## Depression in the Elderly: Study Suggests New Approach to Treatment

**F**or many people, the older years are far from golden. Illness, loneliness, or the death of a spouse or friends can cause depression. Although the elderly make up only 13% of the population, they comprise 18% of all suicide deaths.

Now, a multi-institutional study led by Dr. George Alexopoulos, professor of psychiatry and director of Weill Cornell Institute of Geriatric Psychiatry at the Westchester Division, suggests that older patients' suicidal thoughts and depression tend to go away more quickly

when their primary care physician uses a depression care manager to help identify depressed patients, offer treatment for depression, and encourage patients to adhere to treatment.

The findings of the PROSPECT study (Prevention of Suicide in Primary Care Elderly: Collaborative Trial) were published in the March 3 issue of the *Journal of the American Medical Association (JAMA)*. Collaborators included researchers from the University of Pennsylvania, the University of Pittsburgh, the National Institute of Mental Health, and Weill Cornell.

**"Recognizing and diagnosing late-life depression is complex because patients and families often blame their symptoms on aging or on medical illnesses."** — Dr. Martha Bruce

"It is critical to improve the care of late-life depression because depression itself is painful, increases the risk of suicide or death by other medical illnesses, and causes disability and family disruption," said Dr. Alexopoulos, principal investigator of the study.

"Recognizing and diagnosing late-life depression is complex because patients and families often blame their symptoms on aging or on medical illnesses," said Dr. Martha Bruce, professor of sociology in psychiatry at Weill Cornell, who was the lead author of the JAMA paper and co-principal investigator of the PROSPECT study.

The PROSPECT study focused on primary care patients because two-thirds of elderly patients with depression receive care for depression from their primary care physicians and rarely follow through when referred to a mental health specialist. Treatment intervention focused on the use of non-physician depression care managers (trained social workers, nurses, or psychologists) because the average primary care doctor sees four patients in >>> page 3

# Vascular Biology: Cellular Movers and Shakers

Second of two articles highlighting research at Weill Cornell's Center of Vascular Biology

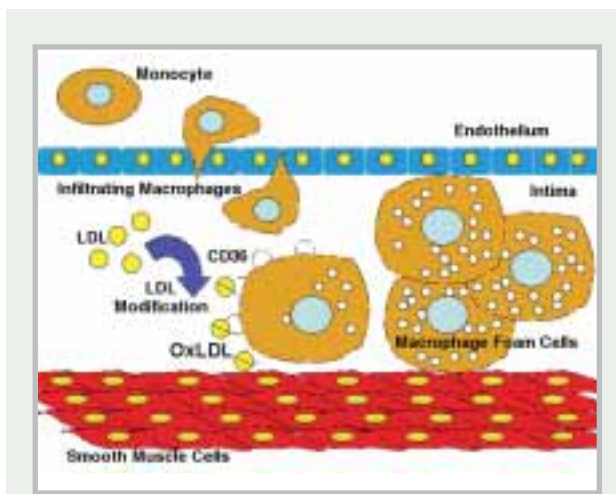
While they normally float in the blood stream, white blood cells can sometimes crawl out of blood vessels, armed and ready to slay bacteria and knit together wounds. Sounds helpful, right? Well, not always, says Dr. William Muller, professor of pathology and laboratory medicine, who is coming up with new methods to stop the cells in their tracks.

The movement of a certain type of white blood cell, known as a monocyte, into the body's tissues is thought to be the first step in the process leading to inflammation and the development of atherosclerosis that may eventually cause a heart attack. As part of an NIH program project grant directed by Dr. David Hajjar in Weill Cornell's Center of Vascular Biology, Dr. Muller, Dr. Frederick Maxfield, chairman of the Department of Biochemistry, and other researchers are studying the molecular signaling that is the "open sesame" that allows monocytes to pass through the endothelium, the layer of cells lining the blood vessels.

"The endothelium allows them to enter, the cells ingest oxidized LDL, or 'bad' cholesterol, and become a type of cell known as a foam cell," said Dr. Muller. "The foam cells die, release their contents, and start off a chronic cycle of inflammation that promotes the formation of atherosclerotic plaque."

Dr. Muller and his colleagues have recreated this scenario in the laboratory to study this interaction, known as the atherosclerotic microenvironment. "We have a system in which monocytes move across cultured endothelial cells and into an extracellular matrix, where they turn into foam cells," he said. "We are going to use this system to learn how to turn them off because that would nip the atherosclerotic lesion in the bud."

In other research on foam cells, Dr. David Hajjar, director of



**ATHEROSCLEROTIC LESIONS form after white blood cells (monocytes) cross blood vessel endothelium and scavenge oxidized LDL cholesterol via the CD36 receptor. The resulting foam cells begin cycle of inflammation that contributes to vascular disease and heart attack.**

the Center of Vascular Biology, and hematologist Dr. Roy Silverstein, professor of medicine, have discovered that a cell surface receptor called CD36 plays a key role in atherosclerosis. In addition, Dr. Hajjar, collaborating with cardiologist Dr. Antonio Gotto, professor of medicine, discovered that a cholesterol-lowering statin drug can decrease foam cell formation by curbing CD36 and possibly preventing the uptake of oxidized LDL. (Dr. Hajjar, the Frank H.T. Rhodes Distinguished Professor of Cardiovascular Biology and Genetics, also serves as executive vice dean of the Medical

College and dean of Weill Cornell's Graduate School of Medical Sciences. Dr. Gotto is the Stephen and Suzanne Weiss Dean of the Medical College.)

While Dr. Muller and colleagues are looking at the movement of cells that can be harmful, Dr. Katherine Hajjar, Dr. Shahin Rafii, and Dr. David Lyden are looking at the movement of cells that could be helpful. They are studying signaling molecules that spur cells to move from bone marrow to the heart to create new blood vessels, a process known as angiogenesis.

"The hypothesis is that when there is a myocardial infarction, or heart attack, the blood supply is cut off from an organ, and the ischemic tissue sends a signal to the bone marrow to mobilize cells that are progenitors to blood vessels," said Dr. Katherine Hajjar, chairman of the Department of Cell and Developmental Biology. "The progenitors enter the circulation and eventually are incorporated into the damaged heart, a process that is driven by very distinct signaling molecules."

"Our goal is to understand these pathways so we can accelerate tissue regeneration by enhancing tissue vascularization," said Dr. Rafii, the Arthur B. Belfer Professor of Genetic Medicine. "One day, we may even be able to isolate these progenitor cells from either the bone marrow or circulation and directly inject them into damaged tissue."

Dr. Katherine Hajjar and her colleagues are also studying annexin II, a member of a family of clot-busting proteins. Mice that lack annexin II have problems with angiogenesis, and are unable to form new blood vessels in response to growth factors. "We are investigating this mechanism in the hope that it can be exploited to develop an agent that might inhibit angiogenesis in abnormal settings, such as cancer and diabetes," she said.

Dr. David Hajjar is also working with Dr. Steven Gross, professor of pharmacology, to study nitric oxide, a signaling molecule so important it once graced the cover of *Science* magazine as the molecule of the year.

Other principal investigators conducting research through the Center of Vascular Biology include Drs. Craig Basson, Jay Edelberg, Domenick Falcone, Barbara Hempstead, Roberto Levi, Aaron Marcus, and Andrew Nicholson. ■

## the Scope

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## <<<from page 1 Monahan Center

and families to go to your doctor when you are well and to offer them the best in prevention, diagnosis, and treatment of all gastrointestinal cancers in a caring, compassionate environment."

Located on York Avenue and 70th Street in the Medical Center's Stich Building, the Monahan Center is one of only a few comprehensive cancer and wellness centers in the U.S. exclusively dedicated to

**"It is my profound hope that the Monahan Center will make it easier for families to contend with perhaps the worst experience they will ever face by providing all necessary resources under one roof." — Ms. Katie Couric**

gastrointestinal health, providing multidisciplinary care for all gastrointestinal cancers, including cancers of the colon, rectum, pancreas, esophagus, liver, stomach, and small intestine.

"Our vision for the Monahan Center was born out of my discussions with Dr. Mark Pochapin, Jay's gastroenterologist," Ms. Couric said. "I discovered during Jay's illness that the journey following a cancer diagnosis is often a traumatic and harrowing one. It is my profound hope that the Monahan

Center will make it easier for families to contend with perhaps the worst experience they will ever face by providing all necessary resources under one roof."

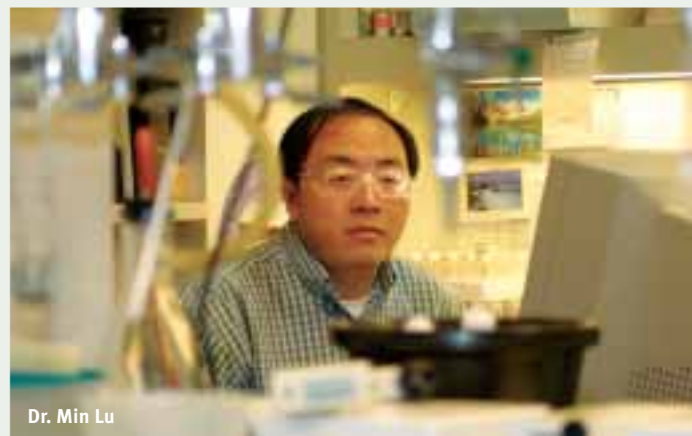
Designed to facilitate education and generate public awareness about gastrointestinal cancers, the center includes two large-screen video walls displaying the latest information on gastrointestinal health for patients, visitors, and passers-by.

"The multidisciplinary approach of the Monahan Center makes it an ideal venue for treating

patients," Dr. Gotto said. "It will provide hands-on experience for our students, many of whom will elect to pursue this area as a specialty and go on to become the next generation of experts."

The Entertainment Industry Foundation's National Colorectal Cancer Research Alliance (EIF's NCCRA), which Ms. Couric founded in March 2000 to raise awareness and research dollars in the fight against colon cancer, provided funding for the Monahan Center. ■

## <<<from page 1 Blood-Clot Inhibitor



Dr. Min Lu

"Insect enzymes have a high ADP-neutralizing activity, designed to keep blood flowing. The human enzyme has a different job that's totally unrelated," said Dr. Lu.

"Using what we call a comparative structural biology approach, we compared the sequence of amino acids — the building blocks of proteins — in humans and insects."

"Based on the sequence alignments of our crystal structure, we pinpointed which amino acids are required for ADPase activity in the insects, and then we replaced the key amino acids in the human version with the amino acids from the insect version," he said. "We took advantage of sucking insects, who use this strategy to maximize their blood-taking from their host."

"Our engineered version of human apyrase, known as HB-apyrase, is a potent inhibitor of platelets, cells crucial for clot formation," said Dr. Lu. "In the future, versions of our HB-apyrase might find applications as therapeutics for stroke or heart attack, which are often caused by blood clots."

However, much more research is needed before any such applications are realized. So far, the researchers have tested the compounds only on platelets in laboratory culture dishes. "This research is fundamental research," Dr. Lu emphasized. "While a therapeutic drug would be a Holy Grail, we don't know if we can achieve that goal tomorrow, in 10 years, or 50 years." ■

*This research was reported in the March 5 issue of Cell. Co-authors included Weill Cornell's Jiayin Dai, Jie Liu, and Yiqun Deng. Thomas Smith of Wyeth Research was also a co-author. The work was supported by grants from the National Institutes of Health (NIH) and the Irma T. Hirsch Trust.*

# First Human Embryo Created after Ovarian Cryopreservation and Reimplantation

For the first time, a cancer patient's ovary — frozen for six years until her cancer was in remission — has been reimplanted under her abdominal skin and used to produce eggs and a single embryo.

Although the embryo did not result in a pregnancy, this unique achievement, led by Dr. Zev Rosenwaks and Dr. Kutluk Oktay, with associates in Weill Cornell's Center for Reproductive Medicine and Infertility (CRMI), raises the possibility that women or girls who need to undergo chemotherapy, radiation, or other ovary-damaging treatments can have their ovaries removed before treatment, frozen, and possibly used to restore fertility or reverse menopause at a later date. The researchers' accomplishment was reported in *Lancet* (March 13, 2004).

"This is the first case in medical history where an embryo has been obtained from frozen banked ovarian tissue after ovarian transplantation," said Dr. Oktay, associate

professor of obstetrics and gynecology and associate professor of reproductive medicine, who was lead author of the article in *Lancet*.

"This research represents a potentially significant reproductive advancement in two respects: first, women can preserve their fertility by freezing their ovarian tissue, and second, pregnancy may be possible even after the tissue remains frozen for a long time," said Dr. Rosenwaks, senior author and director of the CRMI.

The patient, who was diagnosed with breast cancer at age 30, elected to have one of her ovaries removed and frozen prior to beginning chemotherapy. Cryopreservation of her ovarian tissue took place at the Genetics and IVF Institute in Fairfax, Va. Five years later, after successful treatment for her breast cancer, the patient contacted Dr. Oktay at Weill Cornell about using her frozen ovarian tissue and in vitro fertilization in an attempt to become pregnant.

Dr. Oktay and his CRMI associates thawed

15 pieces of the patient's ovarian tissue and transplanted them under the skin in her abdomen. After three months, the tissue began to produce hormones and eggs, and every month the eggs were collected to undergo in vitro fertilization.

"In eight months, we collected about 20 eggs, and eight of those were good enough to be fertilized. We finally got an embryo that made it to the healthy-looking four-cell stage," said Dr. Oktay. "The embryo was transferred to the patient's uterus although she didn't get pregnant. The chances of pregnancy with a single embryo are limited, probably less than 10 percent, so we're going to keep trying."

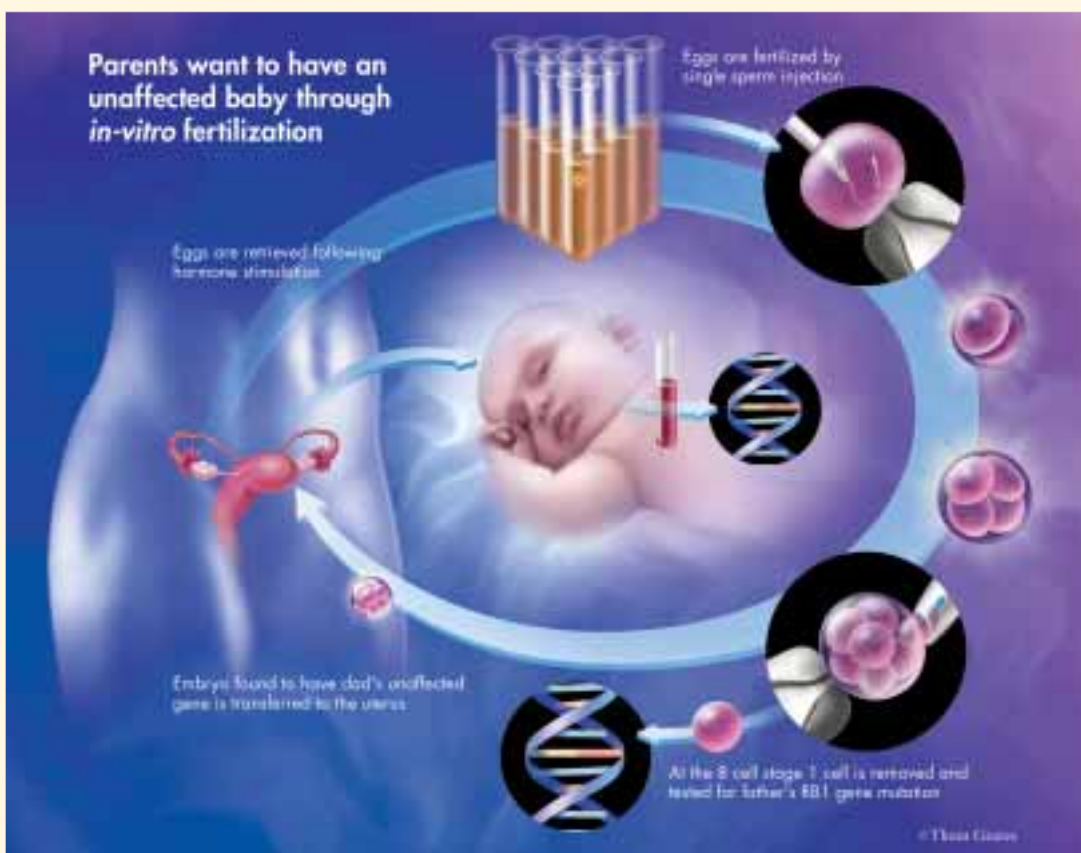
Dr. Oktay noted that ovary cryopreservation and reimplantation could be considered in other clinical situations for both children and adults. "We have patients 6 to 7 years old and up," he said.



**HISTORIC EMBRYO CREATED following ovarian tissue reimplantation.**

There's also the possibility that the procedure could be done on a completely elective basis — to preserve fertility for women who simply want to delay childbearing. "You might actually bank ovarian tissue — potentially as long as you want — and possibly preserve fertility. But this needs to be further studied," said Dr. Oktay. ■

*In addition to Dr. Oktay and Dr. Rosenwaks, co-authors included Dr. Erkan Buyuk, Dr. Lucinda Veeck, Nikica Zaninovic, Dr. Kangpu Xu, Dr. Takumi Takeuchi, from Weill Cornell; and Dr. Michael Opsahl from the Genetics and IVF Institute, Fairfax, Va.*



**SCHEMATIC SHOWING the use of in vitro fertilization and preimplantation genetic diagnosis to screen embryos for the RB1 gene, which causes retinoblastoma.**

whose first child was born with the genetic defect. This youngster developed retinoblastoma at a young age and is currently being treated for a brain tumor.

To try to prevent this from happening again, the mother underwent in vitro fertilization followed by PGD. During PGD, a single cell is collected from each embryo for DNA testing. Embryos that did not carry the retinoblastoma gene defect were transferred to the mother's uterus.

Using this technique, the woman subsequently had two successful pregnancies, resulting in a healthy baby girl and a baby boy.

The father, who carries the genetic defect, was born with retinoblastoma and treated as a child. He has reduced vision in one eye as the result of his disease.

Weill Cornell Medical Center also offers PGD to couples at high risk for transmitting Tay Sachs's disease, cystic fibrosis, sickle-cell anemia, hemophilia, thalassemia, Fanconi's anemia, and other genetic disorders and chromosomal abnormalities. ■

## Babies Born Free of Eye Cancer after Embryo Screen

**EVERY DAY IN THE U.S., A CHILD** develops retinoblastoma, an eye cancer that is fatal if left untreated.

Now, Weill Cornell scientists and physicians can offer some hope to families genetically prone to the condition. For the first time, two healthy children have been born after preimplantation genetic diagnosis (PGD) was used to steer clear of the deadly eye cancer.

Preimplantation genetic diagnosis is used with in vitro fertilization (IVF) to determine the genetic status of embryos before implantation. The technique allows parents to know with reasonable certainty that their child will be normal before the mother is even carrying the child. PGD can virtually eliminate the chance of passing on a genetic

trait from parent to offspring.

Retinoblastoma, the most common primary cancer of childhood, is one such disease transmitted between a parent and their offspring. If a parent has retinoblastoma in both eyes, there is a 50 percent chance of a child being affected.

The collaborative effort at Weill Cornell was led by Dr. Zev

**THREE GENERATIONS OF THE ZIMMERMAN FAMILY (seated), who were the first to benefit from preimplantation genetic diagnosis for retinoblastoma — with Dr. Antonio Gotto (standing, far left), dean of Weill Cornell Medical College; Dr. Zev Rosenwaks; Dr. Herbert Pardes, president of NewYork-Presbyterian Hospital; Dr. David Abramson; and Dr. Kangpu Xu and Katherine Beaverson from the Center for Reproductive Medicine and Infertility.**

Rosenwaks, director of the Center for Reproductive Medicine and Infertility; Dr. David Abramson, director of the Ophthalmic Oncology Center; and Dr. Kangpu Xu, associate professor of embryology and a noted expert in PGD technology.

The babies were born to a couple



<<<from page 1

## Depression in the Elderly

an hour, leaving little time to address issues of depression.

The study included 598 patients 60 years or older who received care at 20 primary care offices in New York City, Philadelphia, and Pittsburgh. The patients had major depression or minor depression that persisted for at least a month. Approximately half of the patients received usual care by their own physicians while the remaining half received the services of a depression care manager.

The investigators examined the patients' level of "suicidal ideation" — or suicidal thoughts — at four months, eight months, and one year after treatment. For patients who had suicidal ideation at the beginning of the study — regardless of whether they had major or minor depression — suicidal thoughts resolved more quickly in primary care practices using care management intervention. Among intervention patients who reported suicidal ideation at the beginning of the study, 71% no longer had suicidal thoughts eight months later. In contrast, only 44% of usual care patients who had suicidal thoughts at entry to the study lost these thoughts by the eighth month of follow-up.

"If Medicare decides to reimburse the intervention used in our study, it may improve the care of depressed elders at a national level and reduce suffering, suicide risk, mortality, and disability. A modest amount of money for trained care managers can buy a lot of health," said Dr. Alexopoulos.

The PROSPECT study was funded by the National Institute of Mental Health. ■

# Baby Born Free of Holt-Oram Syndrome

With the help of Weill Cornell scientists, a young man and his wife now have a healthy baby boy free of a genetic ailment that has plagued the man and his family for generations.

A collaborative team from Weill Cornell's Greenberg Division of Cardiology in the Department of Medicine, the Division of

While many healthy children have been born after preimplantation genetic diagnosis for other disorders, the boy was the first to be born free of Holt-Oram syndrome. In babies who inherit the syndrome, the effects of the condition can be severe or relatively mild. The baby's father, who has the disorder, had some arm and hand abnormalities, as well as a ventricular septal defect that spontaneously closed in childhood.

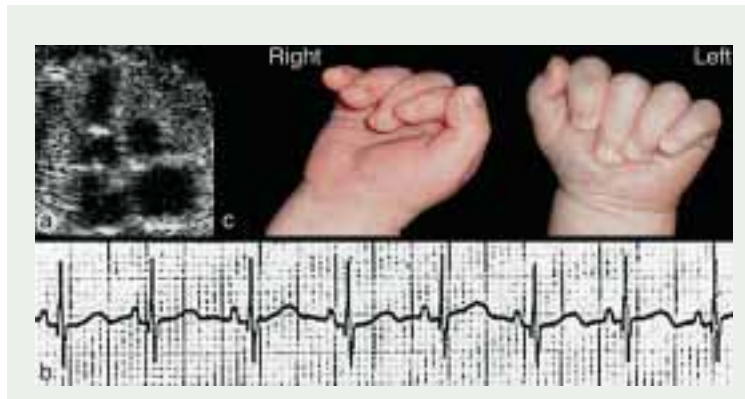
"We have worked with his family for about a decade, and it is very gratifying for our research to be able to help them," said senior investigator Dr. Craig Basson, director of cardiovascular research and associate professor of medicine and associate professor of cell and developmental biology. A clinical report about the case was published in the *American*

*Journal of Medical Genetics*. Co-first authors were Dr. Jie He and Deborah McDermott from the Greenberg Division of Cardiology, Department of Medicine, along with co-authors Drs. Yan Song, Fred Gilbert (Division of Human Genetics, Department of Pediatrics), and Isaac Kligman (Center for Reproductive Medicine and Infertility). ■

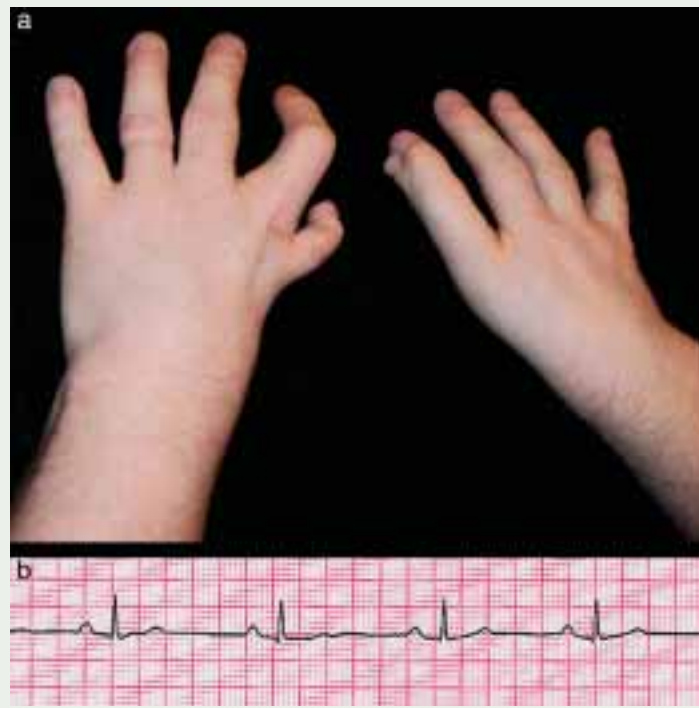


DEBORAH MCDERMOTT, DR. CRAIG BASSON (center), and DR. ISAAC KLIGMAN.

Human Genetics (Pediatrics), and the Center for Reproductive Medicine and Infertility used a research protocol to perform preimplantation genetic diagnosis (PGD). The research study helped the couple to avoid passing on to their child a rare genetic disorder known as Holt-Oram syndrome that can cause birth defects affecting the heart and limbs.



BABY BORN AFTER PREIMPLANTATION GENETIC DIAGNOSIS demonstrated no abnormalities of the heart (A) or hands (C) and had a normal ECG (B).



TYPICAL SKELETAL AND CARDIAC MANIFESTATIONS OF HOLT-ORAM SYNDROME in an adult, including malformations of the hands (A) and slow conduction on an ECG (B).

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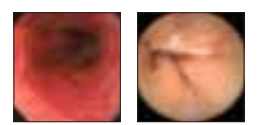
## "Camera Pill" Being Tested for Esophageal Diagnosis

IN THE NEAR FUTURE, determining whether a patient has harmless heartburn or Barrett's Esophagus, a serious precancerous condition, may be as easy as swallowing a camera-equipped pill.

The technique is known as capsule endoscopy, and the "camera pill" device has already been shown to be effective in diagnosing conditions of the small intestine. Dr. Felice Schnoll-Sussman, a gastroenterologist and assistant professor of medicine at Weill Cornell, co-authored a study that found that capsule endoscopy may be a non-invasive alternative for diagnosing Barrett's Esophagus, which is a common result of gastroesophageal reflux disease (GERD). Patients with Barrett's Esophagus are 100 to 300 times more likely to develop esophageal cancer.

"The results of our preliminary study of 53 patients showed that in 92 percent of cases, capsule endoscopy was able to detect when a

The "camera pill" device has already been shown to be effective in diagnosing conditions of the small intestine.



IMAGES FROM BARRETT'S ESOPHAGUS PATIENT diagnosed with traditional endoscopy (pink) and from Barrett's Esophagus patient diagnosed with capsular endoscopy (tan).

patient did not show signs of Barrett's Esophagus," said Dr. Schnoll-Sussman. The findings were recently presented at a meeting of the American Society of Clinical Oncology.

The device used is called the M2A™, a patented technology from Given Imaging, Inc. It received FDA approval in August 2001. ■

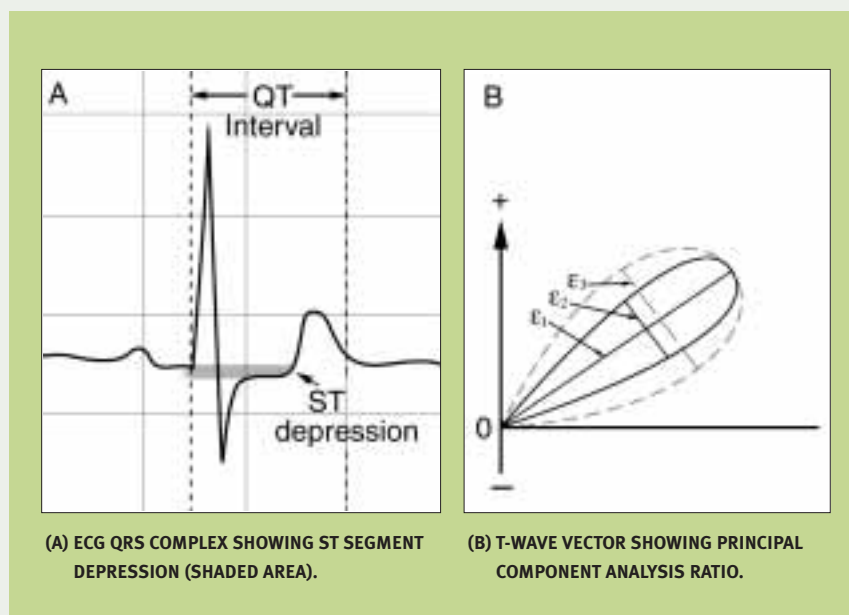
## ECG Abnormalities Can Spell Trouble for Diabetics

DIABETICS WHO HAVE CERTAIN ABNORMALITIES ON an electrocardiogram (ECG) — a measure of the heart's electrical activity — are more likely to die in a five-year period than their peers who have normal ECG results, according to a recent report by Weill Cornell investigators in the journal *Diabetes* (February 2004).

"Because this test can be readily performed, the ECG can be used to identify diabetics who are at increased risk of cardiovascular death or death due to any cause," said lead author Dr. Peter Okin, professor of medicine and director of clinical affairs in the Division of Cardiology.

The study, part of the ongoing Strong Heart Study among American Indians, included 994 participants in their 50s or 60s who had type 2 diabetes. Participants were more likely to die of cardiovascular disease if their ECG showed ST segment depression (a possible sign of heart disease) or an elevated principal component analysis (PCA) ratio (which is linked to a greater risk of heart arrhythmias).

"More study is needed, but it is our suspicion that treating high blood pressure, lowering cholesterol, and controlling blood sugar will make a difference for these patients," said Dr. Okin. ■



The study was funded by grants from the National Heart, Lung, and Blood Institute, and a grant from The Michael Wolk Heart Foundation.

## Growth Factor Boosts Cell Production in Damaged Heart

Injecting a combination of the growth factor PDGF-AB (platelet-derived growth factor-AB) and bone marrow cells into the heart can cause new heart cells to grow in scar tissue, according to a Weill Cornell study conducted in rats.

The finding may one day lead to better treatments for heart attack, which can cause portions of the heart to die and form scar tissue.

Dr. Jay Edelberg, assistant professor of medicine, and colleagues published their results in *Circulation Research* (March 19 print and online issue). PDGF-AB injections boosted the number of heart cells in rats with heart damage similar to that seen in human heart-attack patients. The heart cells, known as myocytes, can beat on their own, and when connected correctly can beat as one unit.

Adding a combination of PDGF-AB and bone marrow cells doubled or quadrupled the number of cardiac myocytes in the heart compared with injection of bone marrow cells or PDGF-AB alone, although more work is needed to get the cells to beat in unison.

Eventually, the researchers hope to find an oral drug to enhance the body's natural ability to repair heart damage. ■

# NEP Loss May Lead to Prostate Cancer

A snippet of protein that sits on top of healthy prostate cells is often lost as the cell morphs into a potentially life-threatening cancer. The protein, known as neutral endopeptidase (NEP), is inactive in about half of all prostate cancers.

Now, Weill Cornell researchers have discovered a major reason why NEP can curb prostate cell growth. It appears that the protein interacts with a powerful tumor suppressor gene called PTEN, according to Dr. David Nanus and his team,



Dr. David Nanus

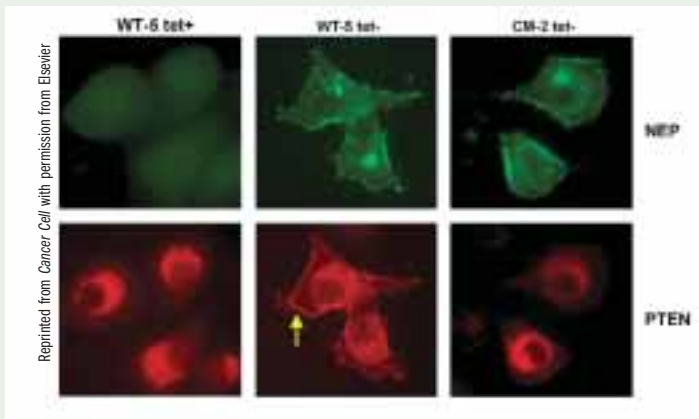
who published their research in the January issue of *Cancer Cell*.

“A lot of people are studying PTEN trying to figure out how it works, and what our research has shown — and it’s the

first time it’s being reported — is that NEP and PTEN interact,” said Dr. Nanus, an associate professor of medicine and urology. “NEP stabilizes PTEN and allows it to localize in certain areas of the cell, which makes it more of an aggressive tumor suppressor. If NEP is lost, PTEN is not going to function, or at least not as well.”

PTEN is one of the most common tumor suppressor genes that malfunctions in cancer cells. The finding could one day lead to new treatments for prostate cancer.

“We are doing a number of studies trying to re-express NEP in prostate cancer cells to try to inhibit growth using a gene therapy approach,” said Dr. Nanus. “That’s all in the lab right now, in animals, but we hope, if it’s successful in animals, to move it on to patients.” ■



NEP RECRUITS PTEN TO THE PLASMA MEMBRANE. WT-5 cells expressing wild-type NEP and CM-2 cells expressing mutant NEP were cultured with (+) and without (-) tetracycline and stained with an anti-NEP antibody (upper panel) and anti-PTEN antibody (lower panel). PTEN is intracellular in cells lacking NEP (left) or full-length NEP (right). In cells expressing NEP (center), PTEN is recruited to the plasma membrane (arrow).



Dr. JoAnn Difede

## Virtual-Reality Therapy Helps Patients Overcome Fears

**WHETHER IT’S A FEAR OF FLYING, PUBLIC SPEAKING, OR SPIDERS, DR. JOANN DIFEDE**

knows what can help — confronting the fear. But scheduling a visit to the tarantula section of the pet store is often too traumatic for those in the grip of a serious phobia. That’s where virtual reality comes in.

Dr. Difede, director of the Anxiety and Traumatic Stress Studies Program in Weill Cornell’s Department of Psychiatry, uses a virtual-reality helmet to immerse patients in a three-dimensional environment that safely exposes patients to what they fear most.

“In order to get better, patients must confront their

fear,” said Dr. Difede, an expert in the treatment of post-traumatic stress disorder (PTSD).

Dr. Difede and Weill Cornell offer virtual-reality environments that address a fear of flying, public speaking, heights, and spiders. They also offer an environment that simulates downtown Manhattan and the World Trade Center, for those experiencing PTSD related to 9/11.

Weill Cornell’s program is one of the few virtual-reality facilities in the nation and the only one in the Northeast. The virtual-reality project is funded by the National Institute on Drug Abuse, Pfizer, Inc., Dell Computers, and the Paul Allen Foundation. ■



Dr. Cynthia Pfeffer

## When a Parent Commits Suicide: Study to Look at Children Left Behind

**HOW CHILDREN ARE AFFECTED BY THE DEATH OF A LOVED ONE HAS** been an area of particular interest to Dr. Cynthia Pfeffer, a noted childhood bereavement expert. Now with a two-year grant from the American Foundation for Suicide Prevention, she is launching a study to find out if a parent’s suicide can affect a youngster’s psychological, physiological and physical growth.

“This new study,” says Dr. Pfeffer, professor of psychiatry, “will allow us to better understand the process of grieving in children. It will help us begin to make sense of a traumatic event such as suicide.”

Each child’s height and weight will be recorded at regular intervals, and levels of the stress hormone cortisol will be measured in both children and the surviving parents. The study will also include a comparison group of children who were not exposed to suicide.

Anxiety, depression, alcoholism, drug addiction, and financial instability can increase the risk of suicide. Because these issues tend to run in families, the study is of particular importance. “These children are at a higher risk of committing suicide themselves,” notes Dr. Pfeffer. “By intervening, we have the potential to prevent this.”

Eventually, Dr. Pfeffer’s study will include about 50 families. ■

## Is It the Flu or Anthrax?

**Study from Weill Cornell lessens the confusion**



Dr. Nathaniel Hupert

public health and medicine at Weill Cornell.

Dr. Hupert and colleagues have developed a set of questions for physicians to use in the aftermath of a suspected anthrax attack on a large population center.

Their conclusion? If there’s a sore throat and runny nose, the culprit is more likely to be a viral respiratory tract infection, but clusters of unusual symptoms including non-headache neurologic symptoms such as dizziness and visual changes, nausea, vomiting, and shortness of breath should raise the possibility of anthrax in patients who might have been exposed.

Their findings were published in the *Annals of Internal Medicine* (September 2, 2003). ■

*In addition to Dr. Hupert, co-authors of the study in the Annals of Internal Medicine were Dr. Alvin Mushlin, Dr. Mark Callahan, and Dr. Gonzalo Bearman, who is now at the Medical College of Virginia, Virginia Commonwealth University.*

**F**ive people in the U.S. died of inhalational anthrax in 2001 in a still-unsolved terrorist attack that caught many doctors off-guard and unprepared.

“Four of the 11 patients who developed anthrax in 2001 were originally sent home with other diagnoses,” said Dr. Nathaniel Hupert, assistant professor of

# Supporting Scientists on the Frontlines of Discovery



Amelia Panico

Postdoctoral associates and fellows form the backbone of Weill Cornell's research enterprise. In laboratories throughout the Medical College, more than 300 recent Ph.D.s and M.D.s ("postdocs") conduct laboratory investigations in nearly all clinical and basic science departments and medical disciplines. They provide the expertise and intellectual resources Weill Cornell and its principal investigators depend on to produce important and timely scientific discoveries. In the process, postdocs gain the skills, experience, and credentials they need to secure junior faculty positions in academia, or to launch careers in industry or government.

As part of the campaign for *Advancing the Clinical Mission*, Weill Cornell aims to raise \$3.5 million in endowment to support postdocs. The establishment of a new Office of Postdoctoral Affairs at the Medical College is a major component of this initiative.

"Postdocs, like graduate students, make an enormous contribution to our research enterprise. Establishment of the Office of Postdoctoral Affairs to address the special needs and concerns of postdocs is a top priority that reflects how highly we value these young scientists at Weill Cornell," said Dr. David Hajjar, executive vice dean of the Medical College and dean of the Weill Cornell Graduate School of Medical Sciences, who oversees the Office of Postdoctoral Affairs (OPA).

Serving as the faculty director of the Office of Postdoctoral Affairs is Dr. Joel Pardee. (Dr. Pardee also continues to serve as associate dean of the Graduate

**DR. JOEL PARDEE, faculty director of the Office of Postdoctoral Affairs, and KAREN SHERMAN, administrative director.**

School of Medical Sciences.) Karen Sherman serves as administrative director of the OPA.

The OPA functions as a first-ever "home" for postdocs working in various laboratories. Serving as an important information and referral source for postdocs, faculty and administrators, the OPA acts as an advocate for postdocs within the administration, addressing issues of concern to postdocs and resolving individual problems. By providing a central source for promoting ideas and issues important to postdoctoral fellows, faculty mentors, and administration, "The mission of the Office of Postdoctoral Affairs is to improve the quality of life for the hundreds of postdoctoral associates and fellows working in labs throughout Weill Cornell," said Dr. Pardee. "It is also our mandate to aid our faculty in recruiting and retaining the very best postdocs to the Medical College."

Working with the recently formed Weill Cornell Postdoctoral Association and a newly created Joint Faculty and Postdoctoral Advisory Committee, the OPA will review existing policy and recommend new policies in the area of immigration, housing, stipend support, career development and mentoring, among others. In addition, the office will organize social events, provide orientation for newcomers, develop a website and handbook, and help postdocs identify and pursue independent grants. ■

## technology development



Amelia Panico

Dr. Francis Barany

### Making the Most of New Discoveries

#### New Developments in Ligase Chain Reaction

JUST AS IT CAN TAKE YEARS TO GET A NEW DRUG TO MARKET, IT CAN be a long and bumpy road before a new technology finds its niche. Just ask Dr. Francis Barany, professor of microbiology and immunology.

In 1991, Dr. Barany developed ligase chain reaction (LCR), a DNA amplification technique that looked like it would solve several problems better than its popular cousin, polymerase chain reaction (PCR). Though PCR would soon star in a science fiction movie called "Jurassic Park," the technology wasn't perfect.

Because of LCR's potential, the Cornell Research Foundation filed for patent protection and licensed its patent application to Applied BioSystems Inc. Dr. Barany, under a multi-year sponsored research agreement with Applied BioSystems, began to develop applications for the technique, including a genetic test for cystic fibrosis.

In the early 1990s, however, competing technologies hit the scene that seemed to dim the commercial promise of LCR. Undeterred, the Cornell Research Foundation continued to file patent applications on Dr. Barany's new inventions. The intellectual property portfolio grew, and now includes 9 U.S. patents, 16 pending U.S. applications, 2 foreign-issued patents, and 39 pending foreign applications.

By 2004, researchers began to focus on single nucleotide polymorphisms, or SNPs (pronounced "snips"). SNPs make up about 90% of all human genetic variation, and scientists believe they will help identify the genes associated with complex diseases such as cancer, diabetes and mental illness.

In January, Applied BioSystems introduced the SNPlex™ Genotyping System, a product that was based in part on Dr. Barany's efforts. SNPlex promises to be a valuable tool in helping scientists identify and analyze the millions of SNPs in the human genome more quickly, and should also work with research on SNPs in the genomes of other species.

"Because the biotech landscape changes so quickly, in the time it takes to debug a new commercial solution to a problem, the problem may have disappeared," said Dr. Brian Kelly, director of Weill Cornell's Office of Technology Development. "Often, however, a new problem will appear that can be solved by the discarded solution. This is what happened with LCR." ■

## academic affairs and appointments

### Carolyn Reid: Frances and John L. Loeb Librarian



**CAROLYN REID** has been appointed the Frances and John L. Loeb Librarian of Medicine for

Weill Cornell's Samuel J. Wood Library and C.V. Starr Biomedical Information Center.

Ms. Reid had been serving as acting director of the medical library since 2001, following the retirement of former Loeb Librarian Robert Braude.

The position of the Loeb Librarian of Medicine was established by the Medical College in 1984 with a gift from Mr. and Mrs. Loeb, who were generous and longtime supporters of both Cornell University Medical College and The New York Hospital. Frances Loeb, who died in 1996, was a trustee of Cornell University and served as a trustee member of the Medical College's Board of Overseers

from 1983 to 1988, when she became a life overseer. John Loeb, who died in 1996, served as a member of the The New York Hospital's Board of Governors from 1959 to 1972, when he became a life governor.

Carolyn Reid joined the Medical College in 1987 as associate director of the Medical Library. She had previously served as associate and interim director of the University of Nebraska's Midcontinental and Regional Medical Library Program. From 1989 to 1999, she was adjunct associate professor of the Graduate School of Information and Library Science at the Pratt Institute in New York. Among her professional honors are the Medical Library

Association's Estelle Broadman Award for Academic Medical Librarian of the Year (1992) and the MLA's Research Development and Project Award (1986).

Ms. Reid received undergraduate and graduate degrees in library science from the University of Missouri.

### Dr. Olaf Andersen: Meikle Professor of Medical Education



**DR. OLAF ANDERSEN**, director of the Tri-Institutional MD-PhD Program and professor of

physiology and biophysics at Weill Cornell, has been appointed the Thomas H. Meikle, Jr. Professor of Medical Education.

Established in 1998 by a gift from the Josiah H. Macy, Jr. Foundation, the Thomas H. Meikle, Jr. Professorship of Medical Education is named in honor of the late Dr. Meikle, who was the retired president of the Macy Foundation and who also served as dean of Cornell University Medical College (1980-87) and first dean of the Cornell University Graduate School of Medical Sciences (1969-76). The Meikle Professorship is awarded for a five-year renewable term to a full-time tenured professor who has a distinguished record of scholarly



Dr. Nina Schor (far left) with MD-PhD students.

## MD-PhD Students Host Alumna Nina Schor

The Tri-Institutional MD-PhD Program of Weill Cornell, Rockefeller University, and the Sloan-Kettering Institute welcomed back distinguished alumna Dr. Nina Schor for an engaging lecture on January 22.

Dr. Schor, a prominent researcher in pediatric neuroscience, holds the Carol Ann Craumer Endowed Chair in

Pediatric Research and is chief of pediatric neurology at the Children's Hospital of Pittsburgh. She is also professor of pediatrics, neurology, and pharmacology and chief of the division of child neurology at the University of Pittsburgh School of Medicine.

In her presentation, Dr. Schor focused on her research toward developing chemotherapy for neural crest tumors and talked

about her career development, from her days as a graduate student at Rockefeller to her current responsibilities as a researcher, clinician, and administrator.

Dr. Schor earned her first acclaim in science in 1972, when she won the top prize in the national Westinghouse Science Talent Search for high-school students. After graduating from Benjamin Cardozo High School in Queens, she earned her B.S. degree from Yale University (1975), her Ph.D. degree from Rockefeller University (1980), and her M.D. degree from Cornell University Medical College (1981).

After training in pediatrics at the Children's Hospital of Boston, she did a neurological residency at Harvard's Longwood Area Program and then joined the faculty of the University of Pittsburgh School of Medicine (1986).

Her lecture at Weill Cornell was followed by dinner and more conversation with students in the Griffis Faculty Club.

The Tri-Institutional MD-PhD program hosts two alumni lectures each year. ■

## "Match Day 2004"

More than 100 graduating medical students packed Weill Cornell's Archbold Commons Student Lounge on March 18 for "Match Day," the national residency-matching event at which medical students find out which postgraduate training program they will enter after graduation. Toasting the students with champagne, Dr. Antonio Gotto, dean of the Medical College, noted the exceptional matches for the graduating class: "It was an excellent match again this year. We're all very proud of you."

Seventy percent (70%) of the students who matched to PGY1 and PGY2 slots obtained positions at the most prestigious institutions in the country. Forty-two percent (42%) matched in disciplines traditionally associated with primary-care careers: internal medicine (22), primary-care medicine (3), pediatrics (17), and primary-care pediatrics (1). Twenty-three percent (23%) of the class successfully matched in the very competitive subspecialties of neurology, neurological surgery, otorhinolaryngology (ENT), ophthalmology, emergency medicine, radiology, and dermatology.

Thirty-two students will be starting their residencies at NewYork Weill Cornell Medical Center: 8 in internal medicine, 5 in pediatrics, 4 in surgery (preliminary), 3 in psychiatry, 3 in general surgery, 2 in radiology, 2 in urology, and 1 each in anesthesiology, emergency medicine, neurological surgery, ophthalmology, and pathology. Five students are going uptown to NewYork-Presbyterian/Columbia University Medical Center.

Altogether, 58 will remain in the metropolitan area, and 21 will remain in the northeast. ■



CHRISTOPHER TOWE (left), who will begin his general-surgery residency at NewYork-Presbyterian/Weill Cornell, celebrates his "match" with friends.

## Graduate School News

### Prospective students enjoy the "New York Experience"

The Graduate School welcomed 100 prospective students to a recruitment weekend in February dubbed the "New York Experience." Now in its seventh year, the two-day event is a chance for a select group of students to hear firsthand from faculty and current students about programs of study at the school and get a taste of life in New York City.

Dean David Hajjar spoke at the opening breakfast, updating the students about the new tri-institutional programs in chemical biology and computational biomedicine and shared some of his own experiences as a postdoctoral trainee at Cornell in the 1970s.

"At the time I was choosing an institution to do my postdoctoral work, I had no idea what it meant to study in New York City. I learned quickly from faculty and colleagues that being where the best

biomedical research occurred, there would be a critical mass of creative, front-rank scientists who would help accelerate the pace of my career. It was true in the 1970s when I was a postdoc, and it's true today. By coming to New York, students enter a flourishing scientific community that will enrich their lives for years to come."

A common theme emerged at the faculty and student meetings during the weekend: if you choose to come to Weill Cornell, you are entering a collaborative environment that is truly unique. The three powerhouse institutions that form the cornerstone of the biomedical community — Weill Cornell Medical College, the Sloan-Kettering Institute, and Rockefeller University — offer students unparalleled opportunities to work with top scientists, hone their skills, and move forward toward the next breakthroughs in biomedical science. ■

## Archbold Commons Gets "Makeover"

On March 4, students were welcomed to a ribbon-cutting celebration for the renovated Archbold Commons Student Lounge in the Weill Education Center. The refurbished space now features new lighting, leather seating, and new carpets. In addition, food service will be provided by a new vendor, Pyramid Coffee, offering gourmet coffees, lunch, and assorted pastries and snacks. At the opening celebration, students enjoyed a delectable dinner catered by Pyramid Coffee.

"We wanted to warm up and brighten the space with a lounge atmosphere that is student-friendly for social gathering and studying," said MD-PhD student Michael



CUTTING THE RIBBON for the new Archbold Commons Student Lounge: (from left, front row) Dr. Carol Storey-Johnson, Jillian Polis, Michael Keyoung, and Joseph Habboushe; (second row) Bill Cunningham, Nady Richard, and Jennifer McCartt.

Keyoung, who helped plan the refurbishment during his term as student representative on Weill Cornell's Board of Overseers. The new lounge is a place students can and will enjoy, he said, adding, "It will foster an even more nurturing community." ■

accomplishment and is involved in the active teaching of medical students.

Dr. Andersen, who joined the Medical College in 1973, is a nationally recognized membrane physiologist and expert on the modeling of membranes. He has made major contributions to the understanding of the structure of ion channels, trafficking of ion transporters, and the mechanism of membrane protein folding.

Since 1996, Dr. Andersen has also served as director of the Tri-Institutional MD-PhD Program conducted jointly by Weill Cornell, the Sloan-Kettering Institute, and Rockefeller University. "Under Dr. Andersen's leadership, the

Tri-Institutional MD-PhD Program has become one of the top joint-degree programs in the country," said Dr. Antonio Gotto, dean of the Medical College.

Dr. Andersen's teaching activities include lecturing in three courses — "Molecules to Cells" and "Human Structure and Function" in the Medical College and "Frontiers of Biomedical Science" in the Weill Cornell Graduate School of Medical Sciences. He also supervises journal club sessions and has been a tutor in the Medical College problem-based learning sessions.

Dr. Andersen received his medical degree from the Copenhagen University Faculty of Medicine (Denmark).

## Siegel Distinguished Professorship of Clinical Medicine Established; Dr. Joseph Hayes Appointed First Siegel Professor



Weill Cornell Art & Photo

Weill Cornell Medical College has established the Herbert J. and Ann L. Siegel Distinguished Professorship of Clinical Medicine, and DR. JOSEPH HAYES has been appointed the first Siegel Professor.

Establishment of the Siegel Professorship follows a \$2 million pledge made in 2002 by Mr. and Mrs. Siegel, which has been fulfilled. Mr. Siegel, former chairman, president, and director of Chris-Craft Industries, has been a member of Weill Cornell's Board of Overseers since 1998. The Siegels have been generous supporters of the Medical College. Previously, in 2000, they endowed the Ann L. Siegel Research Scientist as part of the Structural Biology Initiative in the Strategic Plan for Research.

Dr. Hayes formerly held Weill Cornell's Irene F. and I. Roy Psaty Distinguished Professorship of Clinical Medicine. A cardiologist who trained at The New York Hospital, he has been

affiliated with the Medical Center for 40 years. He has served as director of the cardiac graphics laboratory (1970-76), director of the training program in internal medicine and vice chairman of the Department of Medicine (1988-96), medical director of the clinical information system (1996-2004), and associate dean for billing compliance (2000-2004). In 1992, he was honored for his exemplary contributions to the Medical College when he was named an honorary fellow of the college's Alumni Association. Dr. Hayes received his medical degree from Georgetown University. ■



## Naming of Cardiology Division Honors Maurice and Corinne Greenberg

The naming of Weill Cornell's Division of Cardiology in honor of long-time benefactors Maurice and Corinne Greenberg was celebrated at a ribbon-cutting ceremony held on February 2.

The new name — the Maurice R. and Corinne P. Greenberg Division of Cardiology — commemorates the Greenbergs' ongoing commitment in many areas of the NewYork Weill Cornell Medical Center, including cardiovascular research and patient care.

"The Greenberg family and the Starr Foundation have continually demonstrated their steadfast

leadership in support of cardiology," said Dr. Antonio Gotto, dean of the Medical College. "Without their forward-thinking and generosity, the scope and success of our cardiology program would not have been possible."

Through the vision and leadership of the Greenberg family, the Division of Cardiology has recruited physician-scientists of the highest caliber, acquired a supercomputer that made possible the world's only three-dimensional computer model of atrial fibrillation, and is now in the process of upgrading many of its facilities, including laboratory space dedicated

**DR. ANTONIO GOTTO (far left); CORINNE GREENBERG; MAURICE GREENBERG; and DR. HERBERT PARDES (far right), president and CEO of NewYork-Presbyterian Hospital, perform the ceremonial ribbon-cutting at the dedication ceremony.**

to innovative research initiatives such as genomic phenotyping.

Last year, the Greenberg family and the Starr Foundation made generous contributions for cardiology initiatives as part of the Medical College's capital campaign for *Advancing the Clinical Mission* and to support research in molecular cardiology. In addition, the Starr Foundation recently established clinical scholar endowments in honor of Dr. Bruce Lerman, the Hilda Altschul Master Professor of Medicine and chief of cardiology, and Dr. James P. Smith, clinical professor of medicine. The Starr Foundation also gave generously in 2000 to help fund the Atrial Fibrillation Basic Research Program.

Maurice Greenberg is a member of the Medical College's Board of Overseers as well as chairman emeritus and trustee of NewYork-Presbyterian Hospital.

Mr. Greenberg is chairman and CEO of American International Group (AIG), a leading global insurance and financial services organization, and chairman of the Starr Foundation, one of the largest private foundations in the U.S. ■

## classacts

### Graduate Students Mentor Younger Scientists

**WEILL CORNELL GRADUATE STUDENTS AND SEVENTH-GRADE STUDENTS**

from East Side Middle School in Manhattan teamed up again for the Cornell Science Challenge, a joint effort by Weill Cornell Graduate School of Medical Sciences and the East Side Middle School to introduce young students to science and its applications.

For 12 weeks, volunteer students and staff from the Graduate School, Memorial Sloan-Kettering Cancer Center, and Rockefeller University mentored the seventh-graders — teaching them the basics of the scientific method: hypothesis, experimentation, and analysis. The mentors included graduate students, research technicians, postdoctoral fellows, and faculty.

The students' research projects culminated in a poster presentation held at Weill Cornell on March 30 in the Olin Hall gym. Dr. Max Gomez, science and medical correspondent for WNBC-TV, presented awards to the 7th-graders for such categories as "Best Scientific Method" and "Best Presentation." ■



**WINNERS OF THE AWARD FOR "BEST SCIENTIFIC METHOD" with DR. JOEL PARDEE (left), associate dean of the Graduate School of Medical Sciences, and Dr. Max Gomez.**

# the Scope

Weill Cornell  
May • June 2004

## ataglance



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### COVER STORY:

#### JAY MONAHAN CENTER FOR GASTROINTESTINAL HEALTH

Newly opened center focuses on care and prevention for all gastrointestinal disorders.



1

### COVER STORY:

**DEPRESSION IN THE ELDERLY**  
Study suggests new approach to treatment.



1

### COVER STORY:

#### BLOOD-CLOT INHIBITOR CREATED

Insects' enzymes inspire re-engineering.



4

### SCIENCE STORIES:

#### HOLT-ORAM SYNDROME

Parents can avoid passing on genetic disorder with risks to heart and limbs.



5

### SCIENCE BRIEFS:

#### PROSTATE CANCER

Loss of protein (NEP) weakens tumor suppressor (PTEN).



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### TECHNOLOGY DEVELOPMENT

New developments in ligase chain reaction.

7

### CLASS ACTS:

#### TRI-INSTITUTIONAL MD-PHD PROGRAM

Students host alumna Nina Schor.

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### CLASS ACTS:

#### GRADUATE SCHOOL NEWS

Prospective students enjoy the "New York Experience."

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