DO YOUR KNEES FEEL OLD?

YOU DON’T KNOW THE HALF OF IT. ASK LUCY.
OVER THE TRANSOM

DOUBLE TAKE
I recognized almost all of the faces on the back of the Spring 2009 issue. It took me a minute to see my friend Brian Caputo (MD ‘89, Res ‘93) without the thick glasses that he had worn when we were in school together.

I was the 1990 Alumni Scholar, and the Class of 1989 took me under its wing. Brian was especially kind and taught me well. He was always so compassionate. He said that one day near-sightedness would commonly be corrected with laser surgery and planned to be an ophthalmologist.

Brian, you were absolutely right. I hope that you have found the happiness that you deserve.

Erin M. Sabo (MD ‘90)
Bulger, Pa.

Editor's Note: Brian Caputo is indeed an ophthalmologist and is practicing in New Kensington, Pa.

RECENT MAGAZINE HONORS
Carnegie Science Award for Journalism
J. Miksch

CASE District II Accolades
Gold, Periodical Staff Writing

CASE District II Accolades
Gold, Best Article
J. Miksch, “The Investigator’s Path”

CASE District II Accolades
Silver, Covers (Summer 2008)

IABC Pittsburgh Golden Triangle
Award of Excellence, Magazines

IABC Award of Excellence, Feature Writing
J. Miksch, “The Investigator’s Path”

IABC Award of Honor, Publication Design
E. Cerri

Pittsburgh Black Media Federation
Robert L. Vann Media Award
Magazine Features, Third Place
C. Zinchini, “Twins”

We gladly receive letters (which we may edit for length, style, and clarity).

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WARM UP WITH US
Winter approaches. Shirley, here, can attest to that being a bit of a drag. But before we know it, February will be upon us—with Grapefruit League baseball and the promise of a new spring, and sun, in the offing.

For Pitt health sciences alumni and friends, that time of year means renewal as well. Join us for another kind of spring training. At the Winter Academy in Naples, Fla., all-star Pitt researchers will offer insight into exciting new developments in science and medicine.

Reserve your seats for
WINTER ACADEMY.
February 12, 2010
Ritz-Carlton Resort and Spa
Naples, Fla.

Contact: Pat Carver
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It can take as much as a decade to correctly diagnose bipolar disorder. Mary Phillips hopes imaging can speed up the process, saving time and reducing suffering.
BY ELAINE VITONE

CONTRIBUTORS
Artist and illustrator JULIETTE BORDA (“The ‘Now What?’ Field of Medicine”) has been a Pitt Med contributor since the magazine’s inception. Each assignment, she says, is taken on with pleasure. “Elena [Gialamas Cerri] is one of the best art directors I work with these days … plus health-related stories are one of my favorite topics to work with,” she says. Borda sees her style as “quietly expressive, simple, and thoughtful” and counts fashion, signage, city living, film, David Hockney, and the Fauvists as influences. A Carnegie Mellon University graduate and Brooklyn resident, Borda has contributed to many major periodicals—including The New Yorker, which featured one of her illustrations on the cover—and her work hangs in the permanent collection of Pittsburgh’s Carnegie Museum of Art and in the home of actor and author Ethan Hawke.

Our very own JOE MIKSCH (“Wobbly Knees” and other stories) took the Carnegie Science Journalism Award for 2009. Besides all the recognition for his writing he’s been getting, Pitt Med’s associate editor also nabbed a patch from his bowling league for rolling the same score three times in a row. He recently proofread a mystery novel by Joan Rivers for Simon & Schuster and says he is considering writing one of his own, “in tandem with a friend named Tim.” Thanks to a novelist neighbor from El Salvador, he has become enamored with Latin American literature and is considering learning Spanish. “For many years, I’ve had recurring dreams in which I’m fluent in Spanish,” he says. He lives on the North Side with his wife, Colleen; dog, Shirley (shown on the opposite page); and two cats, Nick and Nora. He’d like you to know his house is for sale.

COVER
Our cover girl, Lucy, was found in Ethiopia in 1974. She’s 3.2 million years old, yet not the oldest subject in Freddie Fu’s study of the evolution of the knee. (© Alain Nogues/Sygma/Corbis.)
I am on the edge of mysteries and the veil is getting thinner and thinner.
—Louis Pasteur

Scientists explore a lot of dead ends, and Victor Ambros’ instincts told him that he’d arrived at another. His Dartmouth lab had found a gene in *C. elegans*, a tiny worm, that did not produce the regulatory protein the team had expected. It produced a single strand of RNA only 22 nucleotides long. This was in the early 1990s, and nothing like it had been seen before. The little RNA was interesting, but Ambros suspected it was a curiosity that existed only in worms. He remained a skeptic until 2000, when another lab published a paper which showed that a second example of this microRNA, as it came to be called (miRNA), was conserved across a wide range of living things—from plants to nematodes to sea urchins to humans. Ambros says that after he read that paper, he stared out his window for 10 minutes, reorganizing his view of the universe.

Since then, scientists have sequenced many thousands of examples of miRNA. They’ve learned that they function as gene silencers—regulating the expression of genes critical to normal development and biological function—and occasionally as gene activators. Viruses manipulate their hosts by targeting miRNA pathways, and dysfunction of miRNA activity leads to some cancers (in which case they act as oncogenes); but happily, in some cases, miRNAs act as tumor suppressor genes. For his work, Victor Ambros won the Lasker Basic Medical Research Award in 2008 and during our recent, annual Science Festival, our own 2009 Dickson Prize in Medicine.

Three years ago, here at the medical school, Bino John and collaborators accidentally discovered RNA even smaller than micro. It was a perfect example of chance favoring the prepared mind. His lab was probing a 23-nucleotides-long miRNA from the Kaposi’s sarcoma herpes virus. Bino had refined the northern blot technique to make it more sensitive, and the group unexpectedly detected RNA that was only 17 nucleotides long. They were then able to sequence a great number of what Bino dubbed usRNAs (usually small RNAs) from a wide variety of tissues. Bino was stunned to find that usRNAs appeared to outnumber miRNAs in their samples. Much like miRNA, one of the functions of usRNA seems to be silencing specific genes.

We are only beginning to understand the importance of usRNA, but, as with miRNA, we can bet that this finding will not lead to a dead end. Several companies are aggressively working to develop small molecules that act on miRNAs—to inhibit or activate their role in diseases such as cancer. All based on a chance observation in an “elegant” worm! What better rationale for the pursuit of basic science?

Everything in biology is in equipoise: Our cells synthesize proteins and degrade them. We produce genetic instructions when needed and silence them with miRNA and usRNA when they are not. The English author and mystic James Rhoades once wrote:

*It is the joy of joys, / To thrill co-operant with the primal cause / Of the unswerving laws / Which hold in everlasting equipoise / Those balances of God, / The visible and invisible Universe.*

Arthur S. Levine, MD
Senior Vice Chancellor for the Health Sciences
Dean, School of Medicine
FOOTNOTE

Down by 12 in the final round, Scott Itano (MD ’09) wagered all his points and answered correctly: “Hypoglycemia.” Itano competed last summer in Next Top Doc, a quiz show on the satellite radio station ReachMD. He faced tough competition from some of the sharpest medical students in the nation, making it to the quarterfinals. Itano’s new challenge is his residency in family medicine at the University of Washington’s Swedish Medical Center.

BURKE ELECTED TO IOM

Donald Burke, dean of the University of Pittsburgh Graduate School of Public Health, director of Pitt’s Center for Vaccine Research, associate vice chancellor for global health, and professor of medicine in the School of Medicine, has been elected to the Institute of Medicine (IOM). Burke, an MD, joins 15 current and former School of Medicine faculty in this august society of investigators.

IOM members provide consultation and advice to the government and the private sector to improve health care nationally. Over the course of his lengthy career, Burke has contributed to the use of computer modeling of infectious diseases. He is now working on computer models to chart the likely progress of the evolution of infectious microorganisms, the response of the host, and the behavioral changes of an infected population. —Joe Miksch

TRACKING SUPERBUGS

The emergence of “superbugs” that are resistant to treatment has raised adrenaline levels at U.S. hospitals. In 2007, the Journal of the American Medical Association estimated there were more than 78,000 cases of health care–associated MRSA (methicillin-resistant Staphylococcus aureus) infection in 2005 alone. The University of Pittsburgh’s Lee Harrison is intent on reining in the superbug problem. He’s getting help from the Commonwealth of Pennsylvania.

With colleagues, Harrison, an MD professor of medicine, epidemiology, and infectious diseases, will tap into a $4.7 million grant from the Pennsylvania Department of Health to take on C. difficile, A. baumannii, and MRSA, sometimes deadly bacteria that are to blame for a large proportion of drug-resistant hospital-acquired infections. The grant will establish a Center of Excellence in Prevention and Control of Antibiotic-Resistant Bacterial Infections, based in Pitt’s School of Medicine, that will attempt to understand how these pathogens develop, how they avoid death at the hands of antibiotics, and how the infections spread. —JM
In his third year in the University of Pittsburgh School of Medicine, Michael Cho’s life is fairly typical—going through his rotations, planning for the future. The years leading up to this point, however, were anything but typical. After entering Cornell University as a premed, Cho switched his emphasis to film, art history, and French. When Cho graduated he moved to Los Angeles, where he studied filmmaking.

From that point, he directed 10 documentaries—including *Another America*, which focuses on relations between African Americans and Korean immigrants in Detroit. The urge to study medicine, though, never left him, and, after acquiring a postbaccalaureate certificate in premedicine at Scripps College in Claremont, Calif., he enrolled at Pitt. He hopes to find a way to combine the art of filmmaking with the science of medicine in his practice. He does not find this combination unusual. Referring to the building across Fifth Avenue from the old Children’s Hospital site, Cho noted, “It is called the Medical Arts Building, after all.”

On the disparity between filmmaking and medicine
It is disparate and not at the same time. I think they have a lot in common, because you’re always dealing with people, finding out about their history, what makes them tick. And so, in a way, being a doctor and being a documentarian [are both] like being detectives.

On why he re-entered medicine
I received a grant to travel to the ethnic minority border regions in China. So when I was travelling in China and Korea I came across traditional healers, and I was fascinated by what they did. I had some treatment through a healer there and [thought], Wow, this is amazing.

On combining film and medicine
My scholarly project looks at using patient stories, and I hope to make it an Internet-based piece. The start of it was the idea that med school research has shown that [student] empathy levels peak after the first year [of school, then drop off]. I want to find a way to address that issue, to have people see the person behind the illness.

His question for us
In a world of algorithms, is there a role for creativity in medical decision making?

—Interview by Joe Miksch

Shanti Pinto may be working with a secret ingredient in embryonic stem cells. Pinto, a medical student at the University of Pittsburgh, suspects that hemopoietic cell kinase (HCK) maintains pluripotency—the ability to become many different cell types—in embryonic cells, because HCK disappears when stem cells differentiate. She is interested in whether HCK might be able to confer pluripotency to all cells.

A Research Training Fellowship for Medical Students from the Howard Hughes Medical Institute has allowed Pinto to focus on this project with Pitt’s Thomas Smithgall, a PhD, the William S. McElroy Professor, and chair of microbiology and molecular genetics.

Pinto is one of five Pitt med students in 2009 to receive the $38,000 grants, which cover salary and lab expenses. That’s more students to receive HHMI funding than in any previous year at the medical school.

Christopher Fung—who, like the other awardees, is taking a year off from school to focus on research—is working in the Pitt lab of Jennifer Grandis, MD professor of otolaryngology. Using blood samples from head and neck cancer patients, Fung investigates the effect of certain mutations on the development and treatment of the disease. Awardee Ezra Mirvish researches cancers caused by viruses. His sequencing methods may allow him to pinpoint viral genes in tumor cells so that therapies can be developed against a given virus.

HHMI awardees John Evankovich and Nicholas Maurice are both researching the liver. Evankovich studies the molecular mechanisms of liver damage resulting from reperfusion of blood to the liver after surgery. Because the same process damages other organs after surgery, Evankovich’s efforts to reduce the damage could be used in a wide variety of surgical settings. His surgeon mentors are Pitt’s David Geller, Richard L. Simmons Professor of Surgery, and Allan Tsung, assistant professor of surgery. Maurice, working in the lab of Pitt’s David Perlmutter—an MD, chair of pediatrics, and Vira I. Heinz Professor—researches alpha-1 antitrypsin deficiency, the leading genetic cause of liver failure requiring transplantation in children.

—Brandon Ellis
**Class of 2013 Cheat Sheet**

We thought you'd enjoy meeting a few of the members of the Class of 2013 whose bios turned our heads.

Ka’ohimanu Dang, the only native Hawaiian member of the class, saw her grandmother die at age 48 of colon cancer, detected late and undertreated by her physicians. Dang worked for nine years in biomedical research, with the idea that if clinicians couldn’t help her grandmother, then research could. But after noticing the skepticism of the native Hawaiian community surrounding medical research and practice, Dang got another idea. “If I as a doctor say, ‘You don’t have to be scared of this,’ [people are more trusting],” she says.

Fellow first-year Brady Mock loves experimentation, a good trait for a med student. A former state champion wrestler from Utah, he has also dabbled in ballet, wakeboarding, and bungee-jumping. Medicine is an experiment for him, too. He is the first from his family to enter the medical field.

Zachary Tano, a graduate of the U.S. Naval Academy, was drawn to medicine after a memorable tour of duty in Afghanistan. While helping the U.S. Navy Civil Engineer Corps build facilities for the Afghan police force, Tano interviewed many Afghans in local hospitals and felt a strong desire to do something about their poor standard of care.

This spirit of caring and giving extends to Michelle Garcia, who designed a program at the University of San Francisco in which students could donate their excess meal plan dollars to supply family shelters in the area. —BE

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**FOOTNOTE**

You don’t have to be a star athlete to have a bobblehead doll made in your likeness. Renowned University of Pittsburgh orthopaedists Freddie Fu (MD ’77, Res ’82) and Christopher Harner (Res ’86), for example, are immortalized in nodding-doll form.

When members of the 2007 Department of Orthopaedic Surgery residency class prepared for the end-of-year skit roasting their attendings, they kidnapped the mini Fu and Harner and made a video, complete with voice-overs, of their mentors traveling through the world of Pitt orthopaedics.

Then they had bobbleheads made of themselves as a parting gift to Fu and Harner. The dolls now stand sentinel, encased in glass outside Fu’s office, nodding in affirmation at their inspirations.

---

**CLUES TO A CANCER VACCINE**

Thanks to a clue provided by the healthy immune system, Olivera Finn believes she may be on to a path that could lead to a cancer vaccine.

Finn, a PhD who is Distinguished Professor and chair of the Department of Immunology in the University of Pittsburgh School of Medicine, found that some healthy people naturally developed an immune response to a protein produced by cells infected with chicken pox and also made in excess in many cancers. Vaccinated mice exposed to a cancer cell line that overexpressed the same protein, called cyclin B1, were able to reject the formation of tumors.

Earlier, Finn developed a vaccine to boost immune response against MUC1, a protein abnormally produced in colon cancer. Because these immune responses are natural, Finn says, there is less concern that boosting them could lead to autoimmune disease.

Finn’s study on cyclin B1 was published in August in the *Proceedings of the National Academy of Sciences*. —JM
Appointments

Michael Boninger has dropped “interim” from his title. He’s now the chair of the University of Pittsburgh Department of Physical Medicine and Rehabilitation. The MD has a track record of research that extends from the basic—such as the physiology of muscle—to the applied, engineering medical devices to aid with injury rehabilitation. He is a member of the National Spinal Cord Injury Association’s Hall of Fame.

Boninger’s department stands out for its research activity; it ranks first in National Institutes of Health funding. (Find out more about his faculty’s intriguing studies—from getting stem cells to act their age to mind-controlled prosthetic limbs—in our p. 23 story.)

David Lewis is the new medical director of Western Psychiatric Institute and Clinic of UPMC and chair of Pitt’s Department of Psychiatry. He follows in the footsteps of David Kupfer and Thomas Detre, who led the department—and, in the case of Detre, the entire academic medical center—to national prominence.

Lewis, the UPMC Professor in Translational Neuroscience who was elected to the Institute of Medicine in 2007, is an MD and a noted expert in schizophrenia. He joined the Pitt faculty in 1987 and has served as a professor of psychiatry and neuroscience as well as director of the Translational Neuroscience Program. Lewis, author of more than 300 publications, has been recognized with a number of honors, including the Stanley Dean Research Award from the American College of Psychiatrists. Floyd Bloom—former editor of *Science* and former director of the Scripps Clinic and Research Foundation (where Lewis was a visiting scientist)—has said that Lewis “is one of the two or three most outstanding translational neuroscientists of his generation.”

The department of the future, says Lewis, will engage in clinical studies and also build on the foundations of the basic sciences of psychiatry: “There are many fundamental fields of knowledge on which our clinical practice rests—neuroscience, psychology, epidemiology, genetics, to name a few.” Among other priorities they’ll pursue, he expects Pitt faculty to move the field toward rational preemptive interventions. “This is particularly important in psychiatry, because in many ways the target symptoms we treat now are far downstream in the disease process. Many of our treatments are analogous to what a patient with cardiovascular disease receives after a myocardial infarction.”

Donald Yealy is now chair of Pitt’s Department of Emergency Medicine. Yealy, an MD, was vice chair of the department before assuming his new position.

The department has been a worldwide leader in the clinic and the lab for the past 25 years. That presents a challenge, he says: “There’s nothing for me to fix. What I need to do is make sure things continue that way. You either get better or get worse; there’s no standing still.”

Yealy’s own work is wide-ranging. He has examined, among other issues, the differences in the severity of illness experienced by emergency department patients of different races who have congestive heart failure. —Erica Lloyd & Joe Miksch
COOL DOWN

On a bright July morning in a quiet two-story house in Allison Park, Pa., a pile of dry wood catches a spark. Within minutes, the room’s contents ignite, and flames spread to the adjacent room. Pulses racing, three firefighters reach the scene, pull a hose from their engine, and rush into the smoke-filled building.

Outside, three more firefighters are doing their part to ensure the safety of their brethren in peril: chilling out in lawn chairs?

Simmer down, now. It’s all in the name of science.

The blaze is one of several staged this day at Allegheny County Fire Academy. It’s part of a FEMA-sponsored study on the most common killer of firefighters, on duty or off: cardiac arrest.

David Hostler, a University of Pittsburgh PhD assistant professor of emergency medicine as well as founder and director of Pitt’s Emergency Responder Human Performance Lab (ERHPL), designed the study.

The heat, dehydration, and exertion that come with firefighting have long been thought to cause a cascade of inflammation that strains the cardiovascular system. But until now, there’s been very little research on how the process works—or how it might be prevented.

Hoping to find answers, Hostler has teamed up with Joe Suyama, assistant professor of emergency medicine at Pitt and medical director of ERHPL, and Steven Reis, Pitt professor of medicine and emergency medicine and associate vice chancellor for clinical research. All three have some experience in volunteer firefighting. Hostler has spent more than 20 years in turnout gear; he’s now an active firefighter/paramedic in O’Hara Township.

Today, after each simulation burn, the firefighters try out cool-down methods borrowed from NASCAR racers—submerging their forearms in ice water; wearing vests lined with cool liquid; and sitting in an air-conditioned room. Pitt undergrads carefully document heart rates and core temperatures.

“Feels pretty good,” says Francis Deleonibus, assistant fire chief of operations, as he sits in a specially designed lawn chair with ice-water pools in place of armrests. “I can see myself on the beach in one of these.”

“The fire service has always been a calling to a certain extent,” says Hostler, “but we also have to remember: It’s a job we need to go home from at the end of the day.”

—Elaine Vitone

—Photo by Martha Rial
Residents gather at the site of a bomb attack in Kirkuk, north of Baghdad, Iraq, in June. At least 65 people were killed when a truck packed with explosives detonated outside a mosque.
BLASTS TO THE BRAIN
THE NEW WARTIME EPIDEMIC
BY REID R. FRAZIER

If World War I brought shell shock, and the Vietnam War introduced the world to post-traumatic stress disorder (PTSD), the wars in Iraq and Afghanistan are etching a new entry in the lexicon of battlefield medicine: blast injury. There have been more than 80,000 detonations of improvised explosive devices in Iraq in the past six years, accounting for more than 60 percent of American and coalition-force casualties and the deaths of thousands of Iraqi civilians.

Typically, injuries in the “blast zone” are numerous and simultaneous—the blast can shred internal organs with shrapnel or shear off a limb. Among the most vulnerable areas in a blast is the brain. The brain can be confused, deformed, pierced, and damaged from secondary trauma such as ischemia, edema, and hemorrhage.

Armor, helmets, and better battlefield medicine have saved thousands of soldiers in these conflicts. (The killed-to-injured ratio in Iraq and Afghanistan is 1-to-10, compared to 1-to-2.5 for all other American wars.) But survivors are often severely injured. Soldiers with traumatic brain injury (TBI) induced by a blast suffer from headaches, dizziness, vertigo, gaze instability, and motion intolerance. Complicating care for these soldiers is the fact that blast TBI shares symptoms with PTSD. Military doctors and researchers are now trying to sort through the chaotic pathogenesis of this new, war-borne disease.

A team of University of Pittsburgh researchers led by Patrick Kochanek—an MD, director of the Safar Center for Resuscitation Research, and professor of critical care medicine, pediatrics, and anesthesiology—is helping the Department of Defense in this effort.

Kochanek and colleagues have found that blast TBI is quite different from “civilian” TBI, like the kind typically sustained in a car crash. “Say your head hits a windshield: You have this big, focal contusion. It’s a big focal area of badness that will ultimately be lost,” Kochanek says. “In blast TBI, the area of injury is far more diffuse.”

In studying the neuropathology of blast, Pitt researchers have found that, unlike its civilian cousin, blast TBI appears far more damaging to the synapses, axons, and dendrites of the brain—its white matter connective tissues and cables. These are the lines through which the electrochemical signaling of neurotransmission occurs.

“We’re getting an idea of how different this is from the conventional [civilian injury] model,” Kochanek says.

One culprit in the prevalence of axonal injury seems to be the increase in calcium signaling that occurs during blast TBI. Researchers have found that calcium pours through ion channels in injured neurons, releasing proteases suspected of cleaving proteins in the axons. (The prevalence of these cleaved proteins could serve as a biomarker for TBI on the battlefield.) So Safar researchers are looking at molecules known to moderate the calcium pathway—namely the immunosuppressants cyclosporine and tacrolimus (the now-ubiquitous antirejection drugs tested in organ transplant patients at Pitt). Other team members are researching drugs that target the mitochondria, which are sensitive to “excitatory” calcium signaling.

Blunt TBI commonly occurs alongside other injuries—penetrating wounds, traumatically amputated limbs, hemorrhage. This polytrauma only deepens the severity of brain injury. (In civilian TBI, polytrauma doubles morbidity and mortality rates.) Blood loss is a big factor in exacerbating the brain damage. When the body loses about 30 percent of its blood volume, as in a severe orthopaedic injury like a lost limb, hemorrhagic shock ensues. Blood vessels constrict throughout the body; blood pressure drops off a cliff. This is by design—the body tries to avoid bleeding out and conserves resources for the heart and brain. But when it’s injured, the brain needs blood—with its neuroprotective proteins and molecules—more than ever.

“It’s as if the brain is going through a 100-meter sprint, and you’re depriving it of oxygen,” says Kochanek.

Pumping too much blood into the body can lead to edema, a swelling of the tissues. So the Pitt team is testing blood substitutes that might be able to “thread the needle” by providing neuroprotective molecules without overloading the tissues with fluid. One possible approach is polynitroxyalted pegylated hemoglobin (PNPH)—a blood substitute that has both antioxidant and expansive properties. Preliminary research shows PNPH, unlike standard hemoglobin, does not kill neurons in culture. (The team is also looking at a recombinant hemoglobin that was developed in E. coli and at a Carnegie Mellon University laboratory.) Induced mild hypothermia, an approach developed at Pitt, could also hold promise.

The nature of blast means that treating it will be complicated, says C. Edward Dixon, professor of neurosurgery, director of Pitt’s Brain Trauma Research Center, and a neurotrauma expert working on the project. “You may want to look at several types of treatments,” says Dixon. “There isn’t likely to be a silver bullet.”
When the results of an HIV-prevention study were released at an international conference in Montreal last February, the excitement in the room was palpable. Even though, at just 30 percent efficacy, the findings weren’t statistically significant, this was no small victory. It was the first time any medical product had been shown to reduce the incidence of HIV in women.

“It was quite intoxicating,” says Sharon Hillier of that electric day at the Conference on Retroviruses and Opportunistic Infections. “A colleague told me, ‘The first air flight was just a few feet off the ground. You have to take that first short flight before you can soar across oceans.”’

The study, dubbed HPTN-035, tested the efficacy of topical microbicide gels in preventing HIV infection. Two gels were tested against a placebo gel and against a no-gel control in more than 3,000 women in Southern Africa and the United States. The gel that was most effective was PRO 2000, which hinders HIV from attaching to target cells in the genital tract.

HPTN-035 was conducted by the Microbicide Trials Network, an international collaboration headed by Hillier and headquartered at Pitt. (Hillier, a PhD, is also a University of Pittsburgh professor of obstetrics, gynecology, and reproductive sciences, as well as vice chair for faculty affairs and director of reproductive infectious disease research in the Division of Reproductive Infectious Diseases and Immunology.)

The National Institutes of Health founded the network in 2006 to bring together investigators in the United States, Africa, and India developing new HIV-prevention strategies. It’s an urgent need, says Hillier; although AIDS treatment has advanced significantly in recent years, treatment alone can’t change the trajectory of the epidemic, which now affects 33 million worldwide. For every two people who receive treatment for the disease, five more people become infected.

Further, the old “ABC’s” prevention mantra of the past decade—abstain, be faithful, and use condoms—isn’t enough, especially for women.

“Abstinence arguably isn’t really a choice for many women,” says Hillier. “And condom use is not something women can control.”

The network is now testing the safety of a microbicide gel in a population researchers have found to be one of the most vulnerable: pregnant women. Pitt’s Richard Beigi, assistant professor of obstetrics, gynecology, and reproductive sciences, leads this phase I study, which is the first of its kind.

The network designed VOICE (Vaginal and Oral Interventions to Control the Epidemic), the first study to ask these questions. It began enrolling participants at sites in Southern Africa in September.

The network is exploring several AIDS-treatment drugs that might also be used as preventative drugs, an approach known as pre-exposure prophylaxis. One such agent is tenofovir. Hillier’s co-PI at the Microbicide Trials Network, Ian McGowan—Pitt professor of medicine in the Division of Gastroenterology, Hepatology, and Nutrition with a joint appointment in the Department of Obstetrics, Gynecology, and Reproductive Sciences—helped develop the drug.

McGowan is now working on two phase I trials of tenofovir’s safety, acceptability, and ability to be absorbed for use in anal sex, where the risk of HIV infection is 20 times higher than in vaginal sex. Rectal-microbicide research has long been underfunded, but has finally been embraced for its potential to combat the epidemic, McGowan reports. They’re trying two methods: tenofovir topical gels and tablets taken orally.

In July, Hillier received the Thomas Parran Award from the American Sexually Transmitted Diseases Association, a lifetime achievement award honoring her work in prevention and treatment of sexually transmitted infections. It’s a fitting tribute; the award was named after Thomas Parran Jr. (1892–1968), who was the first dean of Pitt’s Graduate School of Public Health. He, too, believed in the power of prevention and labored to bring to light a disease people would rather not think about: His focus was syphilis.

Nearly a century later, the story of AIDS is similar, Hillier notes. It’s a devastating disease that this country spends a fortune treating, though we neglect the prevention side. But Hillier and friends are hoping to help change that.

“What we’re hearing from colleagues and from study participants around the world is that this has given them hope,” she says.
Fifteen years ago, Steven Shapiro made a breakthrough in emphysema. He and his research team isolated and cloned an enzyme called macrophage elastase, or MMP-12, and went on to prove that it causes the deadly disease that chews up the elastic fibers of the lungs, at least in mice. Smokers, who gasp for air once their lungs turn baggy, have a high concentration of macrophage elastase, and mice that lack this enzyme are protected from smoking-induced emphysema.

Then five years ago, Shapiro, the Jack D. Myers Professor and chair of the Department of Medicine at the University of Pittsburgh, and Pitt’s McGarry Houghton, assistant professor of medicine, were conducting another lung study and made a startling discovery about macrophage elastase: The same enzyme that can be deadly also fights bacterial infections in the lungs and likely elsewhere in the body.

It was another eureka moment for Shapiro, as thrilling as his first discovery. “We know the bad things it does. But Mother Nature is too smart to make things that are only going to hurt us,” says Shapiro. “They have to have some physiological function, too.”

Shapiro and Houghton, who are both MDs, recently published their results in Nature. They are hoping their findings may lead to a potent new weapon against antibiotic-resistant “superbugs.” Collaborating with a structural biologist, they’ve begun working on a new antimicrobial drug.

“While our focus has been on understanding the biology of disease,” Shapiro says, “it sure would be nice to see something that came out of our research that actually helped patients.”

Their research is particularly relevant because of the proliferation of superbugs resistant to antibiotics, raising the fear that we could revert to the days prior to penicillin when routine infections could be life-threatening.

“Organisms are getting smarter and more resistant to antibiotics,” Shapiro says. “These superbugs are scary. We need fresh ideas to fight infections.”

MMP-12 is found in the macrophage, a cell that attacks invading bacteria. Houghton and Shapiro believe that the amino acid sequence of the antimicrobial portion of MMP-12, located in the tail of the enzyme, is unique in nature.

They tested the antimicrobial properties of MMP-12 on laboratory mice; half of the mice were genetically altered so that they had no macrophage elastase. The mice that lacked the enzyme hunched over and died when exposed to bacteria. The control mice with the enzyme thrived.

Shapiro and Houghton need to conduct more research to see whether the antimicrobial part of the enzyme would be safe for humans. They are also investigating whether macrophage elastase stops tumor cells from proliferating, as early evidence suggests.

The two researchers made their discovery while testing a mistaken theory regarding complications that can occur after bone marrow transplants.

But some of the best scientific discoveries come from mistakes, notes Shapiro: “If you are going to stick to your story, you are never going to get anywhere.”

Shapiro is so devoted to pulmonary research that he once started smoking for three months to serve as his own control group for an experiment. He stopped puffing after the widely watched experiment. (Many of his colleagues thought the effort was crazy.) Still, he remains devoted to studying emphysema and looking for treatments for other aspects of chronic obstructive pulmonary disease, or COPD. The disease is the fourth-leading cause of death in our country and is expected to be the third-leading cause of death in the world by 2020, he says. Although the incidence of smoking has gone down slightly, it has not yet been reflected in a lower incidence of COPD.

“I would love for everyone to stop smoking today,” Shapiro says. “But you would still have a whole generation of diseased lungs.”
How does one make a lemur walk a straight line? The answer: grapes. But the real question being asked is, “What does the evolution of the knee tell us about the best way to repair ours when the anterior cruciate ligaments snap?” That answer is a bit more complicated.

If a layman takes even a very close look at the ACL, it looks like one bundle of fibers connecting the femur to the tibia. The ligament (which is actually two ligaments, the anteromedial and posterolateral—more on that in a bit) stabilizes the knee while allowing for extension of the leg and rotation of the joint. It’s a pretty important piece of anatomy, especially for the professional athlete, but also for the weekend warrior and, frankly, anyone who wants to walk without pain. Worldwide, surgeons perform about 800,000 ACL procedures each year.

Freddie Fu (MD ’77, Res ’82), an MD as well as David Silver Professor and chair of the Department of Orthopaedic Surgery at the University of Pittsburgh, has been repairing ACLs since 1982. More than a quarter-century later, he frets that he—and every other orthopaedic surgeon in the world—might have been doing it wrong.
Well, “wrong” may be too strong a word. ACL repair, as it’s typically practiced today, does a fine job of getting folks back on their feet. Professional athletes often return to the field cutting, accelerating, and jumping as well as before. The regular guy can walk, jog, or bowl as well as before. In many ways, contemporary ACL surgery is good enough, but Fu is firmly convinced it can be better.

Fu’s known as a pretty energetic fellow. He’s made surgical “house calls” to Saudi Arabia, Turkey, Brazil, and Hong Kong. He takes care of the joints of University athletes and professional jocks— Steelers, Pirates, and Penguins. He’s repaired the anatomies of ballet star Mikhail Baryshnikov and five-time Tour de France winner Miguel Indurain. (Fu himself rides about 100 miles a week and sponsors a professional team—the Freddie Fu Cycling Team of the Allegheny Cycling Association.) Thank-you notes from patients famous and humble decorate his office-suite walls.

He’s often pictured, tuxedo-clad, in the society pages of Pittsburgh newspapers. He’ll do as many as 12 surgeries a day. And, if a reporter happens to have a small question about something going on in his department— something that any number of Fu’s accomplished staffers could answer—it’s not unusual for Fu to respond himself, calling from China at 3 a.m. his local time. “I’m worldwide,” he says with a shrug and a smile.

Sitting with him at a conference table in his Kaufmann Medical Building office soon turns into a scene of controlled (at least as far as Fu is concerned—it didn’t seem so to an overwhelmed visitor) chaos. “Bring me that paper,” he shouts to a vacant doorway. Sure enough, the paper, carried by one of his many assistants who had passed by in the hall, arrives. “Where’s that diagram?” Same thing. As Fu speaks, it seems as though he might fly out of his chair. It’s almost as if he’s disappointed that his mind can be in many places at once, but his body cannot. His is a fast-paced world, yet Fu is dedicated to finding a way to slow down ACL surgery.

With all the documentation he wants in hand, Fu begins to elucidate his vision of a more perfect ACL surgery.

“The mainstay of [ACL] surgery was to do it fast and efficiently,” Fu says, fast and efficiently.

Then Fu slows down a bit—speaking at a more conversational pace and gesturing less frantically. “We’ve gotten a false sense of security, because we’re used to doing it this way, and it seems to work. But five to seven years after [a procedure], people get a significant amount of wear and tear. If you wait long enough, bad things will happen.” These “bad things” include arthritis and joint instability and could require another procedure.

Perhaps if Fu could determine “more scientifically,” as he puts it, how nature, through evolution, wants the knee to be structured, he could develop a surgical technique that would fix the ACL as nature intends it to be.

The path to a better understanding and more precise surgery involves the aforementioned lemur, a bear, a tiger, a springbok, a kangaroo, goats, humans, a mandrill, an ostrich, a gorilla, Lucy the famed 3-million-year-old hominid, some 50-million-year-old fossils, and some pretty advanced technology.

In the course of his career, Fu has repaired more than 5,000 ACLs. When he began operating, he’d open the knee, harvest a ligament graft from the patient’s hamstring or from a cadaver, and replace the torn ligament. With the advent of arthroscopic surgery, there came to be much less cutting; however, the template remained the same in terms of using just one ligament to replace two and not being particularly precise regarding where the replacement ligament joins the femur and tibia.

Yet two sets of investigators described the ACL as a double-bundled structure in the late 1930s and early 1940s. After that? Not much happened along those lines for a long while.

“Until about five or 10 years ago, nobody actually talked about the presence of these two bundles,” says Sheila Ingham, an MD postdoctoral research associate working with Fu. Some people still didn’t believe there were two bundles, and those who did failed to see the importance.

The notion that because the healthy knee has two ACL bundles it should again have two after being repaired crept into the operating suite about a decade ago. On a visit to Japan, Fu observed surgeons attempting double-bundle ACL reconstruction.

“When I came back, I started doing the technique,” Fu says. “But as I started doing the technique, I realized that I needed to learn more about it. Why it might matter.”

Fu set out to confirm that the ACL consists of two bundles and then show that each has important, specific, and separate roles in maintaining the integrity of the knee.

His investigations began with the dissection of knees from cadavers (including a fetus), which unequivocally established that there are two ACL bundles. Fu went back into the annals of human— actually, pre-human—history and examined the knee of the aforementioned Lucy. A model of her fossil is in the care of C. Owen Lovejoy, associate professor of biological anthropology at Kent State University. (Lucy’s remains remain in Ethiopia, where she was found.)

Fu contacted Lovejoy after coming across a series of articles the anthropologist published on the knee in *Gait and Posture.* Lovejoy says he wasn’t particularly surprised to hear from Fu.

“He’s the foremost authority on ACL reconstruction in the world, and as a consequence he’s interested in any research that relates to it.”

Fu, who keeps a replica of Lucy’s femur and tibia in a velvet-lined wooden case in his office, says that examining our distant ancestor went a long way toward confirming his hunch that having a double-bundle ACL is part of what it means to be human.

“She has the double-bundle configuration, and she walked upright,” Fu says. “She’s similar to a human being, not a gorilla—very similar in the soft tissue.”
Fu then had to show whether this fact matters—that the use of a joint dictates how nature allows it to evolve. Enter the lemur.

The lemur in question is Copper, a resident of the Pittsburgh Zoo. He’s 18, docile—“He’s so sweet you can actually go into his cage and pet him,” Ingham says—and is one among many who are giving Fu and his team insight into how form follows function.

At 5 one morning, Copper’s keepers at the zoo took him to UPMC Presbyterian for a CT scan of his knee. “Five people came with him,” Ingham recalls. “They dealt with him, gave him the anesthesia.” Then Copper traveled across town to Pitt’s Orthopaedic Biodynamics Laboratory on the South Side. There, the plan was to encourage him to walk so that Scott Tashman, PhD associate professor of orthopaedic surgery and director of the lab, could record a high-definition X-ray movie of Copper’s gait. (The lemur testing, and examinations of other subjects, was made possible by a grant from the Heinz Endowments.

With zoo personnel at each end of a special runway-like box crafted for Copper, he was coaxed back and forth. “He just had to walk,” Ingham says, “to come and go, come and go, but he got stubborn sometimes.” He would get started, stop, start again, stop again.

“This went on for a couple of hours,” Ingham says. “Finally, he looked at us and kind of said, ‘What do you want me to do?’ And toward the end, he sort of said, ‘Okay, if you want me to walk, I’ll walk.’” A gentle poke, coupled with grapes offered by the zoo’s vet team, finally got the little fellow moving—long forelimbs stretching out, followed by his red rump and rear legs.

Ingham compares Copper’s perambulations to those of a cat. “His gait is similar to most quadrupeds,” she says. “He keeps his knees flexed, which makes them a bit different from ours.” This bended stance and accompanying ease of rotation, she notes, allows for greater suppleness of movement than humans have. “[Lemurs] are very agile animals when they need to be,” she says.

After a couple of hours in Tashman’s biodynamics lab, the team had enough data, and Copper was excused. “At the end he got pizza, and that made him happy,” Ingham says with a laugh. “We wanted to make him jump, but he wasn’t having any of that.”

The biodynamics lab lies along the Monongahela River, on South Water Street. Tucked between the Steelers’ and University of Pittsburgh football team’s practice facility, the UPMC Sports Performance Complex, and the FBI’s local headquarters, the lab is kind of a playground for the kinesiology set. Tashman has become known as one of the foremost designers of X-ray systems for capturing rapid motion. His Pitt lab includes strobing X-ray machines equipped with video cameras that can record between 180 and 1,000 frames per second. The speed, Tashman says, is vital to producing accurate and clear images.

Tashman can start, stop, and rotate the image at will. He can look at how far the ACL stretches and rotates, the structure of condyles (the round, bony projections at the terminus of the tibia and femur in this case), how the bones move in relation to one another, and the degree of force borne by cartilage and the bones during locomotion.

Tashman’s examinations of the nature of the knee—with humans and other primates—are at a fairly early stage. “Part of [the investigation] is about understanding the evolutionary development of the knee and why our knees are designed the way they are,” he says. “That’s more of an intellectual pursuit. But then there’s the possibility of understanding why a specific configuration of the knee might be beneficial for certain activities.”

For example, the work may one day help explain why some people—such as Pittsburgh Steelers receiver Hines Ward—can participate in sports at the highest level without an ACL in one knee and why others can barely walk with a torn ligament.

“There are a lot of theories running around about how structure relates to risk of injury and as to whether certain knees are better designed for certain activities,” Tashman says. “There are a lot of options when it comes to repairing a damaged knee ligament. What we might need to think about is what this person is going to be doing.”

All this, Fu says, will help him and other surgeons change ACL surgery from a one-size-fits-all pursuit to a personalized one.

The team’s animal investigations—part of a collaboration with the Pittsburgh Zoo that began in 2007—are lending further insight
into what the structure of a knee says about what it can, and should, be able to do.

“The animals are critical because we are trying to know why different animals have different sizes of ACL—why some have triple bundles, some have two,” Fu says. “How do these things correlate with animal morphology, and how can we translate this knowledge to humans?”

Ingham says it’s generally accepted that the anteromedial ligament of the ACL stabilizes the knee as it swings forward and back. The posterolateral provides rotational stability. Typically, she says, single-bundle ACL repair includes only the anteromedial ligament, and the patient tends to have more knee rotation than she should. Not good.

“What you see in ACL reconstruction is that after a few years, you develop osteoarthritis,” Ingham says.

“At that point, you either downgrade your physical activity or decide to go swimming [rather than participate in high-impact activities].”

When a zoo animal is anesthetized for any reason, Ingham or her colleagues go to the zoo equipped with a goniometer to measure the rotation and flexion of the creature’s knee. When an animal dies of natural causes, the zoo provides the knee to Fu’s team for dissection and examination of the ligaments.

When Petya the Siberian tiger, for example, had his annual physical, Ingham had the privilege of examining the 15-month-old, 200-pound cat. Small animals, like Copper, she can do on her own, she notes. The bigger, furrier patients require some help.

“Examining them is challenging enough, because we’re trained to examine humans,” she says. “And with the larger animals—bears, tigers, gorillas—two of us have to do the examination.” One holds the leg at a 90-degree angle while the other manipulates the knee, measuring the rotation and extension. “And it’s hard to deal with all that fur and even to find the knee sometimes.”

Ingham admits to some trepidation when working with those outweighing her by hundreds of pounds and bearing sharp teeth. But at the beginning of the project, she got some sound advice about what to do if Petya were to wake up while having his knee twisted this way and that: “Basically, it was, ‘Get out of the room as quickly as possible!’”

In 2007, the zoo’s mandrill, Johnny, was grabbing and poking at his knee. Fu took this opportunity to operate on the living monkey, finding that he had a partial ACL tear and three ACL bundles. Though a full-on fix was impractical, Fu says, he removed some inflamed tissue in Johnny’s knee to reduce his discomfort. Today, Ingham reports, Johnny is pain free and has even acquired a girlfriend.

Ingham calls up an image on her laptop. “This is a gorilla knee. You can see that it has three bundles. What we’ve come to see is that these [three-bundle] animals have more rotation, that animals who live in trees seem to need more rotation than we do.”

A tiger, on the other hand, has less rotational range of motion.

“We asked, ‘Why is that?’” says Ingham. “Well, gorillas are plantigrades [they walk with the soles of their feet on the ground], they move like we do. But tigers aren’t, they move like dogs or cats [on their toes]; they’re digitigrades and have much more range of motion front and back. So—aha!—that’s where the form and function start coming in.”

So if we humans are more like the gorilla than the tiger, yet the gorilla has an extra bundle to help control knee rotation, while we don’t, perhaps, Ingham says, it makes sense to consider that excessive rotation contributes to the development of osteoarthritis in humans with bad ACLs.

If that’s so, she adds, it’s all the more important to repair both bundles in the human knee to ward off degeneration.

Christopher Beard—a PhD, Mary R. Dawson Chair of Vertebrate Paleontology and curator at the Carnegie Museum of Natural History, and an adjunct faculty member in Pitt’s School of Medicine—says that his involvement with Fu began several years ago, when the surgeon invited him to Pitt. Beard and a handful of colleagues made short presentations to visiting scholars about the evolution of the knee in primates and other mammals.

Fu’s team has since examined scores of fossils in the museum’s collection. This work, Beard says, has gone a long way toward confirming Fu’s conviction that nature gave humans a double-bundle ACL for a reason.

“The double-bundle ACL is an ancestral condition among a wide variety of primates and other mammals,” Beard wrote in an e-mail. “Put another way, this strongly suggests that double-bundle ACLs have been conserved by natural selection for millions of years in a variety of different organisms, including humans. So, [Fu’s] surgical technique to reconstruct ACLs in light of this knowledge is obviously the best way forward.”

Lovejoy agrees. “The absolute sanity of [the double-bundle procedure] struck me,” he says. “Mechanically, of course that’s the way you should do it, but it isn’t the standard procedure.”

Yet. The more knowledge Fu and his team acquire, the more Fu looks to apply it to surgery.

‘Let’s say a mechanic wants to replace a fan belt in a car. The vehicle is designed in a
way that, once he opens the hood, it’s pretty obvious where the belt should go—see those pulleys there? But what if the mechanic doesn’t quite place the new belt into the proper slot on the pulleys? Or, if he does put it in the right place, what if he uses the wrong size belt, fails to tighten it adequately, or over-tightens it? It’ll probably work well enough for a while, but sooner or later, the belt will slip off the pulleys or rupture.

Putting the ACL in the proper position—using the double- or single-bundle technique—is a challenge. And this, says Fu, has contributed to the fact that at five to seven years after ACL surgery, many patients report significant pain.

“If you put [the ACL] in the wrong place, the force pulling on it isn’t right,” Fu says. The bone can expand. There are consequences both mechanically and biologically, and people don’t realize it.”

So why don’t surgeons always place ACL repairs in the right place? There are a handful of reasons: an incomplete understanding of the anatomy (which Fu and colleagues are trying to remedy through their research); the fact that presurgical imaging wasn’t so great before 3-D CT scans were used regularly; and the belief that close enough was good enough.

Fu is now convinced that little is more important to successful ACL repair than replicating native anatomy. Close enough won’t cut it any more. “With nonanatomical placement, you can have abnormal kinematics of the knee, and that will cause it to wear out,” Fu says.

When a surgeon does a single-bundle ACL repair, even if the graft is put precisely where it should be, only 40–60 percent of the native anatomy is replicated. Fu says. If he were to do a double-bundle repair, that percentage would come closer to 90 percent.

The thing is, this type of ACL surgery takes more time, requires a defter surgical touch, and, at the end of the day, might not be for everyone. And, frankly, says Fu, he’s not entirely sure that it will improve patient outcomes enough to justify the difficulty. Of course, one reason for this uncertainty is that double-bundle surgery hasn’t been around long enough to do long-term studies.

Fu’s dedication to the idea of anatomical reconstruction applies regardless of whether single- or double-bundle reconstruction is appropriate for a patient. In either case, lack of attention to detail—typical ACL repair surgery has been so mechanized that it can take less than a half-hour to complete—can result in surgeons placing the anteromedial bundle in the insertion site where the posterolateral bundle belongs and vice versa.

Putting tab A into the wrong slot C can have unfortunate consequences for those assembling IKEA furniture. It’s no better for an ACL patient.

“We did a study with a goat,” Fu says. “We matched it right, and we matched it wrong. We saw osteoclasts [cells that destroy bone] much more when we put it in the wrong place. That makes sense. You have the wrong tunnel, and you put [the bundle] in the wrong place, and the function will not be right. It’s simple.”

Fu has taken steps to ensure greater accuracy in the placement of ACL bundles as well as in how much graft to use.

“It takes time to change bad habits. I had to shed bad habits, but right now I would say that I’m pretty anatomical,” he says.

Several elements factor into deciding where the new ACL bundles ought to be inserted in the femur and tibia. Looking for the remnants of the torn bundle is a good first step toward finding out where the new one should go. Once the insertion sites are defined, Fu breaks out—get ready for this high-tech tool—a ruler. He then measures the length and width of all four (if it’s a double-bundle procedure) insertion sites.

“I guess it’s not hard to do this,” Fu says. “But in every case we use the ruler and take about five more minutes to do these measurements. It helps us make decisions about what to do.” Otherwise, range of motion will be limited, bone may impinge on tendon, and tension on the tendon will be stronger than normal. For all these reasons, the graft can fail.

Accounting for precise variations in individual knee anatomy—how large the insertion sites are, as well as how far apart they are—allows Fu to customize the tunnel and graft size for each bundle. It also makes notchplasty—the shearing of bone to prevent tendon from rubbing on bone—a thing of the past.

“The truth is that if you put an ACL exactly where God gave you an ACL, there will be no impingement.” And the native anatomy won’t be distorted.

So, during your surgery—a procedure that mimics native anatomy if Fu has his way—how about a sandwich?

C. Owen Lovejoy, Fu, and Lucy share a moment together.
“Fewer than three out of 10 people who suffer severe vision impairment even leave their homes.”
A NEW CENTER FOCUSES ON RESTORING VISION
BY CHUCK STARESINIC

AN INVISIBLE PROBLEM

On the door to Lieutenant Ivan Castro’s room at National Naval Medical Center in Bethesda, Md., Major General Gale Pollock found a handmade sign that read, “Use Vision Precautions.” (In other words, as you enter this room, don’t assume the soldier inside can see you or anything else.) As an army nurse, it was Pollock’s job to check on the wounded soldiers in the naval hospital. Never mind that she was a major general and chief of the U.S. Army Nurse Corps. She was an army nurse.

“He didn’t track me when I came into the room,” Pollock recalls. “So I put my hand on him when I got there, so he’d know where I was.”

How are you doing?
Crppy.
What’s going on?
I’m blind.

Castro didn’t say a word about his other injuries, which were extensive. A mortar blast had killed two army snipers standing next to him on a rooftop in Iraq. The force of the explosion broke Castro’s arm and left the bone protruding. It broke his nose,
We don’t realize how many there are who are struggling.”

are an embarrassment to anyone who ever was, is, or will be a Ranger. You are a quitter.

Castro rolled up on one elbow and yelled: I told you I’m blind!

Pollock yelled right back: And I told you you’re a quitter! I’ve got other blind service members in the military. So what the hell is your problem? You are a quitter.

Just a few years earlier, Gale Pollock admittedly did not have much of a handle on the extent of vision problems among service members and veterans. Then, she learned that 10–13 percent of all the combat injuries in Iraq and Afghanistan involve the eyes. As she dug deeper, the extent of the problem began to emerge. It has only grown larger as the wars have dragged on.

“We have just over 100 now in the military who have had one or both eyes enucleated,” Pollock says. “We have over 1,000 who are legally blind.”

Pollock and her staff then began to ask what there was to offer these folks, soldiers and civilians alike. She was not impressed with the answers.

“Fewer than three out of 10 people who suffer severe vision impairment even leave their homes. That’s why it’s an invisible issue in America, because they are not out there. We don’t see people struggling. We don’t realize how many there are who are struggling. We occasionally see someone with a white cane or a guide dog, and we think, ‘Look how well they are getting along!’ And we falsely assign that positive to the entire community of vision impaired. But it’s a continuum, and the people you see out there are the risk takers and the ‘Don’t you tell me I can’t do that’ kind of person. … At the other end you have people who are so chronically depressed that they are suicidal. Then you have the bulk of them in the middle.

“My role as a nurse,” says Pollock, “is to raise people to their highest level of functioning, regardless of their injury or disability.” She started talking with the blind and injured, she says, telling them, “Hi. I’m your new big sister, and I’m going to find a way for you to have a higher quality of life.”

She traveled to different research centers and talked with clinicians focused on the eye. Along the way, she met Joel Schuman, professor and chair of the Department of Ophthalmology in the University of Pittsburgh School of Medicine, and Alan Russell, a Pitt University Professor of Surgery and director of the Pitt/UPMC McGowan Institute for Regenerative Medicine. Russell and Schuman were taken with her single-minded attention to getting science out of the lab and into the clinic, where it could help people struggling with their vision today.

One of the first things Pollock would learn about Pitt was that a collaborative culture permeated the place. When she met Schuman, an expert in glaucoma, he was deep in conversation with Russell, who might not have known much about eyes at that point, but knew a great deal about the body’s inherent ability to heal and regenerate tissue.

These scientists, Pollock realized, were not just talking about correcting damaged vision with better lenses, implants, or transplants. They were talking about a fundamentally different approach—coaxing the body into growing new corneal tissue to replace scar tissue, for example, or getting a severed optic nerve to reconnect on its own. Both of these are tissues that, once damaged, do not heal in any meaningful way. These scientists believed they could change that.

As Russell puts it, regenerative medicine is about “accelerating the pace at which the body heals itself into a clinically relevant time scale. Instead of ameliorating symptoms, we will regenerate lost function of the body.”

Louis J. Fox is a guy who knows how to both work hard and enjoy the rewards that hard work brings. Or, put another way, he’s a guy who doesn’t know how to sit still.

“I’m a type A personality by genetics,” he says.

Until 1999, Fox made a living as a senior executive at Gerald Metals, in Stamford, Conn. He ran its global precious metals trading and financing group. He often worked 12–14 hours a day. For fun, he piloted his own plane.

He “retired” in 1999. Fox’s idea of a retirement activity involved starting a gold commodities trading company. (More on that later.)

At the beginning of 2000, just as this happy, successful commodities trader entered what was expected to be a blissful, relaxing, and productive phase of life, Fox noticed that the vision in his right eye was a little off. Something wasn’t quite right when he closed his left eye and tried to read the traffic signs. He found an eye doctor who told him his vision was 20/25 in that eye. For a guy who’d recently been 20/20 or better vision impaired, this was not good.

For the most part, the human eye is a nonvascular organ, meaning its various parts do not contain blood vessels. The exception is the retina, which makes up the entire back wall of the globe that is the eye. More than half of the inner surface area of this globe is the retina, which is suffused with a network of blood vessels. The central retinal artery delivers oxygen-rich blood to this network through a single entry point in the back of the eye. Once depleted of its oxygen, blood leaves the eye via the central retinal vein. In Fox’s right eye, a blockage occurred in this vein, and the blood began to back up in the eye. The central part of the retina, which corresponds to the center of one’s field of view, was beginning to swell and bleed. The retinal tissue was becoming damaged.
When Fox asked his doctor what could be done, he was told, “Not much.” It could heal itself, but it might not.

Fortunately, Fox still had excellent vision in his left eye. He applied for and received a waiver from the Federal Aviation Administration to fly as a pilot with monovision. Three years after his right retinal vein occluded, he woke up one morning and noticed something wasn’t quite right about his left eye. Fox was among the 6–14 percent of people with central retinal vein occlusion who experience it in both eyes, leaving him unable to drive a car, let alone pilot an airplane.

One day, his wife, Dorothy Fox, called him into the room to catch a segment of the CBS television show Sunday Morning. It was all about vision restoration at the University of Pittsburgh, where he received his undergraduate degree in 1964. Being a Pitt grad, Fox went ahead and called the University and soon found himself in touch with Russell and Schuman.

On a subsequent visit to the Pitt campus and the McGowan Institute for Regenerative Medicine, Fox was bowled over.

“You have to understand, the world I come from—the commodity world—is a very different-thinking kind of world,” he says. “It’s dynamic. In the world of commodities, every day is different. It’s never the same, and you can’t get stuck in old ways of thinking. Well, you can, and people do, but the real successes are because it’s so dynamic and people see that. That mentality seemed to pervade the whole Pitt/UPMC/McGowan medical community. And it was both refreshing and exciting.”

Fox was in a good position to recognize this sort of thinking. When he “retired,” he and some partners started buying a lot of gold-mining properties with the intention of drilling them and developing gold reserves. “We weren’t going to mine the properties,” Fox says. “We were going to hold the properties and develop the reserves with the view that we thought gold was going to go up significantly higher. We were more right than we ever thought, because in 2000, gold was around $200 an ounce. Today, it’s about $950 an ounce and looking like its going higher.”

In 2009, Fox announced a $3 million commitment to what is now the Louis J. Fox Center for Vision Restoration of UPMC and the University of Pittsburgh, a collaborative effort of the UPMC Eye Center and McGowan. UPMC has pledged to match all such philanthropic donations to the center.

As of 2008, the Fox Center is under the leadership of executive director Gale Pollock, now retired from the army.

“I f a mammalian fetus loses a limb in the first trimester, it regrows it,” says Russell. “But this ability is lost as we age. A child who loses a fingertip in the first six months of life regrows it. By age 5, they do not.” McGowan Institute researchers are finding ways to kick-start these dormant abilities of tissue regeneration. And what they are doing seems to apply to every organ system in the body.

The Louis J. Fox Center for Vision Restoration applies this same sort of thinking to the eye. The work of Stephen Badylak, Pitt professor of surgery and director of tissue engineering at the McGowan Institute, is a perfect example. Badylak’s lab constructs scaffolds around which the body regenerates new tissue—a lost fingertip, for example. They start with an extracellular matrix derived from pig bladders that are essentially washed of all cells, leaving connective tissue that comprised the structure of the organ. The body seems to recognize biochemical signals from the matrix as a summons to populate the scaffold with cells and generate new tissue. The scaffolds are eventually absorbed, leaving no trace. Recently, Badylak’s lab began to ask whether they could convince the body to repair a severed optic nerve.

“You can have a perfectly functional eyeball, but if you don’t have the nerves to convey those signals back to the brain, you don’t have vision. We don’t have the skills to repair a severed optic nerve,” says Badylak, but he adds that the body probably does. He says it’s too early to say exactly how his lab needs to shape or apply the matrix to accomplish this. He also doesn’t know if it will be necessary to seed the matrix with neuronal cells or stem cells from the patient, but he’s optimistic it will work.

“Imagine the optic nerve as a telephone wire with loads of cables running through each wire. We would form a sleeve around the severed ends of the optic nerve that would contain not only the guidance cues to say the severed nerve should grow in this direction, but also cues that would promote actual cell division and elongation of the dendritic processes and the axonal processes. I think, frankly, that it will be a tube-shaped sleeve that is going to get our best first results.” He says the questions then become: Do we need to add a cell component? Do we need to fill the sleeve with a gel form of the matrix to help promote this?

As with the optic nerve, doctors have few options when it comes to repairing damaged corneas right now. This clear covering that permits light to enter the eye is a fascinating tissue. The outermost layer consists of cells that regularly slough off and regenerate. Superficial scratches and wounds to this layer leave no permanent scars. But the innermost layer is a different story. The cells and proteins that make up this layer are rigidly structured to be both strong and transparent. An injury or infection that damages this innermost layer will lead to the growth of scar tissue that lacks the proper structure and is not transparent.

Roughly 10 million people on the planet have cloudy corneas that they can’t see through properly. To date, the only cure is corneal transplantation, a procedure that is very common and highly successful in this country. As a nonvascularized organ, the cornea is immune-privileged, meaning it does
tissue. “There wasn’t any inflammation. There had the ability to completely reconstruct the Funderburgh says. The stem cells apparently therefore have cloudy corneas.

Institute, but the new Fox Center for Vision has long been associated with the McGowan these cells we could maybe take care of corneal times to make sure we were really right. It was

components of the cornea’s structure, including a protein called lumican, which is key to the proper structure and transparency of the cornea. What would happen, Funderburgh asked, if these cells were injected into a damaged cornea?

Their experiment was a cautious first step—they injected human corneal stem cells into mice that cannot produce lumican and therefore have cloudy corneas.

The results were kind of shocking, Funderburgh says. The stem cells apparently had the ability to completely reconstruct the tissue. “There wasn’t any inflammation. There wasn’t anything obvious going on—it was just that the mouse corneas got clear. They took this matrix, which was improperly put together, and which we always thought was like cement, and they turned cloudy corneas clear. And when we went back to look at the collagen structure, it had changed also, so it was kind of shocking. We had to do it a few times to make sure we were really right. It was a very exciting possibility that just by injecting these cells we could maybe take care of corneal scars without having to do a transplant.”

With his interest in stem cells, Funderburgh has long been associated with the McGowan Institute, but the new Fox Center for Vision Restoration brings more attention and more resources to bear for moving discoveries like his to the clinic. With Pollock’s enthusiastic support, he’s exploring how to culture these cells in such a way that the FDA will approve them for use in a clinical trial.

“Gale Pollock,” he says, “is the kind of person who walks into your office and says, ‘Okay, when are you going to help my sol-

Before the wow’d audience at the press conference, Jernigan correctly described the shapes and directional arrows placed on the screen in front of him.

In the coming year, researchers at the Fox Center for Vision Restoration hope several dozen people who have lost their vision will test the latest version of the BrainPort.

“This device is not going to give you vision. But it makes a huge difference.”

“I’ve always been what is known as a ‘grind and find’ biochemist,” he says with a laugh. “I’ve spent my whole career taking tissues apart and looking at the molecules and seeing how they fit together and how they work.”

Recent discoveries have Funderburgh looking to get his lab’s discoveries on the fast track to the clinic. He and his colleagues were the first to discover, isolate, and culture stem cells from the innermost layer of the cornea. (A Japanese lab published a similar description around the same time, and these may prove to be the same cell type.) They found that these cells, even after many rounds of expansion in the lab, continue to produce the biochemical components of the cornea’s structure, including a protein called lumican, which is key to the proper structure and transparency of the cornea. What would happen, Funderburgh asked, if these cells were injected into a damaged cornea?

A t a press conference in May 2009 announcing the $3 million commitment from Louis Fox, retired Marine Corporal Mike Jernigan demonstrated a futuristic, experimental device called the BrainPort.

Like Castro, the U.S. Army Ranger blinded in battle, Jernigan was blinded in an explosion in Iraq. A pair of artillery shells had killed one of his fellow Marines and wounded three others. Of the survivors, he was the worst off. The front of his head caved in. Traumatic brain injury only begins to describe his case. His forehead was gone, and 45 percent of his brain crushed. Somehow, thanks to a Kevlar helmet, Jernigan says, there was no penetrating brain injury. He says that he had 30 major surgeries in 12 months and “flattened” during three of them. He lost both eyes.

But at the press conference in Pittsburgh, Jernigan, sporting a pair of black wraparound sunglasses, placed a small plastic device (an IOD, for intra-oral device) on his tongue. Electrical cables connected the IOD to the sunglasses, which have a tiny, unobtrusive camera mounted on the bridge. Jernigan, who has no eyeballs, sat before a black felt screen with white shapes. As the camera picked up the images, data were transmitted to the IOD, which contains a grid of tiny electrodes in contact with Jernigan’s tongue.

“It feels like putting a 9-volt battery on your tongue,” says Jernigan. Pollock describes the feeling as “like champagne bubbles.”

The BrainPort is being developed at the University of Wisconsin and field tested here at Pitt, among other places. The information conveyed from the camera to the tongue makes its way to the user’s visual cortex.

“This device is not going to give you vision,” says Jernigan. “But it makes a huge difference. It might not be vision, but it’s not total darkness, either. A device like this can give a person like myself a lot of hope and a lot of excitement about where this technology can go.”

To all appearances, Jernigan does not have trouble venturing out of his house. He is a political science major enrolled at the University of South Florida. He uses a guide dog to get around. (Although he has a BrainPort at home, he doesn’t use it much—testimony to the refinement required before the device will help a large number of people in daily life.)

And Ivan Castro, whom Gale Pollock reached out to in his Bethesda hospital bed by directly challenging him, has remained in the army, been promoted to captain, and met the challenges of his postinjury life head on.

“I think he did six marathons last year,” says Pollock. “I saw him finish the Boston Marathon. He and some of his colleagues I am absolutely focused on helping now. We are going to demonstrate to the world that life does not stop if you’ve lost your sight.”

To convey the plight of those with lost vision, Pollock often describes a wide spectrum of activity, with Jernigan and Castro occupying the “go-getter” end and a more reclusive majority taking up the rest. But Jernigan is quick to counter that the spectrum may not be as wide as it first appears.

“When I first came home, I was scared to leave my apartment,” he says. “I was scared to walk past the sidewalk and get into the parking lot, because I was afraid I’d get hit by a car. And that’s the type of stuff you deal with. I had a tight family and a lot of support, and I went to counseling. If it wasn’t for that, I don’t know what would have happened. And that’s what a lot of people don’t understand. Everyone looks at me as the person who can’t be stopped and doesn’t let anything get in his way, but nobody realizes that I’m three steps away from being reclusive. That’s just how it is.”
Cane resting on her one good leg, Kimmy Perilloux rolls up her long-sleeved T-shirt. The exterior of her arm still looks strong, but signs of diabetes line the inner arm: There is a thick bandage on the biceps, toward the armpit, where she received her insulin injection earlier that morning. Three off-white furrows appear near the wrist, where a surgeon inserted fistulas for dialysis treatment.

Physician Michael Boninger asks Perilloux to extend her arms and turn her palms up. He presses down on them gently. “My arm hurts,” because of the fistulas, she explains. Boninger stops.

Boninger had begun the exam by reviewing Perilloux’s medical history, a particularly long one for a 46-year-old. Diagnosed with
In the Department of Physical Medicine and Rehabilitation, faculty are researching better ways to deal with, slow, or reverse the decline of the body.
that could restore tissue and increase function.

recovery, new technologies, and biologic therapies

table destruction of the body—whether destroyed

The rehab docs in PM&R are researching bet-

(NIH) funding for departments of its kind.

number one in National Institutes of Health

the helm of a research juggernaut that now ranks

“Are we getting less pain and

stress injuries for wheelchair users. “In physical

medical arts—making the best of impaired bodies

He has authored pioneering studies in repetitive

He received a bachelor's degree in engi-

engineering from Ohio State University, then got

“Have you long-term contact with

patients—you're not dealing with emergen-

cies,” he says of his chosen field. “And,” he

continues, “patients get better. It's about them

I had a kid who came into the hospital;
[he] was riding his bicycle and was hit by a

car. Had a brain injury and really came into

Boninger also directs the Institute for

WINTER 2009/10

A SIDE EFFECT OF MODERN MEDICINE

Boninger is a trim, buoyant man who rises at

5 a.m. and gets on his elliptical trainer, where

takes up on doctoral student papers and

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Sowa, Pitt assistant professor of physical medicine and rehabilitation, thinks there's a better inflammatory patch in the area. For his neck, dynamic balancing exercises and to use an anti-

This is curious, she notes, because he uses it all the time.

For the hip, Sowa writes a script for his physical therapist to put James through standing on one leg. Sowa checks his hip alignment, which seems fine, before she tells him it's okay to place his foot down again.

James is here because of chronic muscle pain in his hip and spasms in his neck, which he's had since an 8-year-old hit him in the eye with a tennis ball last year. His wobbly performance on one leg tells Sowa that his hip abductor (the outside of the thigh) is weak. This is curious, she notes, because he uses it all the time.

For the hip, Sowa writes a script for his physical therapist to put James through dynamic balancing exercises and to use an anti-inflammatory patch in the area. For his neck, she sends him to a massage therapist.

These therapies will probably reduce the inflammation responsible for James' pain, but Sowa, Pitt assistant professor of physical medicine and rehabilitation, thinks there's a better way to treat patients like him. She's researching the molecular pathways that lead to inflammation in pursuit of biomarkers that could spill out more precisely what's causing these problems and, more importantly, whether the solutions she's given him are working.

Among those who could benefit from such a test would be the large numbers of Americans who suffer from lower-back pain. Lower-back pain, a by-product of a sedentary lifestyle, will afflict about 9 in 10 Americans at some point in their lives. Estimates put the health care cost of lower-back pain at around $32 billion per year, making it the most expensive nonlife-threatening condition. But for the enormity and ubiquity of the problem, we still know relatively little about the mechanisms that cause it or remedy it. Exercise is good for the back, of course, but how much, and what kind? The question of dosage in exercise is very much unresolved, according to Anthony Delitto, professor and chair of physical therapy in Pitt's School of Health and Rehabilitation Sciences.

“We're flying blind as far as dose is concerned,” says Delitto, who has studied the enormous health costs lower-back pain incurs. “We want to be a little more enlightened about dose. We could be underdosing, for all we know. At the same time, we have a patient sitting in a chair in front of us, and [she wants] to be treated.”

Delitto is collaborating with Sowa on biological research into the role exercise plays in reducing inflammation.

Sowa, who has a PhD in biochemistry and an MD, takes cultured invertebral disc cells and gives them a “workout.” In a specially designed chamber, she applies stretch and compression forces that mimic exercise. At certain levels of exercise, the cells produce lower levels of inflammatory molecules. Above a certain threshold, the exercise appears to be damaging—the inflammatory molecules increase. Experiments in rats have produced similar results. (She wagers that exercise could be a better anti-inflammatory than ibuprofen, but has yet to do a head-to-head comparison.) Sowa hopes her research will lead to a biomarker that can give real-time updates of a treatment's efficacy.

A biomarker would be helpful for James, the former tennis pro who had a hard time standing on one leg.

And a biomarker assay would give Sowa a real-time read on the exercises she's prescribed for him. Do they reduce the seroprevalence of inflammatory markers, like interleukin-1 and nitric oxide? What about molecules that reduce inflammation? A test for TIMPs, a group of protease inhibitors that limit the inflammatory cascade, could provide a glimpse into how James' stretching and balancing exercises are working on the molecular level.

MRI and other imaging technologies offer little insight into the molecular pathways Sowa is interested in, especially in the short term.

“The biomarkers potentially could show up in minutes; you could do the exercise regimen, sample the blood, and immediately know, 'Did you do the right thing, or not?'”

GETTING STEM CELLS
TO ACT THEIR AGE

Since stem cells were discovered in the 1960s, researchers have held out hope that they could be used to boost recovery within the deteriorating body. Despite the high hopes, success with stem cell therapies has been elusive. When transplant-
ed into a new body, stem cells from older people tend to die off quickly, form scar tissue, and fail to divide rapidly enough to make a difference.

But what if these cells were sent to the gym? That's more or less a question being asked by Fabrisia Ambrosio, a PhD assistant professor of physical medicine and rehabilitation, physical therapy, and orthopaedic surgery. Ambrosio and her collaborators at Pitt explore the possibility that electrical stimulation and exercise—two standard physical therapy interventions—can help improve the performance of transplanted adult stem cells.

Ambrosio says that even when an adult stem cell from a younger donor is injected into the body of an older person, the grafted cells tend to behave like the cells in their new environment. It's as if these young cells are like children sent to live in a nursing home, she notes.

They take a look at the '50s furniture, the Perry Como records, and black-and-white television. Before long, they start wearing track suits and queuing up for the Early Bird special.

“I'm trying to refurbish their environment, put in modern contemporary furniture, so even the old, resident stem cells can say, 'I need to spruce up my place here,’” says Ambrosio.

With “e-stim” and exercise, transplanted stem cells in mice reproduce more quickly and don't die or form scar tissue as quickly as those in a control group.

Both of these therapies increase blood supply to the affected area. Ambrosio thinks this could be a factor in improving the vitality of grafted stem cells. “I think that exposing the stem cells to either nutrients they need or growth factors they need—or even contact to stem cells in other locations—[is what's] allowing them to behave better.”

Ambrosio has also found that stem cells in older patients might be made to “act younger” through such methods.

This could have serious implications for older patients, like those who've suffered a fall, which can often set off a cascade of additional health problems. “Our idea is if you can give [patients] a little bit of a jump start by injecting their own stem cells, then can you speed up the healing process and get them back faster to doing the things they were able to do before.”

PITTMED
THE MYSTERIES OF THE INJURED BRAIN

The most common type of traumatic brain injury occurs in a car crash. The brain stem and neck act as a fulcrum, accelerating the frontal lobes into an impact with a hard surface—a windshield, a dashboard. Patients lose memory of the crash. As they recover, they go through a stage called “agitation,” during which they are edgy, angry, unsure of why they’re in a rehab ward. Sometimes, they get violent.

“You’ve got to be able to duck quick,” says Amy Wagner, also of the Department of Physical Medicine and Rehabilitation. Wagner, an MD, studies the neurobiology of the injured brain.

Critical care docs often prescribe anticonvulsants and antipsychotic meds to curb some of the behavioral effects seen in agitation. That’s probably a good thing. But Wagner has found that different physicians prescribe these meds for different lengths of time. Some prescribe them longer than indications would warrant. So she studied the effect that long-term dosage has on brain injury patients and found that longer dosage times can hurt the brain’s long-term recovery.

She’s also looking at how variations in the dopamine transporter gene affect a patient’s recovery. Dopaminergic stimulants—like the popular drug Ritalin, indicated for ADHD—help brain injury patients wake up, improve attention and motor processing speed, and increase their levels of arousal. Wagner wants to better understand the relationship between dopamine, the genes that regulate dopamine’s movement through the brain, and the structures in the brain that dopamine and its stimulants target. Her next project will look at whether gender and hormones play a role in modulating dopamine transmission after brain injury.

As with most research about the brain, Wagner’s subject is shrouded in mystery. Thousands of genes and molecules are involved in neurotransmission—she’s chosen a few that seem likely to play a part in recovery.

Wagner knows the damage brain injury can wreak on a patient’s life. While rounding on rehab wards, she sees people who, in an instant, have lost their fundamental purchase on reality. She sees a lot of hardship, yet little could be more interesting to her than trying to understand and fix something as complicated as the injured brain.

“The fun part and challenge in brain injury is that everybody’s brain injury is different,” Wagner says. “We don’t really know everything about the normal state of the brain, and we certainly don’t know much about the injured brain.”

HOW TO MAKE YOUR ARM MOVE WHEN YOU DON’T ACTUALLY HAVE ONE

The stereo speakers in the room hiss with static, and a cluch of guys in lab coats and paper booties do the scientific equivalent of a sound check before a rock show.

“Is that all L6 or all L7?” asks Douglas Weber, Pitt assistant professor of physical medicine and rehabilitation as well as bioengineering, to a roomful of grad students and postdocs huddled around a bank of humongous computer monitors.

“That’s all L6,” says one of his PhD students, James Hokanson, referring to the purple waveform on his screen. The wave is based on an electric impulse being recorded near the L6 dorsal root ganglion of a cat in the middle of the room.

Weber holds one of the cat’s rear paws in his hand. As he strokes the fur, a crackling, popping, Geiger-counter-like sound peaks across the speakers (which are, by the way, “classic Bose 301s” that Weber’s had since he was an undergrad). Waves splutter in the many tiles on Hokanson’s screen. The sound is the cat’s nervous system, firing off a report from skin cell to brain: “Something’s touching my fur.”

The electrodes in the cat intercept the signal and carry it to the speakers and computer.

Weber is trying to map the neural network involved in proprioception—the body’s understanding of where its different parts are in relationship to one another. His focus is neural prosthetics—the cybernetic science that could one day help an amputee move a robotic arm just by thinking.

To do that, neuroengineers like Weber must map how the limbs report to the brain sensations like how heavy an object is and whether it’s hot or smooth.

Each of the 90 electrodes implanted in the cat can listen in on two or three neurons. Weber points to a messy waveform on one of the screens. Hokanson hits a few keystrokes and the scribbles change color—from one big scribble of white to two distinct waves—one short and red, the other longer and yellow. These represent the electrochemical banter of two neurons in the leg, caught on tape by a 10-micron-thick platinum electrode.

Weber is one of several Pitt researchers working on basic research underlying neural prosthetics—that group notably includes Andrew Schwartz, professor of neurobiology (who was Weber’s PhD adviser at Arizona State University). Monkeys in Schwartz’s lab are able to move an artificial limb—just by thinking.

Wei Wang, an MD/PhD assistant professor of physical medicine and rehabilitation, has partnered with Weber to map the motor cortex of the brain. They’d like to be able to wire the cortex to a prosthetic arm. When the brain “thinks” a movement, the arm would get the signal, and move.

As a preliminary step, Wang and Weber are studying the brains of young patients with epilepsy. In these children, the seizures are severe enough that surgery to remove the problematic part of the brain is recommended. To do this, a neurosurgeon implants cortical electrodes (via craniotomy) to determine what functions the patients may lose if the section is removed. Wang and Weber are piggybacking on this procedure by inserting their own microelectrode arrays and putting patient volunteers through a series of basic tests.

On his laptop, Weber keeps a video of one of these tests in which a 12-year-old girl plays a primitive video game (actually, an early version of Super Mario Bros.) without using her hands. When she “tells” him to, Mario jumps, hits a cauldron, and Ping!, the cauldron turns into a coin.

It’s basic stuff—the girl controls only one degree of freedom (down and up; a researcher controls the character’s lateral movement on the screen). But Wang and Weber say they are getting closer to determining what parts of the brain control which motor functions.

They aren’t able to record individual neuronal signals, but they might not need to in order to work a robotic arm. If each neuron is the equivalent of a fan in a stadium, the electrodes can pick up a cheer from a single section. Because of redundancies in the brain, eavesdropping on a cheering section may be just as good, if not better, than listening to each individual fan.

“When you’re moving your hand, you’ll see all these neurons around a given part of the brain get excited,” Wang says.

The field holds promise that, soon, a robotic arm could be manipulated from the brain.

But when? “We’re at that difficult point in the development where it’s like, ‘Okay, are we really ready to start doing this work in patients?’” Weber says. “At some point we need to decide, ‘Okay, we know enough about the signal processing; we know enough about how the signals change over time. We’re ready to do this.’”

To protect privacy, patients’ names were changed in this story.
NEW ANATOMICAL EVIDENCE OF BIPOLAR DISORDER | BY ELAINE VITONE

TRAPPED MINDS
About 15 years ago, Colin Davies (we’ve changed his name), an Oxford-educated Londoner in his early 20s, became depressed and went to see a psychiatrist. His doctor gave him a prescription, and once the pills started to work, things were glorious.

Not only had the crushing weight of his darkened mood vanished, but in its place came a feeling so incredible he couldn’t cram all his enthusiasm into the daylight hours. He hardly slept or ate, but he didn’t feel tired or hungry. He binged, partied, and took everything and everyone in his life for granted—but he was too euphoric to notice.

And then, months later, all the joy rushed out of him. He told his doctor the medication wasn’t working anymore and asked for another. Once those pills kicked in, the unstoppable Super Colin Davies was back … for a while. He raged on like this, caught in a cycle of self-sabotage, for a decade. When he was feeling high, he cheated on his partner, shouted, and even struck his child. And then there were months when he was so low he could barely function.

These images (DTI) show a brain anomaly that may be a biomarker for a predisposition or vulnerability to bipolar disorder. They were taken in healthy children who have a parent with the disorder. The white squares highlight abnormal white matter in the right prefrontal cortex. This anomaly is similar to what is seen in adults who have been diagnosed with bipolar disorder.
“It was so tragic,” says psychiatrist Mary Phillips, who began treating Colin when he was in his mid-30s. “He ended up with no job, no partner, no access to his children, and this awful mood disorder.”

But Phillips realized Davies’ disorder wasn’t clinical depression, as his previous doctors had assumed. By the erratic way he behaved in her office, it was clear to her that he had bipolar disorder, one of the most severe of all psychiatric illnesses.

Marked by swings between mania and depression, bipolar disorder affects 2 percent of the population and is notoriously difficult to diagnose. When people with bipolar disorder seek help, it’s almost always when they’re depressed, rather than when they’re high. (Phillips’ exam with Davies was a rare exception.) At the clinic, they’re virtually indistinguishable from people with unipolar depression. If misdiagnosed and given antidepressants, those suffering from bipolar depression turn manic, then swing between emotional extremes even more drastically. The would-be cure brings out the worst in the disease.

People with bipolar disorder commonly spend a decade trying to get the right diagnosis. By that time, many end up like Davies.

“With very good training and a lot of experience, you can hone your skills and get a very good idea of what diagnosis the person may have,” says Phillips, who treated many mood-disorder patients in London throughout the 1990s. “But it takes a long time to ask all the right questions. We desperately need biological tools.”

Phillips has been a leader in the field of psychiatric neuroscience since it began 25 years ago with the emergence of brain-imaging technologies. In 1997, she published a paper in Nature on the neurobiology of the emotion of disgust. It was the first study ever to link an emotion to a site in the human brain.

After investigating obsessive-compulsive disorder and schizophrenia for several years, Phillips came to the University of Pittsburgh in 2003 to focus primarily on bipolar disorder. She’s now a professor of psychiatry, director of the Functional Neuroimaging Program, and codirector of the Brain Imaging Research Center. (She’s also a consultant/professor for Cardiff University’s Department of Psychological Medicine in Wales and a visiting professor at the Institute of Psychiatry in London.) Of the numerous neuroimaging studies she has published in the field’s premier journals, her September 2009 Biological Psychiatry paper stands out. It established, for the first time, a pattern of distinguishing anatomical characteristics that separate bipolar disorder from unipolar depression.

Phillips is 5-foot-10 with long brown hair; a quick, alto-pitched British accent; and an obsession with her e-mail account. To stay in touch with her armies of collaborators around the world, as well as mentees and colleagues down the hall, she’s plugged in from 6 a.m. to midnight, seven days a week.

She’s been pleased to find that her work is more valued in the States than back home. Across the United Kingdom, many psychiatrists openly decry psychiatric neuroimaging as an unjustifiable expense—why do it when you can diagnose patients by talking to them? Others call brain scans superficial snapshots that can’t even scratch the surface of the complex human mind.

Phillips says that if you had chest pains, or a broken limb, or a serious problem with any other part of your body, your doctor wouldn’t just ask you where it hurts and treat you based on that. So why should the brain be any different? The expense of neuroimaging is coming down, she reports. And she asks us to consider the toll on these patients and their families as they struggle through years of anguish. Some of these cases result in suicide, she reminds.

When the Pittsburgh Post-Gazette reported her landmark study this summer, she received dozens of e-mails of support.

“My poor soul/daughter/husband/wife is sick but can’t get the right diagnosis, said some.

Others said they suspected they themselves had bipolar disorder. They asked: Can I come in and see someone? Can I have a brain scan? And they wrote: Thank you for helping me understand that it’s not my fault and that I’m not a bad person.

Phillips wrote each correspondent back, connecting them with local resources and, when requested, with members of her staff who screen and coordinate study participants. She also thanked them.

“All of it’s been incredibly positive and very touching,” she says. “It’s made me think I must be doing something right.”

In Phillips’ Biological Psychiatry study, participants sat in a scanner and looked at a series of pictures—faces exhibiting extreme emotions like fear, anger, happiness, and sadness. About half of the participants were in a state of depression and had previously been diagnosed with bipolar—I—the most severe form of the disorder. The other half were controls.

Facial expressions have universal meanings for all of us, regardless of language or culture. It’s a gift of our evolution as primates, a way to pass on essential messages quickly and without uttering a sound. The simple act of looking at a face evokes a powerful empathetic response in the brain—emotional contagion, as it’s called—whether the person realizes it consciously or not. Phillips was one of the first to use contagion to map emotions in the brain, a technique that’s widely used today.

As the test subjects completed the exercise, Phillips’ team paid close attention to the uncinate fasciculus, one tract in the vast network of wiring that enables brain regions to communicate with one another. The uncinate fasciculus connects the amygdala (an almond-shaped bulge at the bottom of the brain that helps us process the emotional impact of our experiences) to the orbital prefrontal cortex (a region at the front of the brain that helps us control our behavior). The orbital prefrontal cortex regulates the amygdala as brakes do on a car.

In another study, Phillips and Pitt’s Amelia Versace found that in people with bipolar disorder, the fibers of the uncinate fasciculus were thinner than normal on the left side of the brain, the side that’s generally associated with positive emotions. This anomaly may explain the difficulty in putting the brakes on positive feelings. Hence mania.

On the right side of the brain, which is associated with negative feelings, the uncinate fasciculus fibers were thicker and more criss-crossed than normal. This suggests a tendency to get caught in a loop of negativity. Hence depression.

In another imaging study of unipolar depression, Phillips and Versace found no abnormalities on the right side of the brain—and on the left, the uncinate fasciculus was thicker than normal, not thinner.

“That kind of makes sense,” says Phillips. “Too much of a brake on that side means [people with unipolar depression] are always going to have difficulty feeling positive.”

Virginia Woolf wrote of how the family curse of mental illness plagued him with “violent states of excitement and states of utter apathy.”
Phillips has been awarded funding from the National Institute of Mental Health to use brain imaging to further identify and confirm abnormalities that could help distinguish between bipolar and unipolar depression.

Her team uses a combination of imaging technologies: fMRI (functional magnetic resonance imaging), which tracks blood-flow increases throughout the brain, and DTI (diffusion tensor imaging), which maps the wiring that connects brain regions. DTI is a much newer technique and a welcome one. Blood flow alone can’t tell the whole story.

If there’s a glitch affecting one region of the brain, to some extent, another region (or regions) will pick up the slack. Phillips’ team is showing how these altered networks behave by imaging both function and fine-detail structure at once and in real time. Their hope is that imaging could eventually help psychiatrists not only diagnose mood disorders, but also prescribe and refine treatments, as well as track patients’ progress—a potentially life-changing prospect for people who struggle through the frustrating process of finding just the right drug combination and dosage.

Jorge Almeida, a Pitt postdoctoral associate, began his research career under Phillips’ wing four years ago. Back then, he expected the pathophysiology of psychiatric disorders would be his focus—and the idea of his work having any clinical implications in the foreseeable future didn’t even occur to him. Since working with Phillips, neurological biomarkers have become his mission. “It’s all happening so fast,” he says. “It’s like cancer research was 30 years ago.”

Phillips mentors more than 20 emerging researchers and does a bang-up job in spite of the breakneck speed at which their projects are growing and evolving, her protéégs say. When they present their work at conferences, Phillips makes sure to introduce her mentees to all the big names. When they knock on her door seeking advice, she welcomes them in with a smile. And her e-mail replies are lightning-fast.

“I don’t know how she does it,” Almeida says, laughing. “I try at different times of the day, I try on weekends. She always writes back right away with helpful comments on the papers we’re working on.”

“Because [Phillips] has worked in other disorders, she’s able to come up with more general theories that might apply,” says Natalia Lawrence, a former-mentee-turned-collaborator at Cardiff University’s Wales Institute of Cognitive Neuroscience.

Phillips’ team is working on studies of bipolar II disorder, the less severe version of the disorder that is even more elusive. For these individuals, the depression side is evident, but the other extreme, dubbed hypomania, can be tough to pin down.

Hypomania, as its name suggests, can manifest as a toned-down version of mania—a hyper, life-of-the-party feeling—but it can also feel more like irritability and anger on a short fuse. Even after finally arriving at a diagnosis, people with bipolar II often have a very hard time accepting that they have it and taking medications. The mood-stabilizer drugs used to treat bipolar disorder can cause patients to feel emotionally flat, drowsy, or nauseated or to experience other unpleasant side effects.

“As far as they’re concerned, they’ve just got to wait to find the right antidepressant,” Phillips says. But when she’s shown patients their scans and explained the results, the reaction has been quite different. “It helps people more readily accept the appropriate treatments if they know there’s a scar or a broken circuit.”

Bipolar disorder is an ailment of many guises, a range of combinations of symptoms in varying degrees. Psychiatrists who’ve labored to decipher these subtleties know well that it’s probably overly simplistic to say that there are only two types of bipolar disorder, either I or II. More likely, there’s a whole spectrum of gradients in between, each with its own set of symptoms and pathologies, though this has yet to be proven. Phillips hopes to pursue this hypothesis with Holly Swartz, also in the Department of Psychiatry.

As if bipolar disorder weren’t devastating enough, it often comes with other problems—namely, insomnia and risk-taking behavior. That can add up to a real powder keg. No one knows why these particular issues are such common twofers or threefers—comorbidities, in clinical parlance. To get to the bottom of it, Phillips’ team is comparing the genetics of mood control and sleep problems with brain imaging.

A century before Colin Davies’ illness took hold of him, a fellow countryman named James Kenneth Stephen—a first cousin of novelist Virginia Woolf—began acting odd. Woolf wrote of how the family curse of mental illness plagued him with both “violent states of excitement and states of utter apathy.”

During his monthlong manic periods, Stephen blew his money on useless trinkets and strange clothing. He rode around Cambridge all day in a horse-drawn cab, then arrived home, wild-eyed and frenzied, and rushed inside, leaving his father with the bill. At one point, he ran through the streets stark naked. He was institutionalized soon after, in November of 1891.

At first, he lashed out, destroyed the furniture, and struck a staff member. Then came depression. Then a cheerful and vigorous phase. Then irritability.

In mid-January, the depression returned, and Stephen fell into an unyielding trap of the mind; he couldn’t eat or sleep. His face slowly, his pulse racing, he lay there mumbling, “It’s too late,” as he wasted away. He died on Feb. 3, 1892.

In the days before lithium, this is how many people with severe bipolar disorder spent their final days. One 1933 study found that 40 percent of bipolar patients who died in the hospital succumbed to “manic exhaustion,” like Stephen. Suicide also was common.

Today we know that, if left untreated, bipolar disorder causes deterioration—tiny lesions in the wiring of the brain—that worsens over time. The earlier treatment begins, the less deterioration patients will suffer throughout their lives. And the better they’ll respond.

What if bipolar patients could confront the disorder as early as childhood or adolescence? What if they could contain bipolar disease before it had a chance to rob them of even one day of healthy adult life?

Phillips’ lab is partnering with the Child and Adolescent Bipolar Services Clinic at Western Psychiatric Institute and Clinic of UPMC, which is devoted exclusively to the treatment and study of bipolar disorder in the youngest populations. Working with Boris Birmaher, Pitt’s endowed professor of early onset bipolar disease and a professor of psychiatry, and David Axelson, director of the clinic and Pitt professor of psychiatry, she’s beginning to look at the brains of children who have just received a diagnosis, as well as children who are at risk because of a family history.

They’re charting out how it all begins, watching what changes from the very first manic and depressive episodes.

Phillips reminds us that scientists are just beginning to pierce the mysteries of the mind.

“We really only know, I would guess, about 5 or 10 percent of what there is to know in terms of brain circuitry problems—at most,” she says.

Still, she’s unfazed.

“We have a lot of work to do; so no weekends off.”
The RUSKIN CROWD

HOW MOREHOUSE MEN MADE THEIR WAY NORTH

BY ELAINE VITONE

Morehouse men and others at their 1974 graduation from the School of Medicine (from left): William Hicks, Herbert Chissell, Brian Bowles, Everett Cantrell, Marion Williams, Charles Hefflin, John Houser, William David Moore, and William Cleveland.
In September 1970, Bill Cleveland (MD ’74) gassed up his yellow Volkswagen Beetle and left Atlanta for Pittsburgh. It was 700 unairconditioned miles in the summer heat—the sort of epic road trip that gives a young man at a pivotal moment in his life plenty of time to second-guess his choices.

But not Cleveland. He’d done his homework. There was no doubt in his mind that he’d chosen well when he chose the University of Pittsburgh School of Medicine.

That year, medical schools across the country had made unprecedented efforts to diversify enrollment. Cleveland and several of his classmates at Morehouse College, a college for African American men, had been offered scholarships from schools across the country. But to their disappointment, when they went for their interviews, most of these programs had confessed they were accepting only one or two African American students that year.

“We’d just say, ‘We’re from Pitt,’ and they’d welcome us in,” he recalls.

For the next several years, African American med students from Morehouse and elsewhere built a community of friends and neighbors in Ruskin Apartments, now Ruskin Hall. (It was difficult to find Oakland landlords eager to accept Black student as tenants, some recall.) They walked to and from class and work together, commiserated over the rigors of their training, bonded in ways you can only do by poring over physiology notes together for 12 hours at a stretch. They built what remain some of the closest and most lasting friendships of their lives.

Cleveland says he and his old friends didn’t want for much during med school, but they agree one key ingredient was missing: There were few Black mentors at Pitt—no strong role models with whom they could identify, no blueprints for the future.

“So, at the group’s most recent reunion, like being 6-foot-1 and playing in the NBA. It doesn’t mean you can’t do it; it means you have to bring something else to your game.”

“There’s something about cancer that negates a lot of that,” said oncologist Bill Hicks (MD ’74), a professor of medicine at Ohio State University. “If people think you might be able to help them, they don’t care what color you are.”

The gathering harkened back to those Friday nights 40 years ago, when a group of Pitt students would show up at a party full of total strangers and be welcomed inside.
I advise you to take time to understand that there is a common goal, to become a physician. Everyone on this road has a common goal, to become a physician. This trail is unique—because it requires that you set aside competitiveness with each other. Your goal is for everyone seated here to complete the journey successfully.

For the first time in your lives, some of you will greet patients along your path with words that will become very familiar over the next several years: “Hello, I am a student doctor here to evaluate you.”

The right sleeve has a dark-brown faded stain. This one is blood.

I was a third-year student, rotating on trauma surgery, when a patient with a stab wound to the chest arrived. I watched in fascinated horror as the trauma surgeons opened his chest and asked me to put pressure on the aorta while they repaired the hole in his heart. The only aorta I had ever seen was in the anatomy lab and in textbooks.

The surgeon guided my gloved hand into the patient’s chest and instructed me to push. The hole in the heart was repaired; I watched the heart fill with blood and slowly begin to contract. I felt the pulsations in the aorta, and the trauma surgeon asked me to let up the pressure. The patient survived, and I was astounded by what I had seen.

Lesson: This is why we are here. The joy we get from helping a patient is beyond description. Do not, however, let this success inflate your ego and make you feel infallible. You will make mistakes. We all do.

There are five red-pen marks across the back of the coat. Sara, a 23-year-old, arrived in the medicine clinic intoxicated and high on a variety of drugs. I listened to the secretary and nurse discuss “the drunk dirtbag” and ask the physician whether they should have security throw her out.

I was sent in to interview her and, with trepidation, I entered the room. An hour later, I emerged with the five red marks on my jacket.

Sara had told me that her husband had raped and beaten her last week and had stabbed her five times in the back. She demonstrated this with a marker pen on my back. She was here seeking refuge and help with her addiction.

Lesson: Do not judge your patients until you have walked a mile in their shoes.

Most of us have had a very sheltered life. It is our responsibility as physicians to try to understand our patients’ challenges in life and to factor them into our decision-making.

I treated a gentleman last week with a blood sugar of 550 who was diagnosed with diabetes two weeks earlier. [Normal blood sugar is 80 to 100.] He told me that for lunch, he had had a large plate of spaghetti and a piece of cake.

When I inquired about diet education, he told me that they had given him a book on diabetes in the clinic. When I asked whether he had read it, he looked at the floor and quietly mumbled, “Ma’am, I can’t read.”

Clearly we had failed this gentleman as care providers.

I quietly put my white coat back into the cupboards and pondered what I could tell you today.

I have some advice for all of you as students, physicians, and individuals.

As a student: I advise you to take time for yourselves. Go for a bike ride, take a walk, enjoy a movie with friends.

As a physician: Understand that there are times when it is necessary to accept the inevitable—and comfort alone is what you will be able to offer your patient and the family. You will be privileged to witness birth and be present at death. When you are faced with a 98-year-old with multiple system failure or a 36-year-old with end-stage metastatic cancer, do not run from the room ordering more medication and calling for resuscitation.

Sit down, hold the patient’s hand, comfort with medication if necessary—and accept that this, too, is one of your responsibilities.

As a person: I advise you to set your priorities and place family and friends at the top. The people sitting in this room have been with you throughout your journey. They will remain your support system through this trek as well. This is perhaps your greatest challenge.

Tomorrow, you take your first steps along this new path. May your journey be filled with laughter and good memories.
TRUE TO HIS ROOTS
A MODERN-DAY “BENEVOLENT INDUSTRIALIST”
BY SHARON TREGASKIS

John Rangos was just a few months old when the crash of 1929 brought the U.S. economy grinding to a halt. Most working-class families struggled to put food on their tables and keep their homes. Yet, like every youngster in Weirton, W.Va., a mill town 30 minutes from Pittsburgh, Rangos had two free medical exams every year; if either had revealed the need for follow-up care, that would also have been provided free of charge. In the summer, Weirton children swam in a community pool while their parents hit the links at a community golf course. Credit for these and many other local philanthropic ventures goes to magnate Ernest Weir, who recruited immigrant laborers from Poland, Greece, Finland, and Hungary to work for him at what would become National Steel. Weir was a “benevolent industrialist,” says Rangos. “Not only was he the biggest employer, but he cared about the community.”

Eight decades later, the founder of Pittsburgh-based Chambers Development Company—now part of Waste Management—credits Weir with inspiring his own modern-day blend of business and philanthropy. In 1990, he endowed the original John G. Rangos Sr. Research Center at Children’s Hospital of Pittsburgh, and his eponymous family foundation also supports research at Johns Hopkins, Duquesne, and Carnegie Mellon universities. In October 2008, the new 10-story, 300,000-square-foot Rangos center opened on the 10-acre Lawrenceville campus of the new Children’s.

“There is nothing more productive than the research that brings about medical solutions,” says Rangos, who joined the Children’s board of trustees in 1990. He traces his commitment to biomedical inquiry to his maternal grandfather’s battle with leukemia. When the man who had raised Rangos died at Presbyterian University Hospital, a physician pleaded with the family to allow an autopsy so doctors could better understand why the 84-year-old Greek American sailor had withstood the disease more than a year longer than most patients. They made an impression, says Rangos, “describing what they could learn from research that they could use to treat patients in the future.”

The research excellence Rangos has championed throughout his nearly two decades on the Children’s board bolsters clinical care and facilitates the recruitment of top scientists, says the hospital’s physician-in-chief and scientific director, David Perlmutter, who is also the chair of pediatrics for the University of Pittsburgh. “John Rangos has been a leader on the board for pushing Children’s Hospital to have a world-class vision,” he says. “His influence has always been in the right direction. In very few words he gets straight to the point, and he always supports the move that has the potential to make important changes for the future.”

BOOSTER SHOTS

The Class of ’59 has stumbled upon a recipe for great reunions, says Howard Reibdord (MD ’59): Start ‘em early and keep ‘em going. Reibdord, a retired pathologist, organized reunions beginning in the 1960s. Through the years, members of the class gathered at resorts like Nemacolin Woodlands and Hidden Valley. They took cruises and getaway weekends together. As a result, this year’s 50th reunion in May drew a crowd and revealed an authentic esprit de corps.

Nancy Swensen (MD ’59) and husband Harold Swensen (MD ’58) hosted a reunion dinner for more than 50 at their Pittsburgh home. Richard Finder (MD ’59), who was unable to travel from Florida on reunion weekend, came to town several weeks later with his wife and threw a party for all the members of the class in the Pittsburgh area.

Discussion at these events frequently turned to a desire to make a gift to the School of Medicine as a group. Many alumni talked about their interest in directly supporting Pitt med students in their efforts to become successful, caring physicians. The class decided to establish a competitive clinical fellowship for a sophomore medical student to work with a disadvantaged population. It’s fair to say they’re well within reach of their long-term goal of $50,000, with $34,000 raised or pledged as of Sept. 15. —Chuck Staresinic

FOR INFORMATION ON GIVING TO THE SCHOOL:
Deb Desjardins, 412-647-3792 or ddeb@pmhsf.org
On the web: www.giveto.pitt.edu/
CLASS NOTES

’50s Basil Rudusky (MD ’59) has authored a new book, Forensic Cardiovascular Medicine (CRC Press, 2009), which he describes as being of interest to not only physicians, but also to those in the legal profession who handle cases involving cardiovascular medicine. Rudusky has performed independent medical examinations and provided expert testimony for more than 30 years. His book contains the first complete classification system for myocardial contusion and blunt cardiac trauma. With the advent of better seatbelts and airbags, people are surviving accidents suffered at higher speeds, says Rudusky.

’70s Paul Paris (MD ’76) may be stepping down as chair of the University of Pittsburgh’s Department of Emergency Medicine, but he is still imagining ways to save lives and reduce health care costs. As director of UPMC’s EMS activities, Paris teaches EMTs about preventative medicine in the home through a program called Emed Health. Instead of waiting for a patient to refracture a hip in a fall, EMTs are checking for loose electrical cords and shag rugs and teaching patients balance exercises and tai chi. According to Paris, this approach prevents emergencies and ultimately cuts the high costs of emergency and nursing home treatment. Starting in January, Paris will start teaching a different group of cost-saving mid-level providers. He will be medical director of the newly accredited physician’s assistant program in Pitt’s School of Health and Rehabilitation Sciences.

Robert Johnson (MD ’77) is head of rheumatology for the new Virginia Tech Carilion School of Medicine and Research Institute. The goal of the school is to “train physicians who will be excellent clinicians and will continuously incorporate knowledge gained from the practice of research and scientific inquiry into their everyday practice of medicine,” he reports. Johnson has been involved in medical education for 26 years. He says he honed his teaching skills in the U.S. Navy, where, during a 28-year career, he won many teaching honors, including the Master Teacher Award, given by the Navy’s chapter of the American College of Physicians.

During her latest trip to Zambia, Jeannette South-Paul (MD ’79) spent days in a conference room, using flip charts and posing questions to her Zambian colleagues. “If you had to design something, what would you do?” she asked them. “Where are your priorities?” It was part of the planning for a workshop held at Pitt in September, “Improving Maternal and Child Health Outcomes in Zambia.” South-Paul, chair of Pitt’s Department of Family Medicine, received a $20,000 grant from the school’s Global Academic Program, funded by Pitt’s Center for Global Health, so that she could host top Zambian medical professionals. She did not, however, tell Zambians how to improve their health care system. Instead, South-Paul emphasized an approach in which physicians from both countries could learn from each other. Hypertension and diabetes are common chronic diseases in both Zambia and the United States, especially in poor populations. South-Paul enlisted a Zambian agriculturist to explore aspects of the American and Zambian diet that cause these problems. “I’m trying to be a little more creative and multidisciplinary,” South-Paul says.

’80s When the Pittsburgh Penguins first won the Stanley Cup in 1991, the presence of the cup in Charles Burke’s backyard drew about 20 people. In August 2009, 350 fans flocked to his backyard. Pittsburgh hockey fans are now familiar with the tradition that each member of a championship team gets to keep the Stanley Cup for one day. Burke (Orthopaedic Surgery Res ’86) has been head team physician for the Penguins since 1988.

Some of his friends don’t understand why, but Burke has always preferred to stay in the background with the Penguins. He has been in one team photo since 1988. He takes every precaution to avoid his name appearing in the newspapers. And he sits with the masses instead of bench-side at home games. Burke, who also has a busy orthopaedics practice at UPMC, has been a hockey fan for years, and he played Division I hockey at Harvard University.

Peggy Hasley (MD ’85, Internal Medicine Resident ’88, Chief Resident ’89, General Internal Medicine Fellow ’91) was a bit flummoxed three years ago when a nurse called to ask whether she would help teach a course about treating patients who had liver transplants. Busy with patients at UPMC Montefiore, Hasley at first declined, but when the nurse struggled to find another physician, she accepted the offer. Since the 1980s, the number of patients living many years after organ transplants has skyrocketed, but knowledge of how to treat such patients long-term has lagged behind. Because Hasley, a Pitt associate professor of medicine, was caring for an increasing number of transplant patients, she soon became fascinated by the topic and saw the need to add to the scant literature.

Her manuscript “Primary Care of the Transplant Patient” will appear in the American Journal of Medicine in March 2010, and Hasley envisions it as a manual for care. “The presence of immunosuppressants affects the prevalence and severity of chronic medical illnesses that are the bread and butter of primary care medicine, such as hypertension, diabetes, high cholesterol, and vascular disease,” she says.

’90s Constantin Aliferis (Biomedical Informatics PhD ’98) directs the Center for Health Informatics and Bioinformatics at New York University. He is involved in 15 research projects, including a study of the AKT1 protein, which is known to be involved in the development of lung cancer. He uses a Bayesian network, a system of algorithms designed to represent causality, to find the upstream genes

Every August, the Pitt med family welcomes a new crop of medical students during the White Coat Ceremony, where, typically, a faculty member helps each student into his or her first white coat. This year, two students were met onstage by their fathers, each an alumnus of the school. Greg Hoyson (MD ’82) placed the white coat on the shoulders of daughter Katherine (right), and William Steinbrink (MD ’74) did likewise with his daughter Julie (above).
James Gammie felt like he’d come across this before. Where was it? The cardiac surgeon was looking at a patient with aortic stenosis—a narrowing around the aortic valve that obstructed oxygen-rich blood as it flowed from the left ventricle into the descending aorta. He could hear the telltale murmur when he placed his stethoscope over the base of the heart—starting softly, rising in intensity, and tailing off to a whisper again.

The patient needed an aortic valve replacement—open-heart surgery that involves stopping the heart and relying on a heart-lung machine while surgeons replace the valve. But this patient was too sick for all that. He was at high risk for stroke.

Back in Pittsburgh in the late ‘90s, Gammie recalled, he’d seen a case like this as a thoracic surgery fellow. On a pediatric rotation, he’d witnessed an uncommon procedure—in instead of replacing the valve, surgeons had done an aortic valve bypass. The team cored a hole in the tip of the beating heart and inserted a cloth-covered tube to bypass the obstruction. The other end went to the aorta. It looked difficult, a bit bloody, and a bit bit crazy. But it had saved a very sick child who was unable to withstand the standard valve replacement.

Gammie (Res ’96, Fel ’99) is an associate professor of surgery at the University of Maryland. He took his idea to his division chief, Bartley Griffith (Res ’77, ’79, ’81, Fel ’78), who had been one of his mentors in Pittsburgh and had himself been a Pitt chief resident in thoracic surgery. They located the surgeon who originated the procedure in the 1970s, John Brown of Indiana University in Indianapolis; he sent them a video to help them prepare.

Since that first bypass in 2002, Gammie has performed around 50 aortic valve bypasses. He calls it an “orphan operation.” He believes it never became widely used because of the difficulty of working on a beating heart. Nevertheless, it has a 35-year track record, and patients are still living who had one more than 25 years ago. “We believe that it’s associated with lower risk of stroke,” says Gammie. “And we’re working on making it minimally invasive—our last four or five operations were done through 3-inch incisions.”

Gammie and others have adopted this orphan, going so far as to form a company, Correx, to automate the most challenging maneuver in the procedure. They have patented a device, not yet licensed for use in humans, that punches the hole in the heart and inserts the bypass valve.

“What we do right now is we use a knife. We make a little hole in the tip of the heart, and we stick a Foley catheter in there—a balloon—and we blow it up. Then we have a round coring knife, and we core out this hole and place a finger in it. So there’s an exciting moment when you get 50 cc’s of blood squirting at you. What the device does is it automates that whole process so that you don’t lose any blood at all. It makes it simple, safe, and accessible.” —CS
Allan Drash helped lead a quiet revolution, he liked to say. When the pediatric endocrinologist came to Children’s Hospital of Pittsburgh in 1966, medical care for children with diabetes was primitive. Drash, a professor of pediatrics at the University of Pittsburgh School of Medicine, was one of a handful of physicians who dramatically advanced the field of pediatric endocrinology in the ensuing decades.

In 1967, Drash published evidence that most children with diabetes were insulin deficient (rather than being resistant to the insulin they produced), thus confirming that there were two types of diabetes. At Children’s, he created a diabetes care program that advanced a novel team approach involving the patient’s family, dietitians, physicians, and educators. That model is now the gold standard.

Collaborating with Lewis Kuller, Distinguished Professor of Public Health in Pitt’s Graduate School of Public Health, Drash gathered and laid out the data showing that diabetes was a disease with genetic, lifestyle, and cultural components. The diabetes registry and clinic that grew from these efforts was the largest in North America, making Children’s Hospital of Pittsburgh the place to be for the study of diabetes in children.

Drash considered himself a teacher and physician first. He counseled countless parents and children to live life fully and to never give up on their dreams.

—Chuck Starsinic

Richard Raizman began practicing in Western Pennsylvania as a gastroenterologist in the 1970s. He grew frustrated with the state of care. In a gastroenterologist’s office, patients who needed endoscopy couldn’t get anesthesia or all the high-tech monitoring that goes along with it. But going to the hospital for those things increased the cost, hassle, and the stress levels of his patients.

“A lot of doctors talked about starting outpatient surgery centers,” says Frank Costa (MD ’80, Res ’86), “but nobody did it. That’s the difference between Rich and everyone else. He was not just a visionary; he could put his vision into action.”

Raizman started the region’s first such surgery center with Costa, a urologist, in 1992. Regional hospitals were opposed—they were gaining steady income under the status quo. But Raizman contended that Pittsburgh’s eastern suburbs were underserved by hospitals. The Monroeville Surgery Center was an instant success in its very first year. In 1996, the center was acquired by UPMC.

Raizman displayed a great deal of energy and personal devotion to the causes he believed in. He traveled to Dharamsala, India, many times to donate medical equipment and offer his expertise to Tibetan refugees there. An enthusiastic polo player, he started a Polo for the Cure event that raised more than $1 million for cancer research in the course of 17 years. He was on the Board of Visitors at the University of Pittsburgh School of Medicine, where he helped start a new area of concentration in global health and donated money to create a scholarship. Through Raizman’s estate planning and a combination of other gifts, the University created the Raizman Vaccine Laboratory in Biomedical Science Tower 3 in 2005. A more recent major Raizman gift led to the creation of a liver and neuroendocrine cancer treatment center within the Thomas E. Starzl Transplantation Institute.

Raizman was medical director at the surgery center he created. “Even two weeks before he died, he was doing endoscopies on patients,” says Costa. “He didn’t have to, but he had such a commitment to them. He was driven to the very end to provide competent, compassionate care.” —CS

IN MEMORIAM

’40s
Benjamin Weisband
MD ’41
AUG. 17, 2009

Morry Shapiro
MD ’42
AUG. 2, 2009

’50s
Clinton Lowery
MD ’55
SEPT. 9, 2009

’60s
Carl Marnatti
MD ’61
SEPT. 15, 2009

’80s
Brian Emery
MD ’88
SEPT. 10, 2009

Bernard Miklos
MD ’56
SEPT. 10, 2009

’90s
...
The patient was young, nervous. It was the mid-1970s, and, with a diagnosis of hairy cell leukemia, his anxiety was well warranted. “I told him I needed to do a splenectomy,” recalls oncologist Harvey Golomb (MD ’68). “It would work for a bit.” The patient had a son, only 8, he said, and he wanted to see the boy celebrate his bar mitzvah. Would surgery buy him enough time? “I said, ‘I don’t know. Let’s see what we can do; get started.’”

Three decades later, the patient called back. The leukemia had re-emerged, and his blood counts were dropping again. “I said, ‘We have lots of good agents; we’ll get you started,’” Golomb recalls. “He said, ‘My grandson is 8; I want to see him bar mitzvahed.’ I said, ‘No problem.’”

When Golomb first put a sample of hairy cell leukemia under a scanning electron microscope in the early ’70s, he was a fellow at the University of Chicago. Back then, a patient with the disease was lucky to get an accurate diagnosis in time for surgeons to remove his spleen, the only treatment then available.

Today, Golomb serves as chief medical officer and professor of medicine at the University of Chicago Medical Center and has more than 350 publications to his name—many on hairy cell leukemia. The lot of people with the disease has improved, too: A five-day course of outpatient chemotherapy yields complete remission in 90 percent of cases. In the last 15 years, says Golomb, who was awarded the 2009 Philip S. Hench Distinguished Alumnus Award, he has lost only one patient to hairy cell leukemia. “When I diagnose it now and talk about treatment,” he says, “I talk about a chronic disease not so different from diabetes. They should live as long as anyone else in their age cohort.”

A native of Squirrel Hill, Golomb credits Pitt med fraternal collaborators Bernard Fisher (MD ’43), now a Distinguished Service Professor of Surgery, and the late Edwin Fisher (MD ’47), a professor of pathology from 1958 to 1985, with vital contributions to his intellectual development. After two “dreadful” months assisting Bernard Fisher on kidney transplants and abdominal aorta repairs in his fourth-year surgical rotation, Golomb finally revealed his dismay. “I said, ‘This is horrible; it’s ghastly.’ Bernie said, ‘Oh, I just fill in because they need someone to do it. I’m interested in these cancer cells in the lymph nodes.’” Then he took Golomb to his office, projected a series of Kodachromes on the wall, and explained his groundbreaking inquiry into the progression of breast cancer metastasis. Golomb was fascinated. Edwin Fisher, an expert in electron microscopy, cultivated his protégé’s imaging skills during the spring of 1968, providing training that placed Golomb stateside during the Vietnam War at the Armed Forces Institute of Pathology in Washington, D.C., where he developed techniques for investigating the surface topography of cells using transmission and scanning electron microscopy.

As Golomb deployed that training at the University of Chicago, the rare and relatively obscure hairy cell leukemia caught his eye. “It was a fantastic picture,” he says, “totally different from anything else with its huge, undulating ruffles.” He launched a comparative morphological study. Inevitably, his requests to pathologists for samples yielded calls from hematologists and, later, visits from patients who provided blood samples and sought treatment. Within a few years, Golomb had amassed a roster of some 700 patients and embarked on a quest for new treatments. “I’m just thrilled that I had the opportunity to call on some tools to keep people alive another year or two until I had the next tool,” says Golomb. “And now they’re alive 30 years.”
To celebrate Charles Darwin’s 200th birthday and the 1859 publication of *On the Origin of Species*, we asked some Pitt med-ers and friends of the school this question: Is there anything about the way the human body has evolved that you would have recommended against, had you been consulted?

“Aging!!”

Mary L. Phillips
Director of Functional Imaging in Emotional Disorders
Professor of Psychiatry, University of Pittsburgh

“I would have recommended that we live longer and reproduce less.”

Arthur S. Levine
Senior Vice Chancellor for the Health Sciences
Dean, School of Medicine
University of Pittsburgh

“There should be a way to indicate how a person is going to die. That way we could prevent certain deaths, like those related to heart disease or cancer, with earlier detection.”

Freddie Fu (MD ’77, Res ’82)
David Silver Professor and Chair, Orthopaedic Surgery
University of Pittsburgh

“Probably the biggest problems caused by our unique evolutionary history result from the adoption of bipedal postures by our ancestors sometime prior to 4 million years ago. This led to the bizarre ‘S-shaped’ vertebral column of humans (technically known as lumbar lordosis), which causes chronic lower-back pain in many people. Likewise, bipedalism has constrained human obstetrics, because there are limits to how large the birth canal can be without compromising bipedal locomotion. This explains why women walk and run (on average) in a less energy-efficient fashion than men do, and it also explains why labor is so long and arduous in humans.”

K. Christopher Beard
Adjunct Professor, University of Pittsburgh School of Medicine
Curator and Mary R. Dawson Chair of Vertebrate Paleontology
Carnegie Museum of Natural History

“As a DNA repair person, my chief complaint is that for some reason placental mammals evolved to not express photolyases. These are enzymes that directly reverse DNA damage caused by UV light (sunlight). If humans still expressed these, the rates of skin cancer would be negligible.

“Big mistake!”

Laura Niedernhofer
Associate Professor of Microbiology and Molecular Genetics
University of Pittsburgh

“There are so many I don’t know where to start. Our birth inlets and outlets are too small. Our anterior abdominal wall is too weak. The frontal sinuses give me (and most others) headaches for no reason. Our lower lumbar column is too lordosed. Those are starters. Of course, orthopaedic surgeons will give you many that they confront every day, but they are more anatomically detailed. Take for example the femoral head epiphysis—it is relatively easily disrupted during growth and can slip away from the femoral neck, which can lead to avascular necrosis. There are many defects at that anatomical level—the skeleton seems to be riddled with them.”

C. Owen Lovejoy
Associate Professor of Biological Anthropology
Kent State University
Collaborator with Pitt’s Freddie Fu

“The human body is the most perfect machine ever assembled—a combination of strength, dexterity, and resilience. It is the only machine that gets stronger with use, rather than wearing out. With sufficient training, humans can run a horse to death. Our crowning achievement is the amazing human brain, with the ability to reason, plan for the future, and decipher complex problems.”

Bert W. O’Malley (BS ’53, MD ’63)
Tom Thompson Distinguished Professor and Chair
Molecular and Cellular Biology, Baylor College of Medicine

—Compiled by Jamar Thrasher
CALENDAR
OF SPECIAL INTEREST TO ALUMNI AND FRIENDS

For information on an event, unless otherwise noted, contact the Medical Alumni Association: 1-877-MED-ALUM, 412-648-9090, or medalum@medschool.pitt.edu. www.maa.pitt.edu

MASTER SURGEON LECTURE SERIES
DECEMBER 16
8 a.m.
Lecture Room 5, Scaife Hall
“Mitral Valve Surgery in the 21st Century”
Ronald V. Pellegrini, MD, Speaker
For information: www.surgery.upmc.edu

WINTER ACADEMY
FEBRUARY 12
Ritz-Carlton Resort
Naples, Fla.
For information or to request an invitation:
Pat Carver
412-647-5307
cpat@pitt.edu
www.winteracademy.pitt.edu

HEALTH SCIENCES ALUMNI RECEPTION
APRIL 10
Phoenix, Ariz.
For information:
Pat Carver
412-647-5307
cpat@pitt.edu

STARZL LECTURE
APRIL 14
4 p.m.
Lecture Room 6, Scaife Hall
For information:
www.surgery.upmc.edu

MEDICAL ALUMNI WEEKEND 2010
MAY 21–24
Reunion Classes:
2000 1995
1990 1985
1980 1975
1970 1965
1960 1955
1950

ALUMNI BREAKFAST & MEDICAL SCHOOL TOUR
MAY 22
9 a.m.
Scaife Hall

REUNION GALA
MAY 22
6 p.m.
LeMont, Pittsburgh

UPCOMING HEALTH SCIENCES ALUMNI RECEPTIONS
Boston, Mass.
Los Angeles, Calif.
Naples, Fla.
New York, N.Y.
Pittsburgh (South Hills)
Raleigh, N.C.
For information:
Pat Carver
412-647-5307
cpat@pitt.edu

TO FIND OUT WHAT ELSE IS HAPPENING AT THE MEDICAL SCHOOL, GO TO www.health.pitt.edu
When you were in med school, you probably tried to peer into your future. Would you become an internist, a cardiologist, a pediatrician? Would you work in a big city practice? A rural town? A major university medical center? Join us May 21–24, 2010, to reflect on your past and all the effort that got you to where you are today.

This year, the reunion gala will be at LeMont restaurant on Mount Washington, whose storied view includes the campus where you began your journey.

Medical Alumni Weekend
May 21–24, 2010
For a list of classes having reunions in the spring, turn to our calendar on the other side of this page.

1-877-MED-ALUM
medalum@medschool.pitt.edu
www.medicalschool.pitt.edu/alumni