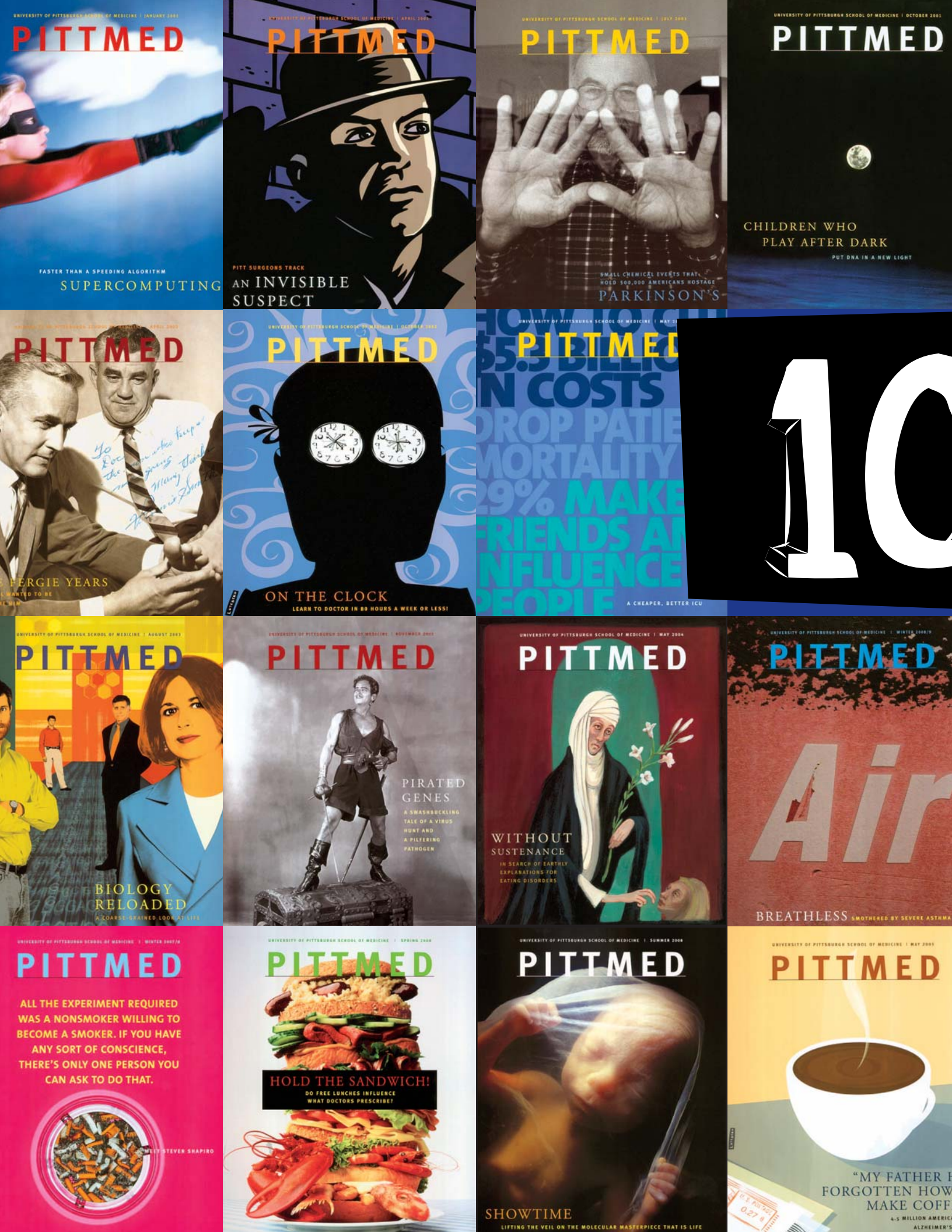

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HOLD THE SANDWICH!
DO FREE LUNCHES INFLUENCE WHAT DOCTORS PRESCRIBE?
PITTMED
SHOWTIME
LIFTING THE VEIL ON THE MOLECULAR MASTERPIECE THAT IS LIFE
PITTMED
"MY FATHER
FORGOTTEN HOW
MAKE COFF

A DECADE OF PITT MED

BY MAGAZINE STAFF AND CONTRIBUTORS

For Ten

For 10 years now, we've followed around doctors walking dark city streets to care for the homeless, bioengineers convinced they can find a way to help veterans regrow limbs, students who'd happily travel several thousand miles to help children orphaned by AIDS. Our days are spent witnessing generosity and genius and mourning and triumph and humility and astonishing aplomb.

As vocations in which practitioners grapple with issues of humanity and mortality as part of a daily routine, or at least as a daily backdrop, medicine and biomedical science are awfully good realms for story fodder. Remember high school English, when Mrs. Finkelbottom taught you about the great themes of literature? You know—Man v. Man, Man v. Nature ... Well, we decided to see how some of the more compelling stories we've told have evolved and how they might fit into such a roster. With apologies to Homer and Hemingway (and with a decidedly medical twist), here goes. Ten years, 10 enduring themes of literature. Thank you for the chance to revisit these characters—and for a fascinating decade.

—Erica Lloyd, Editor in Chief

HEADLINE TYPOGRAPHY | MICHAEL LOTENERO

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Man V. Man

When we met with Paula Monaghan-Nichols for this magazine's very first cover story, she was trying to avoid being bitten by a monster of her own creation ("Killer Mice," October 1999). The uncooperative, genetically engineered baby mouse was the runt of the litter, a mutant with a gene called *tailless* knocked out. Imagine a baby rodent Hannibal Lecter, though not so clever. Her mouse had learning deficits, was fearless, and was, most notably, extremely aggressive. By the time it reached sexual maturity, if left alone with its brethren, it would have fought them to the death and won.

It was natural to wonder, what might such a nasty creature tell us about ourselves?

The mouse and others of its kind are giving us clues as to how we're wired. In the past decade, Monaghan-Nichols, an associate professor of neurobiology at the University of Pittsburgh, has discovered that *tailless* is involved in the production of stem cells. So knocking the gene out of all the brain cells seriously tampered with its developmental pathways. The gene is important to restoring cells in the brain and could hold clues for how certain regions might rebuild from degenerative conditions.



In 1999 we asked, what might a psychopathic mouse tell us about how we're wired?

Monaghan-Nichols later decided to delete *tailless* more selectively. She targeted the cerebral cortex and ended up with much friendlier mutants—not a mean mouse among them. Still, like the knockout mice she bred 10 years ago, these critters aren't at all anxious or fearful.

She was surprised to find that although the mice have much smaller hippocampal formations, that hasn't seemed to have affected their ability to figure out maze puzzles. The hippocampal structure has long been associated with learning and memory. "The hippocampus looks so different from normal, but the animals perform extremely well," she says.

Other knockout animal models, including smaller critters like zebra fish, fruit flies, and the nematode *Caenorhabditis elegans,* are being used throughout the school in powerful ways. *C. elegans*, for example, has helped Gary Silverman, professor of pediatrics and chief of the Division of Neonatology and Developmental Biology, in his studies of a serpin gene, which is protective in epithelial cells in the intestines and lung. We first wrote about his work and worms in November 2004 ("At the Boundaries of Hope"). Now Silverman's microscopic serpin knockout worm is a "workhorse" for drug discovery, as he puts it.

Just a few years ago, researchers were thrilled at the prospect of using live cells in robotic drug discovery systems to look for promising therapeutic compounds. Silverman and his colleagues have refined techniques for using live animals, namely his favorite nematode, to search for an antidote for necrotizing enterocolitis, a condition in which the intestinal wall dies in newborns. "We have a tool that will permit us to identify a drug for a disease that has no known treatment," he says.

"This is an animal that has a full neurologic system," adds Silverman; so his team will know right away whether a compound is toxic. And they can put 50 animals in a microtiter well at once. "That's like screening 50 patients!

"We think this [serpin] pathway is well conserved in worms and extends all the way up to humans," he says.

Likewise, Monaghan-Nichols' *tailless* models continue to intrigue her: "There's no doubt to me that there is a primordial [*tailless*] gene that performed a primordial function and that our proteins have somehow evolved from that." Her knockout mice may even one day give us insight about man's inhumanity to man, or at least how anatomical and other deficits can influence behavior. If she deletes *tailless* from certain regions outside the cortex, she has reason to believe that "maybe the aggression will come back." She hopes so, anyway. —*EL*

the Individual in Nature

"We started out being virus hunters," Yuan Chang told *Pitt Med* in 2003, when asked what had attracted her and her husband, Patrick Moore, to the School of Medicine ("Pirated Genes," November 2003). They wanted to continue the quest, she said, and Pitt offered a chance. "We may not find anything," she warned then, but that disclaimer proved unnecessary. In 2008, they used molecular techniques to show that a virus was behind a rare cancer called Merkel cell carcinoma. This came 15 years after they had discovered the Kaposi's sarcoma herpes virus.

Moore is a professor with appointments in microbiology and molecular genetics in the School of Medicine, as well as in infectious diseases and microbiology in the Graduate School of Public Health. Chang is a professor of pathology.

We photographed the pair lording over a treasure chest and gazing off into the distance. Like all explorers worth their salt, they appear ready to sail into the unknown. Theirs is a classic story of delving into the natural world and returning with treasure.

But the pursuit of these viruses that have forever been part of nature took place not in the field but in a sophisticated molecular biology laboratory using cancerous tissue samples. The use of the built environment to explore the natural history of viruses has expanded greatly at Pitt in recent years.

Pitt's Center for Vaccine Research was launched in 2006 (see our "New Math" story from that November), and it has brought a whole new area of expertise to the University. Its centerpiece is the federally funded Regional Biocontainment Laboratory, which takes up an entire floor of the University's Biomedical Science Tower 3. The lab is rated Biosafety Level III, meaning Pitt researchers can study highly infectious agents such as tuberculosis, dengue fever, influenza, and HIV. Before the lab was built, approximately a half-dozen investigators at Pitt worked in these areas. When the center is fully staffed this fall, there will be 18.

Most notable among the scientists who joined the effort at Pitt is Donald Burke, director of the center, associate vice chancellor for global health, and dean of Pitt's Graduate School of Public Health. Burke is an expert on infectious diseases and biodefense who previously was in charge of military infectious disease research at Walter Reed Army Institute of Research. From early in his career, he has seen the value of computer models used in fields as disparate as economics and engineering, and he has championed and advanced their application to understanding the spread and control of infectious diseases. Pitt investigators like Burke and Bruce Y. Lee (an MD/MBA assistant professor of medicine, epidemiology, and biomedical informatics) have created computer models to help inform policy makers on public health issues. One model contains data points to represent each person in the United States, complete with demographic data. Scientists can enter data related to outbreaks such as the current H1N1 influenza and see the scenarios that could result from such interventions as mass vaccination or limited vaccination.

Thus, questions that would otherwise require a massive natural experiment on a long timeline are quickly explored in the artificial world of the model. —*Chuck Staresinic*



Patrick Moore and Yuan Chang continue to come back with the loot. (Here, they are shown in 2003.)

the Individual in Nature

We used to think of cancer as a foreign invader, a regimented type that overtook one organ after another in an orderly sequence. The thinking was: Find the tumor and cut it out, along with as much surrounding tissue as you can. And if the cancer came back? Well, you just didn't do it right, Doc. Through the first half of the 20th century, cancer literature often read more like radical-surgery how-to manuals than reports on scientific investigation.

Today, we know that cancer is not a foreign intruder, but a disease that lives throughout the body as a whole, traveling the bloodstream and planting new growths wherever it happens upon the right circumstances. We understand that we can't fight it without applying a nuanced understanding of our own biology and the nature of the disease (see "Bad Company," Fall 2008).

In our July 2002 issue, *Pitt Med* interviewed the front man of the very first clinical trials for cancer that, in 1967, finally laid to rest the radical-surgery paradigm ("Bernard Fisher in Conversation"). Fisher's studies set the precedent for the University of Pittsburgh Cancer Institute's (UPCI) growing clinical trial program—now more than 200 active trials strong—and, arguably, the very notion that the science of cancer treatment should be based in (go figure) *science*.



Fisher (MD '43) went on to lead studies of the breast-cancer drug tamoxifen, the first biologically based treatment for cancer, which is still widely used today. In 1998, tamoxifen was found not only to stave off breast-cancer recurrence, but also prevent it from forming in the first place.

Last winter, as part of the centennial commemoration of the American Association for Cancer Research, the editors of *Cancer Research* invited Fisher to write an article detailing the evolution of cancer surgery, and his role in it, for the December issue of the journal.

In February, Pitt honored Fisher when Nancy Davidson, UPCI's new director, gave a presentation as part of Fisher's namesake lecture series. University officials presented him with an honorary degree and played a video tribute to him and his legacy. The event also marked the 90th birthday of this influential scientist, who took on the doubly taxing role of translational researcher before it had much meaning—or much clout.

"The surgeons would say, 'Oh yeah, Bernie Fisher—that rat doctor,'" Fisher recalled with a laugh in the tribute video. "The basic scientists said, 'Oh yeah, Bernie Fisher—the surgeon.' I had a disconnect of who I was and what I was. And that's survived pretty well over the years."

—Elaine Vitone

SINGLE CANCER CELL SEEKS MULTIPLE PARTNERS. AMBITIOUS, HYPERACTIVE, UNSTABLE MUTANT WITH NOMADIC TENDENCIES. REPLY AT YOUR OWN RISK GOOD AT FITTING IN (FOR A WHILE). INTERESTED IN HAVING LOTS OF OFFSPRING.

Taking on cancer today is less about radical surgery and more about understanding the disease's very nature, thanks to early visionaries like Bernard Fisher (shown above).

the Individual v. Himself

In literature, the tragic hero's downfall is his failure to recognize his own fatal flaw. Throughout the history of psychiatry and neurobiology, too, we've struggled to glimpse at frailties within the living brain—to peer inside and understand what brings about some of the most profoundly heartbreaking disorders. Imaging technologies are revolutionizing our understanding of the brain, still many psychiatric conditions, including psychotic disorders and neurodegenerative diseases, remain difficult to reckon with—patient exams and intake interviews being the only diagnostic tools available in the clinic. But emerging research may soon help bring these blind spots to light, both figuratively and literally.

A team at Pittsburgh Institute for Neurodegenerative Diseases (PIND) is working to better understand and treat Parkinson's and other neurodegenerative diseases. Assistant professor of neurology Sarah Berman develops new techniques for studying the critical processes of mitochondria, which have defects in the dopamine cells of Parkinson's patients. And an animal study of a gene therapy for Parkinson's is under way, led by J. Timothy Greenamyre, professor of neurology, chief of the Division of Movement Disorders, and director of PIND, and Edward Burton, assistant professor of neurology and of microbiology and molecular genetics.

Basic science studies and autopsies are bringing schizophrenia's disease process into focus, says David Lewis, professor of psychiatry and neuroscience and director of Pitt's Translational Neuroscience Program and Conte Center for the Neuroscience of Mental Disorders.

Schizophrenia is best known for its characteristic hallucinations and delusions, but an even more devastating side of the disorder is cognitive impairment. Psychosis comes and goes, but cognitive impairment is constant, progressive. It's the best predictor of how functional these patients will be. In "A Chance for Normalcy?" (May 2006), Lewis told us his team had discovered that GABA neurons—neurons that regulate working memory—function improperly in people with schizophrenia.

Last year Lewis completed a proof-of-concept trial for a compound that boosts the signal of these neurons—potentially the first drug to treat schizophrenia's cognitive symptoms. Officials at the National Institute of Mental Health were so encouraged by the biological rationale for this approach they began a multicenter clinical trial before Lewis' study was complete. NIMH trial results are expected to be released in late fall.

Alzheimer's is another disease that has long eluded researchers, its telltale amyloid plaque deposits until recently only visible in the brain through autopsy. In May 2005, when *Pitt Med* did a roundup of science's understanding of Alzheimer's and



In May 2005, writer Cindy Gill shared a story full of love and heartbreak about her Alzheimer's-stricken father, who had forgotten how to make coffee.

Parkinson's ("Stolen Lives"), one of the most promising breakthroughs was a dye that makes amyloid plaque visible in the PET scans of living subjects. The dye had been developed the previous year by Pitt researchers Bill Klunk (professor of psychiatry, codirector of Pitt's Alzheimer Disease Research Center, and director of the Laboratory of Molecular Neuropharmacology at Western Psychiatric Institute and Clinic) and Chet Mathis (director of the UPMC PET Center and professor and vice chair for research in Pitt's Department of Radiology). Dubbed Pittsburgh Compound B (PiB), the dye has been instrumental in thousands of Alzheimer's studies around the world. Surprisingly, these studies have shown that not everyone who has significant amounts of amyloid plaque has Alzheimer's. What other mechanisms are involved? Klunk hopes to find out. His team follows patients with a rare, genetic form of Alzheimer's. Scans from these patients' presymptomatic years will offer a rare glimpse at the disease pathology before amyloid plaque starts to form—and eventually, Klunk hopes, a target for therapy.

Yet PiB has a half-life of only 20 minutes. In the fall, GE Healthcare will begin phase III clinical trials for a more stable version that can be used in the clinic.

"In my future view," Klunk says, "I see people getting their colonoscopy at 50 and their amyloid scan at maybe 65. And if you have amyloid plaques, we hope to have a drug to get rid of it. It's not enough until we get that second part." —*EV*

the Individual v. Himself

"Did I kill the old hag? No, not the old hag—I killed myself!"
—Raskolnikov in Dostoyevsky's *Crime and Punishment*

Hamlet, *Strange Case of Dr. Jekyll and Mr. Hyde*, *Heart of Darkness*—the classics abound with tales of the individual battling against himself, suffering the grim consequences of his actions. It's a recurring theme in medicine, too. In fact, the prevalence of autoimmune diseases like diabetes—illnesses in which the immune system attacks the body's own tissue—appears to be increasing worldwide. But Pitt scientists are devising creative solutions that could help reverse this trend.

Few diseases are as complex as type 1 diabetes, in which the body mercilessly attacks the pancreatic beta cells responsible for producing insulin. But Massimo Trucco, Hillman Professor of Pediatric Immunology and an MD professor of pediatrics, pathology, human genetics, and epidemiology, and Nick Giannoukakis, an associate professor of pathology and immunology, are duping the very immune cells that sicken patients. *Pitt Med* first started tracking this work in our January 2000 issue, and in the summer of 2008 we wrote about an upcoming safety trial involving engineered immune cells.



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The scientists have completed treatment and a yearlong follow-up of seven of 14 adults with diabetes for this trial. They remove dendritic cells from the patients' blood and prime them with molecules that render them incapable of initiating an autoimmune attack. Then they infuse the modified cells back into the body. "The good news is that we see absolutely no side effects," Giannoukakis says of the trial so far. Now the two are gearing up to test a more streamlined form of their therapy—one that relies on injections of tiny primed beads, eliminating the need for tedious dendritic cell removal—in safety trials next year. "I think we're going to have some exciting data coming out in the next three to four years," Giannoukakis says.

Halting the immune attack may not suffice, though—especially if the disease has already killed many beta cells. Some patients will also require pancreatic islet transplantations, but they aren't easy to achieve: One transplant can require tissue from up to six different pancreases, and sometimes repeat surgeries are necessary. To address this problem, Andrew Stewart, chief of Pitt's Division of Endocrinology and Metabolism, is developing beta cells that can regenerate themselves over and over again—which these cells wouldn't normally do. Working with him from his division are Adolfo Garcia-Ocana, a PhD associate professor; Rupangi Vasavada, a PhD assistant professor; Nathalie Fiaschi-Taesch, a PhD assistant professor; and Karen Takane, a PhD research associate.

Oddly, Stewart stumbled upon the idea while researching a calcium-regulating protein implicated in osteoporosis. The pancreas made this protein, too; when it made too much, there were "way too many beta cells," he noticed. Stewart is studying 30 known growth-regulating proteins to see whether tweaking them could boost beta cell replication. So far, he's identified a few. His team "doesn't make beta cells," he explains. "We make them better."

It would be ideal, of course, to prevent such diseases from developing at all—but first scientists must understand the biological pathways involved. This is the purview of Richard Duerr, associate professor of medicine and human genetics, whom we first wrote about in our July 2001 issue. Duerr and his colleagues, as part of an international consortium, are identifying genes involved in inflammatory bowel disease (IBD)—a condition that includes Crohn's disease and ulcerative colitis. (Duerr notes that IBD isn't an autoimmune disease, because the immune system isn't fighting its own cells. Instead, it mounts an overaggressive response to GI bacteria. Yet, the concept is similar.) Since 2001, Duerr and colleagues have found more than 30 gene variants associated with risk for the development of Crohn's. These discoveries have implicated biological processes previously not known to be involved in Crohn's, such as autophagy, the process by which cells recycle their old and damaged bits and break down intracellular bacteria. Autophagy may go awry in IBD and "lead to chronic tissue damage in the GI tract," Duerr explains.

Our greatest foes might well be within us, as Spanish novelist Miguel de Cervantes Saavedra once noted. But that doesn't mean we can't win. —*Melinda Wenner*

When Josh Maloney connected the blasting cap to the quarter-stick of dynamite in his hand, the circuit was supposed to be broken. This one was faulty and closed from the get-go. Two tours of duty in Iraq without so much as a cold, and he blows his hand off during a training exercise in Quantico, Va.

Days later, when he finally regained his wits at Walter Reed Army Medical Center in Washington, D.C., Maloney knew that he wanted to be in Pittsburgh. It wasn't just home. Pittsburgh represented the medical expertise he wanted.

Maloney, a Marine corporal at the time, had no idea just how appropriate his hometown was. Two years earlier, *Pitt Med* had written about W.P. Andrew Lee ("When Being First Isn't Enough," November 2005), Pitt professor and chief of plastic and reconstructive surgery. We described Lee's interest in hand transplantation—a feat he had not yet attempted, though a few dozen transplants had been tried around the world. Lee felt that scientists did not yet know enough about achieving tolerance—convincing the immune system to accept new biological material as self—to attempt hand transplantation.

"I will be disappointed if we don't make meaningful progress on tolerance induction in five years," he said then. In April 2009, Lee led a team that gave Maloney a new hand. They followed that up several weeks later with the first double hand transplant in the United States, this one for a Georgia man who lost his hands to a sepsis infection a decade earlier.



Early in his career, transplant great Thomas E. Starzl seemed to be his own worst enemy.

The hand transplants involved a novel approach to suppressing the immune system that was developed here. Dubbed the Pittsburgh protocol, it involves an infusion of antibodies on the day of the transplant and, 15 days later, another of bone marrow from the deceased donor. The patient then takes a low daily dose of one antirejection drug instead of the more typical three-drug cocktail that carries a higher risk of side effects like diabetes and infection.

"This is similar to what has been done here with patients who have had kidney transplants," says Fadi Lakkis, professor of surgery and immunology and scientific director of the Thomas E. Starzl Transplantation Institute. In the short term, it's clear that these patients do as well as patients on two or three drugs, and they have fewer side effects from their drugs, says Lakkis. What remains to be seen is what happens after three to five years. Will these patients be at higher risk of chronic rejection or delayed loss of the grafted organ?

For patients, transplantation is a long battle against the self—a high-stakes attempt to trick, cajole, distract, or beat down the immune system until it finally accepts new tissue as self. Surgeons have been known to battle the self, as well. Thomas E. Starzl, for one, once seemed to be his own worst enemy. Working since the 1960s to make liver transplantation a viable option for otherwise doomed patients, Starzl developed a monomaniacal drive. His health suffered. Some said he was crazy to try this thing that would never work. Colleagues learned to climb aboard or get out of the way.

As this magazine recounted one of Pittsburgh's epic and storied efforts ("Only Starzl Dared To," May 2006), the surgeon and Pitt Distinguished Service Professor of Surgery eventually succeeded in shepherding liver transplantation into the realm of the possible. When he finally stepped back, there was a thriving field of medicine where only a makeshift outpost had stood before.

His next goal: drug-free tolerance. How close are scientists to achieving that today?

"You are catching me at a pessimistic moment," says Lakkis, with a laugh, before explaining the successes and shortcomings in transplantation research.

He says "the field is not any closer [to drug-free tolerance] on a large scale" than when this magazine covered the topic in our Fall 2006 issue ("Break on Through"). "It is a little closer in terms of small scale. It remains an unpredictable process. You can achieve tolerance in a small number of patients, but we still don't know how you can identify that small group of patients ahead of time." That said, Lakkis rattles off the details of recent promising research endeavors at the Starzl Institute, including labs that modify dendritic cells and antibodies to turn down the immune system.

Lakkis has a more fundamental approach. He studies the primitive immune system of *Hydractinia*, a relative of jellyfish, which detects foreign tissue and attacks it. Despite 800 million years of evolution separating us, humans share some aspects of this innate immune system, which may act as a sort of alarm system to alert our more evolved adaptive immune system to foreigners. Lakkis, along with colleagues at Pitt and Yale University, has identified a *Hydractinia* gene involved and is now looking for human genes that are structurally similar. The scientists hope to define a new mechanism in our innate immune system for identifying foreign tissue. If they find one, it would help demonstrate why transplantation's battle against the self is so protracted—because living things have been protecting this sense of self for at least 800 million years, and probably much longer. —*CS*

The Individual in Society

"True strength lies in submission which permits one to dedicate his life, through devotion, to something beyond himself."
—Henry Miller, *The Time of the Assassins*

Brian Miller is a rare doctor who doesn't wait for patients to come to him; instead, he goes to them, seeking out people in need on the streets, in remote communities, and in their homes. Miller (MD '06), a resident in family medicine at Pitt whom we profiled in the February 2004 issue, says his medical philosophy was shaped by his experiences in the Geriatric Experiences for Medical Students (GEMS) program while a Pitt medical student.

"It made me realize that in the clinic, you really are only seeing a very small piece of what a patient's life is like," Miller says.

Through GEMS, Miller visited geriatric patients in their homes, and his experiences revealed that patients sometimes mask their problems in public. "A lot of my patients get dressed up, groomed up, to come to the clinic, looking their best as they walk through the door," he explains. "Things are often quite different at home." For example, he recently paid a visit to a stroke patient who was not recovering well. "I got to see a little bit about who he was—the golf clubs he had used every day that he's no longer using," Miller says. The contrast between his once happy-go-lucky life and his current plight suggested to Miller that the patient was probably depressed. Now, with proper treatment, the patient "has gotten some of his pep back," he says. Ultimately, Miller explains, when doctors see patients at home—something he plans to do throughout his career—they catch unique glimpses of their lives that provide insights into how best to treat them and prevent future health problems.

Miller also reaches out to other communities. This spring, he spent a month in Arizona working at a hospital affiliated with an Apache reservation. And he's a part of Operation Safety Net, a group of physicians and students with a mobile clinic that travels around Pittsburgh treating homeless patients.

A Pitt experience also helped Brad Dicianno make his unique mark as a physician. Dicianno (MD '01), who participated in Pitt's Area of Concentration (AOC) program in disabilities medicine, is now an assistant professor in the Department of Physical Medicine and Rehabilitation, director of the department's Spina Bifida Outpatient Clinic, and the medical director of the Center for Assistive Technology. He builds control interfaces like joysticks to help people with disabilities—especially those with debilitating complications, such as tremors—more easily operate computers and power wheelchairs. In addition, he is building a "virtual environment" that will assess patients' motor abilities so that he can design custom interfaces suited to their strengths. Ultimately, says Dicianno, who was profiled in our April 2001 issue, "the AOC really did make a difference in exposing me to the needs people have that can be met by technology." *—MW*



J. Nadine Gracia in 2000.

In her medical school interview, J. Nadine Gracia said that she wanted to eventually play a role in forming health policy, recalls Paula Davis, Pitt's assistant vice chancellor for health sciences diversity. It would be difficult to find anyone who followed through on a statement more thoroughly or more successfully in just a decade.

Gracia (MD '02, Res '05) was president of the Student National Medical Association during med school (we first wrote about her in January 2000, "President in Training"), and she is currently a White House Fellow, a program that includes Colin Powell and Wesley Clark as alumni. Gracia works on projects addressing women and girls' health in the outer Pacific Islands. As an assistant to the counselors to the U.S. Secretary of Health and Human Services, she prepares briefs and informational memos to guide policy decisions and leads a departmental work group on the insular areas.

Mentors at Pitt made it possible for her "to be a national leader and a medical student at the same time," Gracia says.

"I received the same level of support at Children's Hospital," she says of her residency experience. "They knew I cared about leadership roles and advocacy." *—CS*



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nonoxide and nitrite are
evealing their good sides.

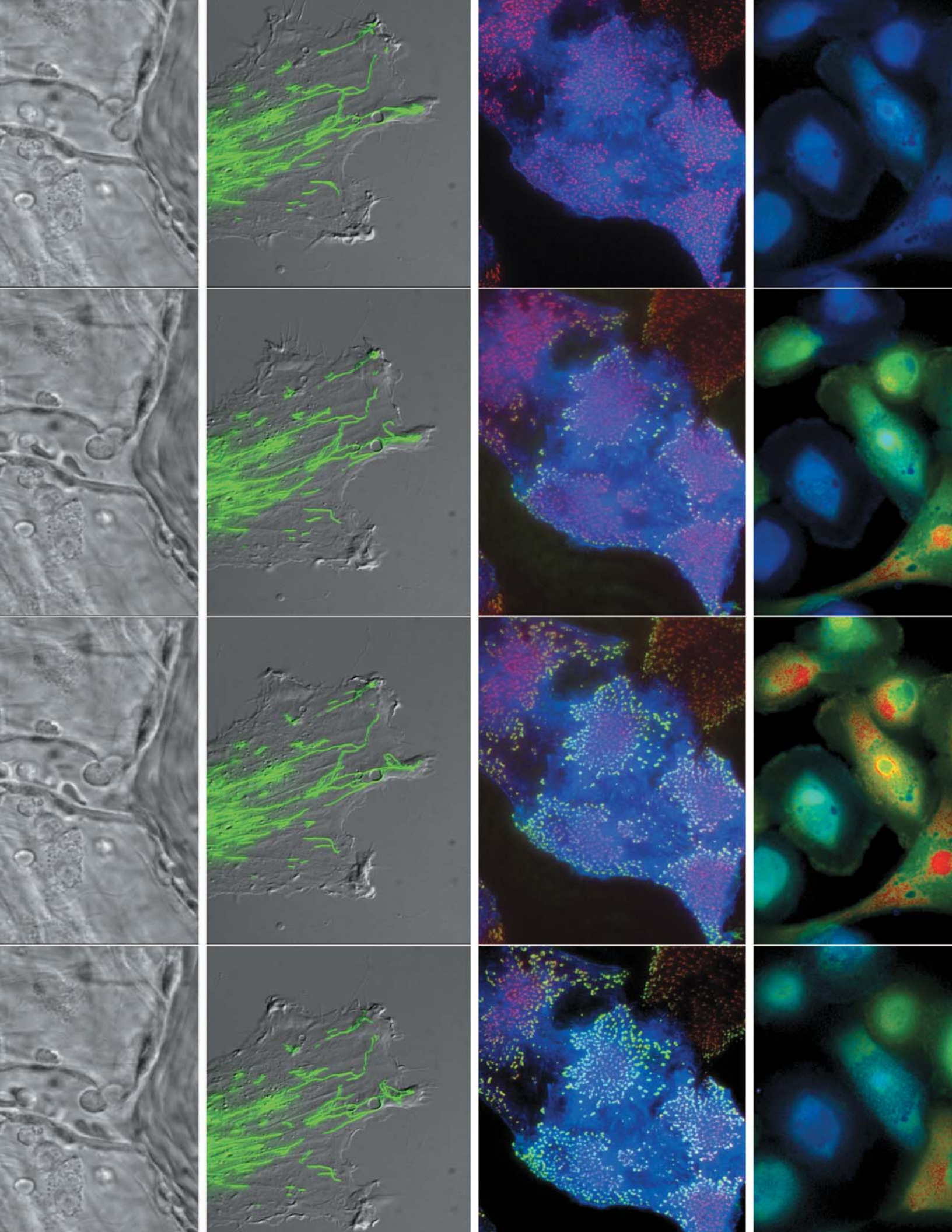
It's shocking to see the younger generation swoon over characters that their elders once wanted locked up. But in the unpredictable world of biomedical research, that is the case with toxic molecules like carbon monoxide (CO) and nitric oxide (NO). They are free radicals—the same ones found in cigarette smoke and automobile exhaust. We've been warned about them, but in the past 10 years, *Pitt Med* has devoted a lot of ink to describing how once-maligned molecules are now studied for their beneficial effects.

A presentation at Science 2008—Pitt's annual science celebration and biomedical mixer—was titled "NO, NO, a Thousand Times NO!" Moderating the program was Bruce Freeman, PhD professor and chair of pharmacology and chemical biology at Pitt, who has spent a few decades at the leading edge of free radical biochemistry. On the docket were four experts in cellular signaling, all Pitt clinicians. One surgeon described how NO was administered to protect his patients' new livers from damage during and after transplantation. And Mark Gladwin, professor of medicine, claimed that our blood cells derive cardioprotective NO from nitrate and nitrite—maligned molecules culled from our drinking water and present in that most evil of foodstuffs, the hotdog. You might recall Gladwin and Freeman's heretical hypothesis from our previous issue ("Welcome to the Dark Side," Summer 2009).

Pitt professor and Department of Surgery chair Timothy Billiar runs a lab that has made real progress on the NO puzzle ("An Invisible Suspect," April 2001). In the late 1980s, his lab showed that an enzyme that catalyzes the formation of NO from oxygen and arginine was expressed in liver cells. He and his colleagues in surgery have since explored the complex regulation and function of this enzyme—called iNOS, for induced nitric oxide synthase—in the liver. In some settings, iNOS contributes to liver damage; in other settings, it protects liver cells from death. The Billiar lab also actively explores the action of NO and iNOS in hemorrhagic shock, sepsis, cell signaling, and programmed cell death.

Elsewhere in surgery, associate professor Noriko Murase is using CO to protect kidneys during experimental models of kidney transplantation and is set to begin a clinical trial in patients this year.

What was once a rogue's gallery of toxic molecules is becoming a physiological hall of fame. Pitt scientists are overseeing big parts of the changeover. —*CS*



the Individual and Technology

"It's almost intelligent, almost sentient," Simon Watkins says with amazement, even though he's watching something he sees every day.

Watkins—PhD professor and vice chair of Pitt's Department of Cell Biology and Physiology, as well as director of the University's Center for Biologic Imaging (CBI)—talks as he runs one of hundreds of cell-in-action videos on his computer. The video is captured from a confocal microscope and a camera recording 150 frames per second. On the screen is a dendritic cell in action. It spreads out in three dimensions, forming what appear to be feet. The feet stretch out and engulf a bacterium, and the dendritic cell internalizes it.

Watkins, Pitt's guru of scientific imaging, arrived here in 1991 and, since then, he says, "The whole field and my existence have changed completely. We can now image so much faster, deeper, and with more colors simultaneously." *Pitt Med* assembled a photo essay featuring the CBI in 2000. It was amazing stuff at the time, says Watkins, but "it was all dead material and all in two dimensions." Today's high-speed, three-dimensional images, he says, represent a sea change. And seeing things happen live and in real time—from a single molecule to a whole cell—provides something invaluable to Watkins: context.

On his rounds of various conferences, Watkins often brings with him a recording of a Steelers game. In the still shot he shows first, quarterback Kordell Stewart is under center at the goal line.

"We can hypothesize what's going to happen next, but we don't know," Watkins says. "You're just looking at a slice of time. A frozen section of time." When the film rolls, Stewart takes the snap from Dermontti Dawson and leaps into the end zone.

But without the context that time provides, you get hypotheses like this:

"A Russian guy comes up to me," recalls Watkins, "and I asked him, 'What do you think is happening?' There was silence. Then he said, 'What I saw was very large men wearing tight, yellow pants. I thought [Stewart] was actually milking [Dawson].'"

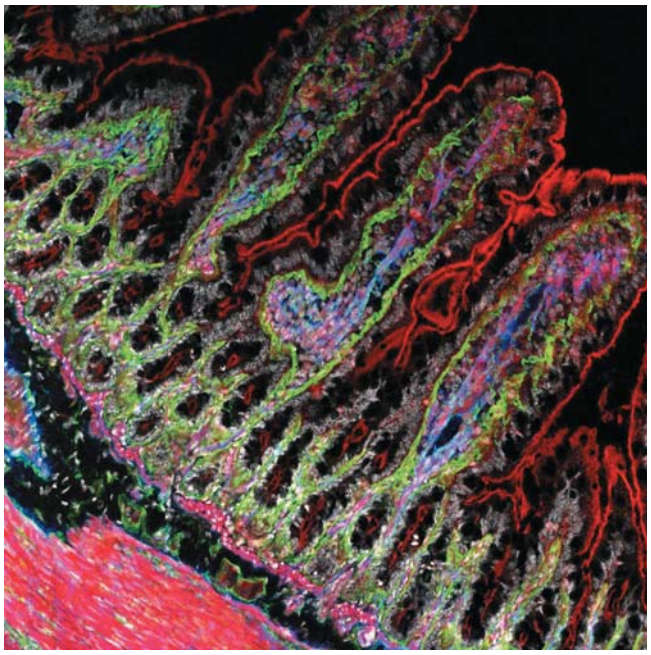
Watkins and the cadre of scientists served by the CBI are also using new technologies and techniques to image living animals. Beating fish hearts and the working pancreas of a rodent have been captured in three dimensions and in real time. Next up, Watkins says, is an entire, living animal.

Not far from Watkins' technological emporium in the Thomas E. Starzl Biomedical Science Tower, Angela Gronenborn does a different kind of imaging, a form of seeing beyond the realm of visible light ("Dark Arts," February 2006).

Gronenborn, a PhD and UPMC Rosalind Franklin Professor as well as inaugural chair of Pitt's Department of Structural Biology, is dedicated to solving the structures of proteins, molecules, and viruses. In 2007, Gronenborn was named head of a National Institutes of Health–funded, $16 million Center for HIV Protein Interactions, based at the University of Pittsburgh. Subsequent work related to that project, Gronenborn says, has resulted in nailing down the structure of the HIV capsid—its protein shell. Her lab also discovered and laid out the structure of a protein, cyanovirin-N, which boasts antiviral properties. These are steps, she says, toward finding vulnerabilities in HIV and possible tools to attack those weak spots.

"I really do believe that we will get the atomic structures of entire cells within the next 10 to 15 years," she says. "The technology is getting there. Also, the architecture and atomic detail of an entire virus—and they're smaller than entire cells—is in reach. People say I'm crazy, that it's science fiction, but I think it will happen." —*Joe Miksch*

LEFT: Simon Watkins has collaborated with Pitt colleagues to see (left to right columns) blood flowing in a live rat (Flordeliza Villanueva's lab), mitochondria in action (Luis Ortiz), a cell having a snack through endocytosis (Linton Traub), and calcium activity in a dendritic cell (Russ Salter).



A section of fixed, frozen mouse intestine imaged a decade ago. Watkins notes, "It is very pretty, but there is no movement, and it's only two dimensions."

Nothing like this had ever been done.

In November 2003, Pitt surgeons revealed to a stunned audience at a neurosurgery conference that they had performed more than 300 minimally invasive brain surgeries through the nose.

Carl Snyderman, professor of otolaryngology and of neurological surgery, and Amin Kassam, former chair of neurological surgery, coined the term "expanded endonasal approach" for the technique that allowed them to reach across the entire base of the skull. Pitt surgeons now routinely reach as far back as the top of the spine, out to the mandibular joint on either side, and forward to the brow.

The discipline, says Ricardo Carrau, professor of otolaryngology and of neurological surgery, "has become a subspecialty, and it's very competitive."

With industry partners, the surgeons have developed a prototype simulator that gives proprioceptive feedback: "When you bite into tissue with an instrument, you want to feel whether you are biting bone, or soft tissue, or tumor," Carrau says.

When we first reported on this technique (May 2005, "Twin Portals to the Brain"), a common postsurgical complication was leakage of cerebrospinal fluid through the opening breached in the base of the skull. Then surgeons reconstructed this barrier using fat or other soft tissue. They now apply a flap of tissue excised from the nasal septum. Because the tissue includes blood vessels, the graft takes to its new home much better than fatty tissue. Previously, says Carrau, "15 to 30 percent of patients needed a second surgery for repair of the leak. Nowadays, it's about 4 percent." —*CS*



Holy numbers, Batman! Using a supercomputing system called "Bigben," Pei Tang's (not shown) group processes data describin 160,000 atoms daily. When we wrote about her studies in 2001, data from 68,000 atoms took 10 days to process. All this crunchi is allowing Tang to reveal how anesthetics work.

the Individual and Technology

Pei Tang knows it takes more than one punch for anesthetic drugs to knock us unconscious. In 2001, we described how Tang, professor of anesthesiology, used the Pittsburgh Supercomputing Center to model the interactions between the anesthetic halothane and a simple ion channel. The number of atoms in her system, 38,724, was considered huge at the time. Now, Tang's group is using "Bigben," a supercomputing system she calls "revolutionary," to model more complex and realistic scenarios. Her postdocs and students feed data from more than 160,000 atoms into Bigben daily, using larger proteins and a wider variety of anesthetic drugs to visualize 20–30 nanoseconds of cell-membrane activity. Multiple models are giving them a clearer picture of what happens at the molecular level under anesthesia. Transmembranous neurotransmitter receptors are like doors to our brain cells. When an anesthetic latches onto a neurotransmitter receptor, the door becomes warped, and neurotransmitters can't function properly. Tang hopes to soon combine her computational and experimental studies to develop safer and longer-lasting anesthetic drugs. *—Brandon Ellis*

With childlike glee, Marco Zenati moves a Microsoft videogame joystick and points to a computer-generated image of a beating pig's heart. "See the probe? It's right next to the left anterior descending artery," he says. In July 2002 ("Mt. Olympus Goes Techie"), Zenati, professor of surgery and bioengineering, worked behind the controls of "Zeus," a robot designed to eliminate hand tremors while operating on the heart. Since then, Zenati has realized the limitations of anthropomorphic robots and teamed up with Carnegie Mellon University's Robotics Institute to develop cardiac robots that look more like snakes than human hands. Preclinical trials on pig hearts are confirming Zenati's predictions. His two newest bots, the Heartlander and Cardio ARM, can reach inside hearts at less invasive angles than previous robots, eliminating the need to deflate a patient's lungs. Cardiorobotics, the Pitt/CMU spin-off developing the technology, raised $11.6 million this summer. *—BE*

Boy meets Girl

Many of the stories in this magazine are, at heart, love stories. If you're going to try to bring about meaningful advances in medicine, passion and devotion seem to help.

Joseph Glorioso, for one, became smitten with the idea of gene therapy in the '90s, when he realized the virus he'd spent much of his career studying was probably the ideal vehicle for delivering therapeutic genes to the nervous system. Most of us would regard HSV1—the herpes simplex virus often associated with cold sores—as an irritant or worse. For Glorioso's purposes, herpes has it all: It naturally travels through neurons, where it excels in settling in and doing nothing.

Glorioso's lab has figured out a way to get it to deliver customized genes on demand while making the virus unable to replicate in the host (actually, most of us have HSV1 in our systems already).

"We've tried very hard to cause disease with these [engineered] organisms, and we just can't do it," Glorioso, professor of microbiology and molecular genetics, says with a chuckle.

There's a slight note of exasperation in his voice, as well. It's been an up-and-down ride for gene therapy devotees. As we reported in a July 2000 article ("Precious Cargo"), questions of safety arose 10 years ago after the death of Jesse Gelsinger, a young man enrolled in a trial at the University of Pennsylvania. Later gene therapy trials in France and elsewhere for severe combined immune deficiency, a.k.a. "boy in the bubble" disease, ended immunodeficiency for 19 of 20 children. But five patients contracted a leukemia-like cancer as a result of the therapy, from which one died. "Four are in remission with immunity still corrected by gene therapy," says Glorioso.

Ever faithful, in the past decade, Glorioso has built a strong gene therapy research program at Pitt with several independent investigators pursuing almost $16 million worth of studies in a wide range of diseases. At the moment, he is most excited about a treatment for chronic pain he developed that's now in a safety trial at the University of Michigan.

"In chronic pain syndrome, even touching the skin hurts," he says. "So these neurons start firing pain signals inappropriately. This kind of pain is a disease. ... People can't go to work; their lives are miserable. Long term, there's no treatment."

Unlike users of narcotics, patients don't build tolerance to Glorioso's treatment. Doctors inject the therapy at the site of the pain, then as Glorioso puts it, "there's this very cool thing that happens." A molecular motor in the nerve carries the virus up the length of the neuron. When it gets to the nucleus, the virus injects its DNA. The viral DNA is then entirely silent except for one gene built to release enkephalin, a naturally occurring substance in our bodies that binds to opioid receptors and relieves pain. The therapy blocks only chronic types of pain—not pangs that might signal a need to remove a hand from a flame, for example.

The biggest issue Glorioso foresees now: cost.

"NIH really doesn't have the money to move these therapies forward." So Glorioso has partnered with a local subsidiary of the Swedish firm Diamyd Medical. Moving forward to the next two clinical trial stages will run "probably $12 million." Yet his commitment is unwavering.

For treating nervous system conditions, he says in a hushed voice, "I think the system we're using is perfect." *—EL*

the Odyssey

It took Odysseus a decade to wend his way home after the fall of Troy. Perhaps he could have used a better navigator.

For some 30 years, Peter Strick has been helping researchers navigate on one of science's great journeys of discovery, the study of the brain. Strick, a PhD who codirects the Center for the Neural Basis of Cognition and is a Pitt professor of neurobiology and psychiatry, maps the circuitry of the brain.

Before Strick published a seminal paper on the topic in 1986, conventional thought had it that discrete areas of the brain performed discrete functions. This part controls thought. This part controls motion. This part controls speech. And so on.

Strick has long been involved in the study of Parkinson's and Huntington's diseases—which are based in the basal ganglia, a group of structures interconnected with the cerebral cortex and thalamus and associated with a variety of functions, including motor control, cognition, emotion, and learning. The basal ganglia were thought merely a locus of motor control before Strick came along. "Parkinson's and Huntington's are very different in terms of symptoms," Strick says, "but they affect different portions of the same neural structure."

This elemental understanding has forced scientists to rethink treatments for neurological disorders. The standard treatment for Parkinson's has been to prescribe L-dopa—a drug used to replace the neurotransmitter dopamine. But today, a neurosurgeon might implant electrodes in the particular neural loop related to the symptoms, a procedure called deep brain stimulation.

The thinking that led to this treatment, Strick says, represents the biggest shift in the past decade of neuroscience. "We now understand that disorders are specific to [brain] systems [rather than just structures], and that the treatment has to be focused to deal with the pathophysiology."

We first wrote about Strick's work in our July 2002 cover story, "The Sweet Science of Movement." Within the past year, the scientist has helped explain why a musician may have the dexterity to, say, play the lyre as adeptly as one of Homer's Sirens. In many animals, the primary motor cortex controls movement through the circuitry of the spinal cord. But "higher" primates, like humans, evolved an area of the cortex that communicates directly with specific spinal cord motor neurons, which instruct shoulder, elbow, and finger muscles to perform. This direct connection, Strick says, accounts for added deftness with small, specific movements.

Karl Kandler is another Pitt researcher erecting key guideposts to help us find our way around the brain. He specializes in the circuits that tell the brain when to go fast and when to lay off the accelerator.

Inhibitory neural pathways, says Kandler, act like a governor on a car engine. The brain may be capable of going as fast as a Ferrari, but it shouldn't; unrestrained neural activity can be the cause of seizures and has been related to schizophrenia.

Kandler, a PhD associate professor of otolaryngology and neurobiology at Pitt, studies the auditory brain system, where many of the pathways are purely inhibitory and well defined. Kandler chose this system for study about 10 years ago, and in October 2002, *Pitt Med* reported ("The Brakes of the Brain") on his early progress that landed him national attention, notably a Presidential Early Career Award for Scientists and Engineers.

Prior to 2005, Kandler reports, it was thought that excitatory neurons—which stimulate cells to act—only released excitatory neurotransmitters such as glutamate and inhibitory transmitters only released inhibitory neurotransmitters like GABA and glycine.

During the past couple of years, however, Kandler has found that in young rats, developing inhibitory neurons in the auditory brain system release glutamate.

More recently still, Kandler discovered that the production of glutamate is vital for the proper development of inhibitory neurons. Mice engineered so they are unable to produce the neurotransmitter, he says, experienced nonconvulsive seizures, indicating that the "brakes of the brain" were not working properly, that the excitatory circuits were overloaded.

If things pan out the same way in humans, says Kandler, it may be possible to use this mouse-derived knowledge to develop drugs to restore the brakes to good condition in people with disorders such as schizophrenia, epilepsy, and tinnitus. —*JM*

Getting into med school can be an epic quest in and of itself. But imagine finally arriving at the school you chose—and that, thank the gods of Mt. Olympus, chose you—only to find out that getting your MD from this particular university would be more complicated than you'd thought.

Sheena Jain (MD '08) recalls feeling a bit anxious at orientation five years ago when she learned about a brand-new curriculum requirement: the scholarly research project. But the project turned out to be a blessing in disguise.

The faculty explained that day at orientation that each student would pair with a mentor who guides her in designing a scientific-research project. As this magazine has reported on a number of occasions, typically the project is a long-term, in-depth study that begins the fall of the second year.

The 270 projects completed thus far have run the gamut, focusing on everything from necrotizing enterocolitis in premature infants to the role of life experience in shaping attitudes in end-of-life care. One student even wrote a medically based mystery/thriller novel.

Working with her mentor, radiation oncologist Sushil Beriwal, Jain did a retrospective, comparative study of clinical outcomes for endometrial-cancer patients who underwent different radiation therapies. Based on the strength of her project, she was asked to represent Pitt at the 2007 Annual Meeting of the Association of American Medical Colleges. Along with two other classmates, Jain answered questions in the exhibit area for conference attendees, many of whom were curious about Pitt's new curriculum, which won an AAMC award for innovation in preclinical education.

Pitt's scholarly research project requirement is designed to give students a preview of the world of academic medicine. It's also designed to create leaders in medicine who can absorb research



Karl Kandler (the tall one) grew up closely observing animal behavior. Now he's the expert on the "brakes of the brain." He's shown here at home in a 2002 photo.

advances, whether or not they have any interest in pursuing a vocation steeped in grants and data.

"This was great for me as a clinician," Jain says of the project. "New research articles are published every day, and you're always going to find contradictory information. I think the only way to gain that appreciation and learn how to read critically is by actually *doing* research."

An added bonus: The scholarly project has also made the dreaded odyssey that is The Job Hunt a little less tortuous. "By far what I was asked about most in interviews was my research," Jain says as she wraps up her last two weeks as a UPMC intern—after that, she's bound for a radiation oncology position at the University of Texas Southwestern Medical Center at Dallas. "If I didn't have that on my resume, I don't know what we would've talked about. Overall, from talking with my classmates, I think our research projects made us much more competitive. We have a real advantage." —*EV*

Coming of Age



Preliminary data from the National Institutes of Health place Pitt and its affiliates fifth among institutions receiving the agency's support.

In 1998, when he took the helm as Pitt's senior vice chancellor for the health sciences and dean of the medical school, Arthur S. Levine had three main goals: Ramp up basic science research, continue the tradition of clinical excellence at the teaching hospitals, and attract some of the best med students in the country.

Done, done, and done.

We reported in 2000 ("His Aim is True") how Levine, an MD, came from the National Institutes of Health (NIH) to fill the rather large shoes of his predecessor, Thomas Detre. Beginning with his leadership of Western Psychiatric Institute and Clinic in the 1970s and later as senior vice chancellor for health sciences, Detre helped transform Pitt from a regional med school best known as the birthplace of the polio vaccine into an up-and-coming national brand.

Under Detre, Pitt's modern academic medical center was born and learned to walk and play with the big kids. Under Levine, it has matured and gotten into poetry, art, home improvement, and marathons. Older and wiser, sure. But slowing down? Don't bet on it.

That's probably a good thing for Pittsburgh. Last year the University brought in about $642 million in outside funding for research and other programs, supporting more than 23,000 jobs; much of the funding relates to biomedical work. The biomedical enterprise that has sprouted around Pitt and UPMC has helped the city weather the country's worst financial crisis since the Great Depression.

In addition to its federal and philanthropic support, the medical school's symbiotic relationship with UPMC, the region's largest employer, has helped it blossom. The teaching hospitals rely on Pitt faculty to deliver care; UPMC in turn invests profits ($146.6 million in 2008) from patient care into research and education. UPMC supports the training of residents and fellows, who are UPMC employees. Other Pitt health sciences schools receive funds, as well.

With the school in a position of strength, Levine created several new departments in the clinical and basic sciences. Two of these—structural biology and computational biology—are now housed in Biomedical Science Tower 3, a $205 million high-tech hive opened in 2005. Levine recruited Angela Gronenborn, a decorated scientist at the NIH, to help design the building and become the UPMC Rosalind Franklin Professor and inaugural chair of structural biology. "I could see the chance for this cross-fertilization of physicians and basic researchers to learn each others' language and push their way forward," says Gronenborn, who was inducted into the National Academy of Sciences in 2007.

The med school has established an Academy of Master Educators to recognize outstanding instructors and steadily shaped its curriculum with the changing nature of medicine. It now requires students to complete a scholarly research project. And fourth-years revisit basic science material after the whirl of third-year clinical rotations. "After you've seen patients with leukemia, it's really good to be able to go back and revisit the science underlying leukemia to tie everything together," says Steven Kanter, vice dean.

Levine has invested in scholarship money to lure top med school students, who now bypass the likes of Stanford, Johns Hopkins, and the Ivies to come to Cardiac Hill. "One of my goals coming in has been to attract a different kind of student—students who would be leaders in their profession," Levine says.

Still, these are daunting economic times, and the future of academic medical centers like Pitt depends on factors that no one, not even Art Levine, can control. Health care reform, in whatever shape it comes, could reduce compensation. More alignment with industry will be necessary, Levine says. But the need should be tempered by policies that keep the medical mission and revenue motive separate, he says. Pitt has already put a lot of thought into how to reduce inappropriate influence (see our Spring 2008 cover story, "A New Diet for Docs"). The American Medical Student Association gave Pitt's efforts very high marks in both 2008 and 2009.

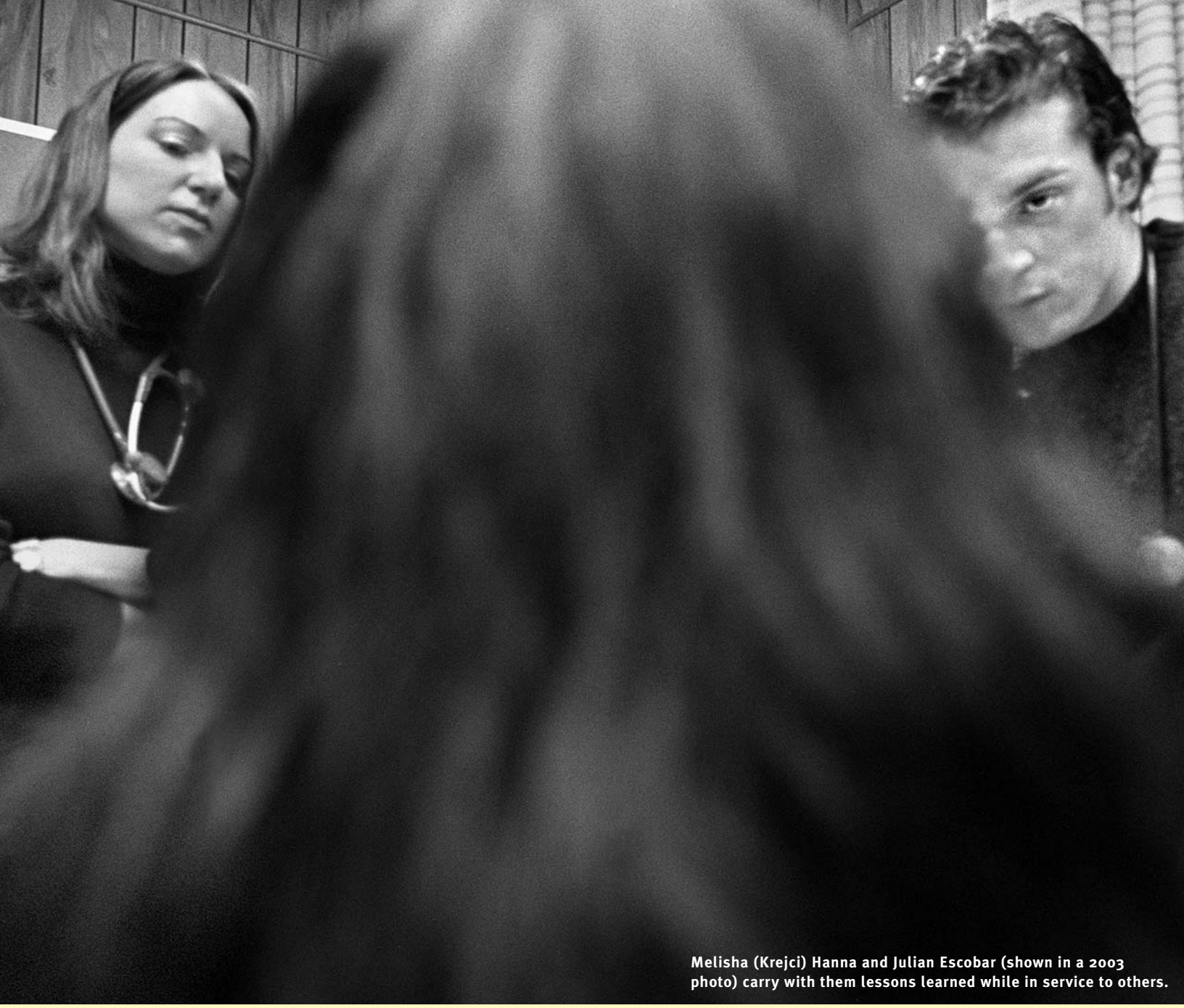
Regardless of the uncertainties, this is no time to wind down on academic medicine, Levine argues: "To prevent a disease, you have to know what's causing it. We can't let up on our support for research."

The academic medical center has grown up. Now, perhaps, comes the hardest part. —*Reid R. Frazier*

The great coming of age stories all function on the mechanics of a simple equation: At some point in our lives, we see things that make us unpack the valise of received knowledge we've carried around up until that point. Huckleberry Finn's eye-opening experience came while sharing a raft on the Mississippi River with an escaped slave named Jim. Holden Caulfield's came on a weekend alone in New York City.

For some Pitt med students, the *bildungsroman* moment comes while serving those in need. In May 2003 ("Modern Day Schweitzers"), we reported on the whirlwind of activity behind Julian Escobar and Melisha (Krejci) Hanna (both MD '04) cofounding Students and Latinos United against Disparities (SALUD), a health service for Pittsburgh's small but growing Latino population. Escobar and Hanna put SALUD together with help from a U.S. Schweitzer Fellowship.

Escobar, who'd grown up in Bogotá and came to Dallas in the early 1990s as a teenager, never considered himself "Latino" before



Melisha (Krejci) Hanna and Julian Escobar (shown in a 2003 photo) carry with them lessons learned while in service to others.

med school. That began to change while working on SALUD, which Pitt med students continue to run. (With a dozen fellows this year, the Schweitzer program remains strong at Pitt, as well.)

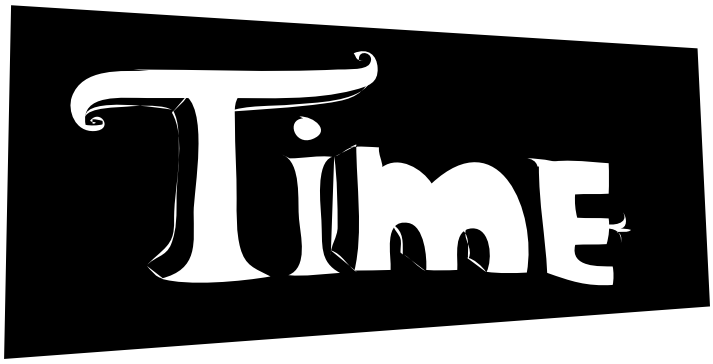
One day in 2003, Escobar was looking for a Spanish translation of the HIPAA statement. He called a hospital office to see whether there were any on hand. "We only have those forms in *American*," Escobar remembers the woman on the other end saying.

"I knew right then that I had this responsibility to educate people around me. I knew I wanted to help the Latino community help itself," he says.

Escobar went on to an ob/gyn residency at Northwestern University. He's now a fellow in reproductive endocrinology and infertility at the University of Texas Southwestern Medical Center at Dallas. His clinic is one of the few of its kind that accepts Medicaid patients, a point of special emphasis for Escobar. "Just because you're poor, or don't speak English, that doesn't mean you shouldn't have access to this care," Escobar says.

Hanna is now at Children's Memorial Hospital in Chicago, where she's completing a pediatric nephrology fellowship and working on a project to improve hypertension screening and care for adolescents from disadvantaged backgrounds.

A long list of Pitt med alums we've chronicled have continued on the path illuminated by their coming-of-age experience. Kate Dickman (MD '09), for example, spent two years in Uganda conducting research on tuberculosis as a Fogarty International Clinical Research Scholar ("Breaking Ground," Fall 2007). She's now in the Boston Combined Residency Program in Pediatrics, run through Harvard and Boston universities. After residency, she'll likely look for a postdoc in public health. At Pitt, she became interested in working with children while volunteering at a pediatric malaria clinic in rural Kenya. Watching children die of a preventable and treatable disease gave her direction and a purpose. "You see something horrific," she says, "and you want to try to make it better." *—RRF*



Authors have long used time as a device in their plots. You could practically hear the clock ticking as we shadowed Brian Pettiford (MD '96, Res '01, Fel '03) during his cardiac surgery fellowship ("On the Clock," October 2002). There were plenty of opportunities for him to wield a scalpel during those 110-hour workweeks, yet scant sleep and foregone family time were part of the price of a now-defunct approach to medical training. Looking back, Pettiford, a Pitt faculty member who will join a private cardiology practice in York, Pa., this fall, says, "If it doesn't kill you, it makes you better."

Not everyone agreed that lives lived in defiance of time was the best situation. An Accreditation Council for Graduate Medical Education standard barring trainees from working more than 80 hours a week—averaged over a month—or shifts longer than 24 hours went into effect on July 1, 2003. Amid growing concern about the effects of fatigue on both patient care and house-staff health, Pitt adopted the standard a year ahead of the national deadline. (Pettiford completed about 90 percent of his training under the old rules.)

The transformation has been profound, says Rita Patel, associate dean for graduate medical education: "It focuses you on the most important things for residents to learn." Today, simulations, podcasts, and online programs guarantee exposure to the unusual cases a resident previously encountered only if she happened to be present when such a patient arrived. Fatigue-recognition training cultivates a shared responsibility for physician health.

The medical center now focuses on strategies for effective patient transfer and team communication. "You're altering the whole culture, moving from a hero-based system—where if you're a patient you hope you hit the right person who can get you out alive—to systemic structures [that] carry you through in a reliable fashion," says Dennis Zerega, vice president for graduate medical education. "It moves from individual heroics to system predictability." *—Sharon Tregaskis*

Why do we age? In a February 2005 headline, *Pitt Med* posed that grammatically simple yet scientifically complex question. Laura Niedernhofer, a Pitt associate professor of microbiology and molecular genetics, proposed that rather than a single underlying mechanism controlling aging throughout the body, aging was probably the result of the gradual accumulation of random damage to cells and molecules. Eventually, the body can't keep up with the necessary repairs.

In the field of aging research, this view has won out, says Niedernhofer, adding, "We are fortunate enough to have the research community embrace our model as one of aging, and we are using it to look for those sorts of 'magic treatments' that might help us live longer and healthier."

The model she refers to is a strain of genetically modified mice deficient in repairing what are known as the interstrand crosslinks of DNA. The mice seem to age in fast-forward, she says, implicating crosslinks in natural aging.

Niedernhofer now works with at least 10 different collaborating labs across Pitt's campus that use her models.

The extent of such collaborations, she says, underscores the growing strength of Pitt as a place for research into aging and DNA repair. Several dozen med school faculty list one or both of these areas among their research interests, including (and this is not a coincidence) Arthur S. Levine, dean of the school and senior vice chancellor for the health sciences.

"I can't think of a better place" to do this work, says Niedernhofer. *—CS*

When the AIDS epidemic first emerged some 30 years ago, it presented the face of a ghoul. Doctors gowned up when seeing patients, even though they knew its pathogen was not airborne.

With the passage of time, the wonder of antiretroviral drugs, and our immense capacity to forget, the old specter has passed, and we now see in its place something totally different—a chronic disease that, many assume, we can live with. That's a dangerous attitude. More than 33 million people now are infected with HIV, two-thirds of them in sub-Saharan Africa. The number of new infections—in the United States, as well—keeps rising. And drug-resistant strains have emerged.

This makes the task before researchers all the more urgent. As we reported in 2002 ("The Virus Keeps Hiding"), Charles Rinaldo, chair and professor of infectious diseases and microbiology in the Graduate School of Public Health and professor of pathology in the School of Medicine, started tracking the health of gay men in Pittsburgh in 1984. The study remains a gold mine for AIDS researchers. Rinaldo's group now focuses on AIDS in its midlife as a pandemic—studying the long-term effects of AIDS drugs and the relationship between HIV and cancer.

It was with samples from Rinaldo's study that John Mellors, chief of the Division of Infectious Diseases and director of UPMC's HIV/AIDS Program, discovered one of the field's best diagnostics—the viral load test.

An HIV vaccine has proved elusive, so Mellors, like many researchers, is focused on prevention. He's looking for new antiretrovirals to treat and prevent HIV-1 infection.

AIDS researchers now face a foe perhaps bigger than the disease itself: the notion that we have the luxury of time to deal with this killer. *—RRF*



Peter Safar's arena was where human lives teeter on the edge.

Death

For a time, Peter Safar cheated death, as we noted in the first issue of this magazine ("Time of Death: Postponed," October 1999). One could make the argument that he cheats it still. His life's work was resuscitation, and his arena was where human lives teeter on the edge—the accident scene, the battlefield, the ambulance, the operating theater, and intensive care. He was a Pitt Distinguished Service Professor and founder of its critical care medicine program. In the wider world, he was hailed as "the father of CPR." To his colleagues at the University of Pittsburgh, he was a dear friend and a mentor without peer.

Safar died in 2003 at age 79, but his legacy thrives. A cadre of Pitt scientists and physicians have carried his research forward. Now his CPR legacy may soon be eclipsed by one of therapeutic hypothermia—chilling patients to save their brain function and their lives.

In 2003, the American Heart Association recommended mild hypothermia for ventricular fibrillation cardiac arrest. Many medical centers have yet to adapt, but Pitt-affiliated hospitals now use hypothermia in about 85 percent of eligible cardiac arrest cases. The data show clear benefit in brain function after recovery. The data are even stronger for the use of hypothermia in newborns with birth asphyxia. All of this stems from decades of hypothermia research conducted at Pitt.

Mild hypothermia is exciting, but deep hypothermia seems downright futuristic. Imagine a high-speed collision in which a person suffers trauma to the chest. Paramedics administer blood and saline, but everything simply leaks out of a tear in the pulmonary artery. Blood pressure plummets, and cardiac arrest ensues. Any trauma surgeon can tell you that this is a lost cause; there simply isn't enough time. To slow the clock, associate professor of surgery and critical care medicine Samuel Tisherman (MD '85, Res '93, Fel '91 & '94) is proceeding with the first clinical trial of emergency preservation and resuscitation (EPR).

Medical personnel will deliver an ice-cold flush of saline through the aorta. It will course through the circulatory system. It will leak out in this case, too—but that doesn't matter, because the patient will be chilled to below 60 degrees Fahrenheit in less than 20 minutes. He'll be left with no heartbeat and no brain activity. A surgeon will repair the injury while the patient has no pulse. Theoretically, this could go on as long as an hour or two. You can bet, however, that the surgeons will try to finish the procedure in closer to 30 minutes. Despite the reams of laboratory evidence and anecdotal "fell through the ice and survived" stories suggesting this will work, nobody likes a patient without a pulse.

Then doctors will gradually rewarm the patient with fluids and the heart should start beating again. Safar himself, who worked to make EPR happen, reportedly described it to a visitor to his laboratory this way:

"He's dead now, but he'll be fine in a few hours." *—CS*