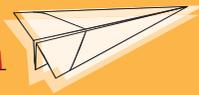


UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | WINTER 2008/9

# PITTMED

*Air*

BREATHLESS SMOTHERED BY SEVERE ASTHMA



**WARM UP WITH US**  
 In mid-February, baseball fans know that Florida Grapefruit League action is nigh. Alumni and friends of the schools of the health sciences also should think of Florida for another kind of spring training. In Naples, they can come together to learn from all-star researchers about what's new and exciting in science and medicine at Pitt.

Reserve your seats for **WINTER ACADEMY**.  
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We gladly receive letters (which we may edit for length, style, and clarity).

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**RECENT MAGAZINE HONORS**

IABC Golden Triangle Award of Honor Magazines

IABC Golden Triangle Award of Honor Magazine Design (E. Cerri)

IABC Golden Triangle Award of Honor Feature Writing (E. Vitone, "What Possessed You?" Fall 2007)

CASE Circle of Excellence Gold, Covers (Winter 2007/8)

CASE Circle of Excellence Bronze, Special Interest Magazines

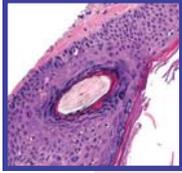
CASE District II Accolades Gold, Magazines

Carnegie Science Center Journalism Award Honorable Mention (J. Miksch)

Pittsburgh Black Media Federation Robert L. Vann Media Award, Photography Honorable Mention (C. Mesa)

# PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, WINTER 2008·9 (NOV/DEC/JAN)  
VOL. 10, ISSUE 4



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## CONTRIBUTORS

Photographer and designer **STEPH HOOTON** [Cover, "Closing the Loop"] cofounded Pictogram Studio in 1988. She says the past 20 years have represented a long-running opportunity to help solve problems—in the case of this issue, how to represent a respiratory ailment through photography.

Her solution? Shooting signs found at gas stations and other locations.

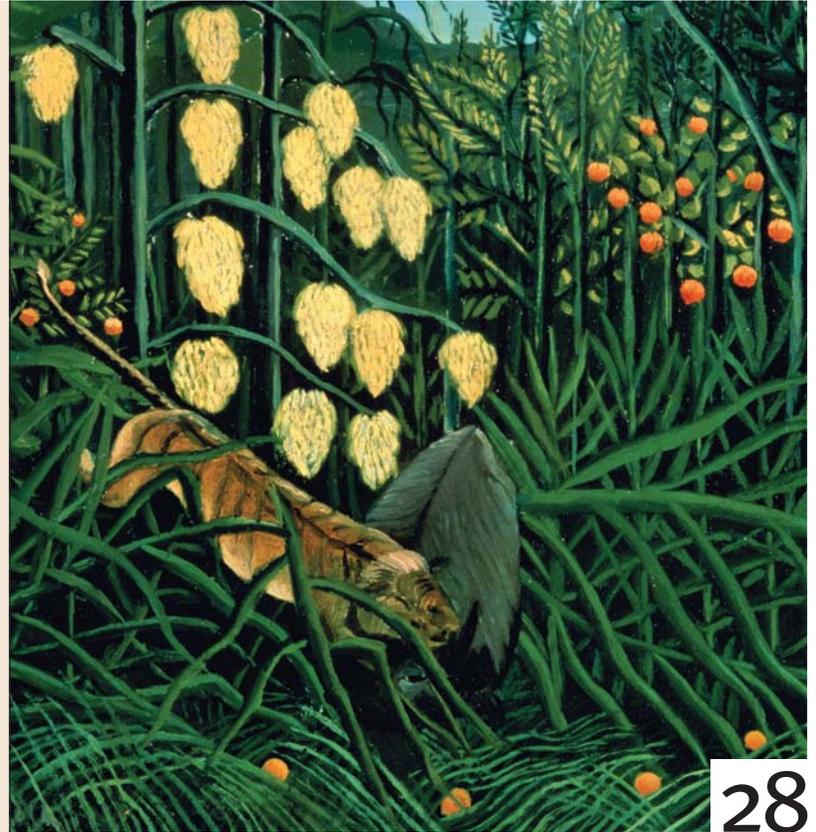
"I thought [the signs] had a lot of character and had a certain quiet power," Hooton says. "There was a lot of power in the story and the way it was written. I wanted powerful images, but I didn't want the images to be literal."

Hooton, a Carnegie Mellon University graduate, lives and works in Maryland. Her other clients have included the National Institutes of Health, Nordstrom, Mobil, and the Jimmy Carter Presidential Library.

While pursuing a master's degree in creative nonfiction writing at the University of Pittsburgh, **ELAINE VITONE** ["A List of Possibilities Yeh Long," and "A Matter of Some Urgency"] wrote about homelessness, including her experiences in Texas, where she edited a newspaper for the homeless. Nowadays, her personal essays explore the finer points of home ownership; she and her husband are fixing up an 85-year-old brick house in the East End of Pittsburgh. She recently wrote about a shelter for disabled dogs in Maryland for *Ladies Home Journal*.

## COVER

Severe asthma can take your breath away. (Cover by Steph Hooton/ Pictogram Studio © 2008.)



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Steven Little's lab crafts synthetic dendrites and Trojan horse drug-delivery systems inspired by nature.

IMAGE ESSAY BY THE LITTLE LABS AND JOE MIKSCH

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A severe asthma attack can feel like inhaling through a straw. Pitt scientists circle from man to mouse and back again to ease each breath.

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W. Chet de Groat has discovered much of what we know about a critical organ system.

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### Nightmares, Past and Future 28

As a callow trainee, Pitt grad Frank Vertosick had the confidence of Achilles. It took a Vietnam veteran to teach the young neurosurgeon humility.

BY FRANK VERTOSICK JR.

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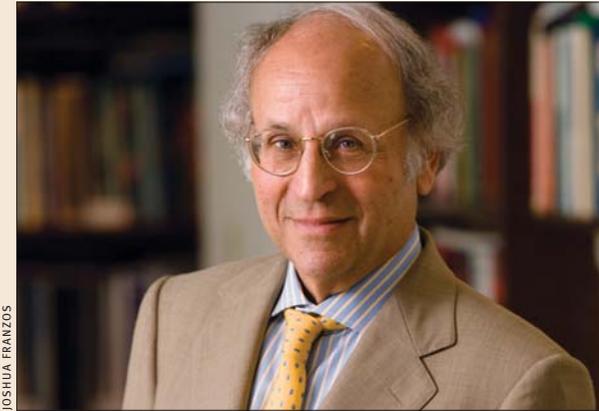
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**T**raditional scientific method has always been, at the very best, 20/20 hindsight. It's good for seeing where you've been. It's good for testing the truth of what you think you know, but it can't tell you where you ought to go.

— Robert Pirsig, *Zen and the Art of Motorcycle Maintenance: An Inquiry Into Values*



JOSHUA FRANZOS

As I write, presidential politics dominate the nightly news. Reflecting on the rhetoric embedded in the headlines, I've been struck by the contrast between public discourse in the political arena compared with the standards that govern the world of science. In the latter, we cultivate respect for dissent and count on the *scientific method*, robust investigation, and peer review to adjudicate competing claims.

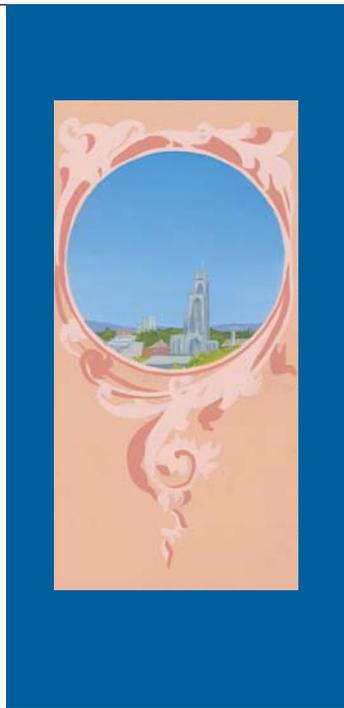
The *scientific method* may not generate easy sound bites or proceed at the pace of the 24-hour news cycle, but it does yield rigorous, intellectually keen, and often profound insights. That understanding is absolutely critical to informing public policy. In fact, Pirsig had it only half right: The *scientific method* is, by necessity, descriptive and thus confined to hindsight. But that doesn't render it irrelevant to the future.

This fall, Dr. Ronald Herberman, director of the University of Pittsburgh Cancer Institute, testified before a subcommittee of the U.S. House of Representatives Committee on Oversight and Government Reform. The subcommittee had invited Dr. Herberman to discuss his concerns about the possible relationship between extensive cell phone use and brain tumors. In particular, he suggests that we don't understand the long-term implications of low-scale electromagnetic radiation on the relatively thin skull and fast-growing architecture of a child's brain. While a few small studies suggest a link between long-term and extensive cell phone use and certain brain tumors, other equally small studies fail to show such a risk. The National Cancer Institute and the American Cancer Society have dismissed Dr. Herberman's concerns as unsupported by currently available data. Moreover, we lack an established biologic theory that would predict such a cause-and-effect link.

Ultimately, more studies are needed—population-based, long-term analyses based on hard data—just what Dr. Herberman recommended: "I cannot tell this committee that cell phones are dangerous, but I certainly can't tell you they are safe. We urgently need to do a study."

On its face, Dr. Herberman's statement applies to any observation in nature, but the scientist's urge to further study, clarify, and interpret doesn't always mesh with the politician's demand for unequivocal, actionable conclusions or the public's desire for easily digested and metabolized certainties. Few of us embrace ambiguity; yet as scientists we often confront the challenge of when and how to communicate uncertainty and how to articulate the questions that often linger when a research project concludes. How then should the scientific and clinical communities balance the public demand for conclusiveness and transparency with our concern for oversimplifying, publicizing, and prematurely resolving the ambiguity often inherent in complex and still inchoate scientific findings? In fact, determining on which side to stand in this balance is the art of science, and, for scientists, there is no "bailout."

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



*Devoted to noteworthy happenings  
at the medical school*

## We Have a Winner

In 2004, transplant surgeon and scientist Thomas Starzl became the first investigator with a primary appointment at the University of Pittsburgh School of Medicine to earn the National Medal of Science, the highest honor bestowed upon scientists by the federal government.

In late August, Bert O'Malley (BS '53, MD '63) became the first School of Medicine grad to make the list.

O'Malley is chair of molecular and cellular biology at the Baylor College of Medicine in Houston. As Starzl is often called the father of transplantation, O'Malley can lay claim to the title "father of molecular endocrinology." His work has uncovered new insights into the function of hormones in normal development and disease states.

O'Malley says he was a bit surprised when told he'd be visiting the White House in September to receive the National Medal: "One never expects this type of honor in one's career, so my initial reaction was that they might have the wrong person." —*Joe Miksch*



**O'Malley receives the National Medal of Science—and a handshake—  
from President Bush.**

## FOOTNOTE

Fearlessness is key for a life spent on stage. But so is caring for your voice. Hence, the Healthy High School Musical workshop. Featuring experts from Pitt's Department of Otolaryngology's Voice Center, the eight-hour workshop gave high school theater students and teachers insight into how the vocal folds work, approaching singing when sick, and then some. Didn't seem to give anyone jitters though. "Is anyone else afraid to sing a high C?" a workshop instructor asked the roomful of teens. No hands rose.

## UP IN SMOKE

Teens, next time someone offers you a joint, remember this: Epidemiological studies suggest a link between heavy marijuana use by adolescents and later development of schizophrenia.

Recent studies by David Lewis, an MD and the UPMC Endowed Professor in Translational Neuroscience in the University of Pittsburgh School of Medicine, suggest a mechanism for the link. Schizophrenia is associated with impairments in the brain's ability to synthesize GABA, a neurotransmitter that is vital for cognitive processes such as working memory.

The brains of people with schizophrenia compensate for GABA deficiency by decreasing the presence of a cannabinoid receptor (CB1R). When CB1R is highly active, it impairs GABA signaling. Marijuana use activates CB1R; the increased activity, in turn, worsens schizophrenia symptoms and boosts the chances of developing the disease among those predisposed to it.

On the plus side, Lewis says, "The findings provide some rationale for a novel drug that ... may increase functionality in people with schizophrenia." —*JM*



CAMI MESA

## A&Q

### Mentoring Evolves

Joan Lakoski doesn't deal in romance—but, professionally, she is something of a matchmaker.

The PhD associate vice chancellor for academic career development and professor of pharmacology and chemical biology undertakes the vital work of helping link med students with faculty mentors and junior faculty with senior faculty mentors. She also builds relationships among the many other permutations of mentor and mentee in the University of Pittsburgh School of Medicine.

Mentoring, she says, helps advance careers, build collegial relationships, enhance faculty recruitment, and reduce the stresses of academic life. "Mentoring is a vehicle for ensuring that we have a culture that tries to utilize everyone's strengths," she says.

#### On the growth of mentoring

We're moving into, as you know, team science. ... These relationships are expanding and growing. Also, careers require tremendous flexibility and resiliency so that you can manage the stresses. Mentoring has really moved from being informally acknowledged to being a formal component of what we do in order to meet the need for better supporting everyone.

#### On the golden rules of the pairing

It's a relationship that has to be built on trust and mutual respect, and both the mentee and the mentor need to provide a safe environment where they can freely exchange ideas. Confidentiality, trust, and mutual respect are, to me, the golden rules.

#### On the endgame

Mentoring not only positions the mentee to get a task done—a research project, a manuscript, an R01 [grant]—but also gives us that collegial support we need that affirms us in terms of our inspirations for ourselves, our vision, and encourages us to take risks. ... To me, that's where the exciting parts of science are, where we're seeing these innovations in clinical and translational research. They're at these boundaries.

#### Her question for us

What are the characteristics of the individual who gave you mentoring advice at a time when it made an impact that still, after all these years, you cherish? —JM

## Next Generation

Late in life, it's not unusual to be diagnosed with high blood pressure or arthritis, but an increasing number of older people are also contracting HIV. Keith Stowell (Res '08), the 2008 recipient of the American College of Psychiatrists' Laughlin Fellowship, sees a number of such patients in his geriatric psychiatry fellowship. In his five years at Western Psychiatric Institute and Clinic, Stowell has seen patients in their 60s who were diagnosed with HIV 20 years ago and others who received their diagnosis 20 days ago. Caring for geriatric patients with HIV or substance abuse disorders interests Stowell because of the wide range of general health problems to be considered in their psychiatric treatment. The field is challenging—soon to be more so as baby boomers age—but Stowell aspires to learn more about the geriatric population through his own work and from his interactions with mentors.

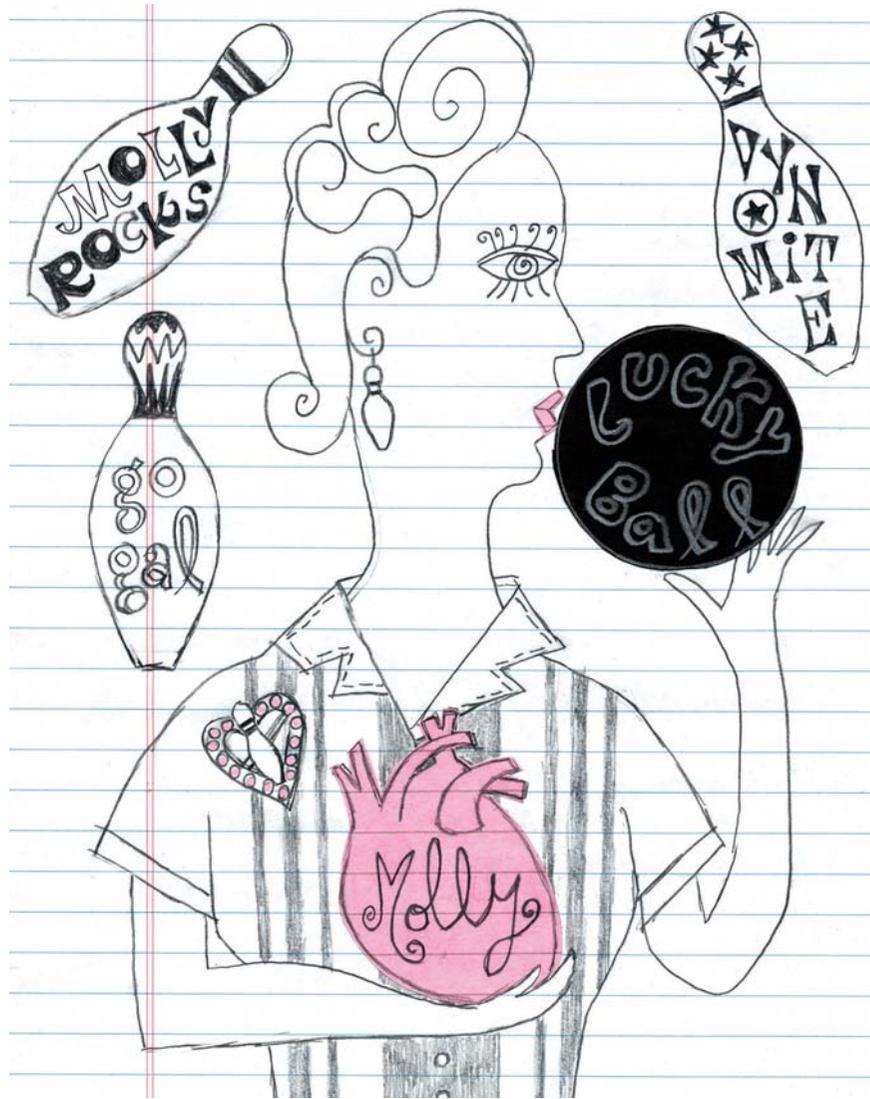
**P53 does to mutated DNA what television action hero Jack Bauer does to terrorists.** The little protein *Science* dubbed "Molecule of the Year" in 1993 identifies mutations and stops them in their tracks—either repairing their sinister deviations or, if they can't be rehabbed, sending them to their deaths. For years, scientists have known of p53's potential as a tumor suppressor protein but have struggled to use it to its fullest; half of all cancers have mutations in p53 and the other half have functioning p53 that is inhibited by other variables. Drew Dudgeon, a pharmacology and chemical biology postdoctoral fellow, received the 2007 Hartwell Fellowship for scientists in the early stages of their biomedical research careers. Together with his mentor, Allegheny Foundation Professor of Pharmacology and Chemical Biology John Lazo, he is screening compounds that may assist p53 in its mission of tumor suppression. The Hartwell Fellowship will provide Dudgeon with \$100,000 throughout two years for research on p53 enhancement for treatment of childhood leukemia. —Hayley Grgurich

## Heart and Soul

When Angeline “Kula” Goughnour awoke after her heart transplant, she found her husband at her side. “You know you rejected it, right?” he asked her. “Yeah, but don’t worry. She won’t give us any more trouble,” Goughnour said. In a few days, it was clear she was right—and the heart came through in more ways than one. After the surgery, she began “talkin’ Southern,” and a new, more forthright side of her personality emerged. Goughnour, a Pennsylvania native, attributed the changes to her new heart—a gift from a 36-year-old woman from Atlanta. “I named her Molly,” she said. “She just feels like a Molly.”

Three weeks shy of the three-year anniversary of her transplant, Kula attended her first Transplant Games at the David Lawrence Convention Center in Pittsburgh as one of 124 local athletes. She competed in the bowling event and, with other conventioners, collected ornamental pins from each of the 32 international teams represented.

A few months after her convalescence, Goughnour wrote to “Molly’s” family, thanking them for her heart. Inside the convention center, her eyes scanned the room. This summer she’d hoped to finally meet Molly’s family at the Games, but understood if it would be too hard for them. “When my dad died in 1986 we donated his corneas,” Goughnour said. “They were transplanted into a blind person, and now she can see. My mom never followed up and contacted the recipient, but after this, I think I will. He had the prettiest blue eyes,” she said smiling. “I could probably pick them out.” —HG



CATHERINE LAZURE

## YOUNG PROFS GET A LEG UP

Being a physician-scientist can be a hard row to hoe. The clinic demands time; so does the lab. And the typical physician-scientist doesn’t get her first major National Institutes of Health grant until she is 43.

Yvonne Chan and Allan Tsung (Res ’08), both 35, are a bit ahead of the game, thanks to the Howard Hughes Medical Institute. The two are among 19 recipients of the HHMI’s Physician-Scientist Early Career Award. Each will receive \$375,000 over five years.

Chan, an MD assistant professor of medicine in the Division of Pulmonary, Allergy, and Critical Care Medicine, will study the immune response to chronic lung infections and its role in the permanent damage associated with obstructive lung diseases.

Tsung, an MD assistant professor of surgery in the transplantation and surgical oncology divisions, will study a signaling molecule called HMGB1 released by injured liver cells.

“I want to have a career in both research and clinical practice,” Tsung says. “This [grant] will help me get started with my basic research.”

It will likely yield other career benefits, as well.

“It doesn’t hurt to have the prestige of an HHMI investigator,” says Chan. —JM

## Doc, May I Have This Dance?

Nearly 5,500 aspiring physicians wanted to be part of the School of Medicine’s class of 2012—just 149 matriculated. Of them, it’s a pretty reasonable guess that only one danced professionally with the *Bill T. Jones/Arnie Zane Dance Company* in New York.

That would be Gaetan Pettigrew, whose mother, Margaret Larkins-Pettigrew (MD ’94, Res ’98), is a Pitt assistant professor of obstetrics and member of the *Pitt Med* editorial advisory board. His father, Chenits Pettigrew, is Pitt’s assistant dean for student affairs and director of diversity programs.

Gaetan Pettigrew is in interesting company. His classmate Alex Singleton is a retired cop. While working in California, he saw the damage that life on the streets can do to young people. Singleton took off his badge and enrolled in a graduate program in psychology. Doing field work, he found that some kids needed psychiatric intervention but had trouble finding psychiatrists interested in taking up the challenge. After talking with his adviser, he decided *he’d* do it.

“So, that’s how I got into medicine,” he said.

Fellow first-year Ajeet Singh Mehta earned his bachelor’s degree from Pitt and was admitted to the School of Medicine under a program that guarantees a spot for stellar high school students who acquit themselves admirably as Pitt undergrads. So did Amar Singh Mehta.

They’re twins. —JM



## SMALL WORLD

For decades, pathologists have relied on microscopes to reveal clues to diagnoses, investing long hours hunched over the lens. But that's about to change. Omnyx, a joint venture between the University of Pittsburgh Medical Center and GE Healthcare, will launch such laborious endeavors into the digital age.

By taking millions of individual snapshots and stitching them together in a single data set, Omnyx's Automated Digital Pathology Imager transforms a glass slide into a zoomable digital image in about a minute. A pathologist can then use the computer screen just like a microscope. The technology allows doctors to use computer-assisted diagnostics for detailed tasks and enables multiple pathologists in disparate locations to access the same file in real time, ultimately providing faster and more accurate analyses.

This digitized panoramic view of a human skin sample (left) shows a hair follicle as well as all layers of the skin necessary for making a diagnostic evaluation.

—Sara Goudarzi

## Appointments

**Bennett Van Houten** joins the School of Medicine as the Richard M. Cyert Professor of Molecular Oncology in the Department of Pharmacology and Chemical Biology. He also will direct the University of Pittsburgh Cancer Institute's Molecular and Cell Biology Program.

Van Houten arrived in early September from the National Institute of Environmental Health Sciences, where he held joint appointments in both the intramural and extramural programs. He is an expert in the mechanisms of DNA damage and repair.

Van Houten, who is a five-time National Institutes of Health Award of Merit winner and an NIH Director's Award recipient, says he had been itching to get back into academia. "The opportunity to be part of a strong and vibrant group that studies genome stability and to be given the resources to allow this group to continue to grow over the next five years is a dream come true."

Another recent arrival is **Guillermo Calero**, an MD/PhD who joins the School of Medicine as an assistant professor of structural biology. Calero served as a postdoctoral fellow with 2006 chemistry Nobel laureate Roger Kornberg at Stanford University and made significant contributions to Kornberg's prizewinning studies of the

process by which genetic information from DNA is copied to RNA.

Calero images very large molecular and macromolecular structures, such as transcription complexes. He uses X-ray crystallographic techniques in his imaging work.

**Mark Gladwin** comes to the University of Pittsburgh as a professor of medicine, chief of the Division of Pulmonary Medicine, and director of the Hemostasis and Vascular Biology Research Institute.

Gladwin, an MD, previously worked at the NIH. His research interest lies in nitrites and how they and other molecules control blood flow and vascular function.

"This is one of the best-funded pulmonary divisions in the country," Gladwin says. "And I'm increasingly convinced it's one of the strongest and most diverse pulmonary divisions in the country, and that's what leveraged me out of the NIH."

The newly created Hemostasis and Vascular Biology Research Institute will study disorders of the blood and blood vessels. It was created with grants from the Institute for Transfusion Medicine and the Hemophilia Center of Western Pennsylvania. —JM



Calero



Gladwin



Van Houten



## THE EYES HAVE IT

There's a nondescript brick house at 54 S. 9th St. on Pittsburgh's South Side. On a warm evening late in August, the guerillas invaded. Armed with tens of thousands of dollars in mobile ophthalmology equipment—including the famed “Better one? Or better two?” machine (that device docs use to check your vision when you're peering at the A-C-G-M-Z, etc., eye chart)—they went about their work, providing free vision care to the city's underserved.

Patients—some Spanish-speaking undocumented workers, some residents of the neighboring Salvation Army shelter, and some working poor—were whisked to the second floor of the building, the Birmingham Free Clinic. There they were tested for cataracts and glaucoma and given eyeglass prescriptions—filled for free—by a half-dozen medical students and ophthalmology residents. (The clinic has multiple health-related uses and is staffed by a rotating cadre of volunteers.)

The three-year-old project, called the Guerilla Eye Service, is

funded by foundation grants and the University of Pittsburgh Medical Center, which donated the van that hauls the team's gear. Evan “Jake” Waxman, an MD assistant professor of ophthalmology and director of the department's residency program, heads the team. He loves the service aspect of what he calls “missions,” as well as what the program does for students and residents who participate.

“Taking care of people who otherwise wouldn't get eye care is very important,” he says. He also says it's important for med students and residents to get involved in community outreach.

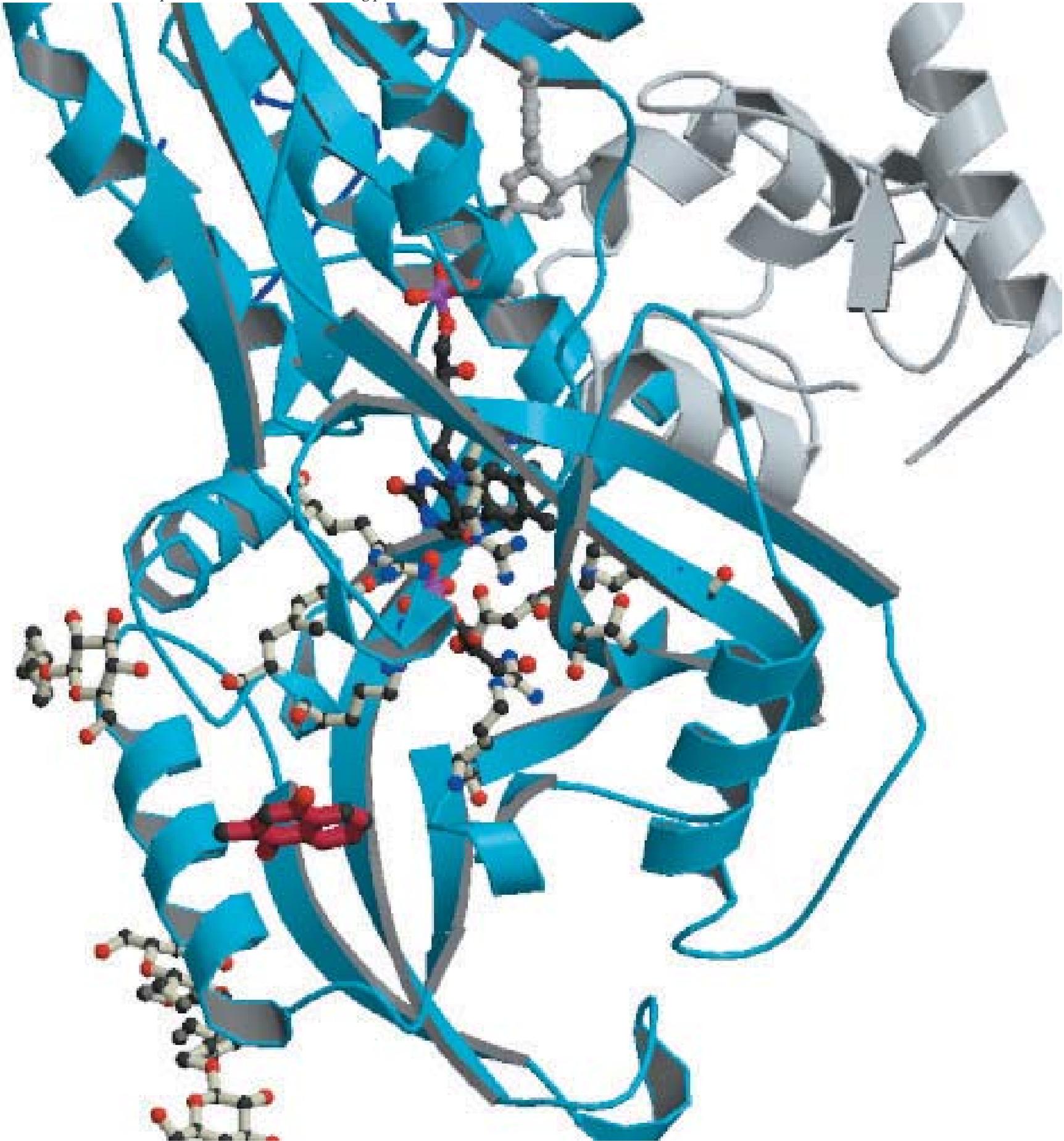
The guerillas also visit sites in Sewickley, Greene County, and Squirrel Hill, seeing close to 700 patients each year. It's a time-consuming project. But, says third-year resident Tim Marra, Waxman meets the challenge with joy.

“He works harder than anyone I have known,” Marra says. “It takes a very special person to do this.”

—Joe Miksch  
—Photo by Jim Judkis

## INVESTIGATIONS

*Explorations and revelations taking place in the medical school*



# A LIST OF POSSIBILITIES

# YEH LONG

## A MISSING LINK IN CHRONIC ILLNESS

BY ELAINE VITONE

In recent years, researchers have begun to find one common denominator in a growing list of chronic diseases: glycerol metabolism. Studies suggest that this process, an intermediate stage in the metabolism of carbohydrates and lipids, can play a part in everything from diabetes and obesity to infectious diseases and even aging.

Unfortunately, our understanding of the precise structure and function of some of the key players in glycerol metabolism falls short. In particular, monotopic proteins—proteins that are partially embedded on the membranes of cells but do not reach all the way down to the interior of cells—pose a challenge. Isolating and studying these macromolecules in their active, normal state—suspended in the semisolid environment of a membrane—is no easy task.

But last year, Associate Professor of Structural Biology Joanne Yeh established the first complete, three-dimensional structure of an enzyme that's common to all living things, and that's crucial to glycerol metabolism—Sn-glycerol-3-phosphate dehydrogenase, or GlpD, for short. The results of the study, which she completed with Research Assistant Professor Shoucheng Du and Research Associate Unmesh Chinte, made GlpD one of only a handful of monotopic-protein structures that have been determined to date.

“I think glycerol metabolism will be on the forefront of developing treatments for these diseases, and so many others,” Yeh says,

**The first complete, 3-D structure of the Sn-glycerol-3-phosphate dehydrogenase (GlpD), an enzyme that's common to all living things and that's crucial to glycerol metabolism.**

“since it is a pivotal yet underappreciated link among some very important metabolic pathways.”

Yeh's team completed their study in three months—far faster than usual—thanks to processes Yeh has fine-tuned over several years. In 2005, she published a paper in *Biochemistry* on novel peptide-based detergents—“peptergents,” as she calls them—that she developed to keep enzymes up and running outside of the membrane and to crystallize them.

Yeh specializes in X-ray crystallography, a technique in which a crystal scatters a beam of X-rays into many smaller ones. The angles and intensities of the beams are used to create a three-dimensional picture of the atoms and their bonds within the crystal.

Most of the study was completed in Pitt's X-ray crystallography facility, which Yeh directs. However, to obtain the best quality data, the team also used a cyclic particle accelerator, or synchrotron, at Argonne National Laboratory in Illinois and another synchrotron at Paul Scherrer Institute in Switzerland. Because time at such specialized facilities is so precious, Yeh's team labored together in Chicago around the clock. In Switzerland, Yeh put in 48 consecutive hours, all solo.

“It's very focused work,” she says, recalling the blur of exhaustion.

Finally, Yeh's team ran their data through advanced computations. After several months, the three-dimensional structure of GlpD emerged, down to the last atom. To make triple-sure their results were solid, Yeh's team solved the structures of GlpD in various states of producing a molecule that is important for cellular energy and fat production. The additional effort gave breadth and depth to their

understanding of GlpD's interaction with the membrane as well as its role in processes related to metabolism and energy production.

In March, Yeh's findings were published in *Proceedings of the National Academy of Sciences*. The paper also won an “Exceptional” rating on Faculty of 1000 Biology, a Web site in which top science faculty across the country highlight noteworthy publications. The rating was the cherry on top for Yeh. “It's really a nice validation of the significance of our findings and recognizes our research results as relevant to not only the structural biology community, but also other scientific disciplines,” she says.

Now, Yeh's lab is teaming up with MDs to make structural studies of human enzymes—specifically, those implicated in cardiac arrest and in metabolic diseases. She's leaving the possibilities wide open, though. After all, the list of opportunities is, well, Yeh long. ■

## NANO NANO

**In October 2007, the journal *Nanomedicine* published Yeh's two-part review of recent developments in nanobiosensors, super-small probes that utilize both biological and electronic features. “Integrating precise atomic, 3-D structure information can harness the innate specificity and sensitivity of biological systems,” she says. “By utilizing structural information, we have produced ultrasensitive biosensors that can be used in medical diagnostic applications. Our goal is to detect abnormalities in cells much earlier than what is currently possible.” —EV**

# PUTTING THEM BACK TOGETHER AGAIN

SCIENTISTS AIM TO MAKE WOUNDED SOLDIERS WHOLE | BY REID R. FRAZIER

Three years ago, Colonel Bob Vandre, then head of the army's Combat Casualty Care Research Program, was in St. Petersburg, Fla., for a U.S. Department of Defense conference on trauma care. Combat casualty care is a “bench to battlefield” discipline, concerned with making medical advances that can have an immediate impact on healing wounded soldiers. Vandre, an imaging physicist and dentist, had helped to create a handheld dental X-ray machine that comes in a padded, waterproof carrying case. He'd been talking with scientists in regenerative medicine and had even collaborated on research with the Pittsburgh Tissue Engineering Initiative, but he was cautious regarding the field's immediate prospects. “I thought it was all tissue cultures, and maybe 50 years from now we'd be able to do something with it.”

Body armor, shorter evacuation times, and improved battlefield medicine have saved thousands of injured U.S. troops in Iraq and Afghanistan. But they come home missing limbs. They are burned, scarred, and otherwise disfigured. The injured-to-killed ratio in all American wars, from the Revolution to Gulf War I, was 2.5 to 1. In Afghanistan and Iraq, that number is around 9 to 1.

So Vandre's jaw nearly hit the floor when he heard a talk at the Florida conference about recent advances in regenerative medicine, particularly lab-grown, transplantable human bladders. The field was much closer to helping wounded soldiers than Vandre had imagined. “This [treatment] isn't 50 years from now,” he remembers thinking. “It's now.”

Vandre spent two years drumming up support in Washington. He pulled together \$42.5 million to fund the newly minted Armed

Forces Institute of Regenerative Medicine, or AFIRM (It's supposed to be pronounced “affirm,” but everyone calls it “A-Firm,” Vandre says.) The White House promptly doubled the budget. And the Pentagon funded two consortiums—one led by the Pitt-UPMC McGowan Institute for Regenerative Medicine with Wake Forest University Baptist Medical Center—to pursue therapies of interest to the military.

The research tackles a wide range of regenerative medicine applications: soft tissue patches cultivated from pig bladders, a cement paste that regrows bone, hand transplantation, a nerve starter tube seeded with stem cells. Many of the therapies mimic processes already found in nature, says Alan Russell, director of the McGowan Institute and a University Professor of Surgery. “The salamander can regrow its heart—if you cut part of the heart out, it will regrow. Why does it happen in a salamander and not in a human—and could it?” says Russell, co-director of the Pitt-Wake Forest consortium.

“People ask, ‘How can you grow a new limb?’ Well, we did it once before—we did it in the womb. If we can understand a lot more about the biological signals that happened then and happen in animals like salamanders and newts, we can begin the process of creating these kinds of therapies.”

To that end, Professor of Surgery Stephen Badylak aims to regrow limbs and digits with biomaterials extracted from pig bladders. The tissue is washed of all cells, leaving behind the extracellular matrix—a honeycomb-like scaffold that attracts stem cells. Badylak hopes army medics can one day suture the material to a severe wound—a shattered arm, a sheared leg—to spur tissue growth and prevent amputation. The key, Badylak says, is getting the



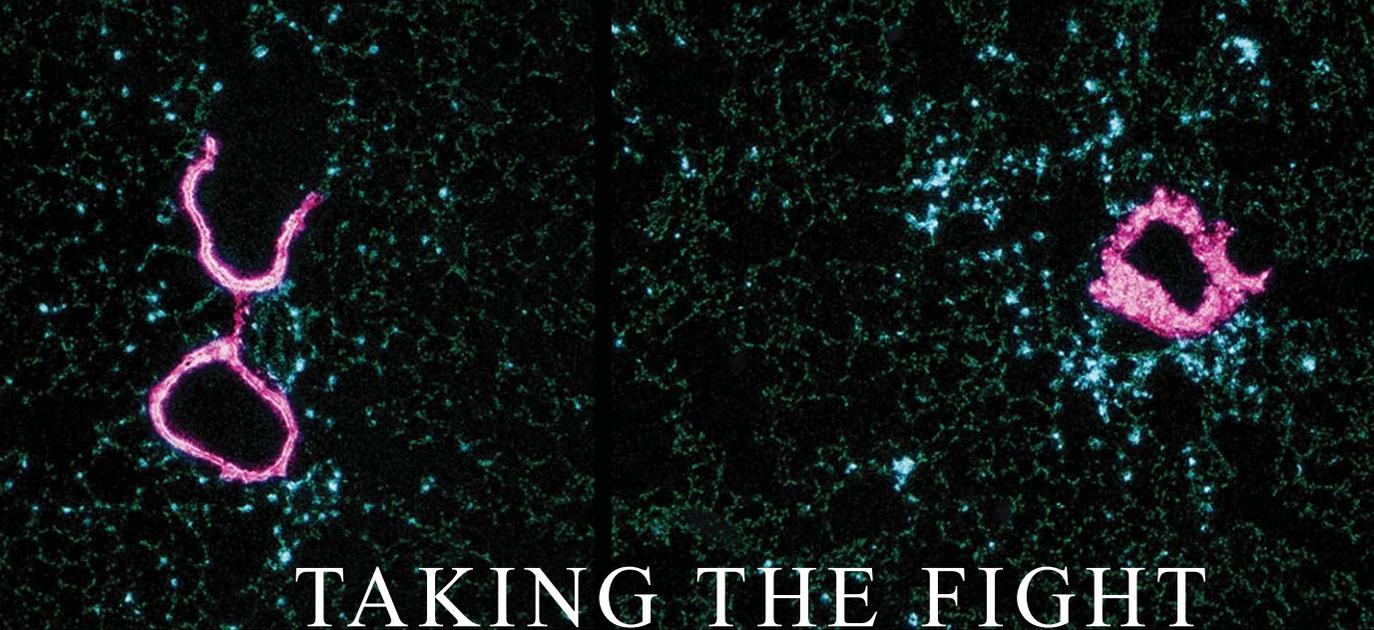
Speedy transport of injured soldiers has drastically increased survival rates in modern warfare, increasing demand for effective wound-healing technology.

signaling right. Normally, cells around a wound tell each other to scar. “We're trying to get the tissue to think, ‘I'm not injured, I just need to grow more tissue.’”

There are more than a dozen other projects at Pitt. Kacey Marra, a polymer chemist and assistant professor of surgery, is working on a tube that will train severed nerves to regrow. A craniofacial team involving Charles Sfeir, Prashant Kumta, and Elia Beniash from Pitt's School of Dental Medicine is exploring a calcium phosphate powder that can be mixed with any liquid—water, saline, even blood—and daubed onto an exposed wound to regrow bone. The substance would behave a lot like Plaster of Paris and could even be applied with a finger. William Wagner, a professor of surgery, is studying a biocompatible patch to treat compartment syndrome, caused when injury-induced inflammation—say, in biceps shredded by shrapnel—causes enough pressure that blood vessels constrict and the tissue dies. Surgical incisions release the pressure. Wagner's patch, seeded with stem cells or special growth proteins, can be sewn directly onto the incised compartment and stimulate regrowth.

It all sounds ambitious, but that's the point, says Badylak, who likens AFIRM to the Manhattan Project or the Apollo missions. “This is not just an incremental advance in a particular disease problem,” he says. “This is true tissue regeneration, replicating what you do as a fetus. Everything we've been taught ever since we started going to school is that human beings cannot regenerate limbs—it's a fact. So the first thing we've got to do is to get over that mindset.” ■

COURTESY U.S. ARMY



IL-22 regulates genes that help make antimicrobial proteins, key to fighting bacterial pneumonia, in airway epithelia. Here, we see two such genes, in pink, after being enhanced with IL-22 treatment.

# TAKING THE FIGHT

# TO PNEUMONIA

A NOVEL TREATMENT EMERGES FROM  
A NEW CELL LINE | BY JOE MIKSCH

**W**orldwide, pneumonia kills more than 2 million children annually. Nothing kills more kids—not even AIDS and malaria combined.

In 2007, Jay Kolls, the Neils K. Jerne Professor of Pediatrics and Immunology in the University of Pittsburgh School of Medicine, discovered a protein target that may lead to therapies to treat bacterial pneumonia and play a vital role in creating a vaccine to prevent the disease.

Kolls, an MD and chief of the Division of Pediatric Pulmonary Medicine, Allergy, and Immunology at Children's Hospital of Pittsburgh of UPMC, says that the first step on the path toward rendering pneumonia impotent came in 1993 with the discovery of interleukin-17 (IL-17A), which is produced by a novel line of cells called T Helper Type 17 (Th17).

"It was found that [IL-17A] regulated neutrophil responses, and we knew that neutrophils [a type of white blood cell that devours pathogens] were critical for host defense against certain types of pneumonia," Kolls says.

This discovery gave birth to the idea that the Th17 pathway could be important to the immune system's defense of cells under assault from the bacteria that cause pneumonia.

Th17 produces a handful of cytokines—proteins that communicate with immune

cells, telling them to go out and take the fight to invading pathogens. IL-17A is involved in regulating neutrophil growth and recruitment, calling the cells into the lung from their perch in blood vessels nearby and, if necessary, ordering up more from the bone marrow.

"A neutrophil only lives eight to 10 hours, so when the lung sustains an infection that lasts longer than that, a signal is sent to the marrow saying, 'I need more troops,'" Kolls says.

Another of these Th17-related cytokines, interleukin-22 (IL-22), was of particular interest to Kolls—its production ramped up concurrently with IL-17A but appeared to serve a slightly different purpose. In 2006, Kolls read a study showing that IL-22 regulates antimicrobial peptides in the skin. The scientist wondered whether IL-22 did the same thing, immunity-wise, in other organs, particularly the lung.

The answer was yes. Examining the immune systems of mice infected with *Mycobacterium tuberculosis*, Kolls found that IL-22 activates a gene called lypocalin-2, which increases the population of antimicrobial peptides that attack invading bacteria. Many bacteria, including *M. tuberculosis*, scavenge iron from the body in order to survive.

"What lypocalin does is actually steal the iron back from the bacteria," Kolls says. "It's not effective against all bacteria, but it's certainly effective against this one."

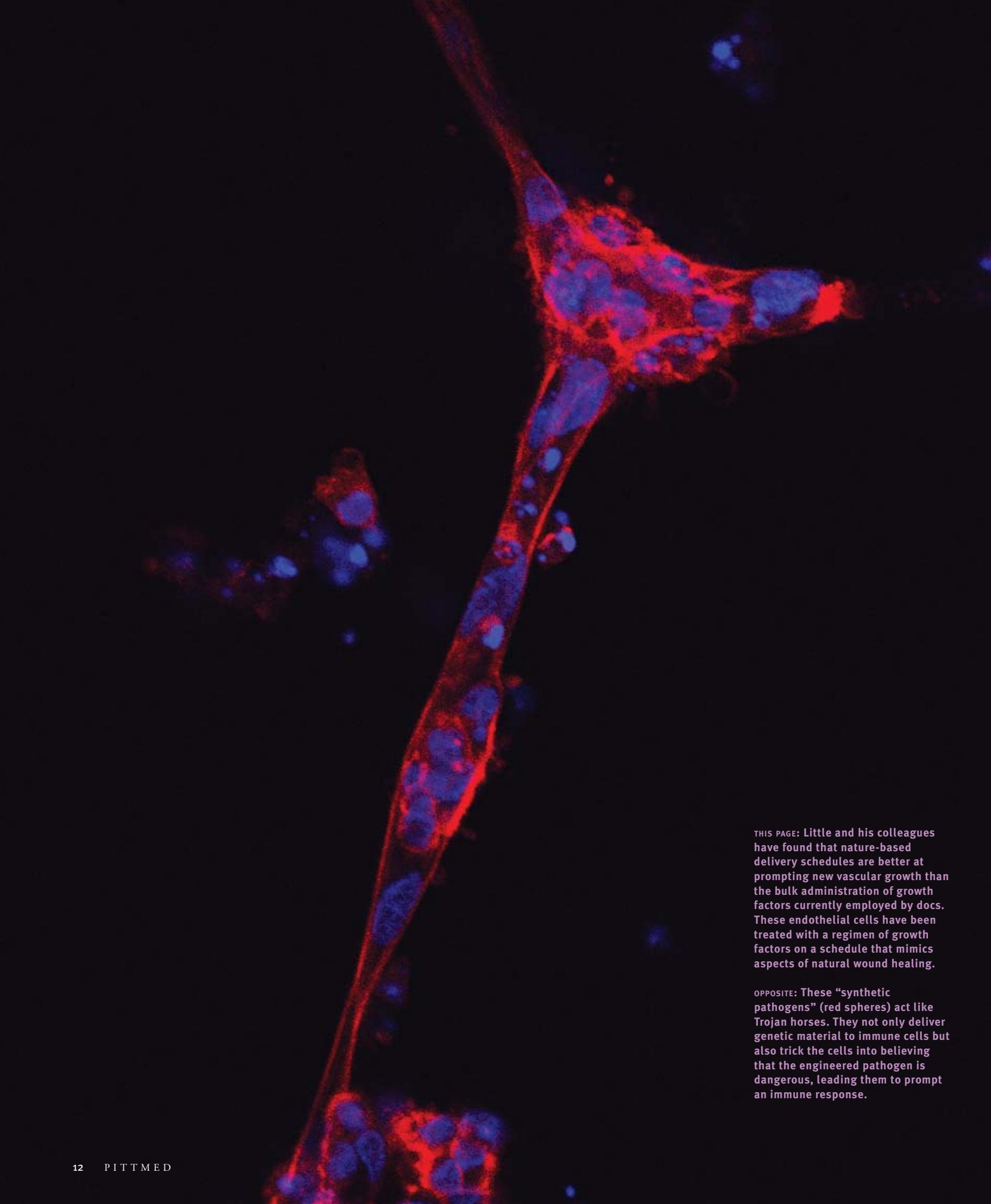
"[IL-17A and IL-22] don't have completely overlapping worlds, but they do both have roles in regulating immunity in the lung," Kolls notes. IL-22's world, though it works in synergy with IL-17A's, might be a bit more important. Mice deficient in IL-17A succumbed to infection in about 48 hours. Those deficient in IL-22 "had trouble within as early as 24 hours," Kolls says.

By increasing the level of IL-22 in the mice's lung tissue, Kolls was able to cure the rodents. More IL-22, Kolls found, meant that there were more iron-stealing proteins and progressively more resilient lung epithelial cells, which could better handle the insults and injuries caused by the pneumonia bacteria.

Kolls says he thinks the process will work the same way in humans. Doses of recombinant IL-22 could be used as a prophylactic treatment against tuberculosis, he says, priming the immune system for a fight.

It will be as much as a decade before IL-22-related therapies are approved to treat or prevent tuberculosis in people, but Kolls' work presages a treatment more effective than antibiotics that comes without the risk of creating antibiotic resistance.

"We could use it as a prophylactic regimen; it could be used as a vaccine," Kolls says. "There's a 5- to 10-year timeline before this could probably happen, but we've learned a lot, and we're making progress." ■



**THIS PAGE:** Little and his colleagues have found that nature-based delivery schedules are better at prompting new vascular growth than the bulk administration of growth factors currently employed by docs. These endothelial cells have been treated with a regimen of growth factors on a schedule that mimics aspects of natural wound healing.

**OPPOSITE:** These “synthetic pathogens” (red spheres) act like Trojan horses. They not only deliver genetic material to immune cells but also trick the cells into believing that the engineered pathogen is dangerous, leading them to prompt an immune response.

IN THE NASCENT FIELD OF BIOMIMETICS,  
THE LAB TAKES INSPIRATION FROM NATURE  
IMAGES | LABORATORIES OF STEVEN LITTLE  
TEXT | JOE MIKSCH

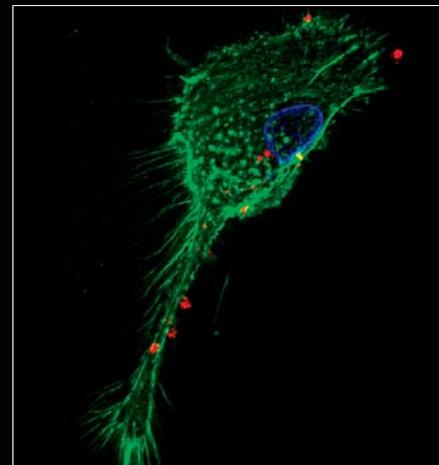
# WHEN MEDICINE IMITATES LIFE

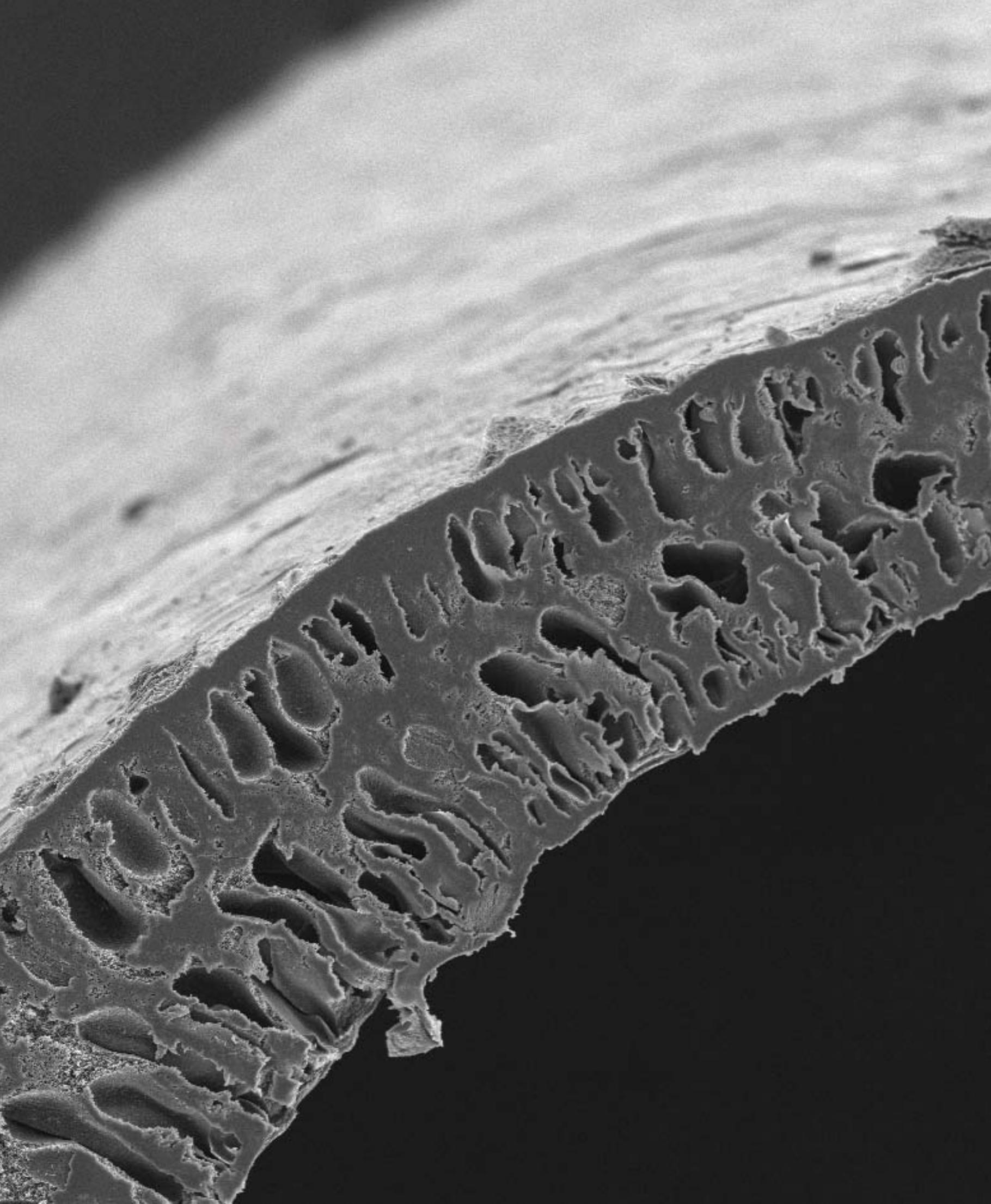
Steven Little, a PhD assistant professor of chemical engineering, bioengineering, and immunology at the University of Pittsburgh, is something of a puppeteer. He doesn't make wooden marionettes dance around a small stage like creatures of flesh and blood, yet he has managed to manipulate what's manmade so it behaves as though it's part of nature.

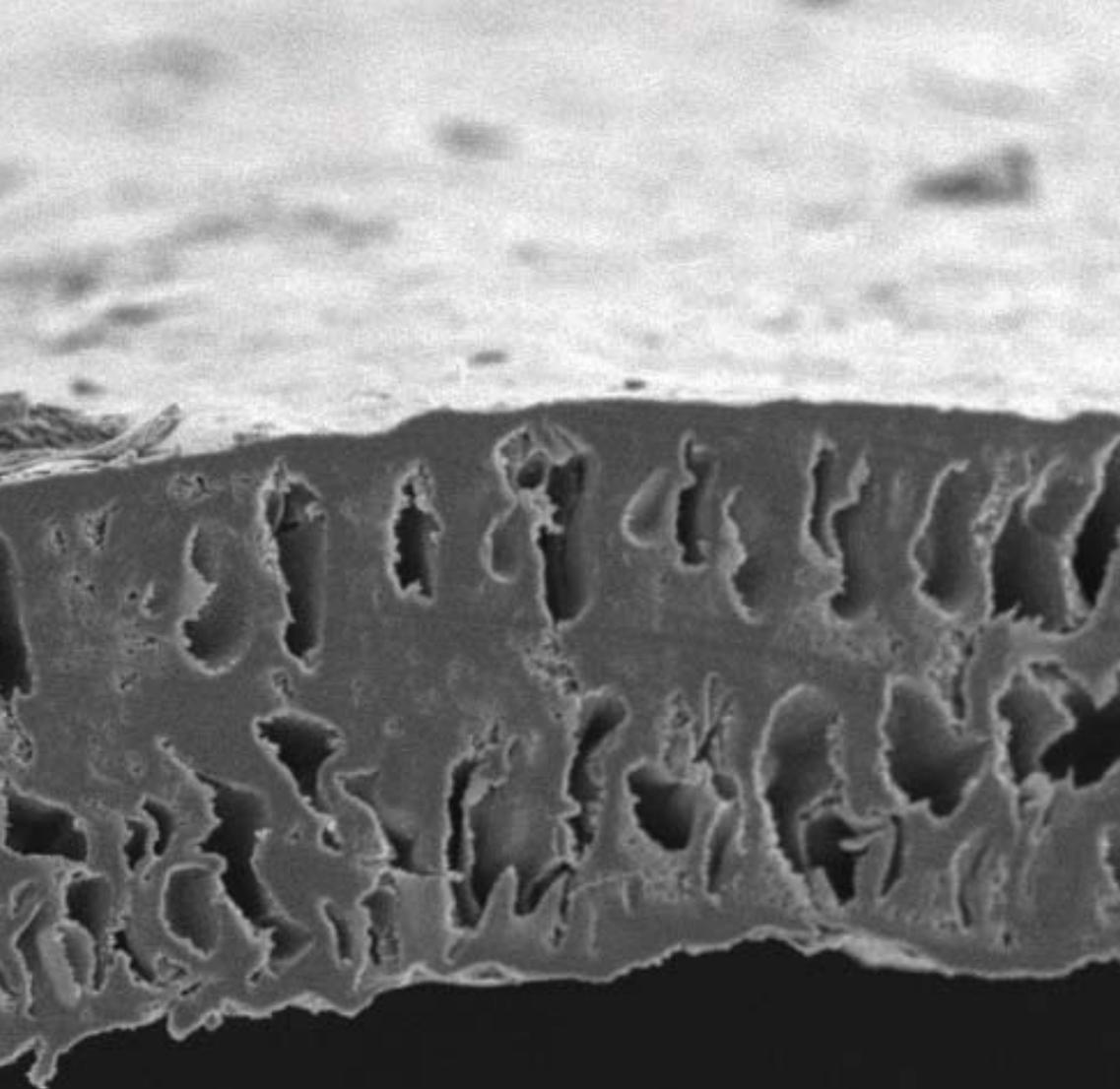
Little is a biomimetician.

Biomimetics, as the word suggests, is the science of making something synthetic act like something that's alive. Little's work represents the melding of myriad disciplines, from immunology to tissue engineering to basic biology. His lab seeks ways to make synthetic cells do the bidding of doctors.

Little and his colleagues have a lot of strings to pull. You have to know how nature works to imitate it successfully. And you have to have the engineering chops necessary to take the lessons nature gives you to create artificial entities that perform like—and maybe even better than—biological ones.

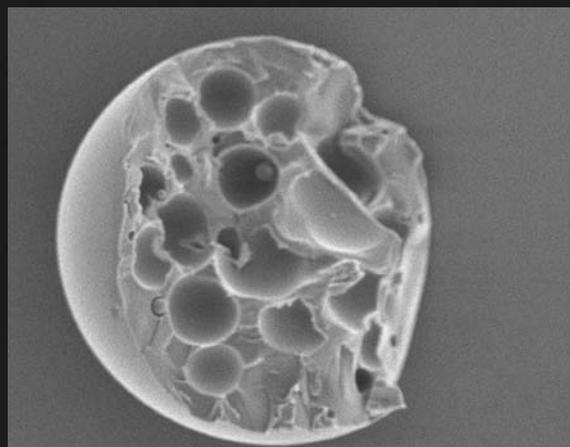




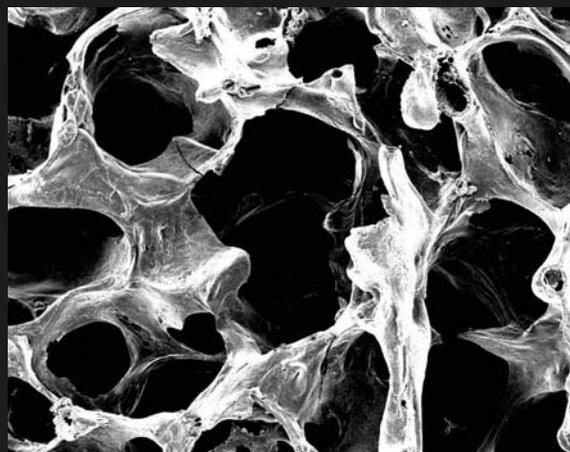


**ABOVE:** A cross section of tiny, porous, hollow fibers fashioned from various inert, man-made materials. Little's group is working toward making networks of these fibers to deliver nutrients, oxygen, and growth factors to wounds.

**RIGHT:** This particle was designed to deliver aqueous drugs, which don't always dissolve simultaneously with the polymer that delivers them. During fabrication Little's lab created "pockets" in the micron-size particles to encapsulate and release the drug. These particles were intentionally frozen at -320 degrees Fahrenheit and cracked open to reveal the interior pockets.



**LOWER RIGHT:** A scanning electron micrograph of a tissue-engineering scaffold made from biodegradable, synthetic polymers. Little's lab is screening massive libraries of materials to choose those that endow biological activity to the surface with the end goal of generating more expedient tissue growth.



Researchers in the Little labs want to accelerate wound healing by using synthetic vasculature to deliver growth factors. (They believe the key is to deliver the factors on a specific order and on a strict schedule.) When the job is done and the wound is healed, Little says, the synthetic system can be dissolved using a fluid containing enzymes.

Another project in the lab seeks to create artificial and biodegradable, yet bioactive, scaffolding to encourage tissue growth.

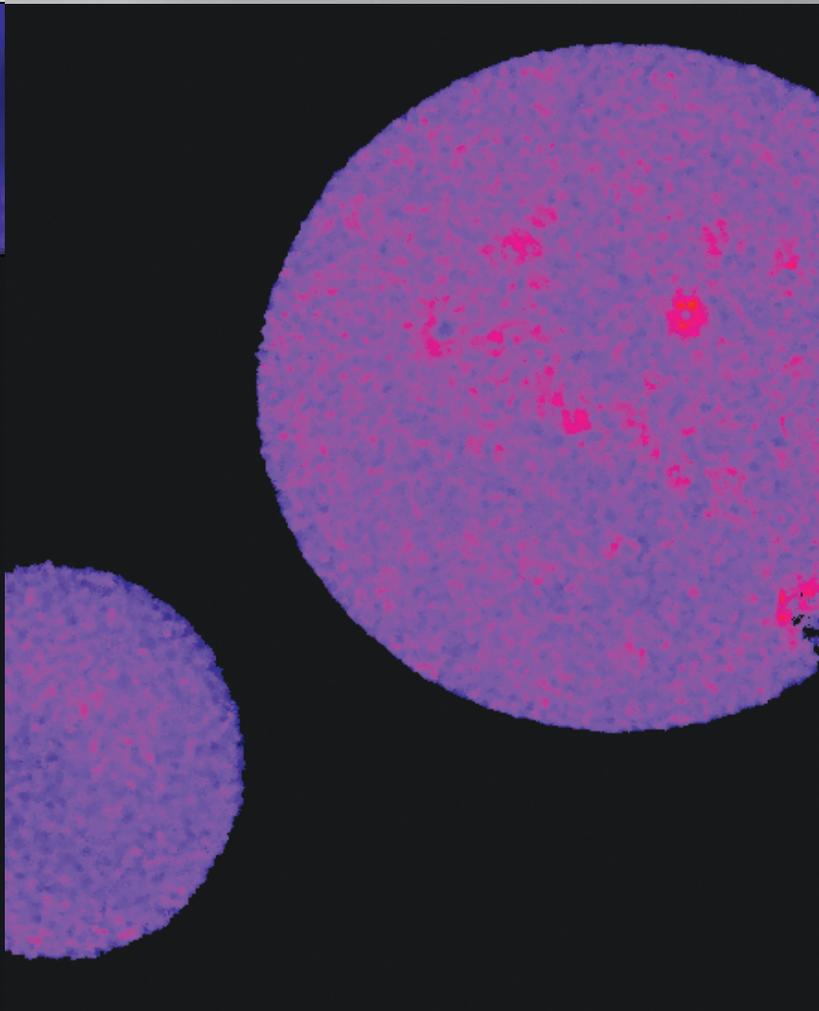
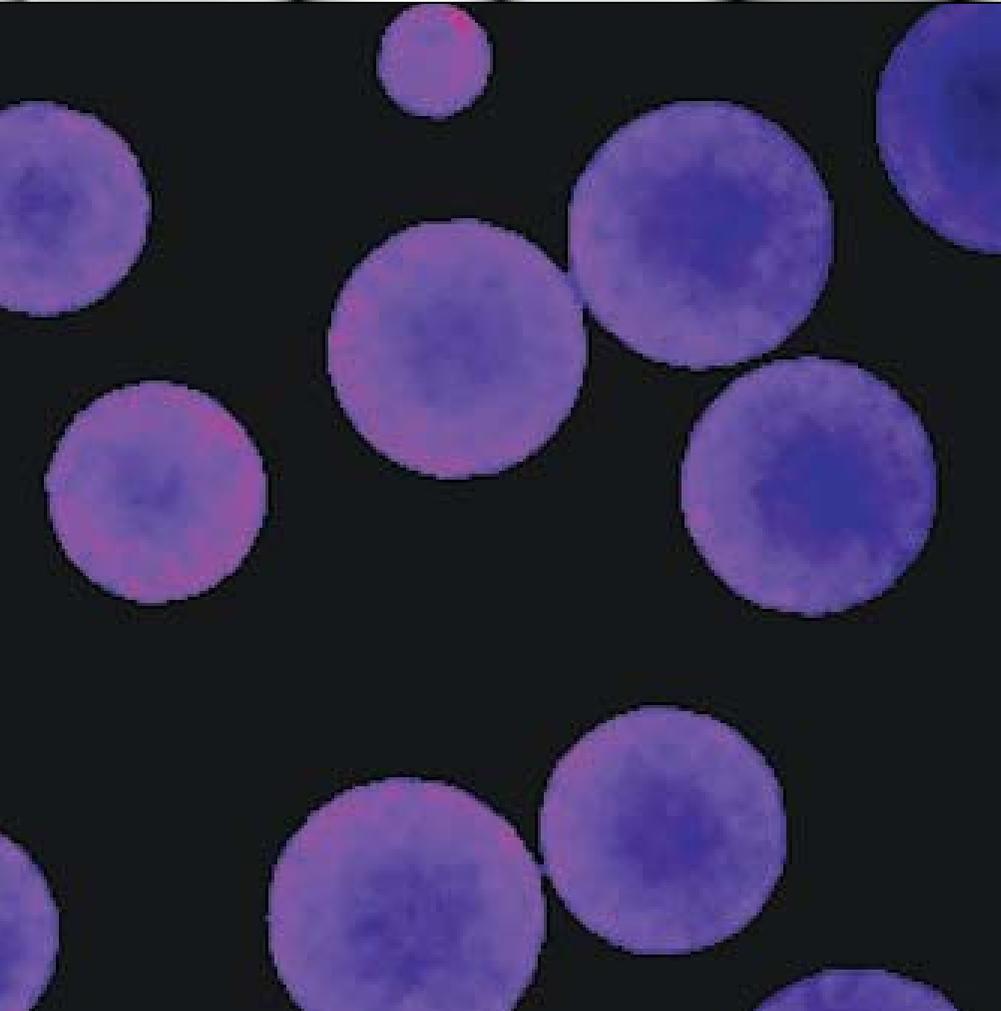
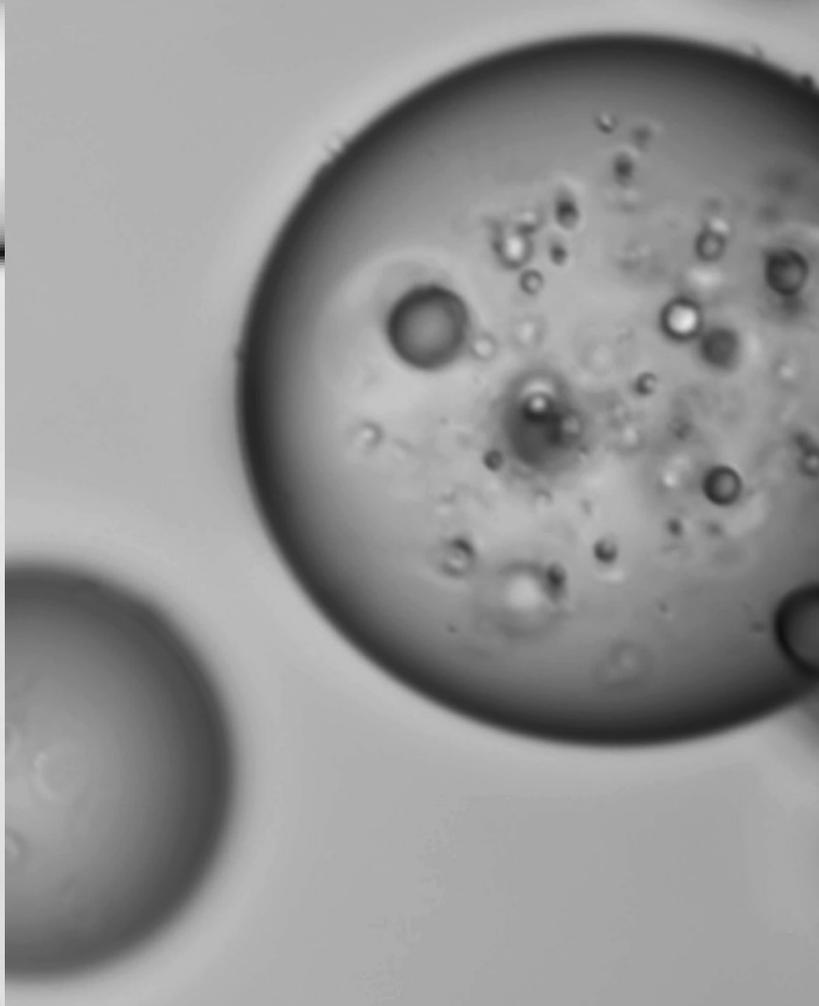
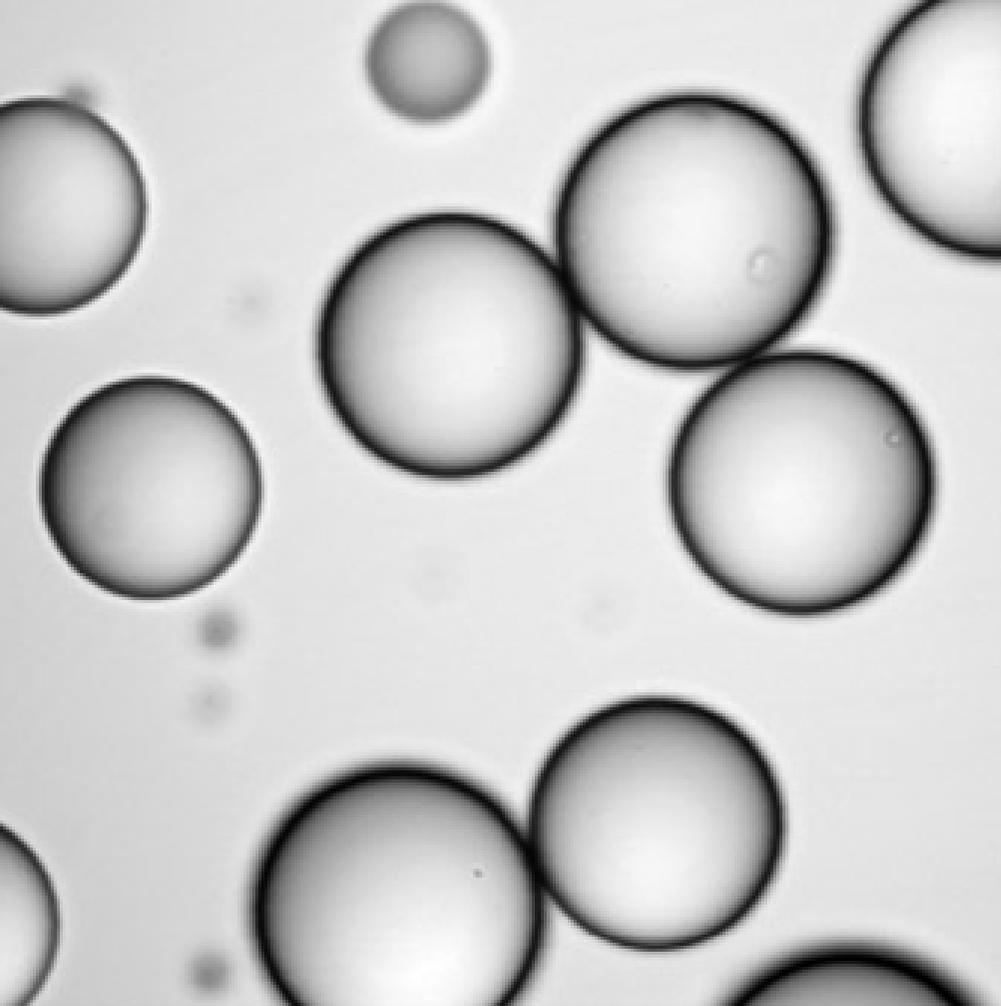
They've also used synthetic pathogens to facilitate delivery of genetic material to immune cells by tricking these cells into thinking they've met a dangerous invader.

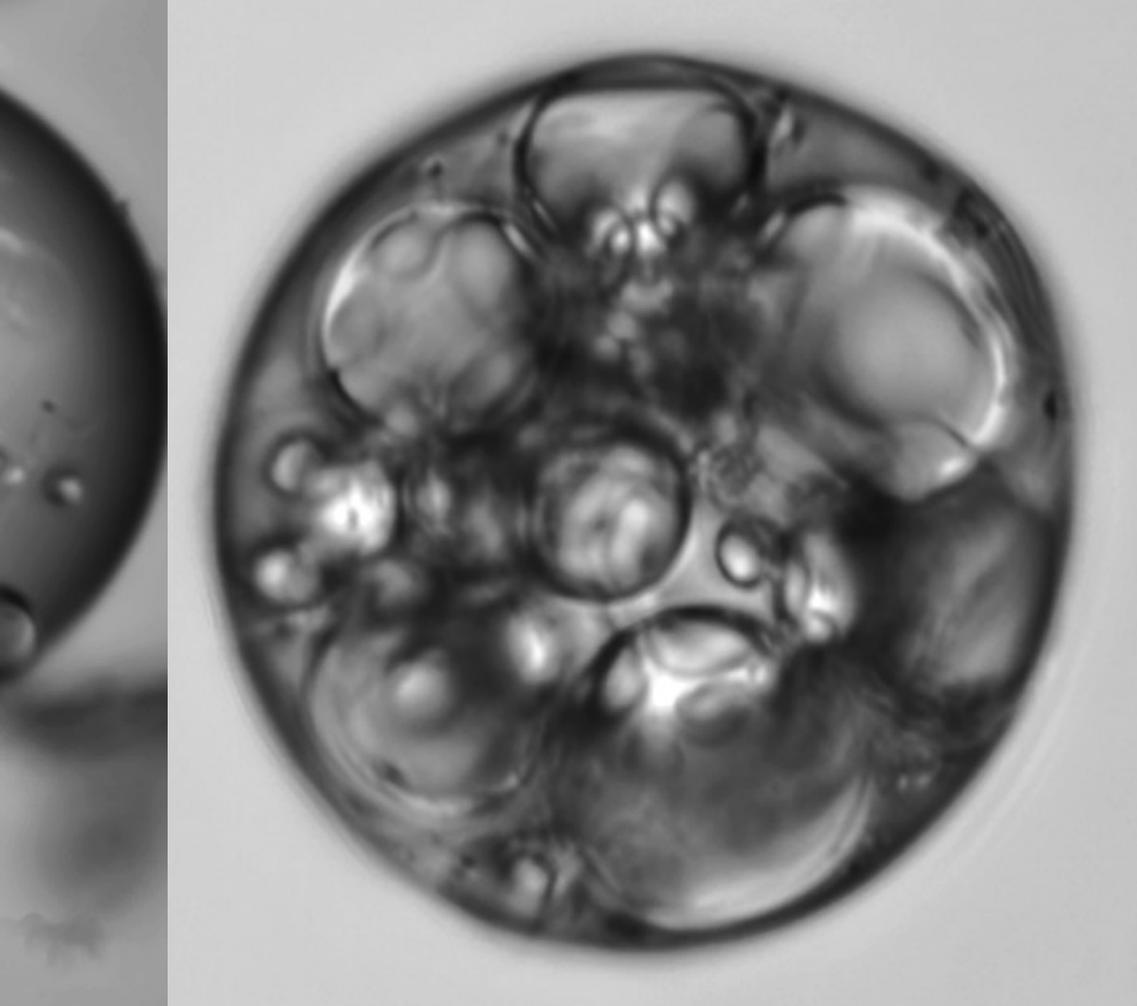
A significant portion of the Little lab's work relates to immunology. In 2007, the Massachusetts Institute of Technology-trained PhD nailed down a few grants to fund research into the development of a "smart" artificial dendritic cell. Not that our immune system's antigen presenters aren't MENSA-eligible in their own right—Little calls dendritic cells "almost sentient"—but he's been able to engineer a homogenous and essentially inexhaustible supply of antigen-presenting cells that can spur or limit an immune response more efficiently than their natural cousins.

The whys and wherefores remain a bit of a mystery, Little concedes, though it's clear that the order and manner in which dendritic cells—natural or engineered—send their chemical signals to T cells affect immune response.

"What I'm talking about is that you have one part of the process and you've got another part of the process. Depending on the way these are oriented or presented, you can get an entirely different immune response," says Little of the chemical signals cells use to communicate.

Researchers in his group are also working to find a way to more accurately target immunosuppressant agents, such as those used to help transplant patients fight off rejection. Immunosuppressant regimens can themselves be highly toxic, but Little thinks it's possible to engineer a drug-delivery particle that will present an immunosuppressant drug to dendritic cells only. Getting the drug directly to the dendritic cell rather than broadcasting it systemwide would allow for lower dosages, thereby reducing or eliminating toxic side effects.





In a somewhat related realm, Little and his collaborators are in the process of making drug delivery vehicles that can be custom-crafted to release a specific drug over a particular time course.

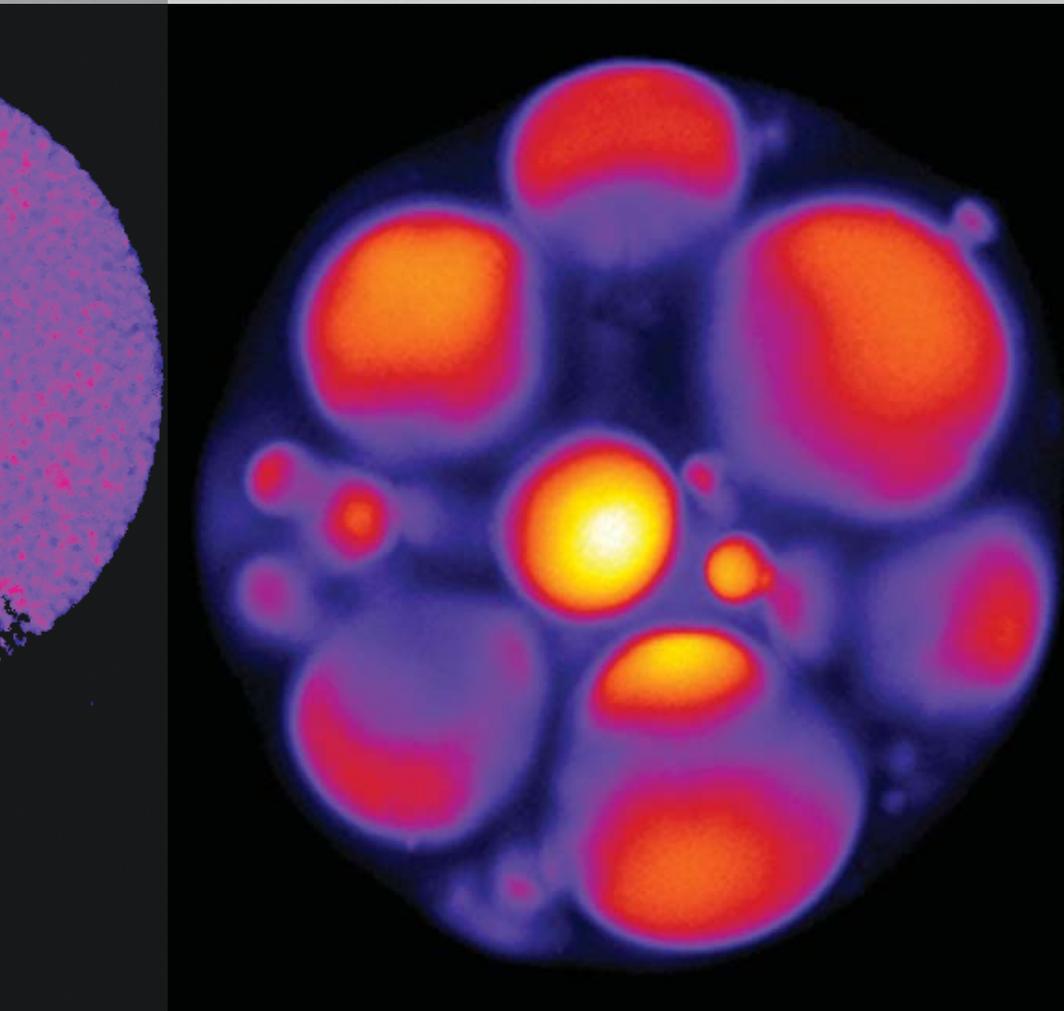
They also are investigating a strategy for summoning cells through the controlled release of chemokines. That is, instead of aiming a delivery vehicle at a cell, the group hopes to use the chemokines to call the targeted cell to a signaling source. Several biological entities use this approach to communicate or signal for help in healing wounds or fighting infection. In this instance, the chemokine may serve as more than a signal—it could potentially lead to a unique biological response. Little says that this approach exemplifies a basic biomimetics principle: Cells are smart enough to know that the context in which a signal is presented is part of the signal itself.

Little says he and his colleagues are at the beginning of what may become a new discipline. This excites him. “Biomimetics is tremendously new,” he says. “We are definitely pushing the limits of what chemical engineers do and what bioengineers do.

“That’s what makes me so excited about it,” he says. “It just looks at this stage to be limitless in what we might be able to accomplish.” ■

**FOR MORE INFORMATION:**  
[www.littlelab.pitt.edu](http://www.littlelab.pitt.edu)

**OPPOSITE:** Little’s group requires an extremely high level of control over the rates and phases of “drug” release from their delivery vehicles in order to simulate biological communication. In these images, Little’s lab has reinforced a hypothetical particle erosion mechanism that is used in mathematical models to predict release of drugs and to rationally design biomimetic delivery systems.



AIK

FROM THE CLINIC TO THE LAB AND BACK AGAIN,  
HARD WORK YIELDS FRESH INSIGHTS

BY CHUCK STARESINIC

# CLOSING THE LOOP ON ASTHMA

Sally Wenzel will never forget the patient who felt he had to ask her, his 28-year-old physician, whether it was okay for him to go fishing on the Chesapeake Bay. He was her elder—a nice man who worked maintenance on a college campus in Virginia. His name was unforgettable because he shared it with a celebrity—we'll call him Ray Charles. His problem was asthma, and he had it bad.

We all take some things for granted. For most people, breathing is one of them. No matter what happens in the course of a day—good day, bad day, sick day, birthday—one expects to move air in and out of one's lungs without even thinking about it. Those who live with severe asthma think about it every day.

Severe asthma is not the same as the mild condition that sent Pittsburgh Steelers halfback Jerome Bettis to the sideline for his inhaler so that he could get back on the field for the fourth quarter. For Charles, an attack felt like he was suddenly breathing through a too-small straw or even a coffee stirrer—an accurate approximation of what happens during an attack.

PHOTOGRAPHY | STEPH HOOTON/PICTOGRAM STUDIO



The bronchial passages constrict and limit the airflow both in and out of the lungs. A bad attack could come on quickly—and without prompt medical attention, it would asphyxiate him.

Nevertheless, fishing on the Chesapeake is not the type of activity associated with asthma attacks. It's not exactly strenuous. Asthma triggers like pollen, dust, and other pollutants are rare on the open water. Wenzel, who was then a fellow in pulmonary medicine, knew that her patient had been doing well in the past year. Moreover, she thought it would be a terrible precedent for her to tell this man that he should not go fishing. She believed that an important part of her job was to enable her patients to enjoy a better quality of life.

But the Chesapeake is a big body of water. So Wenzel told Charles to carry his medications and stay relatively close to shore where he could get medical help in a crisis. It was the early 1980s, and inhaled steroids to reduce inflammation in the lungs were still a decade away. Charles' meds were all slower acting oral anti-inflammatories.

"We didn't really understand the whole steroid thing back then," Wenzel says now.

In fact, the field of asthma was littered with unknowns. Nobody—with the possible exception of pathologists who examined lung tissue postmortem—even knew much about what the inside of an asthmatic's lungs looked like. Living asthmatics were in something of a blind spot for pulmonologists.

The reasons are complex. But they start with perspective—asthma was largely seen as an allergic disease, and allergists did not look inside the lungs of their patients. They

pricked the skin and exposed it to pollen, dust, peanuts, and other allergens. They tried to determine what set off their patients' inflammatory responses.

For pulmonologists, severe asthma patients were, at best, a puzzle and, at worst, a compliance problem. If a patient didn't get better, or if he got worse, it was often assumed that he wasn't following doctor's orders. Pulmonologists blamed emotional disturbances—which they were unable to treat—for exacerbating symptoms. (There is evidence that emotions can exacerbate asthma symptoms, but it's far from definitive.)

Wenzel is now a professor of medicine in the University of Pittsburgh School of Medicine and director of the pulmonary division's Asthma and Allergy Center. Her peers say that she has contributed as much to our understanding of severe asthma in the past 20 years as any pulmonologist. But back when she was physician to Ray Charles, she knew as little as everyone else. She recalls pestering her mentors with questions:

"I would go to my faculty members when I was a fellow, and I'd say, 'These people can get so sick so fast. What's happening, and why?' And no one could give me an answer. They'd say, 'Well, there's probably some inflammation, some swelling of the airways, and muscle spasm...' And that was it!

"This is a disease that is the most common respiratory disease in young people," she says now of asthma. "It afflicts up to 10 percent of the people in the country, and all you can tell me is that there is a little inflammation, swelling, and some twitchy airways? That's not a good enough answer! So I developed this little interest in asthma."

Wenzel applied for her first National Institutes of Health (NIH) grant to study asthma at the Medical College of Virginia, which is now Virginia Commonwealth University.

"No one gave me a chance in—excuse me—*hell* of getting it because the Medical College of Virginia, and certainly the pulmonary division, wasn't known as a research powerhouse," she says. "Oh sure, write it,' they said, 'but we don't think you'll get funded. It will be a good exercise.'"

She did get funded, and other residents and fellows began sending asthmatic patients her way. One such patient was Ray Charles. Wenzel got to know him quite well over the course of a year. He told her stories about his wife and three children, and he really seemed to be doing better when he asked her about going fishing with his buddy.

The next Monday at work, she ran into the chief of the pulmonary division. "So, Sally," he said, "was Ray Charles your patient?"

"What do you mean, *was* Ray Charles my patient?" she replied.

Charles had died fishing on the Chesapeake. He had gone a little too far from shore, and he had an asthma attack. His buddy motored him to the eastern shore, which was arguably less medically equipped than the western shore. By the time anyone could attempt to resuscitate him, it was too late.

Wenzel doesn't ascribe magical properties to earthly events. She's a scientist and a pragmatist. Nevertheless, she says that when she heard of Charles' death, "There was something that said, 'You know this is a problem. And you've been given an

opportunity to help figure it out, because it shouldn't have happened.'

"It probably hit home as hard as anything I could have imagined."

**I**nflammation is good, within reason. It is a defense mechanism. It is how we stay alive despite the onslaught of infection and injury. Inflammation protects the body from invasion by foreign organisms, and it helps to repair damaged tissue.

The inflammatory process begins when cells react to an injury or infection by producing chemicals that signal the immune system. This starts a cascade of events. Blood flow to the area increases. White blood cells arrive in large numbers and consume foreign material and injured cells. In a powerful feedback loop, the white blood cells release more and more chemical signals that amplify and perpetuate the inflammatory response. They also produce toxic chemicals such as oxygen radicals, nitric oxide, and enzymes, all of which help to kill invading microorganisms. All of this is good, so long as the process can be switched off and so long as the inflammation is a reaction to a genuine threat.

Lung inflammation occurs as a result of bacterial and viral infections and because of exposure to air pollution and allergens. Inflammation in the lungs, as in any other part of the body, helps to destroy these foreign invaders and irritants.

In asthma, however, inflammation ceases to be a primarily beneficial process. Perhaps it is an overreaction to something in the air that poses no real danger. Perhaps the body fails to dial back the inflammation as it should following an injury, infection, or exposure to allergens. The persistence and extent of the inflammation begin to erode the person's quality of life.

To make matters worse, the lungs of a person who has weathered repeated attacks of severe asthma begin to show permanent structural changes. Doctors call it remodeling. The thin layer of epithelial cells lining a healthy lung thickens. The smooth muscle cells beneath become a bit spastic, and they fail to smoothly expand and contract the bronchial passages with each breath. These are ominous developments—even if doctors were to find an antidote to the inflammation, the structural transformations would remain, resulting in narrower bronchial passages that no longer function properly.

The chemical pathways that lead to inflammation are fascinatingly complex and poorly understood. Environmental triggers are many and they affect each person differently. Depending upon a person's genetic makeup and general health, a dust storm could trigger a life-threatening asthmatic episode, a brief coughing and sneezing fit, or nothing at all. For the most part, scientists don't know why.

For a physician like Wenzel, the questions from the start were: How do we close the loop

on asthma? How do we make the observations in patients that will tell us why one person has a severe asthma attack when another does not? And how do we find a treatment that will help that one patient?

**N**andini Krishnamoorthy (PhD '08) came to the University of Pittsburgh School of Medicine to pursue a PhD in immunology. In the same way that every creative writing student imagines someday having a book reviewed in *The New York Times*, Krishnamoorthy arrived in Pittsburgh in 2004 imagining her research publications someday appearing in a top-notch journal like, say, *Nature Medicine*. In her case, however, it actually happened, and it happened about as quickly as these things are possible.

Krishnamoorthy's doctoral dissertation led directly to a May 2008 *Nature Medicine* paper that identified a molecule in immune cells essential to the sort of faulty immune response that results in asthma and allergies. Theoretically, identifying a molecule that is critical to the chain of events that leaves a person gasping for breath and waiting for an ambulance can lead directly to new drugs and therapies that target this molecule. (It's important to note, however, that the research subjects here are all mice, not humans. More on that later.)

It started like this: Krishnamoorthy had the good fortune to land in the laboratory of Prabir Ray, an associate professor in Pitt's



**An attack felt like he was suddenly breathing through a too-small straw or even a coffee stirrer, which is an accurate approximation of what actually happens during an attack.**

medicine and immunology departments. Ray has a 20-year track record of delving into the cellular and molecular mechanisms of immune response.

In 1997, Anuradha Ray—now a Pitt professor of medicine and immunology, but then at Yale University with husband Prabir—had published vital insights into the mechanisms responsible for creation of the Th2 cells that orchestrate asthma both in mice and in humans. When Krishnamoorthy began looking for a dissertation topic, the Rays encouraged her to explore the molecular mechanisms that induce asthma in the lung. By that time, Anuradha Ray's group had developed a mouse model of Th2 response in the lung. Timothy Oriss, a Pitt research assistant professor of medicine in the group, published their mouse model in the January 2005 issue of *Immunology*. Oriss had exposed mice to some rather typical allergens and toxins—egg white and cholera toxin, in this case. He wasn't interested in cholera or egg allergies, per se; he was interested in the immune response.

Oriss had found that combining the egg white and cholera toxin significantly altered how the mice reacted. Mice exposed to the cocktail produced a great number of white blood cells called myeloid dendritic cells, which locate foreign material and present it to other immune cells to prime them to attack. The presence of these cells was associated with greater inflammation, including lung inflammation. Mice exposed to egg white alone produced larger amounts of a different type of dendrite—plasmacytoid dendritic cells—that is known to curb inflammation. Predictably, these mice had less lung inflammation. Ray suggested that Krishnamoorthy explore exactly how and why cholera toxin produced its effect on dendritic cells.

Krishnamoorthy took up the challenge. She exposed dendritic cells to cholera toxin, then examined a microarray profile of the genes activated by the toxin. The microarray led her to a gene for a molecule called c-Kit, and her dendritic cells produced a lot of it when exposed to cholera. Most people aren't exposed to cholera, however. Krishnamoorthy wondered what would happen if the cells were exposed to an allergen that people do commonly encounter, like house dust mites, a notorious asthma trigger.

"We found the same result," says Krishnamoorthy. "This was when things got exciting."

C-Kit wasn't new to scientists, but it hadn't previously been so directly implicated in asthma and wasn't typically associated with dendritic cells. It is a signaling molecule that triggers other events in biochemical cascades. If it were present in dendritic cells, the team hypothesized, it probably had an important function in the inflammatory chain of events.

Working with a team of colleagues including Prabir Ray, Anuradha Ray, and Oriss, Krishnamoorthy was able to show that in some instances c-Kit was the very first molecule triggered when allergens were present.

This is not the only immune response in which c-Kit is involved. Neither is c-Kit involved in every allergic response. But Krishnamoorthy, who is now a postdoc in Prabir Ray's lab, believes that her findings open a whole new area of investigation for understanding and limiting inflammation in asthma as well as in other diseases.

Here's one simple reason why it could be a long time before a drug that inhibits c-Kit goes into clinical trials for asthma patients: Krishnamoorthy's research subjects are all mice, and all of Sally Wenzel's patients are humans.

Wenzel says that one of her recurring professional frustrations is "knowing that I will probably never have my papers published in *Nature* or *Nature Medicine* or any of the top journals, because I, in my human systems, can't close the loop."

In this sense, closing the loop means having a theory about what a particular molecule or gene does, then running an experiment to support or disprove that theory. In mice, you have a shot at closing the loop in one paper because you can easily test drugs in mice. It's more difficult in humans, for obvious ethical and legal reasons. Scientists can even eliminate whole genes in mice. That's what Krishnamoorthy and her colleagues did, knocking out the c-Kit gene and creating a population that could not produce the molecule. (When they exposed these mice to allergens, the knockouts lacked the vigorous inflammatory response that normal mice exhibit, lending credence to their theory that c-Kit was important to the allergic response. Loop closed. Paper published.)

Despite the obstacles to closing the loop that a human-focused researcher encounters, Wenzel sells herself short when she says that she "thinks" she has contributed to our

understanding of asthma. Back when she was a young doc with her inaugural NIH grant, she was one of the first pulmonologists to investigate asthma using a bronchoscope. It's hard to believe, but until the early 1980s, there were no invasive studies of asthma patients. No one looked at their lungs.

When she started down this path, Wenzel had herself bronchoscope so that she would know exactly what she was asking of her patients. She learned that she could observe an asthma attack in a small section of lung tissue by introducing a tiny bit of allergen through the scope; she would then rinse the area with saline and study what came out in the wash. Over time, she gravitated toward the severe asthma patients, who needed the most help.

As a result of this work, Wenzel was able to point scientists to the importance of one particular immune cell—the neutrophil—in asthma inflammation. No one had ever looked closely enough to find it in the lungs of a person with severe asthma. Their attention had been on other immune cells seen in milder asthma. Wenzel now believes the neutrophil may be involved in a significant number of asthma cases, and this has important implications for treatment.

Wenzel also was one of the first to biopsy the distal lung in severe asthmatics, taking tissue samples from so deep in the organ that the process had to be guided by X-ray. She has now been doing this work for 20 years and her laboratory has a unique database of clinical, physiological, genetic, and pathologic data from more than 400 people with severe and milder forms of asthma. Using this extensive resource, her lab has been key to documenting and describing the various types and presentations of asthma, which has proven to be both heterogeneous and, nevertheless, comprised of only a handful of phenotypes.

Behind much of these data are patients Wenzel has known for decades. One mom rigged her laundry basket with a homemade bungee-cord harness so that she could drag it around as needed. Lifting and carrying simply took too much effort. When her asthma was bad, her lung function would drop to 30 percent of its usual capacity.

"In the 10 years that I knew her, she had been intubated and put on a breathing machine about six times," says the doctor.

The woman's children had seen their mother lose consciousness and get rushed to the hospital. In elementary school, one of

# CLEARANCE

**It's hard to believe, but until the early 1980s, there were no invasive studies of asthma patients. No one looked at their lungs.**

them successfully petitioned to take a CPR class offered to the high school students—on the grounds that he believed he might need to resuscitate his mom someday.

“The seventh time she had an attack, she died, at age 46,” Wenzel says. “Never did anything to bring this on.” Like Charles, Wenzel calls the woman, “one of the main reasons I’m doing this today.”

According to Serpil Erzurum, codirector of the Cleveland Clinic’s asthma center and chair of the pathobiology department there, Wenzel has informed much of what we know about the architecture of the lung and the changes that occur with asthma and the progression of the disease. “She has been able to describe very specific changes that are now accepted as paradigms of the disease but weren’t completely understood or documented before,” she says.

Wenzel was the person who organized the American Thoracic Society’s workshop on severe asthma in the late 1990s. In a culmination of two years’ work, the committee drafted the definition of severe asthma that now serves as the standard worldwide. The group’s efforts also led to recognition by the NIH of the subset of dangerously ill asthma patients who were not well served by existing medications.

The NIH subsequently dedicated significant resources to a severe asthma research program, for which Wenzel is a principal investigator. Pitt is one of eight centers in the

country funded as a part of the program. Also through Wenzel’s work, a new program in pediatric severe asthma has been initiated.

The side-by-side programs will offer lifelong management of asthma, Wenzel says. Researchers will study the progression of the disease from childhood to adulthood so as to understand the relationship between the two. (Severe asthma in childhood does not necessarily lead to severe asthma in adulthood.) They also will try to determine the role of viral infection and other physiological events in the development of severe asthma. (The woman whose son learned CPR experienced a drastic worsening of her asthma after childbirth.)

An enduring frustration for Wenzel has been the difficulty in closing the loop between the mouse studies in the labs of researchers like the Rays and the asthmatic patients she treats. Just as she arrived at the University of Pittsburgh in 2006, Wenzel wrote an editorial for the *American Journal of Respiratory and Critical Care Medicine* titled “The Mouse Trap—It Still Yields Few Answers.” Chronic asthma is a disease unique to humans, she argued, and while scientists have probed and enhanced their understanding of the mouse immune system, too few basic science discoveries in that species have led to asthma treatments in humans.

“Mice do not have asthma,” she wrote.

Pulmonologist Steven Shapiro—then of Harvard University and now, coincidentally,

chair of Pitt’s Department of Medicine—penned an opposing editorial. Perhaps, he suggested, the trick to animal modeling lies in knowing how far to take the analogy.

Wenzel, along with Prabir and Anuradha Ray, acknowledges that exploring the inflammatory pathways of mice does yield important insights. It may be one-hundredth of all the data from animal models that transfers over, says Wenzel, but it has enabled these colleagues to close the loop at times.

In October 2007, Wenzel and others published a study in *The Lancet* in which they tested a drug designed to block the inflammatory molecule interleukin-4 and its closely related cousin, interleukin-13. Over the years, data from animal models documented in the labs of Prabir and Anuradha Ray had indicated that production of interleukin-4 might be responsible for kick-starting all sorts of immune activity that is ultimately not good for people with asthma. This was thought to be a major pathway. Many of these studies were in mice, but Wenzel used a drug that blocked both interleukin-4 and interleukin-13 in human volunteers. To test the efficacy of the drug, the volunteers then inhaled allergens known to trigger asthma attacks. The drug offered a clear benefit over the placebo.

Loop closed. Paper published. Further trials are needed for this drug and many others to cure this complex, varied disease. But all sides agree that, whether mice get asthma or not, this is what the work is all about. ■



A MATTER OF SOME  
**URGENCY**

SCIENTIST CHET DE GROAT HAS REVEALED  
MUCH OF WHAT WE KNOW ABOUT THE BLADDER

BY ELAINE VITONE

PHOTOGRAPH BY FRANK WALSH

**F**or most of us, spinal cord injury invokes the iconic image of the wheelchair. We assume that what those with impaired mobility want most is to walk again. Our hunch is way off.

In 2004, the Reeve-Irvine Spinal Cord Injury Research Center asked people with spinal cord injuries to rank what would most improve their quality of life. Their answers revealed a powerful theme. Among both quadriplegics and paraplegics, it wasn't mobility that ranked highest but, rather, those aspects of our physiology we shy away from discussing—what even the medical community has traditionally relegated to the catch-bin of “secondary consequences” of spinal cord injury: bladder, bowel, and sexual function.

For 40 years, W. Chet de Groat has devoted his life to studying the sacral nerves, located in the lowest section of the spinal cord and responsible for controlling the autonomic functions of the bladder, bowel, and reproductive organs. A professor of pharmacology and chemical biology and a former director of the pharmacology medical curriculum, he came to Pitt in 1968 and quietly built what remains one of the most prolific laboratories of its kind in the world.

De Groat is 70 years old and stands 6-foot-1 with a full head of white hair. Describing his work, he first breaks down the bladder's complex processes elegantly and succinctly—he's famous for this—and then recites a litany of discoveries, punctuating each with an apology. “Well, I've really beat your ear now,” he says. He prefers to put the focus on those he calls his “scientific children and grandchildren” rather than himself.

Humility seems to run in this family. His mentees often say they owe him their careers, and many are now National Institutes of Health-funded researchers, med school department chairs, and biotech entrepreneurs. Worldwide, the de Groat scientific lineage is helping to improve the health and well-being of people suffering from disorders of the bladder.

“Really, we just stumbled upon all of this,” de Groat says, recalling how he found his calling in 1966, back when almost nothing was known about the sacral nerves. “We found out that the bladder has a lot of interesting properties.”

De Groat was a fellow in Australia, working with neurophysiologists David Curtis and Ronald Ryall to record activity from single neurons in the neck of an anesthetized animal. The trouble was, because of the motion of its lungs, those individual cells were tough to hold onto.

One day, after losing yet another neuron, de Groat and Ryall got frustrated. “Let’s go to another part of the autonomic system,” de Groat suggested. “Something more stable.”

Ryall agreed. “And let’s get as far away from the lungs as possible.”

The good news was that at the bottom of the spinal cord, they could hold on to neurons for hours. The bad news was that there was nothing to record.

The pair found this radio silence odd, and disappointing. But then it occurred to them: Unlike, say, the heart or lungs, the organs at the base of the body are in a resting state for most of the time, except during urination, bowel movements, or sex. Perhaps if they filled the bladder, they thought, those neurons might fire. They tried it, and it worked.

The more de Groat thought about it, the more intrigued he became. Unlike nearly every other organ in the autonomic system, the bladder is controlled voluntarily. Further, babies can’t control their bladders, but adults can—which suggested to de Groat that development plays a role. And finally, he realized that bladder research had the potential to ease the suffering associated with a long list of ailments—incontinence, overactive bladder, prostate disease, and spinal cord injury, to name a few.

It would be gratifying work, and as far as he could tell at the time, it wouldn’t take long. The system seemed simple: Kidneys make urine, the bladder stores it, and the urethra serves as a reservoir. A sphincter muscle at the top of the urethra acts as a dam. When the sphincter relaxes and the bladder contracts, urine flows out.

But the more de Groat studied the bladder, the more he realized there was more to this “simple” system than he had imagined.

In 1970, de Groat found that in many animal infants, urination demands a prompt. A newborn kitten, for example, requires a lick from its mother to spur the process. Without mom, it will die of renal failure.

Though humans don’t require a similar jump-start, we retain the evolutionary legacy of stimulus and response. Hence, when you change junior’s diaper, he wastes no time in making you do it all over again. Once the cloth touches him, it’s beyond his control.

Most of our autonomic reflexes, like knee

jerk, come from the spine, but de Groat’s team found that in infants, the urination reflex is an anomaly. A stimulus like the touch of a diaper sends a message up the spinal cord to a region of the brain stem known as the pontine micturition center, which relays the message back down to the bladder, giving it the green light.

Then, when we’re toddlers, the brain shifts into voluntary mode. De Groat says it’s not clear exactly how this happens, but in adults, the cortex—the part of the brain associated with cognitive control—overrides the reflex.

In the wake of a spinal cord injury, however, the urinary system crashes. At first, the bladder can’t empty at all. Then the system comes online again, albeit transformed.

De Groat’s team found that in a spinal cord injury, the bladder’s wires to the brain are severed forever, and the primitive reflex returns.

In lieu of central nervous system control, the bladder rewires itself using a network of nerves known as silent C fibers. Normally, such nerves would be, well, silent, with only one cue: pain.

After a spinal cord injury, the sphincter and bladder lose their ability to work together. The sphincter doesn’t know when to open, and so the bladder works doubly hard to push urine past. As a result, the bladder muscles thicken—hypertrophy, it’s called. Pressure backs up to the kidneys, dooming them to fail.

Today, ads for drugs to quiet overactive bladder and treat prostate disease are ubiquitous. The bladder is coming out of the closet. Disorders of the urinary system now warrant recognition as more than a strain on our dignity. For newborn kittens, aging humans, and creatures of all life stages between, when the bladder isn’t given its due, the consequences can be debilitating, even deadly.

On a Thursday afternoon in July, de Groat enters his lab in the Thomas E. Starzl Biomedical Science Tower’s east wing. The room feels like the inside of a submarine. Knobs and wires jut out from gadgets that line the walls. Behind the oscilloscopes, speakers, and amplifiers, sheets of copper and aluminum shield the lab from noise. Listening to silent nerves is delicate business.

In the center of the room, Research Associate Yongbei Yu stands at a table that holds the star of the show: a tiny, pink balloon less than an inch in diameter. It’s the bladder and silent-C-fiber nerves of a rat. A transducer—wired to an amplifier on the wall—measures the pressure inside the bladder.

De Groat offers a peek through the micro-

scope. “In the middle, there’s an electrode. The white thing coming over it is the nerve fiber,” he says. “Nice preparation, Yongbei. Are you gonna distend it again?”

Yu nods. She presses a few buttons on a small machine that controls two catheters. One fills the bladder with fluid and the other administers compounds—in this case, potential drugs for overactive bladder. The experiment is part of a study with Professor and Chair of Pharmacology and Chemical Biology Bruce Freeman.

Previously, Yu used this same method in collaboration with de Groat to study ATP, the energy source of the cell, which also works as a neurotransmitter and is often involved in pain.

Now, as the bladder expands with fluid, the speakers begin to scratch with static.

“See the baseline widening?” de Groat says, pointing to a stream of line-streaked paper flowing out of the wall. He raises his voice more still, to outdo the now-swelling noise. “This is what happens in your nerves when your bladder fills up,” he says, and we watch the waves spill out onto the paper, listen to the neurological ruckus fill the room.

De Groat is highly sought after on the lecture circuit and has won six Golden Apple awards for his teaching prowess. When he attends research talks, he’s known to raise a question afterward that amazes speaker and audience alike. “Nobody has ever asked that,” they say. “He thinks like a clinician,” they add—by all accounts, a rarity for a basic researcher.

Watching him now, ears perking for the amplified utterances of a single, tiny nerve fiber, it’s easy to see why he’s such a gifted teacher and speaker. Foremost, he’s a dedicated listener.

At minimum, it takes a bladder-testing marathon of a conversation just to scratch the surface of the de Groat Lab legacy. He won the Urodynamics Society’s Lifetime Achievement Award more than a decade—and 228 papers—ago. Many of the insights that evolved from his early tracing studies 40 years ago have yet to be revised.

Last year, the Christopher and Dana Reeve Foundation honored him with the Reeve-Irvine Research Medal. The foundation’s scientific advisory council chair, Oswald Steward, a professor of anatomy and neurobiology at the University of California–Irvine, calls de Groat the world’s leading expert in autonomic function and a pioneer in translating basic research to the bedsides of patients suffering from disorders of the bladder.

“Chet has built the story from absolutely the ground up,” says Steward. “And his scientific family tree is just truly outstanding—and astounding.”

William Steers, chair of urology at the University of Virginia medical school and editor of *The Journal of Urology*, was among the first of many urologists

to work in de Groat's lab. After he completed his postdoc in 1989, he joined the initial Viagra trials.

"For those of us in the trenches," Steers says, "where we actually see disorders every day, this training gave us a tremendous advantage—in terms of understanding how these things work, why they go wrong, and how we can treat a range of very common yet poorly understood clinical problems."

Apparently, it was a two-way street. Steers remembers de Groat constantly peppering the MDs in the lab with questions: What do you see in your patients? How does this work?

In the late '80s, de Groat published his hypothesis for easing symptoms of overactive bladder in patients with spinal cord injuries and nervous disorders. His theory involved capsaicin, the stuff in hot peppers that burns your tongue. Just as five-alarm chili feels more like a fire drill than an immolation if you eat enough of it over time, he thought overactive silent C fibers in the bladder might also quiet with capsaicin exposure. Initial studies showed promise: Neonatal rats treated with capsaicin were born immune to pain.

At first, the medical community couldn't get behind the idea. Capsaicin is a neurotoxin, after all. The notion of giving it to patients who already had nerve damage sounded ridiculous.

Then London neurologist Clare Fowler, a longtime friend of de Groat's, gave it a shot. She administered capsaicin solution into the bladders of a group of her patients who had multiple sclerosis and severely hyperactive bladders. And just as Fowler and de Groat had hoped, the capsaicin eased the patients' incontinence symptoms.

Fowler's paper was published in *The Lancet* in 1992; de Groat was a coauthor. Since then, a steady succession of even better treatments using the same nerve-numbing concept have followed. Some of them evolved in de Groat's lab.

De Groat collaborator Michael Chancellor, former director of neurological research at Pitt (now at William Beaumont Hospital in Michigan), was the first to use Botox in the bladder. He went on to treat hundreds of patients with overactive bladder and prostate problems and taught doctors around the world his technique. Patients respond very well, he reports. Some have significantly fewer symptoms. "And some are dry," Chancellor says.

"What's really cool is how long it lasts. In the bladder it lasts six to eight months, and in the prostate it lasts a year. That just blew people away."

Chancellor came to Pitt in 1997 as an associate professor of urology interested in developing a new therapy using muscle stem cells. He thought of stress urinary incontinence (SUI) in women—a disorder in which childbirth damages nerves in the bladder, later causing accidents when far lesser strains, like sneezes or laughter, build pressure in

the abdomen. Chancellor wondered: Could stem cells be cultured and injected into the neck of the bladder to relieve SUI symptoms?

"Chet said, 'Hey, run with it,'" he says. "I was able to bounce ideas off of him, hook up with cell biologists in his lab to figure out the models."

Chancellor earned multiple NIH grants for the work, then founded Cook MyoSite, a private firm now conducting FDA-approved trials testing the SUI bladder treatment.

Says Chancellor, "I was only able to do this by the grace of Chet."

**T**he de Groat Lab also aims to understand pain. To this end, Research Assistant Professor of Pharmacology and Chemical Biology Adrian Sculporeanu has been studying capsaicin receptors at the single-cell level for a decade. "It's like fishing," he says. "It takes a lot of patience."

His perseverance is paying off. He and de Groat are finding that these receptors can remain permanently active in certain disease states—a mechanism that, they believe, might explain chronic pain.

Naoki Yoshimura, professor of urology, started in de Groat's lab as a research associate in 1991. Now the two are investigating how silent C fibers control the bladder after spinal cord injury. Their hypothesis: Hypertrophy—that thickening of the bladder muscles—increases the expression of nerve growth factor, which may spur growth in those pesky, not-so-silent-anymore C fibers.

Research Assistant Professor of Urology Changfeng Tai came to the de Groat Lab in 1994. Working with Research Assistant Professor James Roppolo, Tai has published multiple papers on the use of electrical stimulation on the skin surface to control silent-C-fiber activity in the bladder. They found that electrical currents both inhibit and inspire bladder activity, depending on the frequency of stimulation and placement of electrodes.

"We're trying to understand the mechanisms," says Tai, "so we can find a noninvasive way to control the bladder that will cause fewer complications for patients."

Tai and Roppolo are working with Johnson & Johnson to test a disposable patch with stimulator, microchip, and batteries included. A Boston-based company also is developing an injectable electrode to be placed along a nerve.

De Groat often supports his mentees and colleagues in launching new projects, even when he doesn't necessarily agree with their hunches. Such was the case when Lori Birder,

assistant professor of medicine and pharmacology and chemical biology and a former graduate-student researcher in his lab, returned to Pitt in 1997.

Initially, de Groat wasn't on board with her hypothesis that cells of the urothelium—the lining of the bladder that stretches and contracts to accommodate urine—might be a therapeutic target. According to conventional wisdom, the cells were simply a barrier with no active role in bladder function or sensation.

Nonetheless, de Groat gave her space in his lab and, in 2001, she demonstrated that urothelial cells react to stimuli much like neurons and thus have the potential to intensify pain. These preliminary data yielded multiple NIH-funded studies, several of which de Groat collaborates on. (This magazine ran a story on Birder's work in February 2004, online at [pittmed.health.pitt.edu](http://pittmed.health.pitt.edu).)

Once de Groat takes you under his wing, says Birder, the relationship never ends. "He keeps up with everybody's careers," she says, "even after they've moved on from his lab, and really considers how he can help them achieve their goals."

"And I've never, ever heard anyone say anything negative about Chet," she adds, echoing a widely held sentiment among de Groat Lab alumni. "It's like they threw the mold away."

**B**y all accounts, urology is very big in Asia. Throughout the region, the bladder gets a lot more respect than it does here. At meetings for various research and clinical societies, it isn't uncommon to see de Groat posing for pictures or dining with dozens of Asian mentees-turned-colleagues.

When Chancellor heard that de Groat was turning 70 this year, he decided to throw a birthday party for him in September at the Pan Pacific Incontinence Society meeting in Taiwan.

"We've built up so many friends—students from Korea, Japan, Taiwan. I figured it'd be a wonderful opportunity. How else are you gonna get all these people together in one room?"

The planning fast took on a life of its own: de Groat baby pictures, birthday toasts in Chinese and Japanese. Pittsburgh Penguins shirts, hamburgers, and pierogies—anything to recall fond memories of times in Pittsburgh.

"Can you imagine that?" says Chancellor, "Sixty people in Taiwan wearing Pirates hats and going crazy with the Terrible Towels!"

To picture it is to see a scientific family reunion, a proud grandfather's dream realized. ■



A NEUROSURGEON COMES OF AGE  
BY FRANK VERTOSICK JR.

# NIGHTMARES, PAST AND FUTURE

**T**he first years after receiving my driver's license, I cruised the streets with little regard for the dangers of the road. Protected only by the rusting bodies of cheap used cars, I drove with the confidence of Achilles. Until one event penetrated that delusion like the spear that pierced Achilles' human heel.

My revelation came on a snowy Friday evening. Blowing powder dusted the roadway, and I believed the traction was normal. That is, until I reached the first overpass. I hit the shimmering ice and the car's tail began a slow, clockwise spin. My out-of-control Beetle completed one full revolution as it exited the bridge, then regained its footing on the warmer asphalt of the roadway before taking off, straight as an arrow. I continued down the expressway at full speed as if nothing had happened.

But something had happened. My outlook on driving could never be the same again. The experience taught me what the California Highway Patrol's *Red Asphalt* movies in driver's ed did not: how very easy it was to lose control

*Neurosurgeon Frank Vertosick (MD '81, Res '88) penned When the Air Hits Your Brain to chronicle his transformation from intern to chief resident. W. W. Norton & Company originally published the book in 1996. Norton rereleased the paperback this spring with an epilogue. Vertosick, the former president of the Pennsylvania Neurosurgical Society and author of Why We Hurt and The Genius Within, retired from surgery in 2002 because of early-onset Parkinson's disease. He still sees patients in his office in Washington, Pa.*

of a car and die. One instant in complete command; the next, a terrified passenger thrown upon the mercy of fate for survival.

I had been lucky, learning my lesson and paying no price. A Native American proverb states that a child allowed to wander into the campfire learns better than a child told a thousand times to stay away. On that snowy expressway, I had wandered into the campfire and, by sheer luck, escaped unburned.

Before reaching my surgical adulthood, I would again stray into the inferno of overconfidence—and come perilously close to emotional incineration.

Clipping an intracranial aneurysm tests the full mettle of a neurosurgeon—and the residents gauged their machismo using the aneurysm scale. Average on the aneurysm/testosterone scale, I slayed my first (fairly easy) aneurysm six months into my senior residency year. In the second six months, I clipped several more. The number of my successful cases mounted, each smoother than the last. My confidence became dangerously inflated.

“These aren’t so tough,” I remarked foolishly to an attending surgeon.

“You become a neurosurgeon when an aneurysm first blows up in your face,” he replied grimly. “Have you had that happen yet, son?” I shook my head and he just smiled, the knowing smile of a weathered gunslinger talking with a pompous greenhorn who has yet to feel a bullet pierce him to the bone. “Well, when that first one blows,” he continued, “let’s just say the next one you do won’t look quite so easy anymore.”

My senior residency year drew to a close, but because of a sudden change in the schedule, the Veterans Administration beckoned me for three more months of clinical duty. When I took the helm from the previous chief resident, only one patient resided on the VA service: Charles Bognar. Charles, in his mid-40s, had seen some action in Vietnam. He had been at the VA for less than a day. His diagnosis: subarachnoid hemorrhage.

Charles had experienced the worst headache of his life about 48 hours earlier. The pain overwhelmed him like a “mortar burst” as he made love to his wife. His admission CT scan showed fresh blood spilling into the left Sylvian fissure, the large cleft between the frontal and temporal lobes—where the mighty middle cerebral artery lives.

The middle cerebral artery, or MCA, is the

largest branch of the carotid artery within the head, supplying blood to almost two-thirds of the cerebral hemispheres. In the Sylvian fissure, the thick MCA divides into smaller trunks, which exit the fissure and fan out over the brain’s surface. The junction where the MCA subdivides forms a churning vortex of high-pressure blood—fertile ground for aneurysm formation.

MCA aneurysms hide behind the numerous MCA twigs like plump red birds perched in an arterial cage. These vital branches must be sharply dissected away from the fragile dome before a metal clip can be placed; otherwise the MCA might be inadvertently clipped as well, resulting in a stroke.

Charles’ aneurysm resided in the left side of his brain. To a brain surgeon, there are two cerebral hemispheres: The left one, and the one that isn’t the left one. In over 90 percent of right-handed patients, and in the majority of left-handed patients as well, the left hemisphere contains the apparatus for making and comprehending speech, both written and spoken. The right hemisphere does some useful things, too, like helping us get dressed

## I simply did not know the answers. Or worse, perhaps I did.

in the morning and giving us an appreciation of Bach. While a total occlusion of the right MCA will leave a patient paralyzed in the left face, arm, and leg, it will spare the intellect and personality. A similar occlusion of the left MCA amputates the patient from humanity and thrusts him forever into a foreign land, where no one will ever speak his language.

Charles went to the operating room as scheduled. The opening was uneventful and the attending rested in the lounge, available if I “got into trouble.” Using a microdissector, I worked under the microscope to free the aneurysm from the cage of MCA branches so that I could find the neck and get a clip across it. One MCA branch came away easily, then another. I was almost home!

But as I twisted the aneurysm to get one last look at its backside, disaster struck. In a heartbeat, my previously dry operative field turned into a crimson flood. I became paralyzed; blood filled the left side of Charles’ head like a basin and spilled into my lap. My mind went blank. The aneurysm had blown. But where was the tear? And could it be fixed?

“I have some bleeding up here.” My voice quavered as I informed the nurse-anesthetist

of the intraoperative rupture. He bolted from the chair.

“How much?”

“A lot.”

He pulled the emergency light, summoning help.

I screamed for the temporary clip as I relocated the main trunk of the MCA in the bloody maelstrom that swirled within the Sylvian fissure. I placed the clip. The bleeding slowed.

After a brief scrub, the staff surgeon displaced me from the operator’s chair and poked around the anatomy with a suction tip. I cowered, like a small boy awaiting his father’s discovery of a picture window shattered by an errant baseball. In an instant, reduced from brain surgeon to child. In the same instant, the life on the OR table had been laid to waste. Charles’ vast collection of war stories and dirty jokes dissolved from the dying pink circuitry like a Cheshire cat, leaving only the lifeless Sylvian fissure smiling back at me. The temporary clip, on for over five minutes now, left little hope that the precious left hemisphere would survive.

“There is a big hole in the main trunk of the MCA . . .” the staff man grumbled with resignation.

He loaded up an encircling clip, designed to wrap around the entire artery in just such a catastrophe, and crushed it around the MCA. The bleeding stopped, but the branches of the clipped MCA trunk no longer pulsed. In the ensuing minutes, life-giving arteries thrombosed into rods of purple licorice. The staff surgeon shrugged, pulled off his gloves, and yanked down his mask. The act of removing one’s mask and breaking sterility before the wound is closed is symbolic, tantamount to pronouncing the patient dead before he has left the operating table.

“Talk to the family, will you, Frank?”

“Yessir. I will do that.”

Closing the wound took an eternity, a ridiculous, demeaning exercise, a marathon runner slogging to the finish long after everyone else has gone home. I thought about Mrs. Bognar in the waiting room.

In the recovery room, Charles awakened as expected: thrashing his left arm and leg vigorously, but completely motionless in his right arm and leg. When given commands, he

widened his eyes in a bewildered, doe-in-the-headlights stare. His speech, pure gibberish. The left hemisphere was gone. The head gone, the body would not be far behind.

The ensuing days were agonizing. Charles spent his waking hours pounding and twisting the sheets with his left hand in purest frustration, yelling “Yaah . . . yaah” in vain attempts to make himself understood. Rounding on him was torture. The staff surgeon dragged me to see Charles every morning, grimly displaying my mistake like the Ghost of Christmas Future tormenting Scrooge with the outcome of his wasted life.

Mrs. Bognar confronted me every day with an unrelenting bitterness. Nothing the aneurysm could have done would have been worse than this, in her mind. And she was right. She didn’t blame me for the poor outcome of the operation, but she believed that her husband had been deceived about the necessity of the operation in the first place. Statistical operations are hard to explain. They are rolls of the dice, a gamble that operating carries fewer risks than the disease. Anyone who bets the farm and loses winds up feeling duped.

I sank into a deep depression. Ordinary diversions lost all meaning—they seemed trivial when I recalled my patient writhing in his speech-deprived cocoon.

Sleep became difficult. During my waking hours, the final moments before the aneurysm tore replayed in my head over and over again—my own personal Zapruder film. I almost had the goddamned thing clipped! What could I have done differently? If someone else had been doing this case, would things have come out better? Did I play with the dome too long? I simply did not know the answers. Or worse, perhaps I did.

“Death and doughnuts,” our weekly discussion of complications and operative deaths, dispatched the case with little controversy. I thought seriously about resigning and ending my career as an emergency room doc.

I had what it took to face disappointment—or so I believed. But Charles more than bothered me—he tormented me. Charles was the first disaster that was my fault and my fault alone. He didn’t have an incurable disease, he wasn’t ancient and doomed to die of something soon, he didn’t succumb to an attending surgeon, he wasn’t born with cancer of the brain—he placed the delicate porcelain of life into my hands and I dropped it.

At the death and doughnuts conference, I gazed about the room at the dozen or more staff surgeons present, 100 years of neurosurgical experience among them. Surely, these were ordinary men? Their learning curves must have devastated dozens upon dozens of lives. Why were they still sane?

Or were they? During his murder trial, Raskolnikov, the *Crime and Punishment* protagonist, dreamed of a world full of cruel people endowed with such intense belief in their own moral rightness that they never felt the slightest pang of guilt or remorse, even as their world sank into decay. Is that what it would take for me to go on? A blind belief that there was nothing I could have done better, that no one could have achieved a better result than I did on that day?

That is not the way of the scientist, and I still looked at myself as a scientist. Mathematician Jacob Bronowski believed that the credo of science could be found in an Oliver Cromwell utterance: “I beseech you, in the bowels of Christ, think it possible you may be mistaken.” To live with my failures, would I have to exit Bronowski’s self-critical world and enter Raskolnikov’s dreamworld, the megalomaniac’s Utopia?

Five days after surgery, Charles’ dead left brain swelled and smashed the life out of his brain stem. He was placed on mechanical support. During a tense, 10-minute meeting, Charles’ wife and I reached an agreement to withdraw his ventilator. On the seventh post-op day, I went into his room and, armed with the ventilator key, accomplished what four years of living with the Viet Cong could not.

My depression did not relent. I was now 30 years old, engaged to be married, and possessed of only one way, short of flipping burgers, to make a living. If I bailed out now—changed residencies, went to law school, got an M.B.A.—I risked flitting from job to job until I retired, without ever accomplishing anything. Worse, I had no guarantee of being happier or more competent in those fields.

No more second chances. I decided that

my random walk through life must end in neurosurgery.

I refused to operate again for weeks, a feat possible on the slow VA service. Finally I called the chief resident who had trained me. “Quit feeling sorry for yourself,” he told me. “Yeah, it’s a nightmare, but that’s neurosurgery. Land of nightmares. There are plenty more nightmares in your future, pal. The very fact that medical ethics forbids treating your immediate family is proof that we shouldn’t get so involved with a patient that we are made nervous by the possibility of failure. Patients want us to care about them, but they want us to perform with the nerveless demeanor of someone slicing bologna in a deli at the same time. It’s one of those unexplained paradoxes we just accept.”

Eventually, I managed to put Charles behind me. I tossed out my neatly typed resignation letters and halted my searches through the medical want ads. Like Raskolnikov in his gulag, I finally acknowledged that psychopathology is not the way to face difficult responsibilities. Some caring is necessary if we are to be the very best surgeons we can be, even if we can’t be the best in the universe.

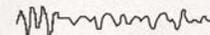
Caring makes the hands shake, but it also makes us dread disaster and work with every fiber of our being to avoid it. Pain, emotional or physical, is the taskmaster of the animal kingdom. The pain of Charles’ death taught me a deep respect for the campfire of surgery. I would mind the heat more carefully from now on.

Three months after Charles died, a thank-you note from Mrs. Bognar appeared in my university mailbox. It read simply: “I know now that you only did your best. Thanks for everything.” I had indeed done my best; my best just wasn’t good enough. I accepted the nightmare of the past and awaited the nightmares of the future. ■

Reprinted from *When the Air Hits Your Brain: Tales from Neurosurgery* by Frank Vertosick Jr., MD ©1996 with permission of the publisher, W.W. Norton & Company, Inc.

## When the Air Hits Your Brain

Frank Vertosick Jr., MD

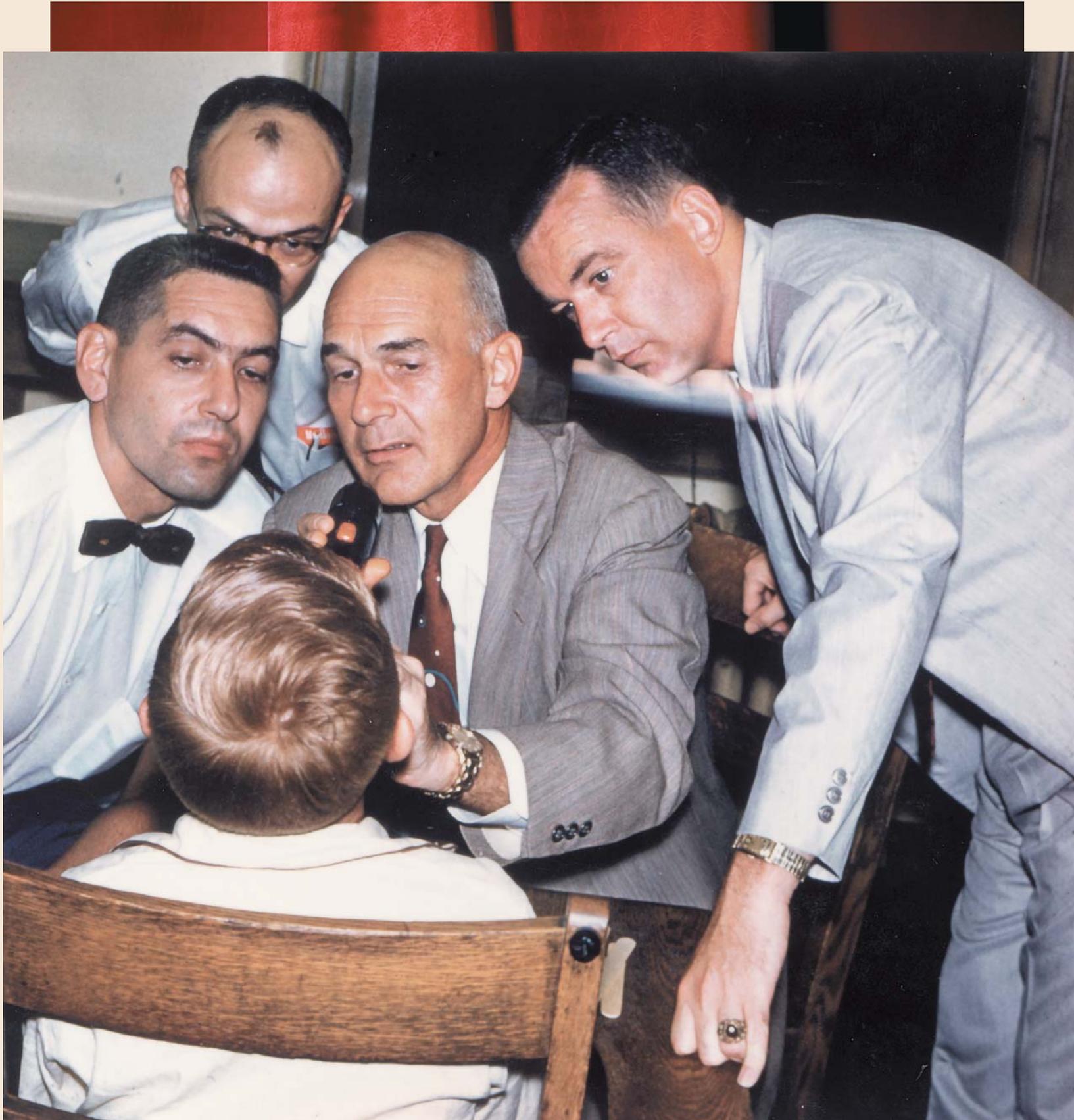


*Tales from Neurosurgery*



**ATTENDING**

*Ruminations on the medical life*



Milt Dupertuis (center), inaugural head of Pitt's plastic surgery program, and residents examine a patient with a cleft lip repair in 1958.

# A CREATION STORY

PLASTIC SURGERY COMES TO PITT

BY MICHAEL FITZGERALD

Jack Gaisford was driving up and down the East Coast in a rented car, trying to find a job before his money ran out. It was 1946, and during World War II, the army didn't spend a lot paying surgeons. Even before he'd been called up, Gaisford's surgical residency at Children's Hospital of Pittsburgh had paid only \$25 a month.

He drove to the University of Pennsylvania, where he'd gone to college on a golf scholarship. Nothing. He went to Georgetown, where he'd gone to medical school. Nothing there, either. But then the chief of surgery at the field hospital in the Philippines, where Gaisford had been stationed for about a year, found him an unpaid surgical pathology fellowship at NewYork-Presbyterian Hospital. That took some string-pulling—the army had called up the young surgeon before he finished his residency, and the hundreds of operations he'd performed during the war didn't count toward its completion. But after 10 months, he had a couple of job offers. The one he took was assistant chief resident in surgery at Children's and Presbyterian Hospitals in Pittsburgh, bringing him back to his childhood home in Western Pennsylvania.

At Pitt, Gaisford assigned residents to help doctors who didn't have assistants. One day in 1948, the schedule included a reconstruction of the cervical esophagus, the portion of the muscular tube connecting the mouth to the stomach where it passes through the throat. Gaisford had performed one prior to his stint in the army, and he remembered it as a terribly difficult operation. There were no residents in plastic surgery—in fact, there was only one plastic surgeon on staff: S. Milton Dupertuis. Gaisford sighed. He couldn't bring himself to assign one of the junior residents to the operation. He'd have to assist Dupertuis himself.

It was a fateful move. Dupertuis “did a remarkable job,” recalls Gaisford, now 93. In fact, the surgeon was so good, Gaisford started assigning himself to work with him on a regular basis. After a few weeks of this, Gaisford asked a question that would change his life:

“Did you ever think about starting a program where you trained plastic surgeons?”

Dupertuis, a shy man, frowned. “Nobody'd be interested in that,” he said. “Nobody.”

Gaisford screwed up his courage. “I don't mean to step out of bounds, but I'm very interested in the work you've been doing, and if you have any interest in starting a training program in plastic surgery, I'd like to be your first resident.”

## Gaisford couldn't bring himself to assign a junior resident to the operation. He'd have to assist.

Dupertuis took him up on it, and on July 1, 1948, Gaisford became the first resident in plastic and reconstructive surgery at Pitt, working for the grand total of \$34 a month. That modest cornerstone turned into a plastic surgery program that has produced generations of leaders in the field. At last count, alumni of Pitt's residency programs in plastic surgery served at one time as chiefs at nearly a quarter of the nation's 88 plastic surgery programs, says W.P. Andrew Lee, a Pitt professor and chief of UPMC's Division of Plastic Surgery.

Gaisford loved the work. But Dupertuis was almost right about the program. Plastic surgery, which draws its name from the Greek *plastikos* “to mold or form,” is a noble pursuit during wartime. Its rich battlefield roots reach back to 800 BCE India, where the practice of amputating a vanquished enemy's nose challenged surgeons to develop techniques for

restoring warriors' dignity, if not their original noses. During World Wars I and II, increasing numbers of soldiers survived what previously would have been fatal wounds and burns. Surgeons endeavored to reduce the physical evidence of those injuries, and the field leapt forward.

But as peace prevailed, the field slipped in prominence, warranting barely an afterthought at most American medical schools. Plus, it took an extra two years of training after the then-standard five years of surgical training. And resources were slim. Dupertuis was known to lug his own instruments—packed in a satchel—from home to office on the streetcar. There was no air conditioning

in the operating rooms in the 1940s, and Dupertuis had to bar the practice of using fans, because they also blew bacteria into the wounds.

Little wonder, then, that after a few months, Gaisford and William White, a hand specialist who met Dupertuis during the war and followed him back to Pitt, looked around and didn't see a second resident on the horizon. If Dupertuis had a prospect in mind, he wasn't saying—he tended to let his hands do the talking for him, even when teaching.

Then, a young surgical resident named Ross Musgrave (MD '43) found himself assigned to the specialties rotation: thoracic, orthopaedic, and plastics at Presbyterian. He could live with chest and ortho, he told John Shirer, the head of Pitt's residency program. But plastics? “They take all day! They put the stitches in and then they take them out, and



COURTESY ROBERT BRAGDON

**By the 1950s, Pitt's plastic surgery reputation was already robust. FRONT ROW: Jack Gaisford, Milt Dupertuis, William White, Ross Musgrave. BACK ROW: Phillip Antypas, Pete Hanna, Frederic Rueckert, Bill LeWorthy, and Bernard Barney.**

they're such fussbudgets," Musgrave said. "I thought you liked me."

"I do, kid," Shirer said.

"Please don't make me do this," Musgrave said.

Shirer was unmoved. "Go on, kid. It'll be good for you."

So in January of 1949, Musgrave found himself scrubbing in with Gaisford and White—Dupertuis was on vacation in Florida. For all of Musgrave's protests, he found he loved plastic surgery. After a couple of weeks, Gaisford and White called Dupertuis at his vacation place.

"He's a live one," they told Dupertuis. And since the trio still lacked a single applicant to succeed Gaisford, they decided to give Musgrave a little push. They called him at home and, after some chitchat, they got to the point. "We hate to do this," they told the unsuspecting young surgeon, "but it's come to the point where we have to know whether or not you want to take the residency in plastic surgery. We have so many applicants that we have to know tonight."

Musgrave paused. "Let me talk it over with my wife a minute," he said. He came back to the phone. "I'll take it."

From there, Pitt's program grew, building around Dupertuis, White, Gaisford, and Musgrave. Soon they were training four residents a year and drawing top talent to Pitt, like Dwight "Pete" Hanna, who would stay on after his residency and become Gaisford's partner and part of the teaching program. It

was a highly accomplished group. Dupertuis, White, and Musgrave would each serve as president of the American Society of Plastic and Reconstructive Surgeons (now the ASPS).

They were very different men, but they worked well together. And they took care of their residents in ways small and significant. When Byron Hardin, a concert-class pianist, would play chamber music with the cello-playing daughter of another Pitt doctor, Pete Hanna would turn pages for him. And when Robert Chase, a resident at Pitt from 1957 to 1959, ran out of money and was going to quit the program, White secretly paid his way on three conditions—that he never say thank you, that he someday do the same for someone else, and that he never tell a soul, a request Chase, 85, has honored in full until now.

In 1959, Milt Dupertuis died of a coronary. At 53, he was president of Presbyterian Hospital, president of the American Board of Plastic Surgery, and president of the American Society of Plastic and Reconstructive Surgeons. By that time, his casual remark to Jack Gaisford—"C'mon boys, who would come to Pittsburgh to do plastic surgery?"—had become a running joke, says Musgrave. "We used to tease him about it, because we were getting very high quality people."

After Dupertuis died, White was named chief. More gregarious than his predecessor, White came to define the program.

White had a capacious appetite for both food and knowledge. They were swashbuckling days for medicine and the country as a

whole. On the spur of the moment, the chief would take the residents to dinner and pick up the tab. At White's home, the residents were treated to "vodscicles"—vodka popsicles their mentor had made himself—followed by a night on the town.

White, who chomped on cauliflower and carrots while holding court in his office with residents, was built like Burl Ives. He threw away his watch because time meant nothing to him, and he was famously late. On days when White had a surgery scheduled to end at 5 p.m., "patients would come to see him and say, 'Do I have time for dinner and a movie, or just dinner?'" recalls Garry Brody, a resident from 1962 to 64. In fact, after White bullied an anesthesiologist to work late one night, an irate Henry Bahnsen, then chief of surgery, fired him.

"We couldn't get over it," says Robert Goldwyn, who did his residency at Pitt from 1961 to 63 after a stint as a surgeon for humanitarian and Nobel Laureate Albert Schweitzer. "How could you get rid of Willie White? That's like firing the Statue of Liberty."

A couple of days later, or so the story goes, White called a staff meeting. His office was lit by candle, and the surgeon was clad in black. Barely visible in the gloom, a pediatric coffin had been filled with the papers published by Pitt plastic surgeons and residents since the program's inception. Later, White called in Bahnsen, who, legend has it, took one look at the funeral setting and the coffin and said, "Willie, you win," and reinstated him.

Not that there was any chance of the program faltering. Pitt was well established by then—"probably the best program in the country," says Brody, and with six teachers, one of the most diverse. White remained chief until his 1977 retirement. Pitt hired J. William Futrell as its chief and first full-time professor of plastic surgery in 1979.

In a sense, later cohorts who came through the program carried on the legacy of early giants like Dupertuis and White. Goldwyn would edit *Plastic and Reconstructive Surgery* from 1980 to 2005. Chase would establish the nation's first integrated surgical training program at Stanford University, combining the general surgical fields with the specialties. Musgrave would go on to serve as a trustee of both the University of Pittsburgh and the University of Pittsburgh Medical Center, as well as governor for six years of the American College of Surgeons.

As a group, they've achieved something lasting, says Lee: "Everyone in our field knows about the long tradition of Pittsburgh plastic surgery." ■

*People and programs  
that keep the school  
healthy and vibrant*



## COLD COMFORT HYPOTHERMIC TREATMENT YIELDS CRITICAL CARE DIVIDENDS

BY HAYLEY GRGURICH  
& MISSY RATERMAN

**L**ou Basenese lay on the sidewalk, flat on his back. Moments before, the 56-year-old had completed a five-mile power walk with his wife, Laura, in their Newport Beach, Calif., neighborhood. Then he dropped to the ground in midsentence, a victim of sudden cardiac arrest. Laura crouched over him, administering CPR. Her two-fingers-to-the-mouth whistle—a sound, Lou says, that could “wake up the dead”—summoned only neighbors. One spoke with the 911 operator, relaying instructions to Laura; another delivered more than 400 chest compressions.

After eight minutes, medics captured a pulse. In the hospital, a medical team detected brain damage. From their perspective, Lou’s prospects for a full recovery were vanishingly slim. A few doctors argued otherwise, and with Laura’s signature, Lou became one of the first patients at Newport Beach’s Hoag Hospital to receive hypothermia treatment using the Arctic Sun, a noninvasive cooling method. It was the summer of 2006.

Gel packs enveloped Basenese’s torso and groin like giant Band-Aids. A bedside machine sent a continuous stream of cold

water through the packs and across his skin, keeping him cool for 24 hours, while his brain convalesced.

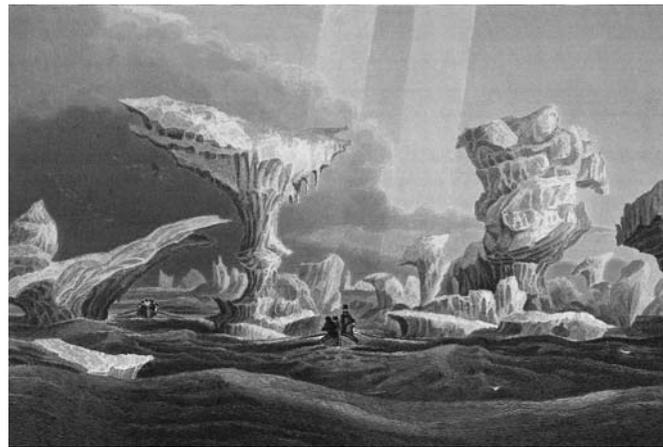
Trauma to any organ triggers a state of hyperthermia, raising the body’s core temperature. The heat acts as a catalyst, signaling the release of excitatory amino acids that destroy the cells of the injured organ. By combating the hyperthermia with cooling agents, doctors hoped to stymie those amino acids and reverse Basenese’s prognosis.

The 56-year-old energy executive shouldn’t have survived. But since a quadruple-bypass four days after completing the Arctic Sun treatment, Basenese has the heart of a 25-year-old, says his cardiologist. And although he had temporary short-term memory loss following the surgery, he has had no permanent brain damage.

Medivance, a Colorado-based company that specializes in the development and manufacture of medical products for therapeutic temperature control, created the gel packs applied to Basenese in the ICU. Now, thanks to Medivance’s chair, Gene McGrevin, a 1966 graduate of Pitt’s College of Arts and Sciences, and his wife, Carol Zord McGrevin, a 1964 graduate of Pitt’s School of Education, the School of Medicine will receive a substantial planned gift for scholarships and research and an award fund for a PhD student in Pitt’s Department of Critical Care Medicine.

McGrevin chose to support Pitt after his involvement in Medivance introduced him to the work of Peter Safar, the late Pitt professor of critical care medicine whose research established the value of therapeutic hypothermia for protection of the central nervous system after trauma and during hypoxia.

Beyond having been inspired by Safar and his Pitt colleagues in critical care medicine, the



**Trauma boosts the body’s core temperature. Hypothermic treatment reduces the damage.**

McGrevins know a thing or two about having big dreams and skinny wallets; both received scholarships during their Pitt days. “Education is one of the most critical variables we have going for us in our society,” McGrevin says. “My wife and I always knew we wanted to do something to give back.” ■

## BOOSTER SHOTS

**W**hen **Robert Georgevich** decided to help others suffering from the lung affliction that had long troubled him, he turned to his most trusted physician for advice. Pulmonologist R. Dean Hautamaki helped Georgevich, who died in October, manage his chronic obstructive pulmonary disease (COPD) for years. Hautamaki talked extensively with Georgevich about COPD research led by his mentor, Pitt pulmonologist Steven Shapiro, who chairs the Department of Medicine here. The result is a \$200,000 gift pledged by the Robert Georgevich Foundation.

**D. Scott and Pamela Kroh** of Latrobe, Pa., pledged a \$50,000 gift to support the diabetes research of Andrew Stewart, Pitt professor of medicine and chief of the endocrinology and metabolism division. Moved by a family member’s diabetes diagnosis, the Krohs were encouraged to learn that Stewart had used data derived, in part, from the Krohs’ support to leverage a \$375,000 grant from the Juvenile Diabetes Research Foundation. Stewart will use the funds to research ways for patients with type 1 and type 2 diabetes to regenerate insulin-producing beta cells. —*Chuck Staresinic*

FOR INFORMATION ON GIVING TO THE SCHOOL:  
**Deb Desjardins, 412-647-3792 or [ddeb@pmhsf.org](mailto:ddeb@pmhsf.org)**



## CLASS NOTES

### '70s

**Chester Lerner** (MD '78), an epidemiologist and director of infectious diseases at New York Downtown Hospital, was three blocks from the World Trade Center on the morning of Sept. 11, 2001. "You could hear the airplane collisions from our hospital, and when you looked out the window, you could see flames coming out of the Trade Center. The hospital was enveloped in a smoke cloud that day," he says. According to Lerner, the hospital treated more than 1,000 patients, including hundreds of firefighters, mostly for smoke inhalation and eye injuries. "The regular job ended, and we focused on triaging the [patients] who came in. The staff of the hospital stayed throughout the day and into the night, but unfortunately there weren't many people to be saved from injuries," he says.

Now the emergency department has been rebuilt to double its size and extra oxygen ports have been installed to help deal with an influx of wounded patients. As hospital epidemiologist, Lerner helps educate and prepare the staff for prospects like pandemic influenza and bioterrorism. He helps coordinate efforts between hospital departments to make sure resources are shared in the event of a crisis. Lerner says he's proudest of his early research, including his 1982 publication in *Annals of Internal Medicine* of some of the first descriptions of the virus now known as HIV/AIDS.

### '80s

On a visit to a comedy club a few years ago, **Jerry Magone** (MD '82) was impressed by

the efficiency with which the staff operated. Drink orders were recorded by multiple servers stationed all over the club, dispensed by a small number of people in a central location, and promptly delivered by others. Magone wondered why prescription orders in medicine couldn't work as smoothly. To learn more about the business of medicine, Magone enrolled at Carnegie Mellon University, receiving a master's degree in medical management in 2000. He is cur-

rently the president of Orthopaedic & Sports Medicine Consultants in Middletown, Ohio. Since 1996, he has helped open new offices, grow the group practice from four physicians to 11, and put his hard-won business acumen to use consulting for other companies.

Psychiatrist **Dale Adair** (MD '85) feels that his patients adhere more to care plans they have a hand in crafting. Adair, a recipient of the 2008 Governor's Award for Excellence, was commended by Pennsylvania Governor Edward G. Rendell for helping prepare Harrisburg State Hospital patients and the community to transition after the hospital closed in 2006. Although he was attuned to their needs, Adair credits his patients for the smooth move. Instead of doctor-patient relationships that are analogous to parent-child dynamics, Adair says he prefers "recovery focused" care, which involves the patient in therapy decisions. Instead of laying down the law, Adair hands his patient a pen to write a plan, because of his belief that people often know what's in their own best interests.

The Trojan horse model suggests a strategy for fighting cancer. Scientists can inject super-small particles filled



Governor Rendell with Adair

## STEVEN DEKOSKY & ROBERTA NESS

### ON THE LAUNCH PAD

Every year, the University of Pittsburgh School of Medicine sends a fresh crop of physicians and scientists out into the world. Any lingering sadness among the faculty is tempered by pride in the accomplishments and character of these graduates as they enter training at some of the finest hospitals and research institutions in the world.

But a medical school is a launching pad for more than students, a fact that became vividly apparent this summer at the University of Pittsburgh. In June, Steven DeKosky, professor and chair of Pitt's Department of Neurology, was appointed dean of the University of Virginia School of Medicine in Charlottesville. (His daughter, Allison DeKosky, received her MD from Pitt this year and began her internal medicine residency at the University of Chicago.) In July, the University of Texas announced that Roberta Ness, currently professor and chair of the Department of Epidemiology in Pitt's Graduate School of Public Health, will become dean of its School of Public Health in Houston. Another former Pittsburgher, Edward Wing, a professor at Pitt from 1977 to 1998 and interim chair of Pitt's Department of Medicine from 1995 to 1997, this year became dean of the school of medicine at Brown University.

Both DeKosky and Ness came to Pitt in the early 1990s, and each has played a part in the meteoric rise experienced by the University's schools of the health sciences.



Colson

with chemotherapy drugs into a cancerous site and, after the tumor cells absorb the particles, trigger release of the chemotherapy drugs. The nanoparticles that MD/PhD **Yolonda Colson** (Immunology PhD '89, Surgery Resident '98) is developing as an associate professor of surgery and of medicine at Harvard Medical School are essentially tiny polymers that trap cancer-fighting drugs inside. Once

they infiltrate the cancerous cells, they release the drugs. This direct route of delivery ensures that the drugs are administered only where needed, thus mitigating or even eliminating the unwanted side effects that conventional chemotherapy inflicts upon healthy parts of the body. Colson is a cardiothoracic surgeon with funding from the National Cancer Institute to utilize near-infrared imaging in lymph node mapping in lung cancer.

## '90s

People with pulmonary hypertension may suffer from shortness of breath, a dizzying lack of blood to the head upon standing, and bloated ankles. They often have the added discomfort of a plastic tube inserted in the chest. Central venous

catheters are the drug delivery method of choice for those with high blood pressure in their lungs.

**Jim White** (MD/PhD '97) hopes that those invasive and uncomfortable measures can eventually be traded in for an aerosol mist. White, the director of the pulmonary hypertension program and assistant professor of medicine, physiology, and pharmacology at the University of Rochester School of Medicine, uses his combination clinic and lab to observe how the disease and its current treatments affect patients. He hopes to develop a new class of drugs to change care for the better.

Classmates of **Louis Rivera** (MD '99) may remember that he was on track to finish his MD in 1998 when a health crisis threatened to derail his studies: He was diagnosed with lymphoma. Yet Rivera came to see this potential setback as an opportunity. He took a year off for research in trauma surgery, working with Pitt professors of surgery Andrew Peitzman and Timothy Billiar on the body's response to blood loss.

"Obviously, it was no fun to have cancer," Rivera says, "but it gave me an opportunity to do basic science research, which I hadn't had any exposure to. I think [research experience] was a really good thing for me to have in terms of wanting to develop an academic career. It was a difficult time, but I wouldn't

change anything. I learned a lot from the experience personally and it didn't set me back professionally."

Rivera, a lieutenant commander in the U.S. Navy, was the ship surgeon aboard an aircraft carrier in early 2008. This summer, Rivera began a surgical oncology fellowship at Roswell Park Cancer Institute in Buffalo, N.Y.

## '00s

As a Pitt resident, **Dina Green** (Internal Medicine Resident '01) got to spend nearly all her free time with her husband, despite the frantic schedule and scant sleep. Pitt coordinated the call schedules for Green and husband **Eric Green** (Internal Medicine Resident '01) for the full three-year duration.

"It was never a situation where one was overnight in the hospital, and one was there the next night so you wouldn't see each other for three days," she says. "Pittsburgh was a place that really bent over backwards to accommodate couples."

Now an assistant professor at Mount Sinai School of Medicine in Manhattan, Dina Green specializes in internal medicine and endocrinology. "Pitt's women's health program was my foundation because I'd say 80-plus percent of the endocrinology patients I see are women," she says. Green focuses on osteoporosis, codirecting a bone density unit at Mount Sinai.

Despite the grueling hours of the internal medicine residency, fatigue never set in on the inpatient oncology floor for **Hussein Tawbi** (Internal Medicine Resident '05, Hematology/Oncology Fellow '08). "I was enjoying doing the real medicine I felt compelled to do," he says. "The patients were a completely different population. They were so attuned to the fact that this fight is teamwork between them and their oncologists."

Currently an assistant professor in the Division of Hematology-Oncology at Pitt, Tawbi received the Paul Carbone MD Fellowship Award from the Eastern Cooperative Oncology Group in 2007. The late Carbone served as president of both the American Association for Cancer Research and the American Society of Clinical Oncology, and the eponymous award supports innovative research in cancer care and treatment. Tawbi's investigations focus on mechanisms of chemotherapy resistance in melanoma, specifically the way cancer cells repair their own DNA to counteract these drugs.

Tawbi heads Pitt's sarcoma clinical research program and is a Pitt PhD candidate in clinical and translational research.

—Meaghan Dorff, Hayley Grgurich



DeKosky

DeKosky came to Pitt to research Alzheimer's disease, the study of which was then centered in the psychiatry department. He spent eight years as chief of geriatrics and neuropsychiatry before becoming chair of neurology in 2002. Neurology was small, but DeKosky successfully moved the Alzheimer's Disease Research Center Grant to the department and landed a few additional research grants to begin growing the work. In 2002, *U.S. News & World Report* didn't even rank the department, and National Institutes of Health (NIH) research funding warranted a departmental ranking of just 39th in the nation. When DeKosky left Pitt, *USNWR* ranked the department 14th in the nation; the department's NIH funding had climbed to 9th among neurology departments.

Ness, an MD who holds secondary appointments in the School of Medicine (in medicine and obstetrics, gynecology, and reproductive sciences), describes what has happened in Pitt's schools of the health sciences, "an almost miraculous expansion."

"When I came, the NIH ranking of the medical school was 22nd," she says. "Now it is in the top 10. [Sixth, to be exact.] Our department is one of the top two in terms of *per capita* funding."

Ness came to Pittsburgh as an assistant professor just embarking on a career. She rose to department chair, and is one of the nation's leading researchers of women's health. —Chuck Staresinic



Ness

# THE WAY WE ARE

## CLASS OF '98

Medical school classmates are close in the same way that siblings are close. They're related whether they like it or not. **Jordan Karp** (MD '98) likes to think that he and his classmates from the University of Pittsburgh School of Medicine Class of 1998 have always had special affinity for one another, however. Their 2008 reunion—attended by more than 30 graduates plus scads of partners, spouses, and children—certainly supports his view.

In addition to the official reunion activities, members of the class gathered for an informal Saturday night dinner at Joe Mama's on Forbes Avenue. Earlier that day, many gathered with their families at the Children's Museum of Pittsburgh.

Karp, an assistant professor of psychiatry and anesthesiology at Pitt, seems too young to have had a physician mentor for 16 years. But as an undergrad, Karp won a fellowship for students interested in careers in neuroscience. He was paired with Pitt's Charles Reynolds (Res '80), one of the leading geriatric psychiatrists in the nation. Karp would go on to complete a psychiatry residency at Columbia University before returning to Pittsburgh for research and clinical fellowships in geriatric psychiatry.

Working closely with Reynolds, a professor of psychiatry, neurology, and neuroscience, Karp researches treatment for older adults who have comorbid major depression and chronic pain.

Karp says that the reunion experience motivated him to join the social networking Web site Facebook, where he stays in touch with many of his classmates.

**Pamela Bensimhon** and **Daniel Bensimhon** (both MD '98) have a unique perspective on medical careers and parenting, and it's not just because they are both MDs. They had twins—twice. One set came in 2002 and another in 2005. Pamela Bensimhon reports that it was an enormous surprise both

times. She had none of the interventions or family history that one might typically associate with fraternal twins. As a pediatrician who specializes in hematology/oncology, she works part-time as a clinician and clinical assistant professor at Wake Forest University Baptist Medical Center in North Carolina.

Daniel Bensimhon is a cardiologist and president of the LeBauer Cardiovascular Research Foundation in Greensboro, N.C. His association with the foundation allows him to pursue clinical research in heart failure while remaining in private practice.

After med school, **Jeffrey Wesolowski** (MD '98) did a radiology residency in Pittsburgh, then a neuroradiology fellowship at Massachusetts General Hospital. He describes his fellowship as two years among some of the best minds in neuroradiology, during which he learned a tremendous amount about the diagnostic potential of new technologies. This was followed by a job that he describes as "9-to-5 assembly line radiology." When he and his partner relocated to Michigan, Wesolowski looked exclusively for academic jobs, and he is now glad to be back among enthusiastic peers working to advance knowledge. He is an assistant professor of radiology at the University of Michigan and associate program director for the radiology residency program there. As a physician-educator, Wesolowski continues to appreciate the problem-based learning sessions (PBLs) that his class experienced in Pittsburgh at a time when very few schools had adopted such innovative teaching techniques.

One classmate of Wesolowski's remembers PBLs differently. She writes that her favorite Pitt memories include "getting a stripper at PBL for Tammy's birthday," and "practical jokes," by which we may conclude, then, that hiring a stripper for PBL is an impractical joke. Current students, take note. —CS

## ROBERT ROGERS

JUNE 9, 1933–SEPT. 4, 2008



Rogers

In a career that spanned nearly four decades, Pitt Professor of Medicine Robert Rogers trained scores of physicians in caring for people with lung disease. At the same time, he developed treatments that led to improved care and quality of life for those patients. Rogers died of complications from prostate cancer at his home in Pittsburgh this year.

For Rogers, a child of the Depression, no opportunity for advancement was to be taken lightly, beginning with education. Born in 1933, Rogers was one of seven siblings. As a teen, he considered pursuing the same occupation as his father, a plasterer with a high school education. According to Rogers' son Rob Rogers, the plasterer's response was, "If you ever pick up a trowel, I'll break your arm. You are going to school."

Rogers' education included both medical school and a pulmonary fellowship at the University of Pennsylvania in Philadelphia. He became chief of the pulmonary division at the University of Pittsburgh in 1980, a position he held until 1996.

Rogers built the division from scratch, says Michael Donahoe (Res '86, Fel '89), a Pitt associate professor of medicine and pulmonary disease specialist who counts himself among Rogers' 90-some trainees.

Rogers developed bronchial lavage—washing the lungs with saline—as the leading treatment for pulmonary alveolar proteinosis, a rare disease in which protein accumulates in the lungs.

In the 1980s, Rogers took up painting, bringing the same passion to his art that he was known for in medicine.

In 2008, the Rogers family started the Bob and Sandy Rogers Endowed Fund to support fellowship training in Pitt's Division of Pulmonary, Allergy, and Critical Care Medicine. —CS



Karp



The Bensimhons



Wesolowski

## IN MEMORIAM

### '30s

**RITA CAREY NEALON HARMEIER**  
MD '39  
JULY 14, 2008

### '40s

**ROBERT LOVE ANDERSON JR.**  
MD '43B  
JUNE 22, 2008

**ALBERT MARRANGONI**  
MD '48  
SEPT. 25, 2008

### '50s

**RALPH LANEVE JR.**  
MD '55  
AUG. 8, 2008

**ALBERT REID LEOPOLD JR.**  
MD '57  
MARCH 17, 2008

### '70s

**DAVID TORKELSON**  
MD '78  
SEPT. 7, 2008

### '80s

**RICHARD BJERKE**  
RES '86  
APRIL 12, 2008

## ERIC PETERSON ENTRUSTED WITH AMERICA'S DATA

BY CHUCK STARESINIC

All around the country today, people fighting cardiovascular disease will enter hospitals. Some will arrive under their own power in emergency departments and cardiology waiting rooms. Others will come flat on their backs, sweating, wincing, and flanked by paramedics. Some will be unconscious.

They will get beta-blockers, statins, and vasodilators; CT scans, angiograms, and electrocardiograms. Drug-coated stents and latex balloons will pry open their occluded arteries. They will have arteries or veins from elsewhere in the body grafted onto their coronary arteries in order to bypass arterial bottlenecks that cut off blood to their heart muscles.

Some will eventually go home with their health relatively intact. Others will not. What determines who has a better outcome?

For Eric Peterson (MD '88), a professor of medicine at Duke University, at least some of the answers are to be gleaned from the reams of data collected from these patients. By mining such data, he helps save lives in hospitals all over the country.

In the mid-1990s, American heart surgeons banded together and began collecting data on

their coronary bypass patients. They put together detailed records on patients' clinical characteristics, courses of treatment, and outcomes.

"But they weren't getting much out of it," says Peterson, who had just completed a cardiology fellowship at Duke. He and his colleagues began to figure out systems to aggregate the data and give reports back to hospitals. They revealed things like whether staff administered the right drugs at the right time to the right patients, whether the proper diagnostic tests were run, and how long patients waited for procedures. Beyond furthering knowledge about what "works," says Peterson, those efforts gave physicians information on how their practices compared with those of their peers. Were they doing what they should in all cases? And were their patients better off for it?

Peterson and his colleagues have shown

that simple things—like the timely delivery of beta-blockers, stents, and angioplasty procedures—often lead to better outcomes. In a national randomized trial, Peterson et al showed that lives were saved by simply delivering quality improvement messages to hospitals, encouraging them to administer drugs and perform interventions according to accepted medical guidelines.

In 2007, Peterson was elected to the American Society for Clinical Investigation, an honor reserved for the most accomplished biomedical researchers age 45 or younger. Peterson, associate director of the Duke Clinical Research Institute and director of cardiovascular research there, is now the principal investigator analyzing every major national cardiovascular registry, including those of the American Heart Association, the Society of Thoracic Surgeons, and the American College of Cardiology.

"Why does the world trust me with its data?" he asks, with a laugh. Answering his own question, he says, "I think, in part, it's because I'm a clinical guy with a lot of quantitative training. ... I can see messages in data. ... Most importantly, I try to give frontline clinicians valuable feedback."

Peterson believes medicine still has room for improvement and that patient registries can drive needed change. He notes that you can go to a Starbucks café anywhere in the country and get the same product and same service 99 percent of the time. But if you enter an American hospital with a heart attack, he says, there's only about a 50–50 chance that you'll get the medicines that could potentially save your life. ■

FRANK HARRIS



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**BOAT MAN WALKING**  
 At 7 a.m. on a brisk Friday in August, Dave Malehorn barrels down a Pittsburgh sidewalk. Alone, the research assistant professor of pathology might not even turn a head. But today he hauls a red, 9-foot kayak, nestled in a modified baby stroller.

“Hey! Is that a boat?” shouts a man from his SUV window. “Yes, it is. It’s a kayak,” Malehorn replies, flashing the driver a smile.

A moment later, a rough curb cut ambushes the proteomics researcher and his kayak. “I’ve inadvertently become an advocate for accessibility,” he says, surveying the worn sidewalk. “Were I in a wheelchair, would I even want to try and get around the city?”

Malehorn began his boat walks to see if he could trek from his Morningside home to one of the city’s half-dozen river access points and soon became a staunch advocate for the waterways. He’s brought the kayak he dubbed “Toy Boat” to work at Magee-Womens Research Institute several times, paddling to Southside Riverfront Park and walking the rest of the way.

In the fall, Malehorn took Toy Boat to tailgate alongside other Panthers football fans, roasting hot dogs over a Sterno-fueled flame. —Missy Raterman



PHOTOGRAPHY BY MICHELLE MALEHORN

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**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.  
Or visit the Web site:  
www.medschool.pitt.edu/alumni

**AAMC PITT RECEPTION**

**NOVEMBER 2**

5:30 – 7 p.m.

AAMC Annual Meeting  
Grand Hyatt San Antonio  
San Antonio, Texas

For information:

Office of the Vice Dean

412-648-9000

vice deanstaff@medschool.pitt.edu

**HEALTH SCIENCES**

**ALUMNI RECEPTION**

**NOVEMBER 20**

6:30 – 8 p.m.

Sewickley Heights Golf Club  
“Alzheimer’s Disease and Pittsburgh  
Compound B”

William Klunk, MD/PhD, Speaker

For information:

412-647-8545

**WINTER ACADEMY**

**FEBRUARY 21, 2009**

Naples, Fla.

For information or to request an invitation:

Pat Carver

412-647-5307

cpat@pitt.edu

**STARZL LECTURE**

**APRIL 1, 2009**

4 p.m.

Lecture Room 6, Scaife Hall  
Clyde Barker, MD, Speaker

For information:

www.surgery.upmc.edu

**MEDICAL ALUMNI WEEKEND**

**2009**

**MAY 15–18, 2009**

**Reunion Classes:**

1949 1954

1959 1964

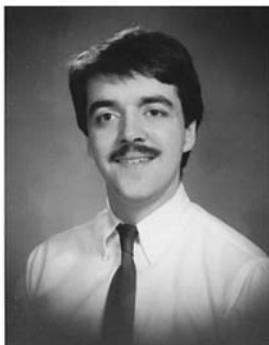
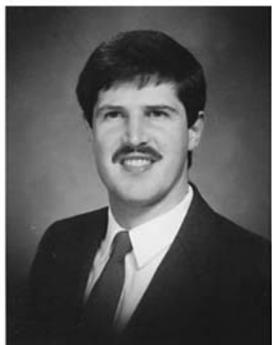
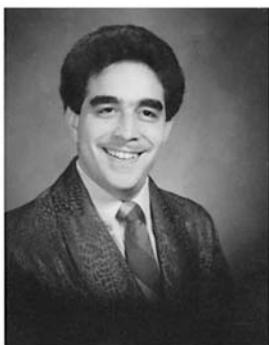
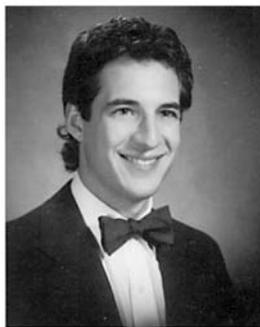
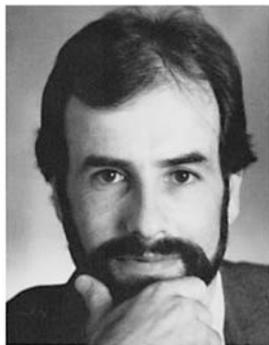
1969 1974

1979 1984

1989 1994

1999

TO FIND OUT WHAT ELSE IS HAPPENING AT THE MEDICAL SCHOOL, GO TO [www.health.pitt.edu](http://www.health.pitt.edu)



## GUESS WHO?

Time to warm up for Medical Alumni Weekend 2009. Dust off your copy of the *Hippocratean*—as we did here with the 1989 edition—and reminisce. Extra credit for anyone who can tell us a good med school story about these or any other members of the Class of '89. Send your stories to [medmag@pitt.edu](mailto:medmag@pitt.edu), or *Pitt Med* University of Pittsburgh 400 Craig Hall Pittsburgh, PA 15260

**Medical Alumni Weekend  
May 15–18, 2009**

For a list of classes having reunions this spring, turn to the other side of this page.

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