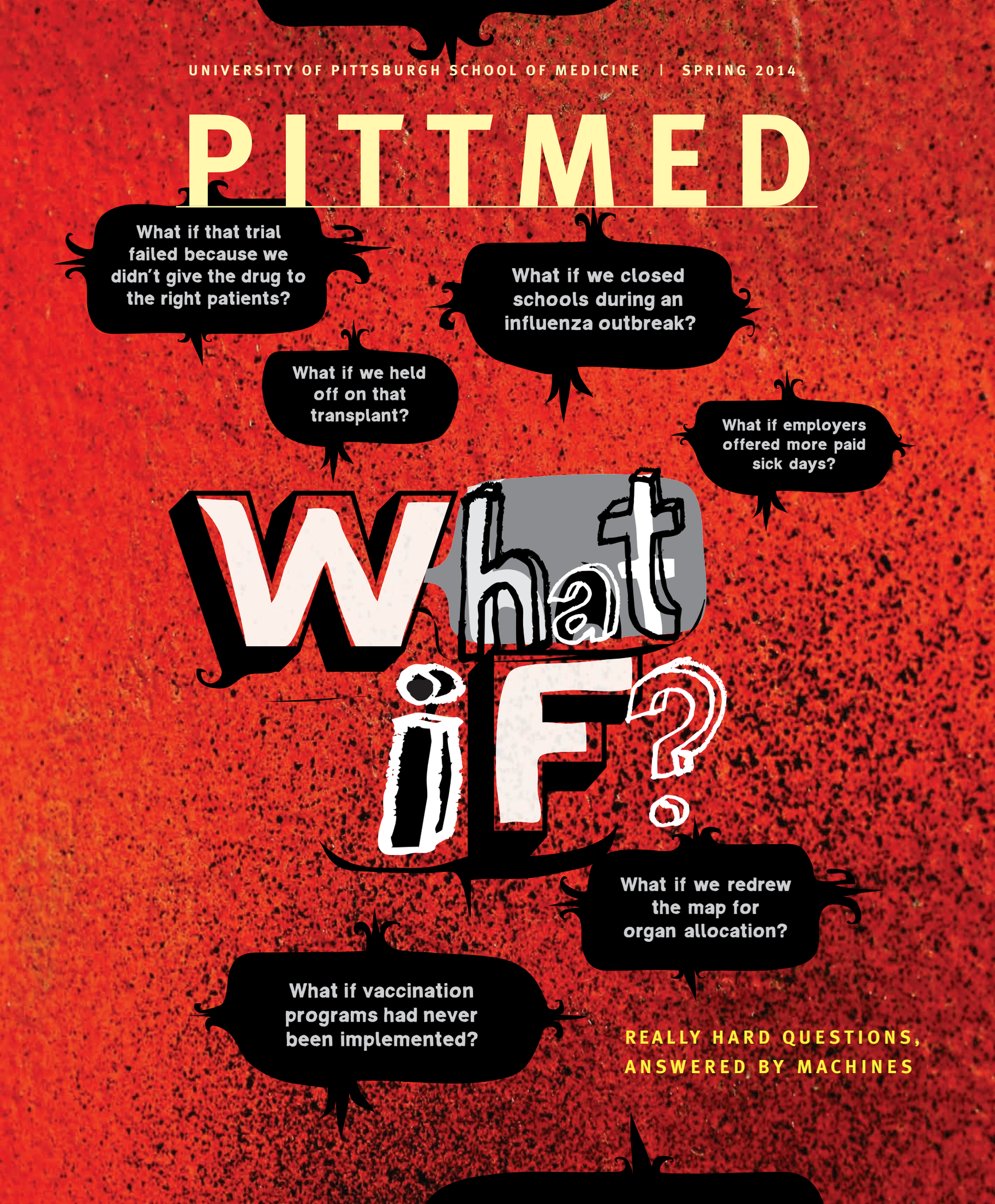
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | SPRING 2014

PITTMED



What if?

REALLY HARD QUESTIONS, ANSWERED BY MACHINES

FROM RUSSIA WITH STAPLES

I recently read Elaine Vitone's accurately written account of Mark Ravitch's trip to Russia in 1958 ("The Surgical Curmudgeon," Spring 2013). I was a surgical resident sitting in the [auditorium at Johns Hopkins] when Dr. Ravitch entered carrying a wooden box containing a unique surgical instrument he had acquired in Russia. Several years later, I was one of the authors on the publication "Clinical Experiences with the Soviet Mechanical Bronchus Stapler (UKB25)." Thank you for honoring my old "chief."

Ronald H. Fishbein
Naples, Fla.

HONORS

This space is typically reserved for magazine honors, but we couldn't resist mentioning that Pitt cleaned up this year at the Carnegie Science Awards, which recognize "outstanding science and technology achievements." Chancellor Mark A. Nordenberg and Jared L. Cohon, the former president of Carnegie Mellon University, were celebrated with the center's highest honor, the Chairman's Award. Five of the eight Pitt honorees were the med school's own, including Angela Gronenborn (Life Sciences), William Federspiel (Honorable Mention), Michael Lotze (Leading STEM Educator), Peijun Zhang (Emerging Female Scientist), and . . . *Pitt Med*'s Elaine Vitone (Science Communicator). The magazine's former senior editor, Joe Miksch, was its honored Science Communicator in 2008.

CLARIFICATION

The cover and other science images from our Winter 2013/14 cover story, "Don't Spare the Horses," originally appeared in *Nature* and should have been credited thusly: Macmillan Publishers Ltd: *Nature*, Vol. 497, Issue 7451, pp. 643-646, © 2013.

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MORE WOW!

For many years, the *Pitt Med* Web site has been utilitarian. Our comrades on Pitt's Web team just made it a heck of a lot better. More interactive! Shape-shifting depending on your device! Prettier! A nice new home for our Pitt Medcasts! It's now live. Check us out at pittmed.health.pitt.edu.

And, between issues, look to our Twitter feed for the scoop from the School of Medicine and the world of science at large.

@PittMedMag

PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, SPRING 2014

VOL. 16, ISSUE 1

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DEPARTMENTS

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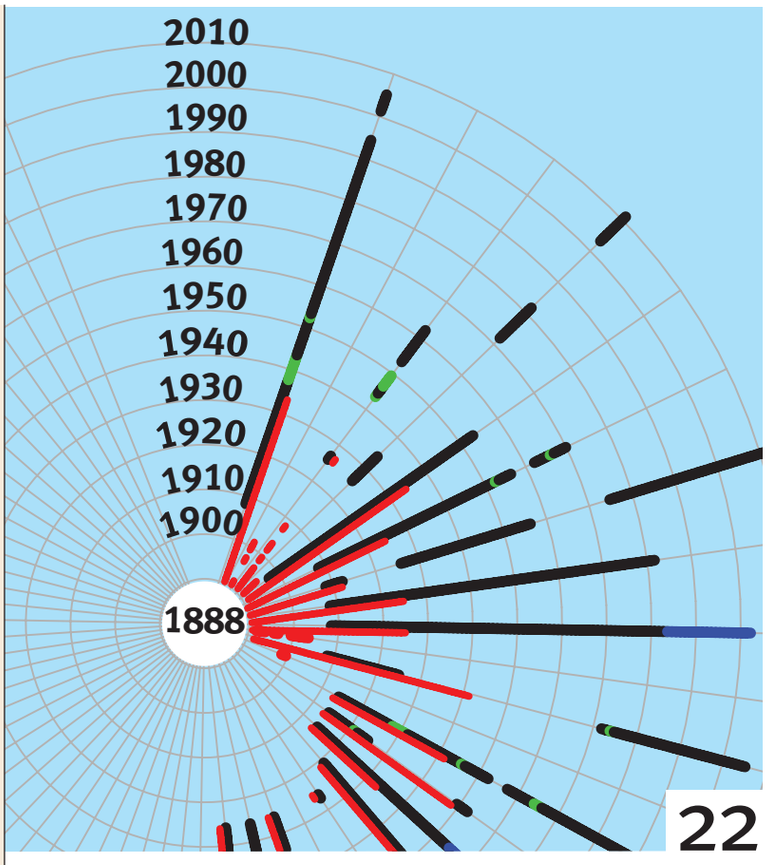
CONTRIBUTORS

JOHN ALTDORFER ["Score."] It's a lot of paperwork for his tax guy, but John Altdorfer says he's never really had a bad day since becoming a full-time freelance photographer. Pre-Internet, he was a writer, but, "Seriously, a picture is generally easier to take than writing a thousand words." (The only writing he still does is for *Pitt Med*.) Seasoned photographers at daily papers helped Altdorfer adjust to the medium ("I couldn't have paid for a better education"), and he quickly learned to always find the interesting shot. He says that the most rewarding part of the job is meeting new people every day: "Whether they're rock stars or local doctors, this job gives me hope every day that the good people in this world will prevail."

BRETT MURPHY ["The History of Disease, In Color" and many other stories] began a pinch-hitting gig on the *Pitt Med* staff four months ago, just days before he graduated from Pitt with a BA in English writing a semester early. Murphy, an Al McDowell Memorial Scholarship recipient, has also been on staff at *The Pitt News*; freelanced for *Pitt Magazine*, *Pop City*, *Next Pittsburgh*, and *Shady Ave. Magazine*; and edited a memoir—not a shabby portfolio for a 22-year-old. And now, the Central Mass. native is packing his sunscreen (guess those last couple of polar vortexes didn't sit well with him). In fall 2014 he'll enroll in UC Berkeley's Graduate School of Journalism.

COVER

Some what-ifs can't be answered in clinical trials. Computational modeling is helping Pitt scientists learn (almost) everything they want to know about health but were afraid to ask. (Illustration: Michael Lotenero © 2014.)



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What If? 12

Modeling in medicine is not just convenient, it also has profound implications, if you ask Yoram Vodovotz. "The conscious mind can't handle more than a few things [at once]," he says. But modeling gives you "the best of both worlds—the rational process that comes out of your conscious mind, integrated with the ability of your unconscious mind." He and others here at Pitt are answering some really hard questions *in silico*.

COVER STORY BY ELAINE VITONE AND BRETT MURPHY

The History of Disease, In Color 22

In a concerted effort (involving 200 million keystrokes and probably a few paper cuts), Pitt's Project Tycho has digitized cases of 56 infectious diseases in every U.S. state and territory before, during, and after vaccination licensure from 1888 to today. The database is helping scientists understand contagion.

BY BRETT MURPHY

Illuminating Work 26

Pittsburgh has shown us what we are made of.

BY ALLA KATSNELSON

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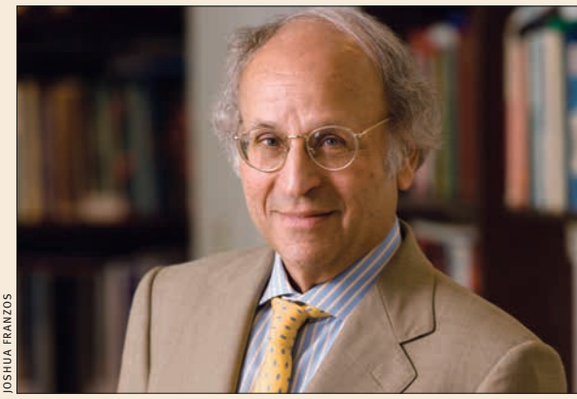


JOSHUA FRANZOS

Can we begin to make our lives once more all of a piece? … When one person taps out a beat, while another leads into the melody, or when three people discover a harmony they never knew existed, or a crowd joins in on a chorus as though to raise the ceiling a few feet higher, then they also know there is hope for the world. —Pete Seeger

Often, when Jonathan Pruitt talks about his research, someone will say, "That's exactly like my workplace!" Jonathan, a behavioral ecologist, is one of Pitt's assistant professors whom I recently invited to speak in my Friday Senior Vice Chancellor's Research Seminar series. He spends his days peering into the webs of social spiders—creatures that, unlike many of the 43,000-plus species in the order *Araneae*, are not loners; rather, they live in colonies. Jonathan has learned that these arthropods are like us in many respects. The roles that these spiders take on within their groups are not determined by the size of their ovaries or mandibles or other aspects of morphology—as previously assumed and is the case with ants—but by their personalities. The social structures which they build are sophisticated.

I was particularly struck by Jonathan's description of a species of social spider found in the Americas, *Anelosimus studiosus*. The fitness of their colonies is determined by the behavioral diversity within them. Some of the spiders build beneficial relations with otherwise parasitic visitors, some are foraging specialists, some concentrate on brood care, some on defending the colony. Not only do the individuals have a propensity for a given behavior, but they are best at the roles they fill. They build on their aptitudes in life, and the group is better for it.

Medicine has something to learn from *A. studiosus*. In recent times, more than 80 percent of health care has been provided by someone other than a physician. With the advent of the Affordable Care Act, we can expect this number to increase; and though that increase is driven by cost concerns and the rising number of insured patients, it is probably a good thing for patients. Nonphysicians can offer substantial primary care and have more time to spend with a patient than is the case with many physicians. Likewise, the modern biomedical research setting is changing. A realization of the complexity and interconnectedness of human biology (note that we now have a Department of Computational and Systems Biology) has researchers collaborating across disciplines as never before—with a diversity of technologies and habits-of-mind.

Studies of engineers have shown that cognitively diverse teams typically outperform others on tasks requiring innovation and exploration of new ideas. But it can take time for both clinical and research teams to gel, and gelling doesn't always happen (especially if we are antisocial spiders!).

Whether we want to break new scientific ground or provide the very best care for our patients, we need to learn to not just work together but to thrive together. How do you build cohesion among persons with different training, expertise, behavior, and perspectives? As authors of one recent meta-review on team science noted, the ability to reflect—on what we each bring to the table, in terms of ability, personality, and our own filters—can make or break a team.

Speaking of thriving teams, here I congratulate Dan McCoy (a Pitt undergrad featured on p. 7). He was a member of the U.S. men's sledge hockey team that traveled to the Paralympics in Sochi this winter. U.S. beat Russia in the finals and brought home the Gold. Truly inspiring teamwork, and I'm also inspired by the spiders!

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

Devoted to noteworthy happenings

at the medical school

IT'S IN YOUR HEAD

A freshman, sitting in history class, started wiggling his fingers in front of his face. *How exactly,* he wondered, *is the brain doing that?* Forty-five years later, Peter Strick, a PhD who leads the University of Pittsburgh's Department of Neurobiology and codirects the Pitt/Carnegie Mellon Center for the Neural Basis of Cognition, is still exploring the wonderfully complex epicenter of human nature. The Brain Institute opened this past winter; it has received funding from the School of Medicine, the Chancellor's Office, and the DSF Charitable Foundation.

Strick says the main goal of the institute is to create a multidisciplinary environment "to ensure financial, intellectual, and technical resources." Five neuroscience centers will be the core of the Brain Institute, which is modeled after Bell Labs, where scientists were given virtual free rein (and nabbed seven Nobel Prizes). Strick wants it to be a place where the thirst for discovery, not grant applications, drives research. —*Brett Murphy*

FOOTNOTE

Pitt neurosurgeon Joseph Maroon met Rajesh Durbal while they were both competing in the final portion of Hawaii's Ironman four years ago. Durbal, who has no legs and one arm, encouraged Maroon to complete the race just as the doc was giving up. Maroon ended up finishing right behind his new friend.

In February, Maroon followed Durbal again, up Mount Kilimanjaro. In the trekking party of 10, everyone, except Maroon (the party's medical director), was missing at least one limb. The point, Maroon told the *Pittsburgh Post-Gazette*, was to show that altitude depends on attitude.

Mark Nordenberg (left) will pass the torch to Patrick Gallagher this summer.

JEFF AHEARN/THE PITT NEWS

Physicist and Alumnus to Lead University

Mark Nordenberg is a tough act to follow. In 19 years as Chancellor, he has guided the University of Pittsburgh to unprecedented heights. So members of the search committee tasked with finding his successor had their work cut out for them. They came through with a surprising candidate and a familiar face—all in one person. On Feb. 8, Pitt's Board of Trustees elected Patrick Gallagher, who will become Chancellor on Aug. 1 when Nordenberg steps down. Gallagher earned his PhD in physics here in 1991 and gave the 2013 commencement address. As the acting deputy secretary of the Department of Commerce and director of the National Institute of Standards and Technology (NIST), Gallagher oversees federal efforts to promote innovation and industrial competitiveness by advancing measurement science, standards, and technology. With a total budget in excess of $1 billion, NIST employs more than 3,000 scientists, engineers, technicians, and support staff.

Gallagher says that one of his goals is to strengthen and build upon Pitt's established partnerships with UPMC, Carnegie Mellon University, private businesses, and government at all levels.

"What I hope I really bring is a capacity to collaborate and build those bridges," says Gallagher. —*Chuck Staresinic*

CAMI MESA

Overheard

Substance Abuse and ADHD

It's getting a bad rap recently—as overdiagnosed and under-monitored. But the truth about ADHD is that it's a very real, very potent mental disorder that ripples through the everyday lives of those it affects. In 1995, Brooke Molina (shown above), a PhD and Pitt professor of psychiatry, joined a multisite study team treating nearly 600 children with ADHD. Equipped with a history of adolescent substance-abuse research, Molina and her colleagues saw the potential for a longitudinal study that would span several years. Molina wanted to understand the link between ADHD and substance abuse. Below, she talks about why young people with the disorder are more susceptible to drug abuse and how that can play out down the road. "Because for the majority of people," she explains, "ADHD doesn't go away."

Nicotine and ADHD

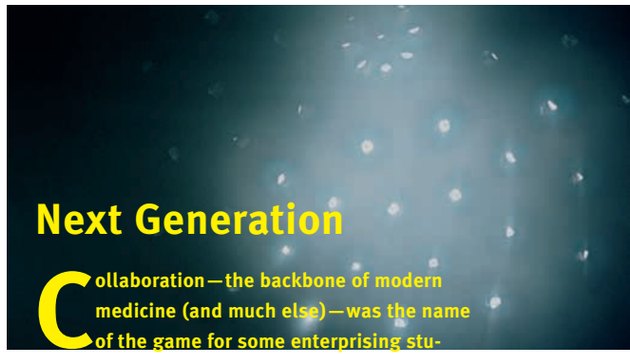
Cigarettes are particularly problematic for people with ADHD. Nicotine seems to target the biochemical deficits of . . . ADHD dopamine regulation. So what happens is people [with ADHD] often become regular smokers. They'll say, "It helps me function, it helps me do better." But then they end up treating the withdrawal more than the ADHD. It becomes addictive and health endangering.

Is drug use a kind of self-medication for them?

Our teenagers with ADHD do not appear to be using drugs and alcohol because they're self-medicating depression. This is often a social thing. Adolescents [with ADHD] often have friends who are users, and that makes them more susceptible. People hypothesize that these kids should be depressed because they're underperforming relative to their intelligence. But ADHD is not about IQ. [You might think] they would get depressed and self-medicate. But we're not finding evidence of that.

The future for these kids

If you go into any treatment facility for addicts, a third of them will have ADHD. But just because you have ADHD doesn't mean you're going to become a drug addict. Our task is trying to understand the various pathways to addiction and use those results to drive the development of treatments to prevent substance abuse and treat it if it does occur. ***—Interview by Brett Murphy***



Next Generation

Collaboration—the backbone of modern medicine (and much else)—was the name of the game for some enterprising students and postdocs at the School of Medicine this year. Some notable players:

Rachel Gordon and Julie Boiko, both pursuing MDs, presented at the Association of American Medical Colleges meeting this past fall on behalf of the Women in Science and Medicine Association. Gordon says, "A big part of what we're trying to do is equalize the playing field across medical schools." Just three student groups were invited to present. Gordon and Boiko's poster detailed what makes up much of their organization's current initiative: introducing key junior faculty skillsets to med students. "Our argument is, yes, students need [to learn] many of the same things being taught to young doctors."

Austin Nuschke, a third-year pathology PhD student, and Donald Taylor, a pathology postdoc, won first place in the Michael G. Wells Student Healthcare Entrepreneurship Competition for their Curostem bio-bandages. Nuschke and Taylor's team has developed a polymer gel infused with a form of adult stem cells (mesenchymal) for healing chronic, external wounds, such as diabetic ulcers. Unlike other dressings, the bio-responsive technology is designed to address the fickle personalities of wounds and heal them within weeks—before they become infected. If the gel proves its mettle in preclinical and clinical studies, its inventors see it saving limbs, lives, and more than $100,000 per patient with dangerous wounds.

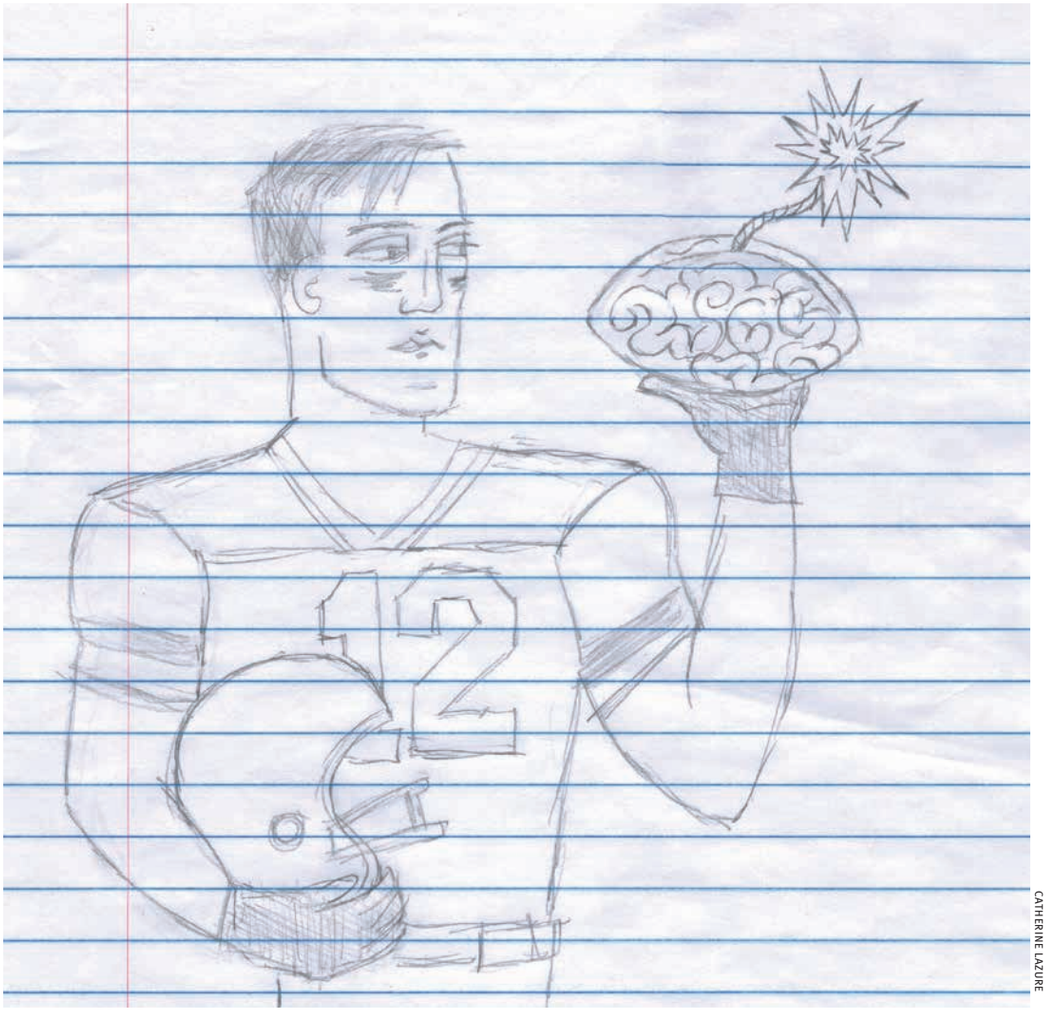
Amanda Gelman, a fourth-year med student, teamed up with a group of doctors, including her mentor Sonya Borrero, an MD, to publish her second paper in her scholarly project on HPV vaccination. "Racial Disparities in Human Papillomavirus Vaccination: Does Access Matter?" appeared in the *Journal of Adolescent Health* last summer. Using a national survey database, the group studied contributing factors in HPV vaccination rates—namely, race, ethnicity, and their relationship to health care access. Gelman says they learned "there's a valuable opportunity to explore preventative strategies at the doctor-patient level." ***—BM***

Strong Safety

Concussions have been the issue du jour recently in the NFL: the subject of lawsuits, editorials, and congressional hearings. In 2009, the league made changes to its health and safety practices, and even its gameplay, in an effort to decrease head injuries.

Now, the NFL and General Electric have given a $300,000 grant to Pitt researchers to study the use of high-definition fiber-tracking, a kind of intricate and colorful brain "X-ray," in determining the exact prognosis of a head injury. Scientists from the UPMC Sports Medicine Concussion Program and Pitt's Learning Research and Development Center (where the imaging technique was developed) will team up on the project.

"We know there are six different trajectories of a concussion," says Michael Collins, a PhD associate professor of orthopaedic surgery and director of the UPMC Sports Medicine Concussion Program. "Cognitive, ocular, vestibular, migraine, mood/anxiety, and neck. But there is no visual marker telling us which will be in play after each concussion." Fifty athletes treated for concussion at UPMC will undergo HD fiber-tracking, which scans the water inside axons to create colorful, detailed images of brain connections. ***—Nick Keppler***



CATHERINE LAZURE

FOOTNOTE

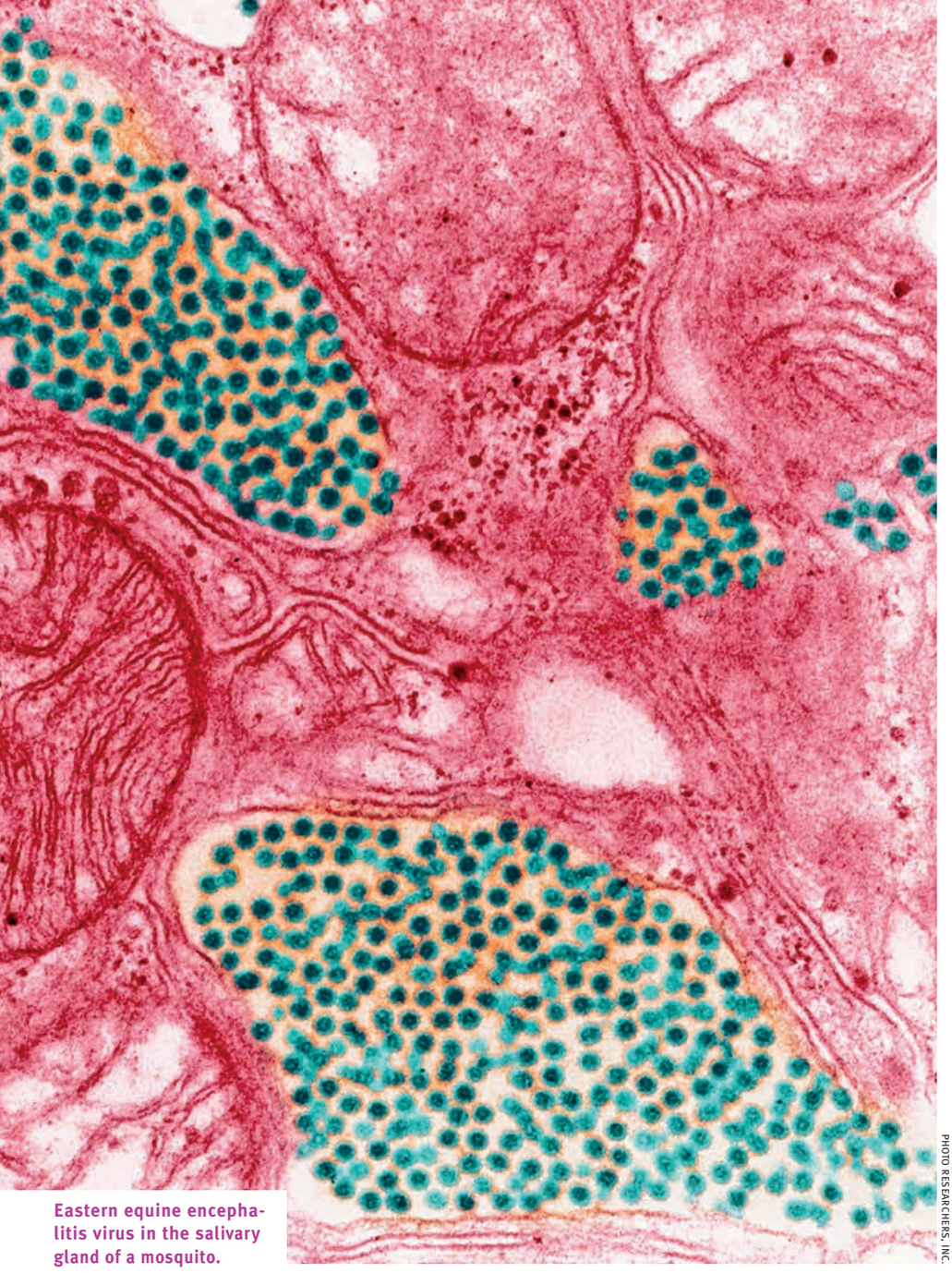
The med school faculty lost control of its students. Just too many give-and-go's and breakaway layups. At a round-robin basketball tourney this winter at the Pete, four faculty and student teams (from the med school and other health science schools) raised money while crossing each other on the hardwood. "Nothing but Netters," the med student squad, took home the trophy. The United Way took home the proceeds.

ONE COAT, TWO COAT, WHITE COAT, BLUE COAT

Seniors at the Pittsburgh Science and Technology Academy, many of whom are aspiring clinicians and scientists, probably didn't imagine themselves slipping into a white coat for many years. But the SciTech Executive Experience, a mentorship program, let them try on a bioscience career and the research attire that goes with it. This year's cohort got started with the "Blue Coat Ceremony," where students were paired with laboratory mentors and draped with official program coats.

For their entire senior year, more than two dozen students spend up to 10 hours a week in research settings at Pitt.

Blue-coaters like Mecia Howard are getting hands-on exposure to medical science. So far this year, Howard has kept busy logging and analyzing data (there's *a lot,* she notes) in preparation for a visual perception study in the lab of Matt Smith, PhD ophthalmology prof. "I've always been interested in neuroscience," the 18-year-old says. "Here, I can learn about how the brain works and responds to the world around it." *—BM*



Eastern equine encephalitis virus in the salivary gland of a mosquito.

PHOTO RESEARCHERS, INC.

TAKING OUT THE BITE

Last September, thousands all over Norfolk County, Mass., stayed indoors at sundown. The towns were under curfew because of a case of eastern equine encephalitis, which is caused by a mosquito-spread pathogen and fatal in 33 percent of cases. Scientists from Pitt's Center for Vaccine Research recently coauthored a *Nature* paper that unpacks a key feature of the disease, which seems to be specific to the Atlantic and Gulf Coast states.

The RNA of the virus binds to the microRNA of the cells of the infected organism, says William Klimstra, PhD associate professor of microbiology and molecular genetics at Pitt. It essentially highjacks the victim's microRNA and replicates within it undetected. And before symptoms emerge and the immune system can react, "the subject is dead," he says. So stopping that binding process—the hijacking—could be the key to a vaccine. ***—NK***

Name Dropping

In a lecture at the School of Medicine on May 13, **Sarah Tishkoff** will explain patterns of evolutionary variation in Africa and what these tell us about "the evolutionary history of modern humans, how people adapt to diverse environments, and the impact on human disease."

Her multidisciplinary lab at the University of Pennsylvania studies different African groups, including click-speaking tribes in the East and pygmy populations in Central Africa. She says studying variation and adaptation can improve "our understanding of the genetic bases for disease susceptibility."

Tishkoff, a PhD and the David and Lyn Silfen University Professor of Genetics and Biology, claims a National Institutes of Health Pioneer Award and the David and Lucile Packard Career Award. She is the first of this year's Laureate Lecturers at Pitt. Others on the vaunted playbill:

Xiaowei Zhuang, PhD professor of chemistry and chemical biology and of physics at Harvard University and member of the National Academy of Sciences, will be here June 4. Zhuang will zoom in on her lab's work with bioimaging at the nanoscale level—single-molecule and super-resolution fluorescence microscopy.

Fellow National Academy member (who is also a member of the American Academy of Arts and Sciences) **Joseph Schlessinger**, PhD professor and chair of pharmacology at Yale University, will be giving a June 26 lecture discussing transmembrane signals and their effect on cell growth and differentiation.

The fall Laureate Lecturer is **Philippa Marrack**, PhD professor of immunology, biochemistry and molecular biology, and medicine at the University of Colorado. (She, too, is a member of both the American Academy of Arts and Sciences and the National Academy of Sciences. The native of England also is a fellow with the Royal Society.) Her Nov. 12 talk will cover an unusual population of antibody-producing cells.

The series wraps up Dec. 10 with **Carla Shatz**, PhD professor of biology and neurobiology at Stanford University and director of its interdisciplinary program, Bio X. She'll talk about critical periods in development and how understanding them can help unlock some of the mysteries of Alzheimer's disease. Shatz has been distinguished with foreign member status with the Royal Society and other honors that, like those of her Laureate peers, are too numerous to mention here. ***—BM***

SCORE.

Alone on the bench, the goalie pops his right thigh out of a prosthetic leg. Then, after a deep breath, he removes his left artificial leg. Now, he's ready to play the game he loves—ice hockey.

The goalie is one of the more than 200 players competing for November's USA Hockey Sled Classic championship at the CONSOL Energy Center, home of the tournament host, the Pittsburgh Penguins.

Nearly all the players have limited or no control of their legs. Some were born with spina bifida. Others suffered spinal cord injuries. Many of the vets in the tournament lost limbs in combat. And, well, these guys know how to *move*.

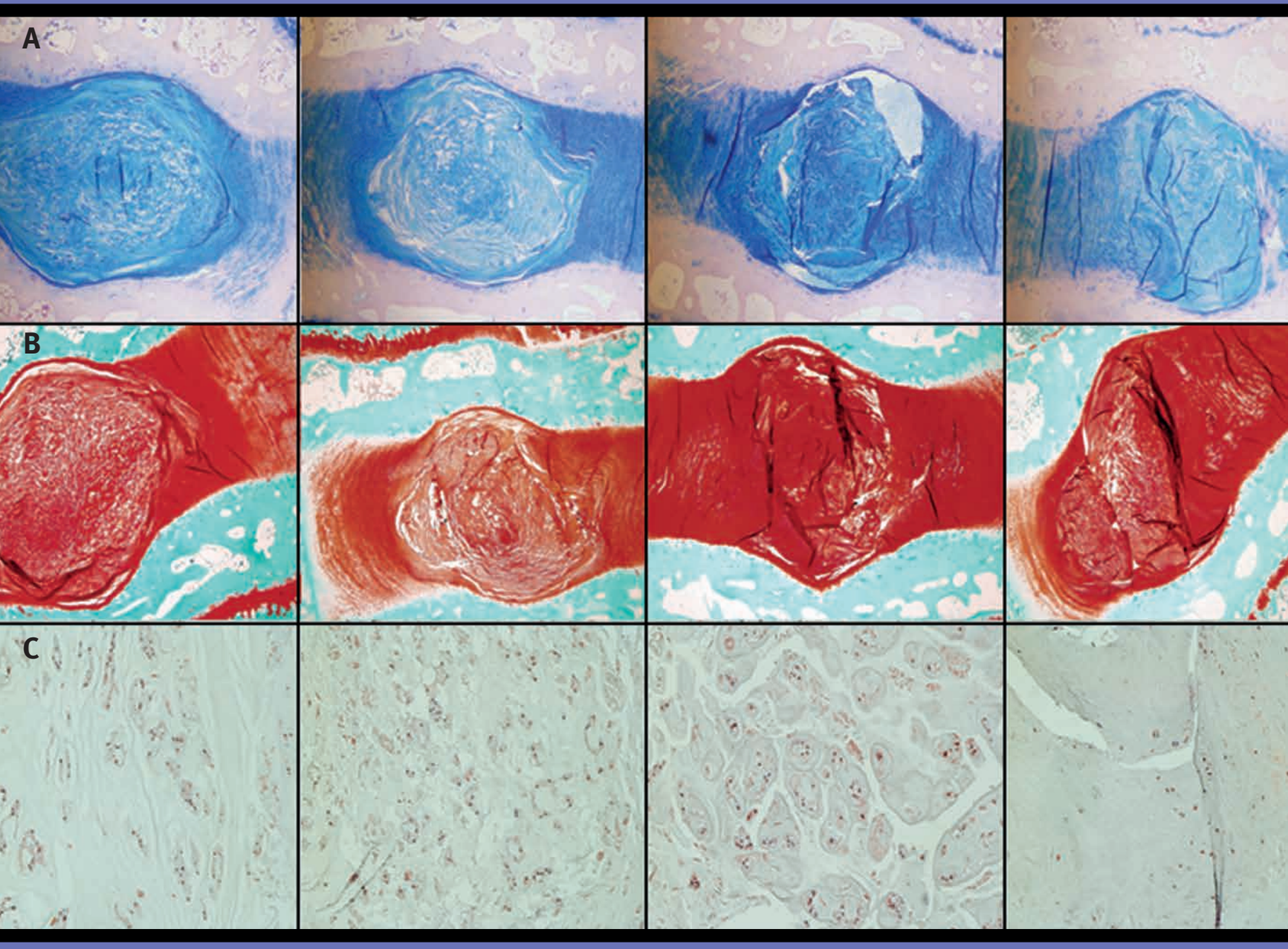
Players propel themselves forward with short hockey sticks (each with a pointed end for pushing) while strapped into hard plastic seats perched on tiny metal frames with twin skate blades. They blaze across the ice at up to 30 miles per hour.

Lee Tempest is a data coordinator at the University of Pittsburgh Model Center on Spinal Cord Injury. The 40-year-old started playing when he was 18, after a car wreck injured his spinal cord. "After years of playing, I feel I can do so much more in all aspects of my life."

Although his Mighty Penguins, sponsored in part by the UPMC Rehabilitation Institute, missed the trophy round, Tempest and his 19-year-old teammate, Pitt sophomore Dan McCoy, understand that the real victories don't show up in the final score. "The game's made me who I am now," says McCoy, watching from the stands. It's given me the confidence to . . . let people know that who I am is not about spina bifida."

McCoy focuses on the action on the rink below. A player unleashes a blistering shot. The puck slips past a goalie's outstretched arm. McCoy smiles. It's a winner. *—Photo and Text by John Altdorfer*

Note: *Dan McCoy went on to play for the U.S. Men's Team during the 2014 Paralympic Winter Games in Sochi; the team took the Gold.*



Using three types of stains, Sowa's work shows that injured spinal discs of rabbits become more damaged (we see less staining and fewer cells) when treated with glucosamine (4A–C) than when they are left alone (3A–C). For comparison, the discs of healthy rabbits not treated with glucosamine (1A–C) and healthy glucosamine-treated rabbits (2A–C) are shown.

CARTILAGE OF CONTENTION

IN ANIMAL MODELS, GLUCOSAMINE SEEMS TO DO MORE HARM THAN GOOD

BY MELINDA WENNER MOYER

One of the most common questions that patients with back problems ask Gwendolyn Sowa, an MD/PhD associate professor of physical medicine and rehabilitation at the University of Pittsburgh, is a simple one: "Should I take glucosamine?"

An estimated 5 million U.S. adults take this supplement, many to alleviate back pain. But there is little research to suggest that it actually works. To get some solid answers, Sowa has been putting glucosamine to the test. She doesn't know yet how the supplement works in humans. But if the results are similar to what she's seen in rabbits, people with lower back pain might be better off without it.

Sowa's investigation into the issue began in 2008, when she and her colleagues exposed cells isolated from the spinal discs of rabbits to glucosamine. They found that the compound reduced markers of inflammation in the cells, and that it also seemed to interfere with the cells' ability to produce matrix proteins important for supporting the structural integrity of spinal discs.

"It was surprising. No one had ever seen this negative effect on matrix proteins," Sowa explains. "We thought that we really needed to confirm this finding to make sure it wasn't an artifact of our in vitro system."

To do so, Sowa and her colleagues used a live rabbit model of disc degeneration associated with lower back pain in older people. Then, Sowa and her colleagues fed the affected rabbits, as well as a group of healthy rabbits, daily over-the-counter glucosamine, in doses comparable to the amount that people typically take. The team periodically evaluated the rabbits' spinal discs using magnetic resonance imaging (MRI), histological studies, and gene expression assays.

Twenty weeks later, "My resident came back with the first set of results, and I was convinced that she'd switched the ID numbers on the animals."

Twenty weeks later, "My resident came back with the first set of results, and I was convinced that she'd switched the ID numbers on the animals," says Sowa.

"On every outcome measure we looked at, we saw this . . . negative effect."

Among other things, the glucosamine appeared to interfere with the production of matrix proteins—and to erode the central gelatinous protective layer found in the center of the discs.

Sowa and her team also noticed that glucosamine reduced inflammation in the disc. Because inflammation is closely tied to the sensation of pain, the finding could explain why people with lower back pain feel better after they take glucosamine. But if "people are taking it and causing damage to their discs, then that's a bad thing," she says.

Sowa stresses that her findings, published online in January in *Spine*, are still preliminary:

"I've had people say, 'Do I stop taking glucosamine?' and I say, 'I don't know, because you're not a rabbit.' It's hard to say how much of this is clinically relevant."

To understand whether this effect is present in humans, Sowa intends to study the mechanism of how glucosamine causes these negative effects on matrix. "Understanding the molecules affected by glucosamine will allow us to answer questions regarding the long-term effects on humans. It will give us the tools to study the immediate response to this compound. Disc degeneration is a chronic process, so it could otherwise take decades to determine the effects in humans," Sowa says.

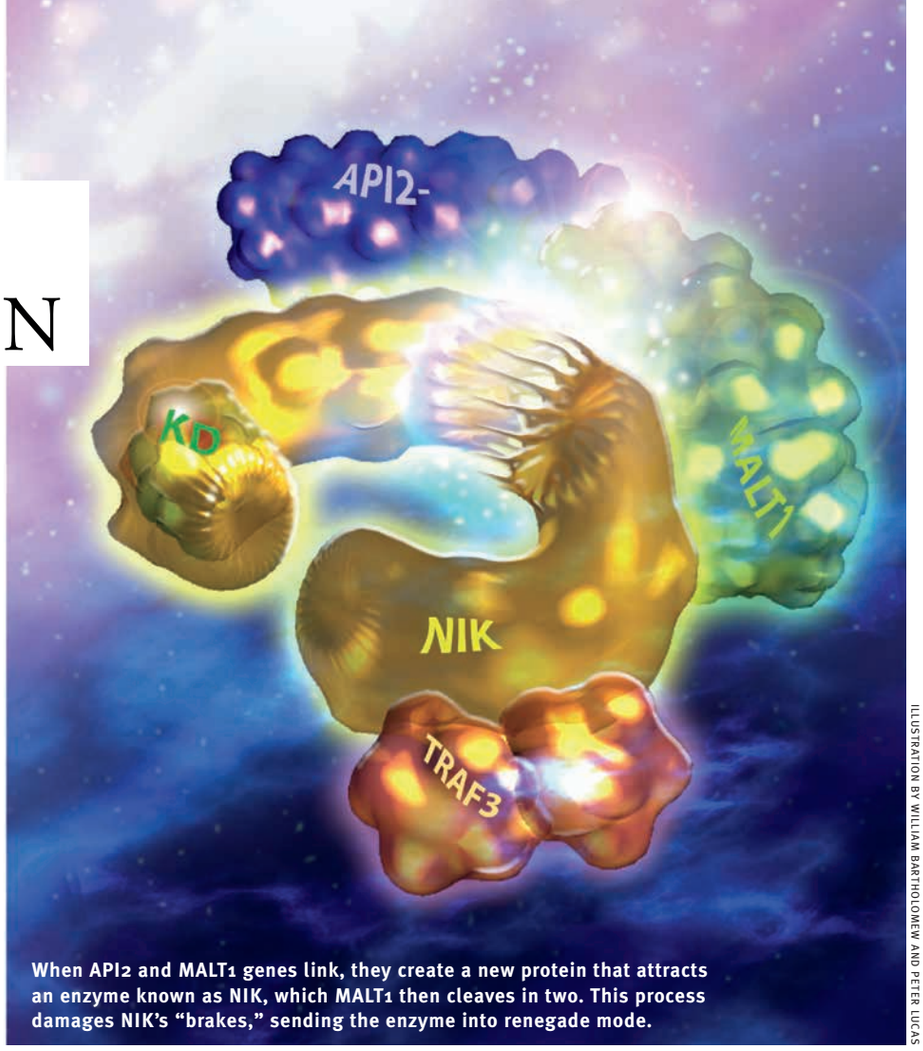
Sowa's work reminds us that just because many supplements and alternative remedies are "natural" does not mean they are intrinsically safe.

"We don't know the risks of many supplements, so patients assume there aren't any," she says. But "not knowing the risks does not equate with not having any risks." ■

FOUND IN TRANSLOCATION

LYMPHOMA BREAKTHROUGH MAY HAVE BROADER SIGNIFICANCE

BY BEN KORMAN



When API2 and MALT1 genes link, they create a new protein that attracts an enzyme known as NIK, which MALT1 then cleaves in two. This process damages NIK's "brakes," sending the enzyme into renegade mode.

ILLUSTRATION BY WILLIAM BARTHOLOMEW AND PETER LUCAS

The Lucases thought they were lymphoma researchers.

So did David Perlmutter, chair of the Department of Pediatrics for the University of Pittsburgh and physician-in-chief and scientific director of Children's Hospital of Pittsburgh of UPMC, when he recruited them from the University of Michigan in late 2012. After all, Linda McAllister-Lucas, MD/PhD chief of service in hematology/oncology and associate professor of pediatrics at Pitt, and Peter Lucas, MD/PhD associate professor of pathology and pediatrics at Pitt, had already done seminal work on the genetic triggers behind MALT lymphoma—a form of cancer that typically proliferates along mucosal surfaces like the stomach. (MALT stands for mucosa-associated lymphoid tissue.)

A little over a year later, it's clear that the lab/life partners' work reaches far beyond the disease they've studied for well over a decade. Since their move to the John G. Rangos Sr. Research Center at Children's, the two have been applying their insights to several other forms of cancer, as well.

The couple first began studying MALT lymphoma in 1999. They noticed that two subsets of the disease are defined by two distinct chromosomal translocations. (Translocations, which pair up segments of genes in the wrong places, are common in lymphomas.) They found that these mismatched couplings give rise to aberrantly expressed versions of the proteins BCL10 and MALT1. When expressed correctly, these proteins play a vital role in the function of lymphocytes (white blood cells). "But if [BCL10 and MALT1 are] targeted by chromosomal translocation," says McAllister-Lucas, "that can contribute to the development of a cancer."

And so began the team's foray into how these triggers fit into a larger picture.

In a 2011 *Science* paper, the couple characterized a third translocation unique to MALT lymphoma: Part of the API2 gene links to part of the MALT1 one, creating a fusion protein that "normally shouldn't even exist in the cell," says Lucas. This new protein attracts an enzyme called NIK. But once NIK is attached to the fusion, MALT1 chops NIK in two.

You might think splitting NIK in two would make it weaker. But when MALT1 cuts NIK, it also slices off an important regulatory portion, sending NIK into a renegade mode and allowing it to act unchecked. Cells, then, are likely to rapidly proliferate, potentially into cancer.

Because NIK functions as a kinase—a kind of enzyme that can alter neighboring proteins—it can influence the life and death of cells. Kinase activity, along with API2-MALT1's NIK-cutting aptitude, is considered potentially "druggable" by the pharmaceutical industry. "There are laboratories that are working on early stage drugs to target MALT1," says Lucas.

Since their own "translocation" from Michigan, the team has been examining the roles these proteins play when they are not in lymphocytes.

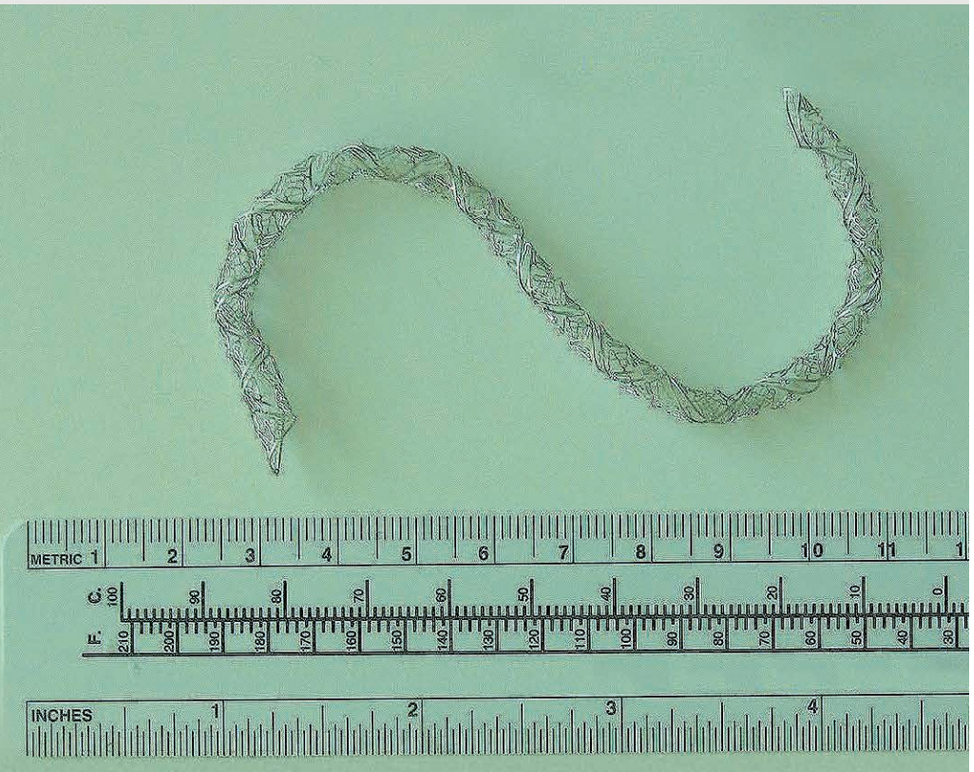
BCL10 and MALT1, it turns out, are present in nearly every cell in our bodies. And even when these genes are expressed normally, they can be stimulated to control cell behavior.

It seems that BCL10 and MALT1 may also play roles in the development of certain breast cancers, hepatocellular carcinoma, and osteosarcoma. The Lucas lab is in the early stages of investigating the role of BCL10 and MALT1 in these cancers. It's an unexpected shift, but a welcome one—like their move to Pittsburgh.

"We actually never intended to leave Michigan," says McAllister-Lucas.

"But over the years," adds Lucas, "we became aware of good departments of pediatrics at various places and good departments of pathology in other places. It's unusual to find really strong departments in both of those areas in the same place like you have at Pitt." ■

Computed tomography image of a magnesium-alloy trachea stent—designed and built by Pitt researchers—that was implanted in a rat. Surface pitting and small fissures on the stent appear as the device degrades (as planned).



This magnesium-alloy stent was developed for an arteriovenous fistula (the connection of a vein and an artery often created for hemodialysis); it's a routine procedure in people with kidney failure. Pitt scientists made the alloy, as well as the coating.

COURTESY S. YARMOLENKO, NORTH CAROLINA AGRICULTURAL AND TECHNICAL STATE UNIVERSITY (TOP IMAGE) AND V. SHANOV, UNIVERSITY OF CINCINNATI (BOTTOM IMAGE).

PEDAL TO THE METAL

THE FAST-EVOLVING FIELD OF BIODEGRADABLE IMPLANTS

BY DANA YATES

To heal by implanting something inside a person that is not *of* the person, like a metal pin, for example, is a feat of biomedical engineering—but it comes with risks, including infection and inflammation. And after the procedure, the implanted metal either becomes part of the person forever or has to be removed later in yet another procedure, which carries its own risks, as well as costs.

But now on the horizon, says a group of Pitt scientists, is the next generation of these devices—metal implants that will do their job and then perform a vanishing act. Biodegradable plastics, such as those widely used in sutures and more recently in cardiac stents, actually aid the healing process. Up next, many expect: biodegradable metals that can do the same, says William Wagner, who is director of the Pitt/UPMC McGowan Institute for Regenerative Medicine and PhD professor of surgery in Pitt's School of Medicine and of bioengineering and chemical engineering in its Swanson School of Engineering.

The McGowan Institute brings together scientists, engineers, and clinical faculty. In 2008, with $18.5 million in funding from the National Science Foundation, McGowan joined a consortium of institutions, led by the North Carolina Agricultural and Technical State University, to develop biodegradable metal implants for surgical use in orthopaedic, cardiac, and reconstructive procedures. The NSF Engineering Research Center for Revolutionizing Metallic Biomaterials (ERC-RMB), as it's known, is producing biodegradable metals designed to promote healing while degrading. It's also supporting research on novel coatings, alloys, and miniaturized sensing systems so that physicians can monitor and control the degradation process.

Across the ERC-RMB team, researchers have developed several device prototypes, including bone-fracture plates and surgical screws. A Pitt crew, for example, has been working with scientists at the University of Cincinnati to develop a stent that will stabilize the arm veins of patients requiring kidney dialysis.

"The field of medical implants has moved to looking at ways to get the body to heal itself," says Wagner. ■


What if that trial failed because we didn't give the drug to the right patients?
What if we closed schools during an influenza outbreak?
What if we held off on that transplant?
What if employers offered more paid sick days?
What if?
What if we redrew the map for organ allocation?
What if vaccination programs had never been implemented?

REALLY HARD QUESTIONS, ANSWERED BY MACHINES

BY ELAINE VITONE AND BRETT MURPHY

ILLUSTRATION BY MICHAEL LOTENERO

A bug goes viral. Inside each unlucky person who takes ill, organs send messenger proteins to one another in crosstalk to fend off infection. Within each of these organs, cells download and duplicate the virus. And all the while, both the cells and the viruses swap data among themselves, gather input from their environments, put it all together, and—most importantly—learn from it. It's reprogram yourself or die.

We biological beings are, at every level, a feedback loop on a mission—an intelligent system.

The machine-learning crowd figured this out decades ago, launching a whole class of techniques and algorithms that took cues straight from the life sciences. Ironically, medicine took a while to warm to the idea of what these two seemingly disparate disciplines, computing and biology, have to offer each other. (Though Pitt's lineage of using computers to solve real-world problems in health care dates back to the 1970s, when Jack Myers, an MD and the late chair of medicine, with Randolph Miller, MD '76, and Harry Pople Jr., created Internist-I, perhaps the first computer-aided diagnostic tool.)

Imagine you want to build a model of a biological process. It's a little bit like perfecting a cake recipe. Say you have 20 ingredients you're considering using. To decide how each variable contributes to the final product, you could go the trial-and-error route, baking Bundt cake after Bundt cake and omitting one ingredient each time. To try changing any two ingredients, you'd have to bake 190 cakes. To change any three, you'd need 1,140. Any four would take 4,845. Or, you could feed all the ingredients into a computer, explaining everything you know about how they interact with one another based on your experience. You could model thousands of what-ifs, coming up with a shortlist of possible recipes—then just bake and taste-test the ones least likely to flop.

In medicine, the "ingredients" for a model might be insights gleaned from the literature, clinical experience, lab experiments, historical records of epidemics, and other data—or some such combination thereof. Researchers run a simulation and check their *in silico* results, as those in the field like to call them, then analyze them for patterns that will inform their "recipe." Then, they gather more data as needed to fine-tune the model and fill in any gaps. Once the model proves viable, they can tweak the dials and test the what-ifs. It's an approach that works well in all sorts of

applications—biomedical device development, disease progression prediction, and so on—and it's holding increasingly more promise as Big Data grows bigger.

Imagine the possibilities with that bug we started with. You could model the molecular process of how it infects cells, duplicates, and spreads throughout the body. You could model disease vectors. (Pitt people have already modeled dengue fever outbreaks at the level of individual mosquitoes.) Take it a few steps further, and you could model how resistance emerges after patients drop various treatments. Drug resistance might then grow to become a population-wide problem. You could model that, too.

Eventually, the medical-computational-modeling community hopes, they'll be able to string all these various pieces together to create one giant *SimCity* of disease, rendering the inner workings of each one of its inhabitants down to the sub-cellular level. Test your what-ifs there, and you could significantly narrow your search for drug candidates, public health interventions, you name it, saving precious time, resources, and lives.

That's the dream. To realize it, Pitt people are delving into difficult questions about health care practice and policy, as well as how the body works. They're building new tools and forging the kind of cross-disciplinary, cross-institutional partnerships it will take to build this *SimCity*. They're asking questions that aren't so easy to ask with a clinical trial. Here are some of the stories behind the work and a few of the intriguing what-ifs these teams are tackling. *—Elaine Vitone*

FIRST, GET THE DATA

In his field, epidemiologist Don Burke, an MD and Pitt Distinguished University Professor of Health Science and Policy as well as professor of medicine, was an early adopter of modeling. His first simulation, which he published in *Nature* in 2004, identified previously unrecognized patterns in Thailand's dengue fever epidemic. He went on to publish similar epidemic analyses for the United States and Central Africa. Following the Sept. 11, 2001 attacks, he designed a smallpox-outbreak model that directly informed U.S. vaccination policy for biodefense preparedness.

Like with all simulation projects, Burke's began with a lot of homework to make sure the model was realistic. "We kept going back to the historical record," he says. (For the Thailand project, his team centralized one province's national reporting on dengue fever going back 30 years.) "And after doing that a number of times, we decided, 'Oh, let's go do it all.'"

By "it all," he meant build a single, centralized, open-source database of all infectious disease cases, everywhere. For as far back as the records go.

A lofty goal, for sure. But by that point—about eight years ago—he was well positioned to build the team that could tackle it. As Pitt's new dean of the Graduate School of Public Health—as well as its associate vice chancellor for global health, health sciences, director of its Center for Vaccine Research (CVR), and UPMC Jonas Salk Professor of Global Health—he'd brought to the University a coveted Models of Infectious Disease Agent Study (MIDAS) grant from the National Institutes of Health. (Pitt has since been named a MIDAS National Center of Excellence.)

To support the MIDAS effort, Burke founded a modeling motherboard of sorts, formally known as the Public Health Dynamics Laboratory (PHDL). A collaboration between Pitt, Carnegie Mellon University, and the Pittsburgh Supercomputing Center, the lab plans to make computational modeling in epidemiology an accessible, everyday tool for students, researchers, public health decision-makers, and anyone else interested. A number of the lab's members are Burke recruits from fields you might not expect in the health sciences—statistical physicists, computer scientists, game theorists, and machine learning experts—whom he proudly calls "hardcore computationalists."

In recent years, PHDL has gone public with that historical database Burke dreamed of. Thus far, Project Tycho, as it's called, includes records for the entire United States, and later this year, the team plans to link it to records from Brazil, Taiwan, and France. The group has also launched FRED, a platform that allows you to simulate the spread of disease from the comfort of your own smartphone. (More on these later—see below and p. 22.) Burke's hope is that the enthusiasm of these early adopters will become … well, infectious. *—EV*

A *WHAT-IF* GENERATOR

Diseases interact with their environment and can't be understood in a vacuum. Like the people who carry them, their reactions differ from scenario to scenario. They're dynamic.

A new modeling platform called FRED—Framework for Reconstructing Epidemiological Dynamics (the acronym honors Fred Rogers)—allows researchers to chart the paths of epidemics and the effects of mitigation strategies, viral evolution, and personal health behavior. "We're trying to tie together things that happen inside human beings and, essentially, the population impact of interventions," says John Grefenstette, a PhD professor of biostatistics in Pitt Public Health and director of the Public Health Dynamics Laboratory at Pitt.

FRED uses census-based, synthetic populations of the entire United States. (What's a synthetic population? Computer-generated data based on actual demographics—"virtually real people without the possibility of a privacy infringement," says Grefenstette.)

The open-source simulator is available online and will be released as an app. It allows you to create a scenario in any U.S. county by controlling "levers"—related to factors like school cancellation days or vaccination rates—that replicate "health-related human behavior based on demographic characteristics."

The tool takes into account the personalities of different places—for instance, an older Pittsburgh population versus a younger Salt Lake City. "Our policies are going to have locally different effects," says Grefenstette.

FRED KNOWS

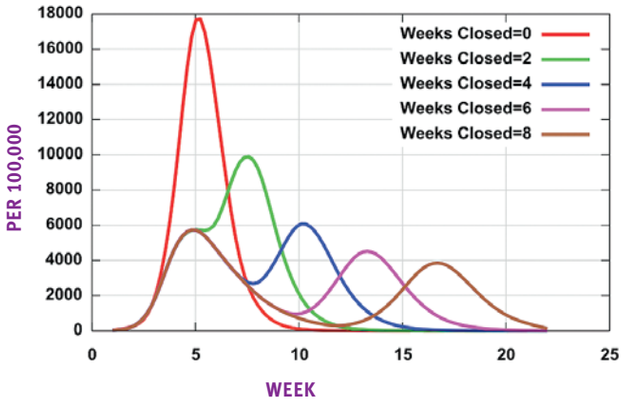
Here's the difference the length of school closures can make on an influenza epidemic in Allegheny County. In this model, schools are set to close after 10 kids get sick.

The top graphs both show that the number of cases is decreased by school closure but not by as much as you might think, though closures do delay outbreaks. (The "attack rate" is the cumulative percentage of persons infected in the population.) When schools re-open, the epidemic trucks on.

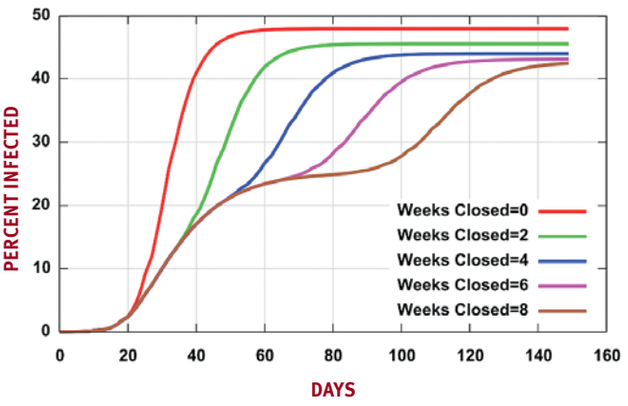
With FRED, you can create animations to see how the epidemic will play out based on the parameters you set.

To try it for your county, go to ... fred.publichealth.pitt.edu/simulator/

FRED: ALLEGHENY COUNTY
INFLUENZA
EFFECTS OF SCHOOL CLOSURE ON INCIDENCE

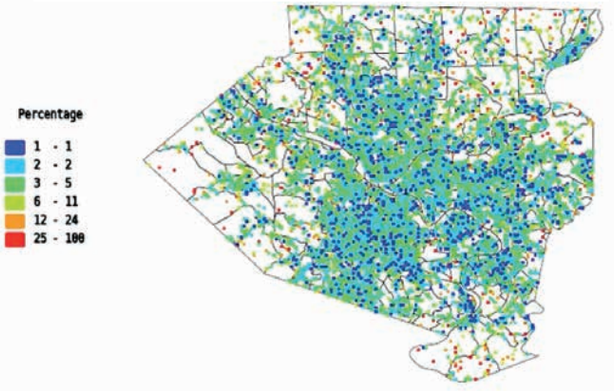


FRED: ALLEGHENY COUNTY
INFLUENZA
EFFECTS OF SCHOOL CLOSURE ON ATTACK RATE



INFLUENZA IN ALLEGHENY COUNTY: NO SCHOOL CLOSURE
DAY (35)

INFLUENZA IN ALLEGHENY COUNTY: 2 WEEK SCHOOL CLOSURE
DAY (35)



What if we closed schools during an influenza outbreak?

What if employers offered more paid sick days?

The thinking behind FRED was interdisciplinary, he adds. "We had people from the department of health, medical doctors, lawyers, statisticians, and computer people [discussing] what would be the highly relevant questions that we could ask with our models." One practical question the team came up with was: *What if employers offered more paid sick days?* They published their results in the *American Journal of Public Health* last year. Using FRED and data from the U.S. Bureau of Labor Statistics, they concluded that just two extra paid "flu days" would reduce workplace infections by almost 40 percent.

—Brett Murphy

SPECIAL AGENTS

An agent-based model, like what FRED creates, simulates activities of autonomous actors (maybe individual pathogens, people, or organizations) and digests how those goings-on influence the system as a whole. The folks who come up with these kinds of models immerse themselves in fields most people have never heard of—game theory, complex systems, computational sociology, and evolutionary programming. (And they probably like *The Sims* video game.) Their models allow the curious to evaluate a design and its effects on people and places without actually implementing it in the real world—say, what a traffic light might mean for commuters on Main Street, the implications of an invasive species entering the Rhine River basin, or the ripple effect of a novel vaccine.

—Brett Murphy and Erica Lloyd

TOP ROW: BMC PUBLIC HEALTH. 2013 OCT 8;13:940. DOI: 10.1186/1471-2458-13-940.
BOTTOM ROW: COURESY PHDL.

WHAT IF THAT TRIAL FAILED BECAUSE WE DIDN'T GIVE THE DRUG TO THE RIGHT PATIENTS?

CATCHING SWELLS

When physicians talk about sepsis, a word they might use to describe it is *cascade*. But the image that comes to mind for these docs is probably not a gentle waterfall. The physiological response that is sepsis can be every bit as catastrophic as a tsunami. And patient outcomes are all over the map—one severely injured patient who ends up with sepsis (a systemic inflammation tied to infections) can do far better than another with more moderate injuries, for example. The rhyme or reason of it all has eluded scientists.

In the late '90s, a few research groups thought sepsis might respond to a TNF-targeting drug as a possible treatment. TNF (a.k.a., tumor necrosis factor) has been used for decades as a sepsis biomarker, a blood test that signals to physicians when the tide is rising. The drug seemed promising at the outset—animal and preliminary human-trial results were encouraging. But a phase III clinical trial was a dud; it had mixed results. Though many patients benefited, many others were harmed.

Frustrated by these and other dead ends in this confounding condition, Yoram Vodovotz, PhD professor of surgery, Gilles Clermont, MD associate professor of critical care medicine, and mathematician Carson Chow—all of the University of Pittsburgh—hatched a plan for a new approach: to build the first *in silico* model of severe sepsis.

Colleagues told them they were crazy. Sepsis is just too complicated to simulate, they said. But that, Vodovotz recalls, was exactly the point.

"The conscious mind can't handle more than a few things [at once]," he says. "But the unconscious mind can do it quite well. My scientific mentors could integrate huge amounts of information and just go, 'I believe the system plays like this.' Really good, experienced doctors do the same thing. [Modeling gives you] the best of both worlds: the rational process that comes out of your conscious mind, integrated with the ability of your unconscious mind."

After reviewing the literature, the team chose biological parameters that appeared to be important in sepsis: the duration of the precipitating infection or injury, the patient's blood pressure, and the level of dysfunction in patient tissues, among others. Using algorithms designed by Chow, they ran the simulations and watched the resulting changes in endotoxin, cytokine, and other protein levels in the hours, days, and weeks after injury. Vodovotz then validated the model by comparing the simulation results to those of his own follow-up studies of cellular processes in the lab. Then the team ran the simulation again.

It's all about relationships, he says. Instead of focusing on the individual players themselves—the various inflammatory markers and whatever molecular processes might be at work within and among them—first look for patterns in how the players affect one another over time: A inhibits B and C, B inhibits C and A, and so on. That makes the time you spend in the lab much more focused and efficient.

In 2004, the team put their model to the test by re-running the failed anti-TNF-drug study *in silico*—and found comparable results in their simulated patients. The silver lining in all this bad news was that the Pitt study proved that modeling sepsis was an idea that could hold water. And unlike with clinical or laboratory trials, simulated sepsis could be rewound, paused for further pondering, and even altered. Scientists could ask important questions, like: Why was the drug good for some people and bad for others? What separates the two groups of patients? Could the trial have succeeded had the drug been given to a more select group of patients?

A decade later, they're still asking these and other questions about sepsis—and much more, as the scope of their work continues to grow. They're studying a number of other inflammatory "cascades," as well, including liver failure and trauma. (For the latter, Vodovotz and colleagues recently launched a 500-patient study to serve as a data storehouse.)

Their findings are nonlinear. So, in the case of sepsis, yes, high TNF levels are a bad sign, but that doesn't necessarily mean that low TNF is a good thing. Inflammation is more complicated than that—but not unfathomable, says Vodovotz.

In addition to some 70 papers illuminating the vast and highly complex ocean that is acute inflammatory response, the team's "crazy" idea (modeling sepsis, that is) has also led to the founding of a field. The Society for Complex Acute Illness, of which Vodovotz and Clermont are cofounders, now has 150 members. It also led to the founding of a biosimulation company in Pittsburgh. Since 2001, Immunetrics has helped some 20 studies build more successful laboratory and clinical trials. —*EV*

WHAT IF WE HELD OFF ON THAT TRANSPLANT?

MODEL PATIENTS

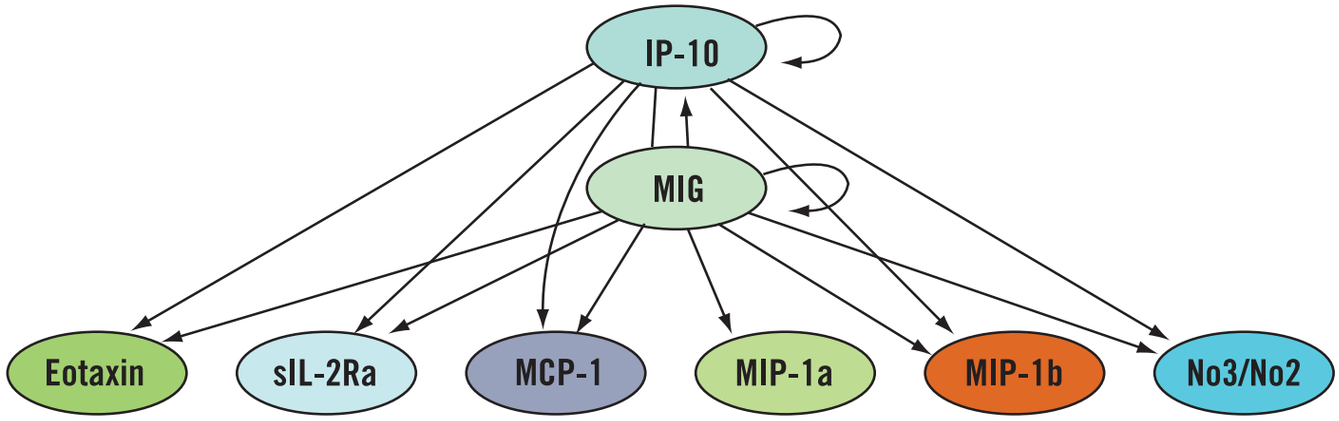
When a patient receives a new liver, not only is she married to a physiologically taxing regimen of immunosuppressants forever, but she's also opening up a daunting new set of what-ifs: What if the transplant doesn't help? What if that organ could have saved the life of someone else on the transplant list?

Mark Roberts—MD professor and chair of health policy and management in Pitt's Graduate School of Public Health and professor of medicine, of industrial engineering, and of clinical and translational science—has been wrestling with these questions for more than a decade.

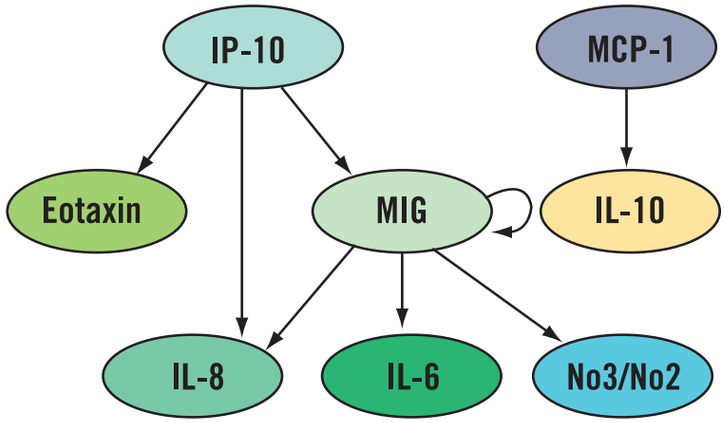
His team gathered and analyzed extensive data on disease progression from patients with end-stage liver disease. From these, the team created thousands of virtual people on virtual waiting lists—a model of every member of the U.S. organ allocation system—"each with their virtual physiologies going on," he says. "And now we can say, 'Okay, what would happen if you changed the rules? What if, instead of [allocating an organ to] the sickest person first, you did the person who would benefit the most? Or what if you eliminated the regional preference?'"

Once recovered, donated livers have a shelf life of 18 hours, tops. In his systematic what-iffing, Roberts has shown that more organs might be transplanted—and more lives saved—in time if the regional map for organ allocation were

SPONTANEOUS SURVIVORS

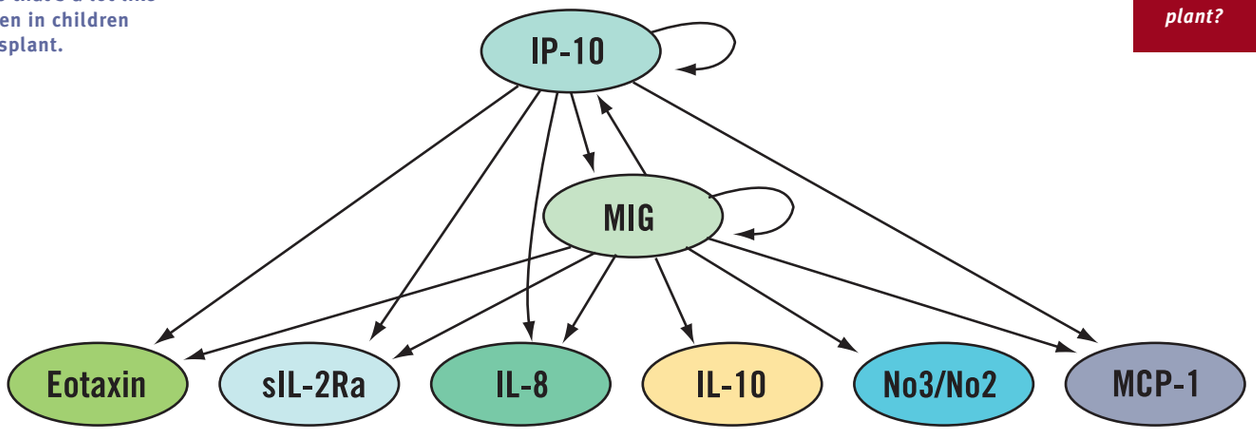


NONSURVIVORS



Previously unpredictable disease progression revealed: Children who spontaneously survive acute liver failure share a network of inflammatory responses that's a lot like what's seen in children post-transplant.

LIVER TRANSPLANT



WHAT CHILD IS THIS? Doctors have always had difficulty predicting which children with liver disease would survive without a transplant. Results from a 14-year multisite clinical study give pediatric specialists a new lens. The graphics shown here plot how various inflammatory mediators interact differently among patient groups with different outcomes. Suddenly, says Pitt's Yoram Vodovotz, the researchers "could easily tell the groups apart." The findings are informing a model that allows the Pitt team to get help treating—for now—virtual patients. They can ask questions like: ***Who needs to get on the transplant list today? And who will do well without a transplant?***

GRAPHIC BY MICHAEL LOTENERO, ADAPTED FROM AZHAR N. ET AL. (2013) ANALYSIS OF SERUM INFLAMMATORY MEDIATORS INDENTIFIES UNIQUE DYNAMIC NETWORKS ASSOCIATED WITH DEATH AND SPONTANEOUS SURVIVAL IN PEDIATRIC ACUTE LIVER FAILURE, PLOS ONE 8(11): E78202. DOI:10.1371/JOURNAL.PONE.0078202.

redrawn, among other findings.

Recently, Roberts teamed up with a Pitt group—including Yoram Vodovotz, of surgery—that's exploring another ethical conundrum in transplant medicine, one that arises in cases of pediatric acute liver failure (PALF). This devastating condition can result from poisoning, acetaminophen overdose, infection, or—as is the case with almost half of these kids—for reasons that are never discovered. PALF can take a child from perfect health to the ICU in a matter of weeks, or even days. Without a liver transplant, many will die. And, for reasons no one can explain, many others won't.

Sometimes, a child is put on the transplant list, seemingly at death's door, and then makes a full recovery before a match for an organ can be found. Which raises a delicate question: Are we doing too many transplants?

And the short answer, says Vodovotz, is, *Yes*.

The team didn't come to this conclusion lightly—or easily. It was informed by the culmination of a 14-year clinical study by a multinational consortium. The Pediatric Acute Liver Failure Study Group, as it's called, was funded by the National Institutes of Health and the National Institute of Diabetes and Digestive and Kidney Diseases and led by Pitt's Robert Squires, professor of pediatrics. The study is perhaps the first to consider the distinct outcomes of the disease—survival with native liver, death with native liver, and transplant—separately, says Squires. (Most of the chidren who were part of the transplant group in the study survived.)

After comparing the inflammatory networks of the patient groups, the team arrived at an intriguing finding: The progression of protein interplay seen in the bloodwork of survivors with native livers and that of the transplant recipients (post-transplant) look markedly similar (see p. 17).

Vodovotz explains that taking blood samples to check for levels of inflammatory mediators has never been helpful in predicting which children could survive without a transplant. But the team found that after drawing blood each day, watching how these levels change, and analyzing how these mediators influence one another over time, a new picture emerged.

"If you look at the network representation, which says how mediators are interplaying with one another, it's a night-and-day difference. You could easily tell the groups apart," he says. The study was published last November in *PLOS ONE.*

Vodovotz and Roberts have started a new model: thousands of virtual boys and girls with PALF, each with his or her own virtual physiology and each facing the decision of whether to get on to the virtual liver-transplant waiting list.

"So we can start doing scenarios and say, 'Let's not transplant this virtual child today. Let's wait until tomorrow and see if [she's] any better,'" says Roberts. "And we can test different strategies for listing a child. We can make reasonable predictions about whether we do that child a service by transplanting [her] or not, and when would be the optimal time to list that child for transplantation." *—EV*

A MONTH'S DIFFERENCE

Female sterilization is the second most common contraceptive in the United States, even though Medicaid patients who elect to have the procedure are subjected to a 30-day waiting period. In a study published in the journal *Contraception* and discussed in a recent *New England Journal of Medicine* editorial, Pitt's Sonya Borrero and Kenneth Smith, both MDs in the Department of Medicine, with collaborators, explored what would happen if policymakers were to revise that rule. Women often request to have their "tubes tied" (tubal ligation) while in the hospital after giving birth. The researchers knew, anecdotally, that the mandate could make scheduling the procedure difficult. Patients with private insurance have no such waiting period imposed on them.

So, what if the mandated month-long lag between the request and procedure didn't exist? After building a model, known as a cost-effectiveness decision analysis, based on real Medicaid data (see the brackets on the right), the team concluded that fulfilled sterilization requests would increase by 45 percent.

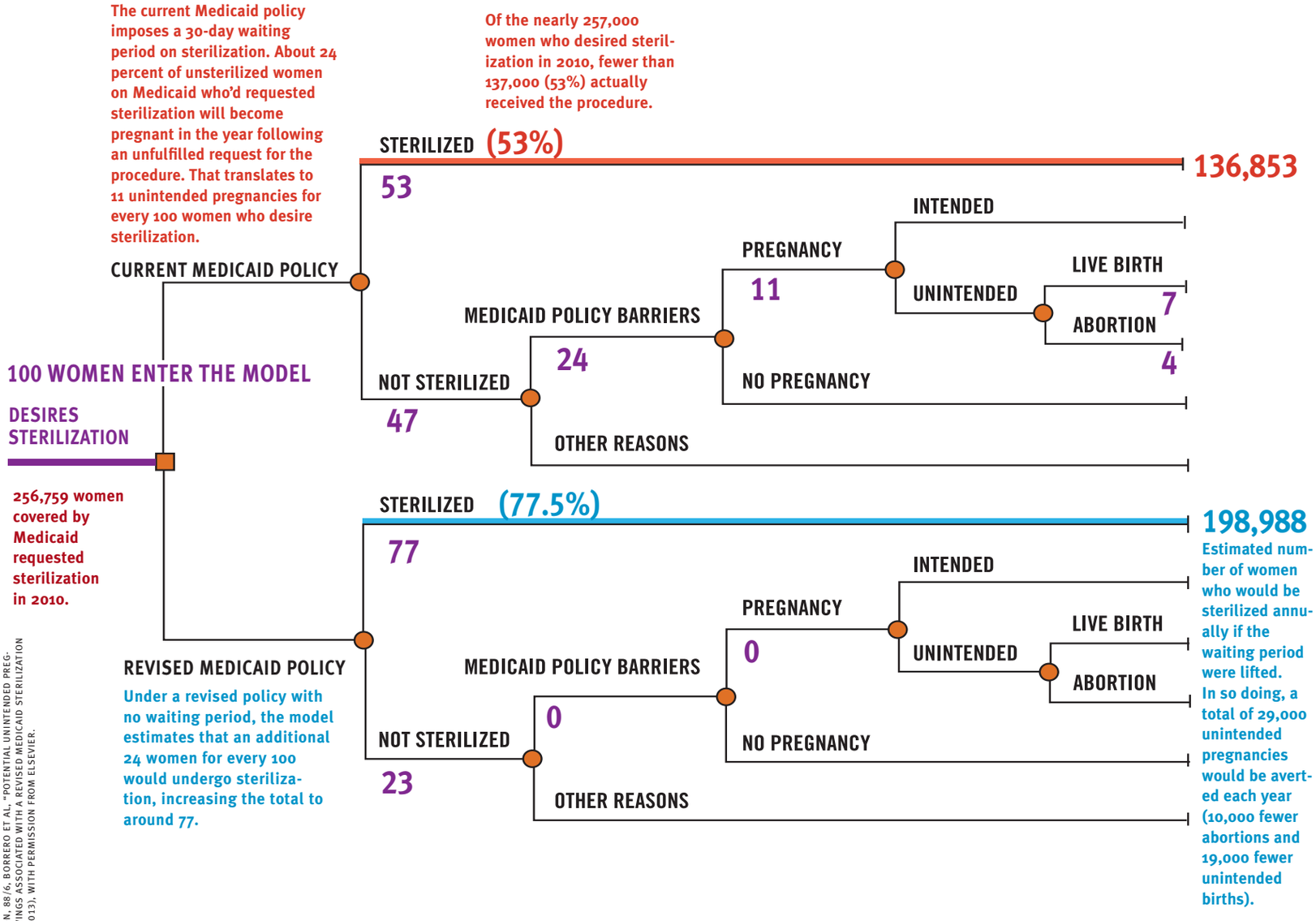
Here's how the analysis works. All women who request sterilization under Medicaid enter the model. The model then simulates potential outcomes over the course of one year. Researchers can compare what happens with the current policy against a parallel Medicaid universe, which simulates outcomes with an imagined revised-policy branch of the model. Under a revised policy, the probability of women actually receiving the procedure increases with the 30-day barrier removed. Smith says that, annually, such an increase could prevent more than 29,000 unintended pregnancies and save the Medicaid program $215 million by avoiding the costs of childbirth from such pregnancies.

The Medicaid rules also require that women sign a consent form. Yet "assessments of the form's readability indicate that it is overly complicated, and its literacy level is too high for the average American adult," Borrero and coauthors write in the *NEJM*. In a related study, a Borrero team found that 34 percent of the women who read the form did not realize that a tubal ligation was permanent, and many did not realize there were reversible alternatives. Any new policy should have more readable documents to ensure that patients understand their options, the researchers say.

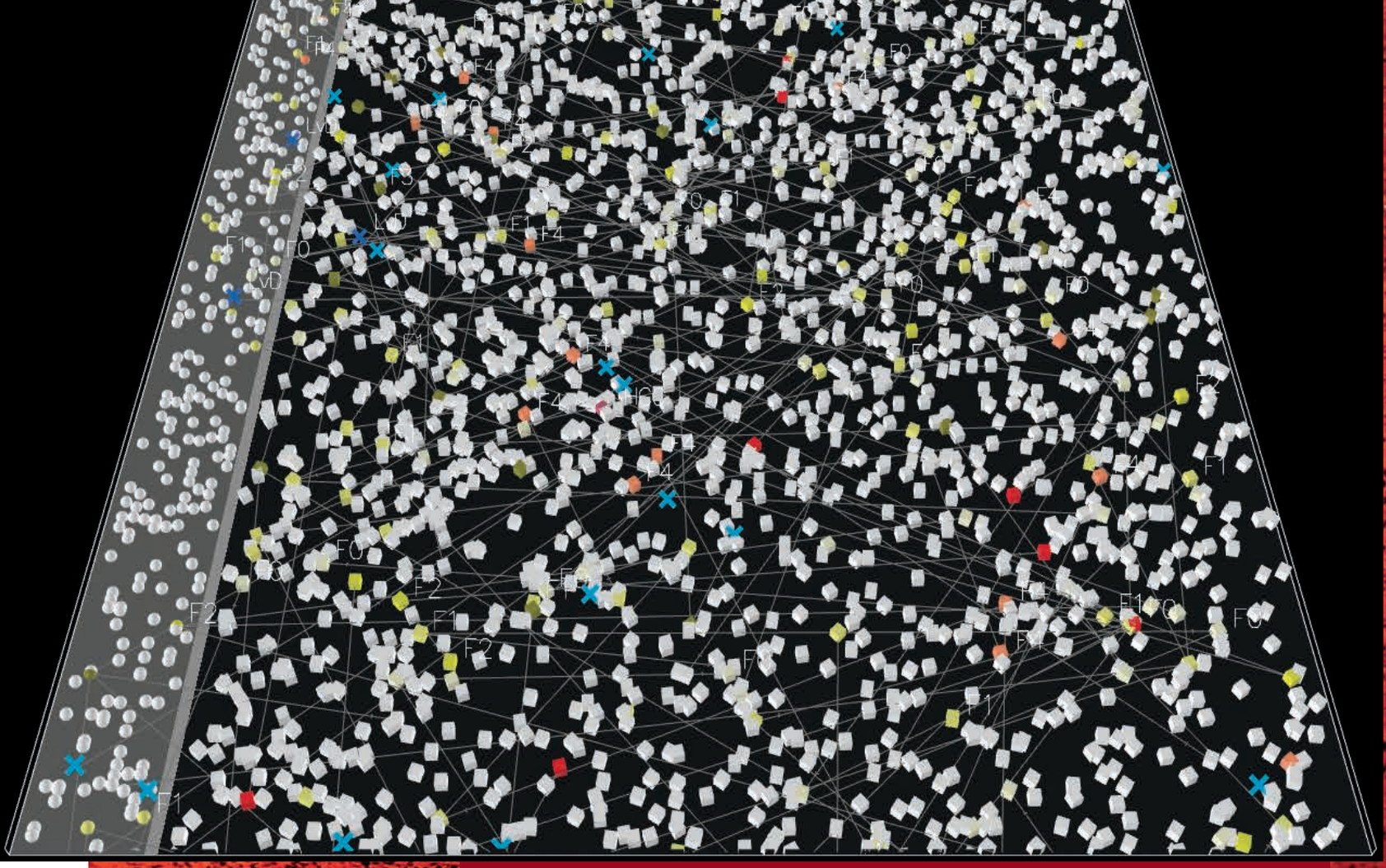
Borrero et al. point out that it is important to be sensitive to the idea that the fertility of the poor seems to be less valued by society. In fact, the Department of Health, Education, and Welfare first established a waiting period in 1976 after numerous troubling reports from that time: Poor women were being pressured into sterilization as part of local or state family planning programs. Health care providers sometimes suggested that welfare and other benefits were tied to sterilization and often didn't get proper patient consents.

Some women are still vulnerable, Borrero notes, pointing out that serious questions have been raised about the sterilizations of 150 women in California prisons between 2006 and 2010.

The *NEJM* editorial authors write, "Although [Medicaid's] policy was designed to protect vulnerable populations, we believe that it does not effectively fulfill that intention—in fact, it restricts the reproductive autonomy of the women it intends to serve." *—BM*



WHAT IF MEDICAID LIFTED THE 30-DAY WAITING PERIOD MANDATED FOR FEMALE STERILIZATIONS?



BOTH SIDES OF THE PRISON FENCE: Screening, and when appropriate, treating, inmates for hepatitis C is probably an effective way to save money and protect society at large from the disease, researchers think—even with treatment costs at about $100,000 a patient. The simulation above shows a 1,000-person sample representative of the entire U.S. population. Incarcerated individuals are shown as dots in the shaded region to the left. The blocks are people living freely in the United States. The lines represent infections spreading from person to person.

THINKING INSIDE AND OUT

More than 3 million people in the United States are infected with hepatitis C, a leading cause of chronic liver disease. Between 50 and 75 percent of them don't even know they have it.

Hep C is often transmitted intravenously. And prisons nationwide—with hep C prevalence documented at rates as high as 35 percent, though no standard screening protocols exist—have become a hotbed for the disease, says Jagpreet Chhatwal, a PhD assistant professor at the M.D. Anderson Cancer Center in Houston. While he was an assistant professor of health and policy management and of industrial engineering at Pitt two years ago, Chhatwal teamed up with Pitt's Mark Roberts, MD professor of medicine, Pitt's John Grefenstette, a PhD and director of the Public Health Dynamics Laboratory, and Tianhua He from Tsinghua University in China. They started developing a model that would answer some questions about hep C: What if prisons routinely screened all inmates for hep C and then treated those found to be infected? What would be the cost? What would be the benefits to society at large?

"If we can model the prison system, we can predict the disease impact on intervening while everyone is still inside," Chhatwal says. Many inmates are released unaware they even have hep C.

Using Bureau of Justice statistics, the investigators developed an "agent-based" model (see "Special Agents," p. 15) to simulate people moving between prisons and society and the spread of hep C. "Imagine you're looking at a video game with individuals moving in and out of the [prison] system with certain disease characteristics," Chhatwal says. The model takes into account variables like disease stage, an individual's behavior, access to treatment, and whether a person is aware of the infection.

With the advent of new drugs last year, Chhatwal notes, "the treatment duration has reduced from 48 to 12 weeks." But because it would cost around $100,000 to treat a single

WHAT IF WE SCREENED ALL INMATES FOR HEP C?

patient, and many inmates show no symptoms, prisons have little incentive to change screening policies. (Once prison officials learn of a case of any illness, law requires that the patient be treated.)

Chhatwal estimates that hundreds of thousands of hep C infections could be prevented in the United States throughout the next 10 years if infections in inmates were routinely identified; however, he notes that the team is still validating its conclusions. (The researchers' final estimates will be published this summer as an abstract in *Gastroenterology*.) With their current software, the researchers can simulate up to a 10,000-person sample; that can take several days. They eventually want to translate the model onto the FRED interface to run simulations on the entire U.S. population of 300 million. (See p. 14 to find out what's new in the neighborhood of mass modeling.)

Chhatwal says the model is predicting that people on both sides of the prison fence would benefit from looking out for inmates with hep C: By neglecting the likelihood of infection among this population, he says, "society will bear the burden at some stage." —*BM*

GRAPHIC COURTESY JAGPREET CHHATWAL

OUT WITH THE OLD, IN WITH THE PNEU

Pitt's Kenneth Smith, an MD and professor of medicine, wondered: Is the new pneumococcal vaccine better than the old? And for whom? These vaccines are designed to ward off bacterial pneumonia, bloodstream infections, meningitis, and other infections.

Using national health databases and what's known as a Markov state-transition model, his team found that the older vaccine, usually given to the 65-and-up crowd, ultimately "costs more and had a somewhat smaller spectrum in terms of the types of pneumococcal diseases that it prevented," he says. (The current standard also recommends it for younger persons with high disease risk.)

Published in the *Journal of the American Medical Association* in February 2012, their paper concluded that the new 13-valent pneumococcal conjugate vaccine (PCV13) makes the most economic and health sense for patients over the age of 50, regardless of their medical condition.

The simulations, Smith adds, were sensitive to "herd immunity" caused by children who'd been introduced to the new vaccine. "Kids get the newer vaccine on a routine basis, and that has changed the types of organisms that are causing disease. It's basically cut down the amount of disease the entire population gets." —*BM*

WHAT IF WE USED THIS NEW VACCINE INSTEAD OF THE OLD ONE?

AND WHATNOT

More than a decade ago, Gilles Clermont, MD associate professor of critical care medicine at Pitt, cofounded Immunetrics—a computational modeling software company that's turned what-iffing into a viable Pittsburgh-based biotech enterprise. Immunetrics is now chugging along without him. More recently, he's been exploring ways to use modeling, machine-learning, and other data-driven technology in new smart gadgets in health care.

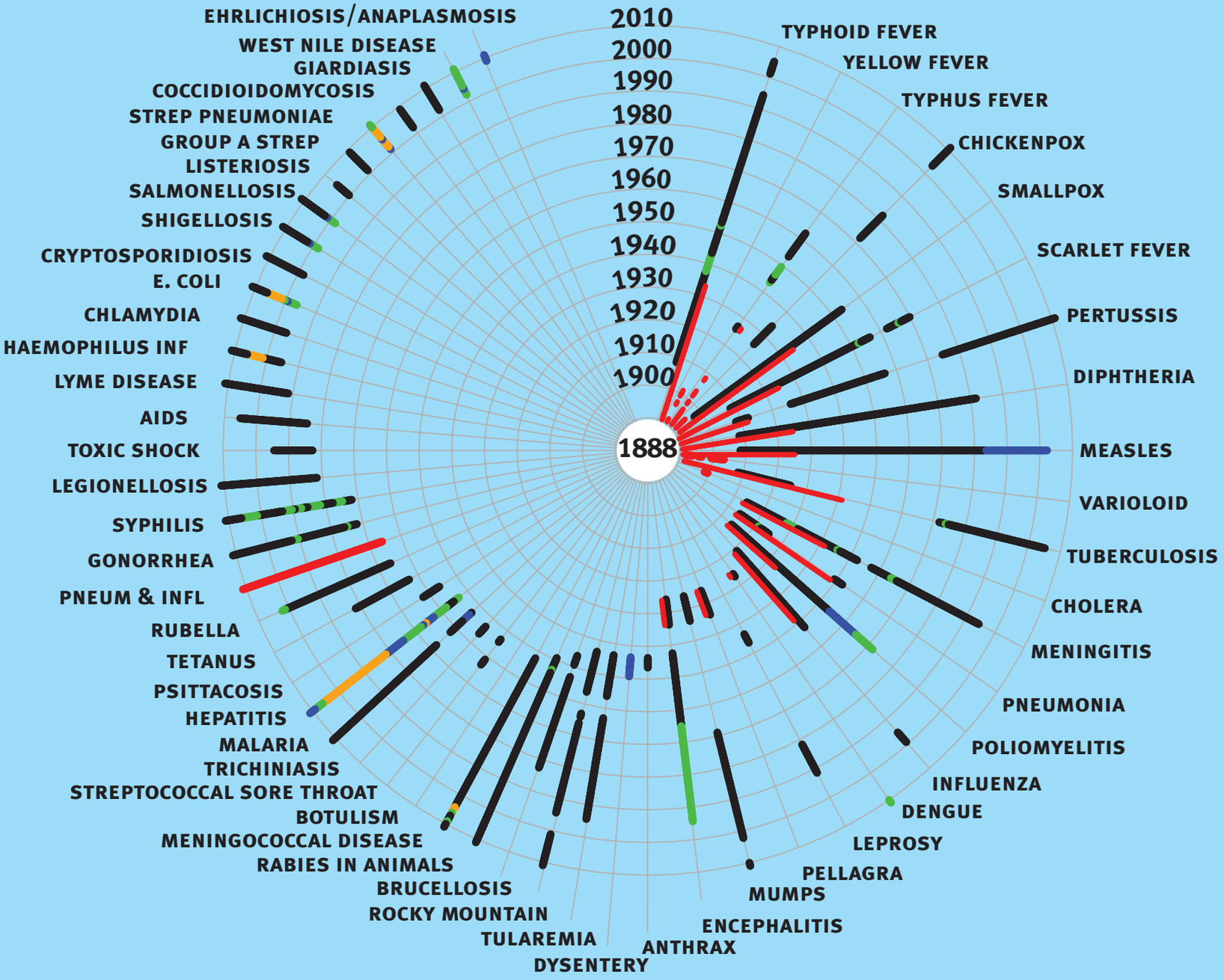
Big Data, particularly the emerging understanding of biology at the mechanistic level, is opening up opportunities for helping patients. Yet, Clermont cautions, "More data does not necessarily correspond with more knowledge. We're really trying to bridge that gap between data and knowledge in novel ways."

On these projects he collaborates with the likes of associate professor of chemical and petroleum engineering Robert Parker; William Kepler Whiteford Professor of Industrial Engineering Andrew Schaefer; research assistant professor of industrial engineering Louis Luangkesorn; professor of critical care medicine Michael Pinsky; and nursing professor of acute and tertiary care Marilyn Hravnak—all of Pitt. Another collaborator is Artur Dubrawski, senior systems scientist at Carnegie Mellon's Robotics Institute. Here are some of the gizmos they have in the works:

- **An artificial pancreas system that maintains desired blood sugar levels in critically ill patients.**
- **An alert system to help physicians flag possible medical errors at the bedside.**
- **A hospital "air traffic controller" on the lookout for ways to keep patient flow humming along smoothly.**
- **A 15-minute health "forecast" system to give critical care docs a heads-up on which patients are headed for trouble—so the physicians can steer them clear of the storm.**

"The more data we have, the more tools we're going to need to cast it—to reinforce, destroy, or remodel our conceptual framework of how the world works," says Clermont.

"This also applies to finance and economics. It's not unique to health care." —*EV and EL*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SMALLPOX
SCARLET FEVER
PERTUSSIS
DIPHTHERIA
MEASLES
VARIOLOID
TUBERCULOSIS
CHOLERA
MENINGITIS
PNEUMONIA
POLIOMYELITIS
INFLUENZA
DENGUE
LEPROSY
PELLAGRA
MUMPS
ENCEPHALITIS
ANTHRAX
DYSENTERY
TULAREMIA
ROCKY MOUNTAIN
BRUCELLOSIS
RABIES IN ANIMALS
MENINGOCOCCAL DISEASE
BOTULISM
STREPTOCOCCAL SORE THROAT
TRICHINIASIS
MALARIA
HEPATITIS
PSITTACOSIS
TETANUS
RUBELLA
PNEUM & INFL
GONORRHEA
SYPHILIS
LEGIONELLOSIS
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LYME DISEASE
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GROUP A STREP
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COCCIDIOIDOMYCOSIS
GIARDIASIS
WEST NILE DISEASE
EHRLICHIOSIS/ANAPLASMOSIS

A DATABASE THAT HELPS SCIENTISTS UNDERSTAND CONTAGION | BY BRETT MURPHY

GRAPHICS COURTESY PROJECT TYCHO

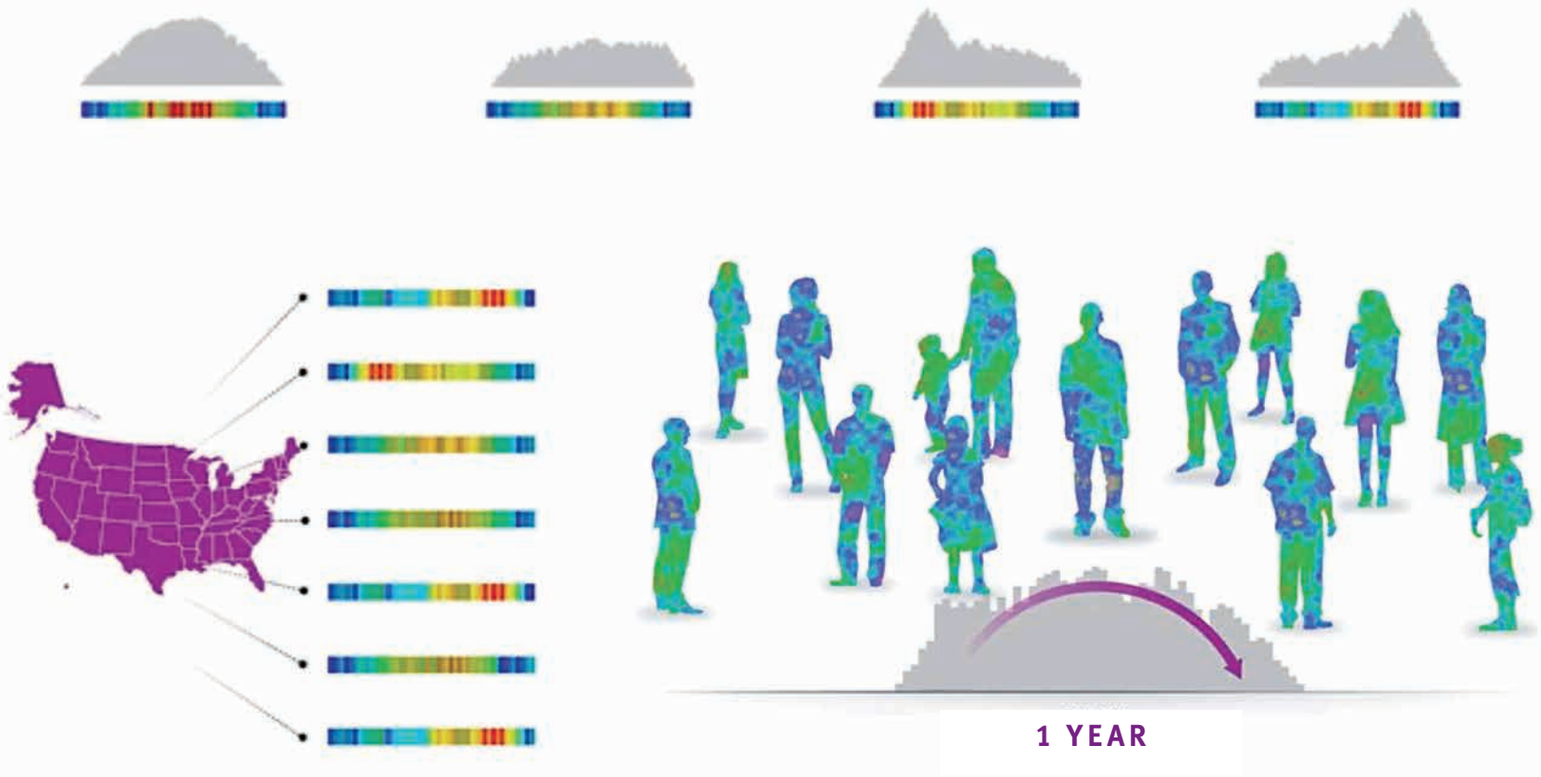
THE HISTORY OF DISEASE, IN COLOR

Tycho Brahe got his nose lopped off over an argument about a math problem. He once refused to get up from a dinner party to relieve himself because he thought it rude, resulting in, probably, a burst bladder that killed him. Yet, his peculiar brand of determination helped give rise to the scientific revolution. The Danish nobleman was among the last great "naked-eye" observers of the cosmos. Before his death in 1601, Brahe passed along his life's work—30 years of detailed observations of the night sky—to his assistant, Johannes Kepler, urging him not to let the fruit of his labors languish.

They did not. Brahe's careful observations became the basis for Kepler's laws of planetary motion, which would, in turn, contribute to Isaac Newton's law of universal gravitation.

This graphic chronicles the history of weekly disease reporting in the United States since 1888. Each concentric circle represents a decade. Moving clockwise, more diseases are reported and filed. Red represents death reports. Other colors represent different categories of reports. For instance, hepatitis began as a single report type, then different case reports led to other classifications of the disease.

WHERE THE DATA COME FROM



Each week, city public health officials report "notifiable" disease occurrences to their respective states. Outbreaks for a given disease can be plotted on an epidemiological curve (purple arrow). Data from all U.S. states and territories—the number of reported cases per week—are compiled at the federal level. Project Tycho digitized these data into color-coded bar graphs for the past 125 years for easy access and analysis. (Red signifies a high number of reported cases and blue signifies a low number.)

Four centuries later, the Pitt researchers who created Project Tycho, a digital database that provides open access to U.S. disease surveillance data, hope they have created a similar foundation for discovery. The newly built epidemiological archive chronicles reports of 56 infectious diseases in every state before, during, and after vaccination licensure from 1888 to recent times.

It took almost three years and more than 200 million keystrokes to create the Project Tycho archive. Many of those workers were University of Pittsburgh undergrads as well as students from Digital Divide Data, a social enterprise that provides jobs and education to young people in Cambodia, Laos, and Kenya. These clerks standardized and organized almost 90 million cases from weekly public health records (paper and PDFs) from all U.S. states and territories, including more than 3,000 American cities. What they wrought: the largest centralized bank of digitized disease surveillance data ever assembled.

And access to it is free, says Wilbert van Panhuis, an MD/PhD professor of epidemiology at Pitt's Graduate School of Public Health and lead investigator for the project. "Our vision was that not only us, but everybody should be able to use this public data for analysis and models." For instance, anybody with enough interest and access to the Internet—a scientist at a university or pharmaceutical company, a journalist, an undergrad—can easily track where and when the polio vaccine was implemented and its efficacy in those cities.

"We hope there are epidemiological, disease-curing Keplers today who will be able to use these data to derive important laws and insights on how epidemics arrive, leave, and interact," says coinvestigator Donald Burke in the project's promotional video. Burke is an MD professor of medicine and of infectious diseases (among other appointments) and dean of Pitt Public Health.

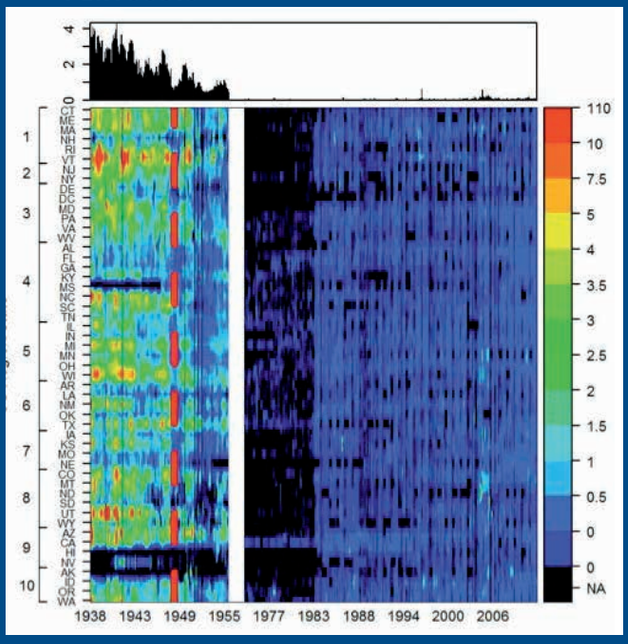
The field of public health data compilation has been fraught with redundancies. Most projects are focused on specific questions; a researcher might toil for years answering a question like, *What effects do condom distribution programs have on the rate of HIV infection in the rural United States?* In search of answers, investigators painstakingly build data sets that often are not shared. And it can be difficult to get funding to create archives with no specific research questions in mind.

Happily, both the National Institutes of Health and the Bill and Melinda Gates Foundation saw value in creating a massive digital archive and funded Project Tycho.

The Project Tycho team has also been inventing new methods to process and analyze public health data. In a November 2013 *New England Journal of Medicine* paper, Project Tycho researchers (from Pitt's public health, medicine, and information sciences schools with collaborators from Johns Hopkins) revealed that vaccination programs

GRAPHICS: THIS PAGE, DOUG FREEMAN/UPMC. ALL OTHERS: W.G. VAN PANHUIS, J. GREFENSTETTE, S.Y. JUNG, N.S. CHOK, A. CROSS, H. ENG, B.Y. LEE, V. ZADOROZHNY, S. BROWN, D. CUMMINGS, D.S. BURKE. CONTAGIOUS DISEASES IN THE UNITED STATES FROM 1888 TO THE PRESENT. NEJM 2013; 369(22): 2152-2158. REPRINTED WITH PERMISSION FROM THE MASSACHUSETTS MEDICAL SOCIETY.

PERTUSSIS



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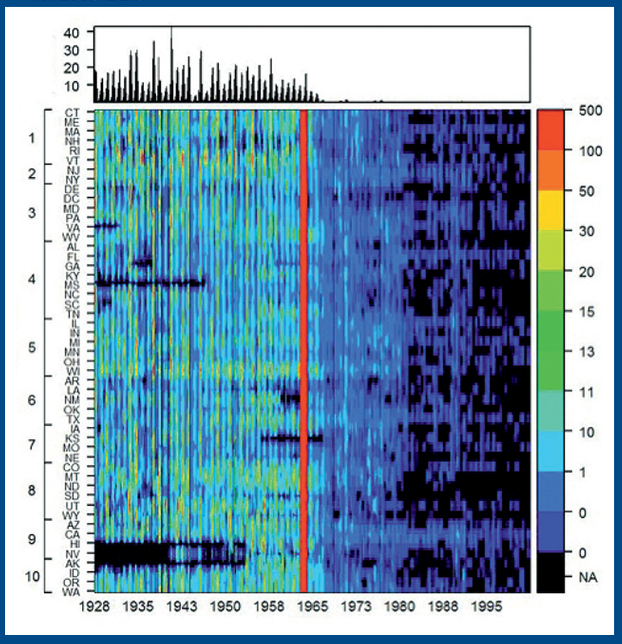
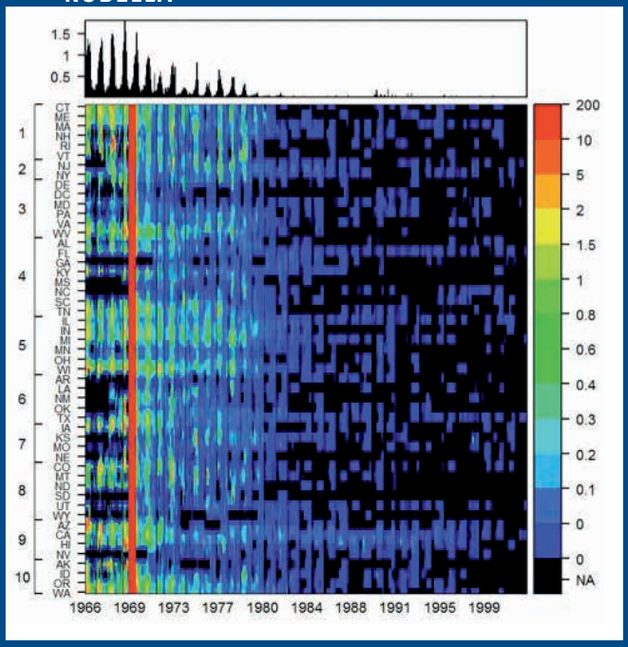
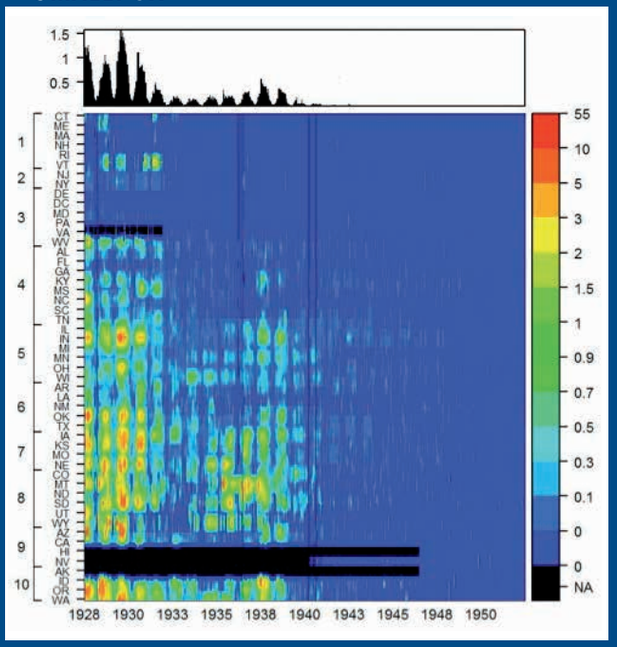


RUBELLA



SMALLPOX



Project Tycho stacks weekly graphs (incidence rates per 100,000) into years and then decades for each state. Before vaccine licensure, epidemics would occur every year across the nation. With each disease shown here, you can see the drastic shift in reported cases before and after the time of licensure—see the red lines. (Smallpox innoculation predates the graph.) The Y axes show U.S. regions/states. The top panels display the weekly incidence rates for all states combined.

Of note is the natural history of pertussis (whooping cough). After vaccine development, we see a dramatic drop-off; between the '40s and '70s, not more than 1 case was reported per 100,000 people nationwide in weekly updates. But recently, because of failure to vaccinate as well as the decline in efficacy of the acellular pertussis vaccine, whooping cough epidemics have been on the upswing.

The Project Tycho team estimates that from 1924 to 2010, 103 million cases of serious childhood diseases were prevented by vaccination in the United States.

for polio, measles, mumps, rubella, hepatitis A, diphtheria, and pertussis (whooping cough) have prevented more than 100 million cases of serious childhood infectious diseases since 1924. Still, some of these pathogens are reemerging. Pertussis vaccines, for example, have been available since the 1920s, but the worst whooping cough epidemic since 1959 occurred in 2012, with more than 48,000 cases nationwide reported by December of that year.

"Parents who question the risk-benefit balance of vaccination may refuse or delay immunization of their children," the Project Tycho team reports, "which leads to local variations in vaccine coverage and increased risk of disease outbreaks." Van Panhuis admits he hopes the project "will introduce new evidence into the debate about vaccination."

The next big step for Project Tycho is to go global. But, Van Panhuis says, technological, economic, and political barriers can hinder cooperation. For instance, developing countries that rely on tourism might be wary of releasing information about epidemics. And they may not even have the means to collect data, let alone analyze them. *What's in it for us?*, the gatekeepers may wonder.

Well, perhaps the lives of millions.

Van Panhuis remains optimistic. He says understanding a disease's narrative, locally and globally, can help move the scientific field forward in developing theories about causation—and then, ways to control or prevent disease. ■

Elaine Vitone contributed to this report.

To take a peek at Project Tycho, visit: www.tycho.pitt.edu

c. 1987

ABOVE: One of Lans Taylor's first fluorescence images: a still of a sea urchin egg injected with fluorescently labeled actin, fertilized, and videotaped to capture the dynamics. The imaging showed an explosive assembly of actin filaments at the membrane, a structure only observed before in fixed, dead cells. (Taylor notes, "This was part of Yu-li Wang's thesis at Harvard, where he was a graduate student of mine." Wang now heads biomedical engineering at Carnegie Mellon University.)

PITTSBURGH HAS SHOWN US WHAT WE ARE MADE OF | BY ALLA KATSNELSON

ILLUMINATING WORK

On a sunny, cold, mid-February morning, Simon Watkins and Claudette St Croix are getting familiar with the insides of a zebra fish embryo. The translucent organism, about one-eighth the size of a kid's thumbnail, rests on the bottom of a glass Petri dish, which the scientists set on the stage of a confocal microscope.

This isn't just any zebra fish embryo. It has been genetically engineered to carry three mutations: one that makes it immobile and another two that make all its blood vessels fluoresce green and all its red blood cells fluoresce red. Watkins and St Croix are using these fish to screen possible new drugs for treating hypertension, so they want to see how the embryo's vasculature changes when they bathe it in different compounds. Using an objective lens specially designed to collect large amounts of light at long distances and at high resolution—crucial for imaging a relatively large, living specimen rather than just a plate of cells or tissue—the duo captures 1,000 images per second.

"These physiological responses are happening so quickly, we can't even see them on [our] computer screen because the screen cannot refresh quickly enough," Watkins says.

It's hard to overstate the importance fluorescence imaging technology has had on modern biology. Open any life sciences journal, and you'll see an array of colorful images delineating life at the microscopic level. Pittsburgh scientists have played a huge part in making this happen.

The human visual system can resolve images coming in at about 25 hertz; many computer screens detect flickering at about 100 hertz (though speeds vary quite a bit); but the cameras Watkins works with capture movies at about 1,000-1,600 hertz. "We have to collect blind, and then do the analysis," he says.

Watkins, the director of the University of Pittsburgh's Center for Biologic Imaging (CBI), presides over a sprawling, 6,500-square-foot suite that houses about 30 microscopes. Between them, these devices can perform close to any feat of imaging achievable today: from three-dimensional views of single molecules to the unfolding of physiological events in the cells of living, breathing organisms. Using genetically encoded fluorescent probes, researchers can simultaneously track the activity of five or six different proteins over time.

It's a striking contrast to the system for detecting fluorescent labels in biological tissue set up by Lans Taylor four decades ago. What was then a state-of-the-art system consisted of a recently declassified night-vision camera hooked up to a Commodore 128-kilobyte computer and a videotape recorder.

c. 1990

The Multimode Microscope Workstation was developed at Carnegie Mellon University in the late '80s and into the '90s. This digital imaging system integrated multiple modes of light microscopy—like image deconvolution (fixing distortions) and 3-D sectioning. It was the first semiautomated digital-imaging light-microscope workstation.

Taylor—now on the faculty at Pitt—is the scientist who planted the seed of imaging innovation in Pittsburgh. (He directs Pitt's Drug Discovery Institute and serves as Allegheny Foundation Professor of Computational and Systems Biology.) Taylor jerry-rigged the Commodore setup when he was a young assistant professor of cell biology at Harvard University. During his PhD work a few years earlier, when he was studying the dynamics of cell motility in amoebas, he realized that fluorescent reagents provided a specific and sensitive way to track cells across space and time. At least, they did sometimes—the fluorescent dyes he used had a lot of problems, like toxicity to cells and chemical instability. Immunologists in the 1940s had learned how to conjugate fluorescent dyes to antibodies, providing a huge boost to the field of immunohistochemistry. But efforts to harness the power of fluorescence for functional studies of the cell were few and far between. By the time Taylor started his own lab in 1974, he was developing his own fluorescent reagents and building imaging systems that could detect the low levels of light emitted. He had an inkling that fluorescence imaging would hit it big as a fundamental technique in the life sciences.

"It became clear when I was still at Harvard in the late 1970s that this was a field that was going to grow," he says, "and that it would require the integration of biology, chemistry, physics, and computer science."

Taylor's hunch about the promise of fluorescence planted a vision in his mind, and he began looking for an institution that was interested in bringing him on to build a center to pull the needed expertise together. The idea struck a chord with Richard Cyert, the late president of Carnegie Mellon University. "President Cyert saw it as a bridge between computer science and engineering—where they had strengths—and biology, where they wanted to grow," says Taylor.

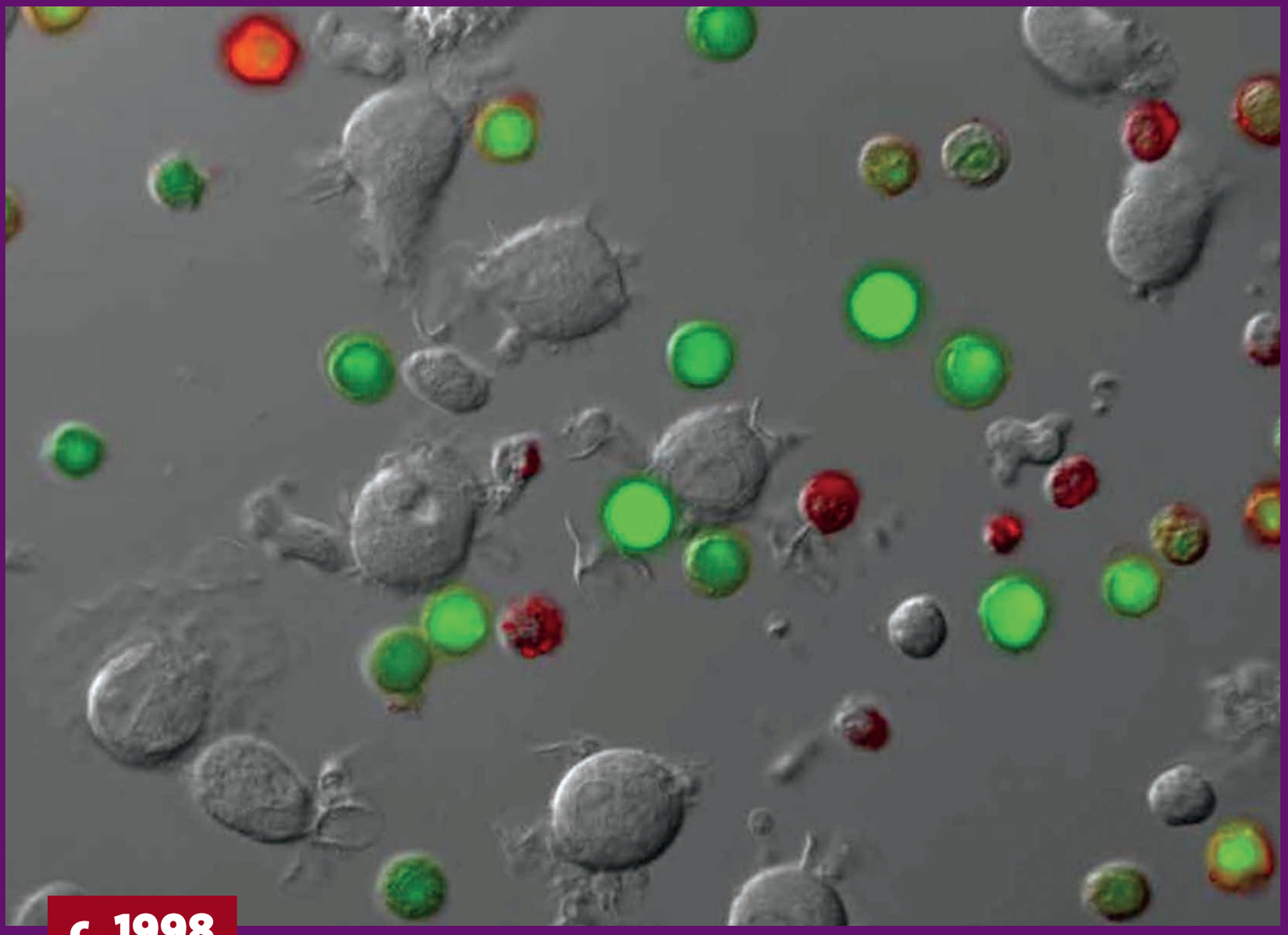
It's hard to overstate the prescience of Taylor and a handful of like-minded scientists. Today, fluorescent probes and detection systems comprise a booming, multibillion dollar industry. Open almost any life sciences–related journal to almost any page and you'll see an array of fluorescence-based colors crisply delineating minute cellular structures or disease markers. Fluorescent probes can be engineered to illuminate specific proteins or cell types, as well as to act as sensors that register changes in physiological phenomena over time. Fluorescence imaging has been used to sequence the human genome, to illuminate cell-signaling pathways, and to guide cancer surgeons. A trio of researchers in 2008 won the Nobel Prize in Chemistry for the discovery and development of the green fluorescent protein, a probe which can be cloned into the genomes of experimental animals and cells. But the sheer number and variety of fluorescent probes and sensors have provided a vast tool kit to biologists seeking to explore almost any question in the life sciences. The imaging center that Taylor launched at CMU in 1982, and its partner imaging center, founded by Watkins at the University of Pittsburgh nine years later, have played a major part in laying the foundation for this methodological revolution. These centers continue to drive innovation in fluorescence imaging technology.

One of Taylor's first recruits in 1982 to CMU's Center for Fluorescence Research was Alan Waggoner, a chemist from Amherst College in Massachusetts. Like Taylor, Waggoner had caught the fluorescence bug in the early 1970s. His interest had been piqued by a colleague at Yale University, neurophysiologist Lawrence Cohen, who wanted to find a way to detect electrical signals in neurons, not by poking them with electrodes but just by looking down a microscope. Waggoner synthesized thousands of dyes before he hit on one that fluoresced upon changes in voltage and was relatively stable and nontoxic to cells.

The collaboration was Waggoner's first experience working with a class of dyes called cyanine dyes. They were the workhorses of the photography industry—developed in the early 1900s and used to increase the range of wavelengths that form an image in photographic film. They were quite bright and photostable. "There was a huge literature on these dyes, but nobody had ever thought much about applying them as labels for biological detection," he says. "I thought that the cyanine dyes could be modified to make them fluorescent labeling agents."

When Taylor brought Waggoner aboard at CMU, he asked the chemist to lead the development of multicolored reagents, labels, and probes. Taylor himself would take charge of inventing better fluorescence detection and imaging systems. Then they'd apply these tools to biological problems. That suited Waggoner

P. 28: COURTESY LANS TAYLOR. P. 29: COURTESY SIMON WATKINS, CBI.



c. 1998

ABOVE: Dendritic cells nibbling on tumor cells. Simon Watkins explains: "This high-speed, long-term, three-color movie helped us understand the basic biology behind a clinical trial with Pitt's Lou Falo (chair of dermatology) and Larisa Geskin. In the late '90s, keeping things in focus for extended periods of time was still very difficult. We used a prototype autofocus device that allowed us to image for 24 hours with no drift—making this study possible. We found that the dendritic cells only consumed the dead (red) tumor cells and seemed to completely ignore the living (green) cells."

just fine. He continued his work with cyanine dyes, fiddling with the chemistry to enhance their brightness and make them even more impervious to bleaching under the light of a microscope bulb. The group devised other probes, as well—both fluoroscent analogues (fluorescent and trackable versions of molecules of interest) and sensors that could detect cellular processes. On the instrumentation side, Taylor and Frederick Lanni, another early recruit to the center, created the so-called standing wave fluorescence microscope, the forerunner of today's super-resolution microscope platforms. The group also hatched several imaging techniques, including one called ratiometric imaging, which allowed researchers to quantify intracellular calcium levels, pH, or other biochemical activities by using a probe that fluoresces to different degrees at two different wavelengths.

As CMU's center continued to grow and innovate, the University of Pittsburgh in 1991 recruited Simon Watkins to start its own imaging center. By then, the field of digital imaging microscopy had progressed to the point where commercial systems using solid state cameras were available, like the Multimode Microscope developed at CMU (see caption on p. 28). However, many biologists continued to use film.

"To take a picture on a fluorescence microscope with film, you'd focus on the image and then press the button and hold it for 15 seconds. And then when you looked at it, the dyes were bleached. And then you'd get the film processed and hope there was an image on it. Isn't that nuts?" says Watkins.

"Everything was slow, everything was dead, and there was no genetically encoded anything."

One advance that changed the status quo was confocal microscopy, a technique invented in the 1950s but commercialized just four years before Watkins came to Pitt. Instead of collecting all of the light emitted by a specimen, confocal microscopy uses a pinhole to reject all but the light in focus. Excluding the flare from fluorescence outside of that region dramatically boosted image quality. By the mid-1990s, this technology had flooded the life sciences world, and Pitt was at the front of the wave. Watkins' facility had acquired four confocal microscopes and was becoming an important resource for scientists at Pitt, as well as at other institutions.


Bruchez


St Croix


Taylor


Watkins


Waggoner

As CMU's imaging center continued to flourish with the help of a National Science Foundation Science and Technology Center grant, Taylor and Waggoner were beginning to feel the lure of the industry world. In 1991, right after Waggoner patented CyDyes, his line of cyanine dyes, the duo decided to spin off a company, Biological Detection Systems (BDS). That company commercialized the dyes as well as the semi-automated imaging system that Taylor had pioneered; BDS was acquired in 1995 by Amersham (another imaging mecca, now part of GE Healthcare), primarily because the four cyanine dyes could separately detect four nucleotides and thus be used in early DNA sequencers. In addition, the dyes were widely deployed in live-cell studies because they allowed researchers to see chemical and molecular events in the context of time and space within cells.

And: "We could actually image and look, and they wouldn't bleach," says Watkins.

With BDS sold, Taylor's feet got itchier. The way he saw it, fluorescence imaging needed to undergo the same kind of revolution that gene sequencing technology was experiencing. Researchers had been able to manually sequence genes since the 1970s, but in order to undertake an endeavor like the Human Genome Project, which launched in 1990, the process needed to be taken completely out of human hands. Similarly, Taylor says, back then it could take days after loading images to complete an analysis with available software. Yet, to track spatial and temporal dynamics in cells, "we needed to go from the kind of human interactive semi-automated microscopes that we were dealing with in the mid-1990s to fully automated," he says. "I decided that although technologically we could have done this at Carnegie Mellon, this was really an industrial task." So while his wife chalked up his departure from academia to a midlife crisis, Taylor set off to launch a second company, Cellomics, in 1996, which created high content screening. This technology automated imaging of cells and small organisms for drug discovery and development. After that, he launched two more companies.

Apart from a brief sabbatical in the UK at Amersham, Waggoner stayed on at CMU; a few years later he began working on a new concept for making modular biosensors that could be designed to follow specific proteins within the cell with unprecedented spatial and temporal resolution. In 2003, the NIH had announced an initiative to fund a network of five multidisciplinary research centers around the country that would develop novel technologies for studying protein function within cellular pathways and networks. Waggoner spoke with Watkins and other investigators at Pitt about applying—an idea that Arthur S. Levine, an MD and Pitt's senior vice chancellor for the health sciences as well as the John and Gertrude Petersen Dean of the School of Medicine, wholeheartedly encouraged.

"Art just said, 'Well, Alan, why don't you go ahead and see if you can put together a proposal and get this thing going—involve some of the University of Pittsburgh people,'" Waggoner recalls. "And that's what we did." The relationship between CMU and Pitt was cemented when they received a $13.1 million grant in 2006.

What Waggoner, Watkins, and their colleagues produced within that framework is powerful technology that can detect an enormous variety of cellular processes in real time. These biosensors consist of a dye called a fluorogen, which fluoresces only in the presence of a protein fragment engineered to activate it, called a fluorogen-activating protein, or FAP. When the two bind, the FAP essentially stabilizes the chemical shape of the fluorogen in a way that allows it to fluoresce. "A simple way to think about it is, if you catch a butterfly, its wings can no longer flap," says Marcel Bruchez, a PhD associate professor of chemistry and biological sciences at CMU who designed the system with Waggoner and Pitt's St Croix, an assistant professor of environmental and occupational health in the Graduate School of Public Health and associate director of the CBI.

"By catching them in a protein, the previously flopping movement of the electron orbits that make up the dye molecule is suppressed," Bruchez says. "Held in that rigid protein environment, the dye can emit light when you shine light on it."

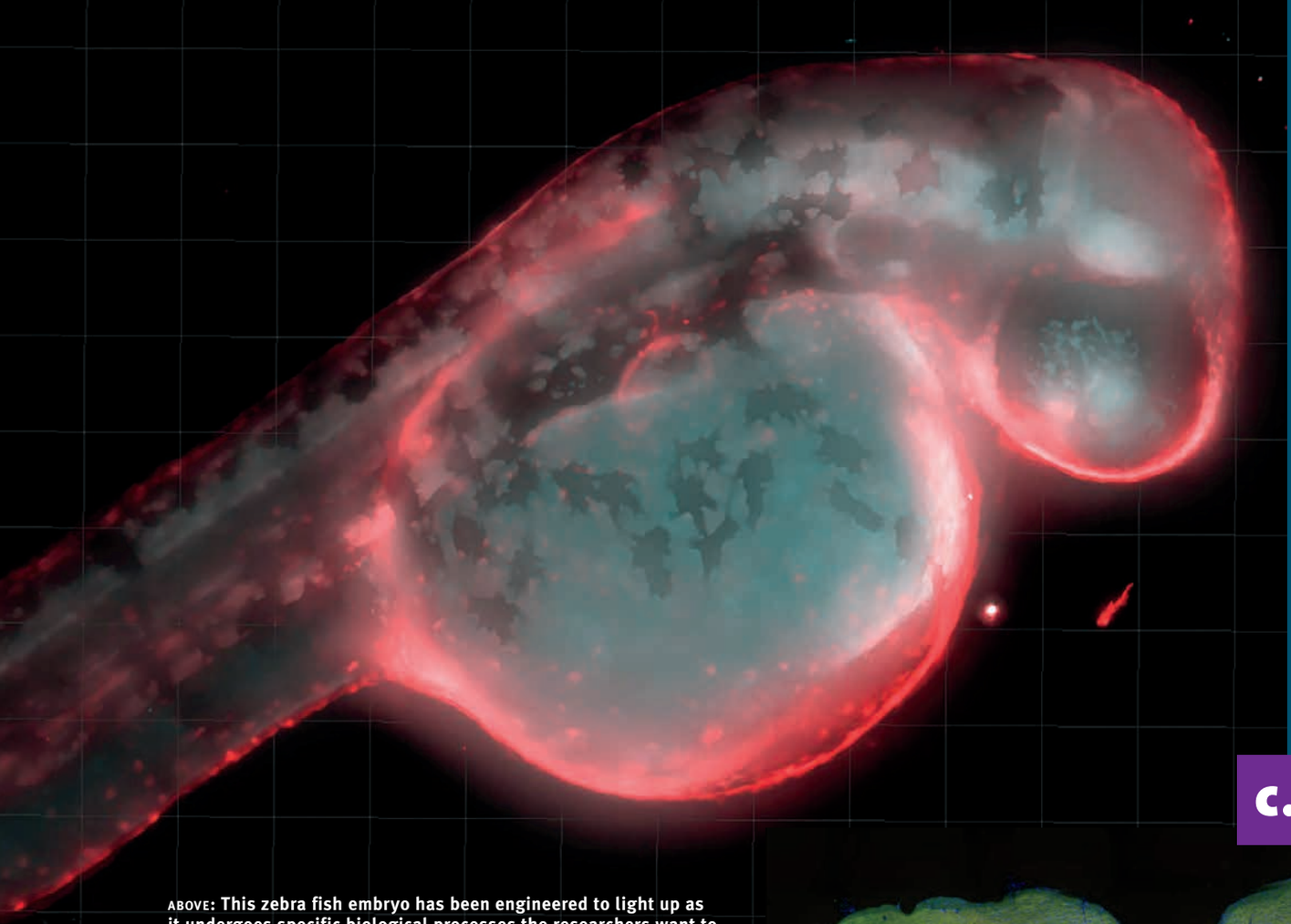
The researchers kept the project moving with weekly informal conversations held at a rotating list of eating and drinking establishments located near the two campuses. The division of labor went like this: CMU researchers would do the chemical fiddling to make novel sensors. Watkins, St Croix, and their crew would test the sensors out in different cell types to show that they worked and then would channel the interest of biologists who might benefit from them. "People walk into Simon's office and say, 'I'm trying to figure this out; how can I do it?'" says Bruchez. "He is really good at mastering the biology that's required to address these problems."

FAP technology has tremendous specificity. For example, it's possible to design sensors that don't pass through cell membranes, and thus specifically detect a protein found only on the outside of a cell; simultaneously, a different color probe can track that same protein within a cell. Along these lines, one application for FAPs is to track the density of proteins called G-protein-coupled receptors (GPCRs) at the cell membrane. GPCRs are a class of molecules mediating many diverse health-related processes. They are targets for about a third of all pharmaceutical drugs on the market, and they accomplish their assigned cellular tasks by communicating with other proteins from a seat in the cell membrane. The FAP assay can quickly screen for GPCR activity by determining how many such proteins have been recruited to the membrane, making it a valuable tool in drug discovery.

Raymond Frizzell, PhD professor of cell biology and director of the cystic fibrosis research center at Pitt, has been using FAPs for cell-surface protein detection as he screens for novel drugs to treat the disease. Cystic fibrosis is caused by mutations in the CFTR protein, one of which blocks the protein's transport to the cell surface. First, Frizzell's group used FAPs attached to CFTR to characterize how efficiently correctors, a class of small molecules designed to correct the function of the protein, brought CFTR to the cell surface.

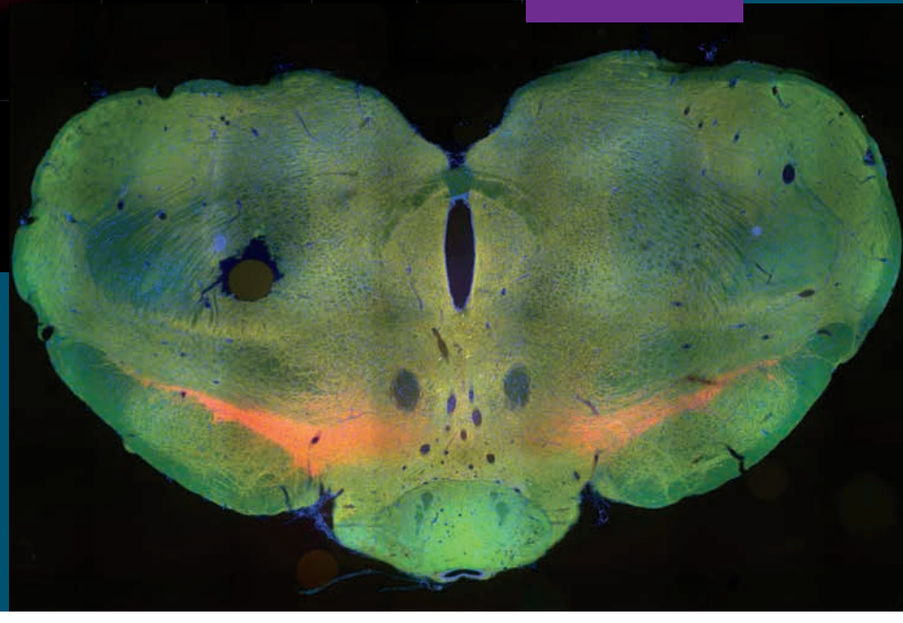
"We could detect very clearly that the protein only got to the cell surface when we used certain correctors or combinations of correctors," Frizzell says.

P. 31: COURTESY SIMON WATKINS, CBI.



c. 2013

ABOVE: This zebra fish embryo has been engineered to light up as it undergoes specific biological processes the researchers want to observe. The powerful and highly specific approach, under development by Pitt and CMU people, involves engineering zebra fish to carry a fluorogen-activating protein (FAP) gene. "This was our first successful trial with the FAP approach in vivo," says Watkins. The image shows blue cerulean dye (tagging the FAP), overlaid with red dye used to light up the FAP protein.



RIGHT: This is a large-area, four-color fluorescent image of a rat brain taken with a multicolor, automated fluorescent microscope capable of collecting very large images of tissue sections in up to five fluorescent colors and stitching all the pictures together so the image looks flawless. Watkins built the scope, using parts he bought on eBay. "It was a summer project in 2011," he says, "and has resulted in multiple high-impact papers." One of those papers showed an image like this, from a study by Pitt's Victor Tapias and Timothy Greenamyre from the Pittsburgh Institute for Neurodegenerative Diseases. The red dye shows fewer neurons associated with the important neurotransmitter dopamine on the right side of the brain; that side has been exposed to a neurotoxin.

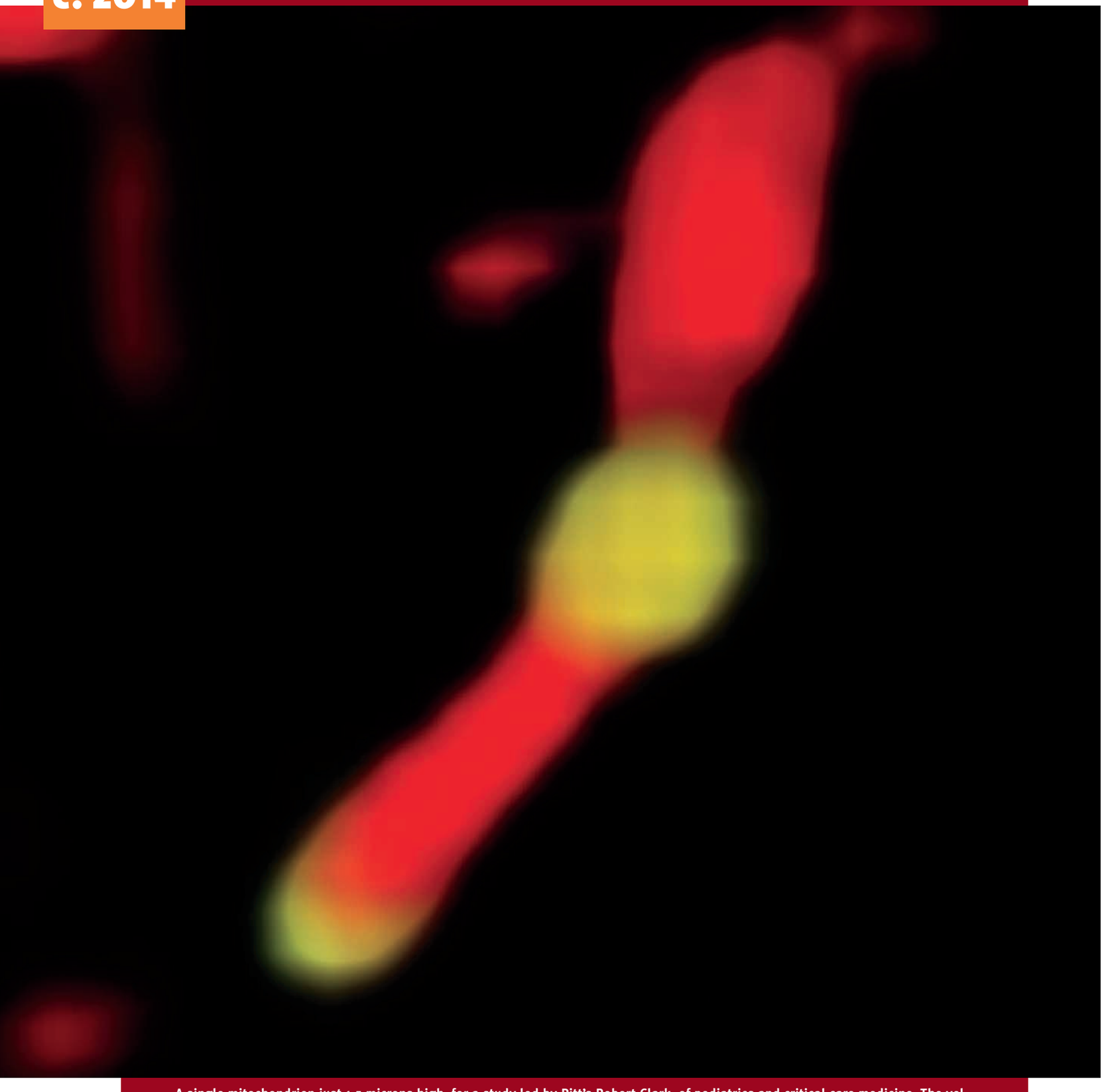
Then, they tested those molecules on cells taken from the lungs of cystic fibrosis patients and grown in a culture dish. Those that got to the cell surface membrane in the first assay were the ones that worked best in the cultured cells, too, validating the use of FAPs to find potential drugs. Frizzell's group is now setting up a high-throughput assay that will use FAPs to screen for more effective corrector compounds.

But FAPs' real superpowers lie in their ability to detect all sorts of physiological changes, such as membrane potential, calcium concentration, pH, or redox state—not just in cells, but in living animals, like the zebra fish Watkins and St Croix have been screening (which was genetically engineered by Pitt's Beth Roman, PhD assistant professor of biological sciences).

"I think this [technique] is going to show us a lot of biology that has been hidden in the cell-based experiments that we've used for almost all of our basic assays," says Bruchez. As he, Waggoner, and Watkins continue to refine the physiological sensors, Michael Tsang, a PhD associate professor of developmental biology, is breeding thousands of zebra fish that will express genetically engineered proteins that make FAP dyes light up in response to changes in calcium concentration. If that works, other sensors will follow.

There are already probes that do that, says Waggoner, but they have big limitations. "Those probes diffuse to wherever they want to be in the cell," he says—which makes it impossible to pin down where the action is taking place.

c. 2014



A single mitochondrion just 1.5 microns high, for a study led by Pitt's Robert Clark, of pediatrics and critical care medicine. The yellow is a compound (Bodipy XJB) made by Pitt's Peter Wipf, in chemistry, designed to scavenge for reactive oxygen species specific to mitochondria (red is a mitochondrial dye). The image shows the chemical is appropriately localized to subregions in the mitochondria. Such super-resolution microscopy "essentially breaks the resolution limit of traditional fluorescence microscopy—and has become very fashionable in the last year or so," says Watkins. The CBI can apply a few technologies to get such results; one of these systems was built by Watkins in 2012 (another summer project).

By targeting proteins specific to the mitochondria, the endoplasmic reticulum, or the cell surface, for example, you can take a reading right there, or follow the signal wherever it goes.

"Then we can ask, *What happens in the normal developmental pathway when these dyes come on? And if we manipulate the system, do we see any changes in the morphology of the embryo?*" says Tsang. "With these new tools [you'll] see these changes happening instantaneously—not just in one cell type or one tissue type, but in the context of a whole organism."

If the technique works, it could give a breathtakingly intimate look at how the ebbs and flows of one cellular mechanism affect another. Does the way that calcium waves are propagated in the heart affect that organ's morphology? Does a neuron firing in one part of the brain affect free radical release elsewhere?

In his role as head of drug discovery for Pitt, Taylor now focuses his efforts on new biosensors and ways of studying activities within many cells or organisms instead of just one at a time. The veteran imager predicts a luminous future for fluorescence technology as researchers gradually master approaches to 3-D imaging in humans, tissue-engineered models, and live animal–techniques.

"I would say there won't be any molecules or biochemical events within cells that we won't have the ability to make a sensor for," Taylor says. And just as FAPs and other fluorescent technologies have shown us fundamental biological processes in cells, other innovations in microscopy are also transforming the field. Just five years ago, the resolution microscopes could achieve was stuck between 200 and 500 nanometers; today, sophisticated super-resolution platforms can achieve a resolution of 20-100 nanometers. (Some get as low as 5 nanometers.)

Of course, there's plenty of work left to do. At present, researchers can only see a few millimeters into living tissue with a microscope.

"It would be great if we could have high-contrast imaging multiple centimeters into animals," says Waggoner. Two other items on his wish list: dyes with infinite photostability (that never fall apart or create reactive oxygen species which poison cells, no matter how much light they are hit with) and dyes with ever-sharper absorption and emission ranges, so that each one gives a narrow and completely isolatable signal.

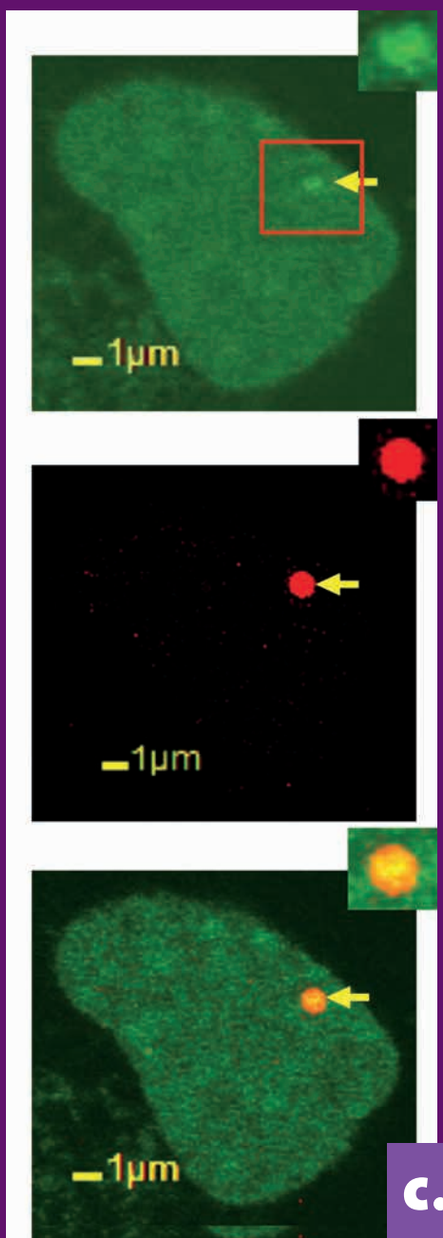
Although the NIH grant that formally intertwined the imaging efforts at CMU and Pitt is now in its sunset phase, there is no sign that the two groups plan to wind down their collective activities any time soon.

Says Waggoner: "It's really best when we work together." ■

Joe Miksch contributed to this story.

FOR MORE HIDDEN ACTIVITIES REVEALED THROUGH CBI'S SCOPES, SEE OUR WEB EXTRA: PITTMED.HEALTH.PITT.EDU

KillerRed dye can be targeted to a particular spot on DNA, where it generates reactive oxygen species upon light exposure. TOP PANEL: As the dye is activated, a repair molecule (NTH1) is recruited to the site of DNA damage within minutes (see arrow). MIDDLE PANEL: Localized KillerRed spot shows the sites of damage at one genome locus. BOTTOM PANEL: Merged view of the first two panels.



A MURDEROUS GLOW

Most fluorescent dyes act as markers or sensors, heralding the presence of a protein or a physiological event. Now there's a way to bring fluorescence into the action with a dye ominously called KillerRed.

For more than a decade, Pitt's Li Lan, an assistant professor of microbiology and molecular genetics, has been studying mammalian cell response to DNA damage. Until recently, she used either a blast from an ultraviolet laser or an enzyme called I-SceI to induce such damage. But it's impossible to pinpoint where exactly on a chromosome a laser hits, and the enzyme, while more precise, creates a cleaner and more artificial break in the DNA than what happens in nature—specifically, in the midst of the production of reactive oxygen species (ROS).

Enter KillerRed, created by Russian scientists, which changes its structure and releases ROS as it absorbs light. It can also be genetically encoded to target a specific location on a chromosome. "KillerRed," Lan realized, "could combine the benefits of the I-SceI system and the laser system." The potent dye could help researchers understand a crucial cellular process.

"Every hour, the DNA in each cell of your body undergoes more than 5,000 breaks," Lan says. Most are quickly repaired, but people in whom that process is impaired accumulate mutations that can lead to cancer and other diseases.

Lan and colleagues figured out a way to fuse KillerRed with a protein that increases gene transcription at a particular location, generating DNA-damaging molecules there. (Her collaborators include CMU's Marcel Bruchez as well as the School of Medicine's Robert Sobol, Bennett Van Houten, and Arthur S. Levine, Petersen Dean and senior vice chancellor for the health sciences.)

Last November, Lan published her first paper using the technique, which showed that damaged DNA is repaired differently depending on whether chromosomes are packed tightly, as they normally are, or unwound, as they become when cells divide.

"It's a big question in the field, but we have not had a good way of analyzing how it happens," says Lan. Until now. *—AK*

c. 2013

SIERRA BOURNE

The unpredictable world of the emergency department meets the rigid constraints of modern medicine: Coming soon to a theater near you. (Above, Ryan McGarry on location.)

CODE BLACK

A CLERKSHIP TURNS INTO A FILM FESTIVAL FAVORITE

BY JENELLE PIFER

Doctors scramble. Dozens shout. Machines beep. A gurney rumbles over tile. A new documentary directed by Ryan McGarry (MD '09), *Code Black,* depicts the emergency department as a living system subject to challenges—extreme waiting lines, long physician hours, and the turbulent emotions experienced by patients and their families. "If you're an outsider, this looks like total chaos," says McGarry in a voiceover. "But as a doctor, I see unity in that chaos. There's a team here in all that coming together to save someone's life."

As a med student at the University of Pittsburgh, McGarry participated in a clerkship and research rotation at Los Angeles County General, which his documentary describes as "the birthplace of modern

emergency medicine." Rather than staffing an emergency department with doctors of varying specialties, in the late 1970s, LA County General leaders decided that training a group of physicians in all aspects of care was the best way to save lives. (Under Peter Safar and others, early reforms were also under way at Pitt.) When McGarry arrived in September 2008, the LA department operated out of a compact, one-room space and thrived using an all-hands-on-deck approach.

"I had no intentions of coming to LA to make a film," says McGarry at a coffee shop in Manhattan, where he is now on staff at NewYork–Presbyterian and assistant professor of emergency medicine at Cornell University. "It was accidental, really, which is often how documentary films get started."

Having studied English as an undergrad and read cinematography journals since childhood, he maintained an impulse toward creative work and recognized early that the hectic environment had real cinematic potential. Just a few weeks into his LA rotation, McGarry began lugging around a 40-pound camera.

"The visual quality of the space—it was literally a 16-by-9 aspect. Most doctors [elsewhere] only take care of one patient at a time in one room. This was like a movie; it had six patients side by side in wide screen," he says.

Initially McGarry wanted to make an experimental, non-narrated film that immersed viewers in the visceral world of emergency medicine. He served as his own film crew and could anticipate where to go next. "With a [larger] crew there would have been a lag time, where I'd have to be like, 'Okay, they're going to cut this guy's chest open next. Let's move over to this corner,'" he says. Instead, the new trainee was able to move quickly, absorbing knowledge himself while capturing intimate shots of young doctors peering into devastated body cavities and shaky med students tugging at their bloodied gloves.

When his four-week emergency medicine clerkship was nearing an end, the University of Pittsburgh gave him an extension to continue filming—a move he calls a "game changer" for the project. The school gave him an additional four-week research rotation, after McGarry demonstrated that he would have a product in the end. The feature-length documentary is now sweeping the festival circuit and earning top prizes nationwide, including Best Documentary Feature at both the 2013 Los Angeles Film Festival and the 2013 Hamptons International Film Festival. The project developed its plotline when McGarry returned to LA County for his residency and continued filming.

By 2012, LA County's emergency department had moved to a new building, a far more modern and sprawling complex that drastically changed how it operated. The team was forced to comply with a slew of administrative and privacy requirements that were simply not an option at the old, relatively antiquated space. (By the way, McGarry was careful to get consent to film anyone appearing in *Code Black*.)

"The new filming was more loaded," says McGarry. "At some point in the documentary process you decide what you want to build your story on, and you go for it."

The focus became a question: How can the unpredictable, team-oriented world of the emergency department function within the rigid terms of modern health care? The new rules forced doctors to spend 8 minutes documenting a 2-minute exam. To maintain patient privacy, there is an endless routine of signing in and out that one physician admitted made him briefly look for the log-in at the bathroom stall.

McGarry narrates the film and serves as its main subject, but the story is completed by the voices of his resident colleagues. Together they represent a new generation of emergency medicine physicians immersed in protocol, policy, forms, and checklists.

In crowded emergency departments, doctors assign a color code to the overall workload, ranking how busy they are from "code blue" to "code black." At code black, "we are so saturated with waiting room volume, admits, and, of course, incoming ambulance traffic, that it feels like the resulting gridlock is an understatement—somehow we're piling multiple, towering layers of gridlock onto more gridlock," says McGarry.

It is entirely possible for a patient at LA County to wait upwards of 14 hours before seeing a doctor. (These are often uninsured patients who rely on the county emergency room for primary care.)

For McGarry, the crowded waiting room is "the most real representation of one of our greatest problems." As a director, he says, "I wanted you to experience what it's like to walk through that waiting room and to feel this canyon of eyes on you, going, 'We're all here.'"

In this way, *Code Black* is exhausting, and it's meant to be. But ultimately, the film has a permeating optimism. The physicians are clearly driven to help their patients. At one point the team rallies to move certain chairs from the waiting room into the treatment area so doctors can visually monitor pending cases (an experiment that doesn't necessarily translate smoothly to every space).

The film illustrates McGarry's wish to inject adrenaline and doctor-patient immediacy back into emergency care. He says that Paul Paris, Pitt's former chair of emergency medicine, with his "get-it-done" style, was an early role model.

RYAN MCGARRY

Watching *Code Black* is exhausting, and it's meant to be.

Today McGarry continues to balance his work in film and medicine. Serving several long shifts in the emergency department each week frees up some blocks of time; he's got several writing and TV concepts in the works.

At film festivals, McGarry no longer stays in the theater to watch the documentary in full. "But I stay for the first 15 minutes to make sure that everyone's okay."

Code Black is graphic. In Aspen, one audience member fainted. So McGarry stays at least for the dramatic opener, he says.

"That's the physician in me." ■

www.codeblackmovie.com

SARA B. MAY

Aftermath of Super Typhoon Haiyan; Koehler's group was the first medical team on site in Tanauan, Philippines.

CLASS NOTES

'80s

At a memorial service for his wife, Jennifer, 48, and two daughters, Hayley, 17, and Michaela, 11, who were murdered during a home invasion in 2007, **William Petit** (MD '82) called on his community to "help a neighbor, fight for a cause, and love your family" in their memory. Seven years later, the Petit Family Foundation has contributed more than $1 million to fostering the education of young people (especially women in the sciences), as well as improving the lives of those affected by chronic illness and protecting and helping those affected by violence.

After the tragedy, Petit, an endocrinologist, left medicine to focus on his foundation work. Recently, he's been exploring a new way to help people, addressing a problem that's been on his radar since his days at Pitt. With a group of MDs and engineers, Petit is developing a noninvasive monitor, "no bigger than a key," that measures glucose levels in saliva rather than blood.

Petit remarried in 2012. His wife, Christine Petit, gave birth to a baby boy, William III, in December.

'90s

For centuries, we thought the sinuses were sterile; infection happened when microorganisms ended up where they weren't supposed to, and the reason infection tended to boomerang back was biofilms—stubbornly antibiotic-resistant stuff. But **Andrew Goldberg** (Otolaryngology Resident '90) had a feeling that wasn't the whole story. Biofilms are found in healthy sinuses, too. Besides, chronic sufferers are often cured even without biofilm-targeting treatments.

Goldberg

In 2012, Goldberg, professor of otolaryngology at the University of California, San Francisco, coauthored a paper in *Science Translational Medicine* debunking this dogma. Using a new genetic analysis technology called PhyloChip, the team found chronic sinusitis patients' sinuses teeming with microlife—and so were the sinuses of their controls. The difference was that the healthy people had more diversity of species, more even distribution between them, and greater numbers overall. Sinusitis, it turns out, is far more complex and nuanced than Goldberg had ever imagined. "There are environmental, host, genetic, and potentially even anatomic factors that all play into the development of this problem in any individual," he says.

Last year, *Orthopedics This Week* named **Brian Cole** (Sports Medicine Fellow '97)—and eight other Pitt med people—among 19 top "thought leaders" in sports medicine in the United States. Cole, professor of orthopaedics at Rush University and team doctor for both the Chicago Bulls and the White Sox, says he was drawn to sports medicine by the opportunity to work with patients who are highly motivated to get better. In June 2013, Cole and his son, Ethan, were part of a medical mission to Kenya in collaboration with Cure International. The mission was to improve the lives of athletes whose injuries had been neglected because of a lack of equipment and expertise.

When **Richard Koehler** (MD '99) and the rest of the team from Mammoth Medical Missions learned about Super Typhoon Haiyan, they were en route to Chiapas, Mexico, for a surgical volunteer mission. It took them only 15 minutes to decide to change course for the Philippines instead. Theirs was the first medical team on the ground in Tanauan, 20 kilometers south of Tacloban City, after the devastating typhoon in November 2013. They performed nearly 150 operations in the 60 hours they were there. Koehler, an avid backpacker and outdoorsman, likens his experience to climbing a mountain. "There's a lot of suffering and misery, but occasionally you get glimpses of the summit. There's a profound sense of satisfaction."

Gonzaga

'00s

Alda Maria Gonzaga (MD '00, Internal Medicine/Pediatrics Resident '04, Medical Education MS '06), director of UPMC's Progressive Evaluation and Referrals Center (PERC), says she strives to see the story behind every patient—and, as director of the Combined Internal Medicine/Pediatrics Residency Program, to instill that sensitivity in her mentees, too. Gonzaga, along with **Reed Van Deusen** (MS '08), oversees patients with chronic early onset conditions such as Down syndrome and autism as they transition from pediatric to adult care. To ease the potentially unsettling move from one phase of life to the next, says Gonzaga, it helps to get to know her patients and their families better. Building these relationships is gratifying for her, as well—it's a "tremendous blessing," she says.

Almost every man who dies of prostate cancer dies with castration-resistant prostate cancer. In August, **Nima Sharifi** (MD '01), who chairs prostate cancer research at the Cleveland Clinic's Lerner Research Institute, published in *Cell* his discovery of a genetic mutation that allows this deadly form of cancer to make its own supply of androgens—prostate tumor fuel—regardless of treatments that target the body's ability to produce it. Sharifi was recognized with the American Association for Cancer Research Outstanding Achievement in Cancer Research Award this spring.

David Levinthal (MD '06, Gastroenterology Fellow '12) describes Pittsburgh as the "perfect place" for his work, citing the support of Pitt mentors Peter Strick and Klaus Bielefeldt, a neurobiologist and a neurogastroenterologist, respectively. And it is complicated work; Levinthal wants to understand how the stomach and other organs are mapped in the brain. Tracing the neurological connections that control the digestive tract will allow doctors to better treat patients with functional bowel disorders and other debilitating conditions that cause problems with swallowing, digestion, and bowel function. Levinthal says that these are not "sexy topics," but the importance of the work to patients' quality of life drives him forward. Forthcoming is a K08 grant from the National Institutes of Health that will fund research on the neural-mapping of the stomach in primates, as well as on altering stomach function using transcranial magnetic stimulation.

In addition to her School of Medicine credentials, **Velma Payne** (Biomedical Informatics MS '08, Biomedical Informatics PhD '10) also has an MS in computer information

systems and an MBA. "I believe technology is a valuable tool to augment medical decision-making within the clinical environment," she writes in her bio. "My goal is to provide tools to clinicians on the front line of medical care that will reduce medical errors and enhance patient safety."

Payne is a postdoctoral fellow at the Center for Innovations in Quality, Effectiveness and Safety, a national center of research excellence funded by the Veterans Health Administration. Her primary interests are the cognitive aspects of medical decision-making and the use of information technology to enhance the diagnostic process and reduce errors.

To date, more than 200 mutations in the PARK2 gene (producer of the protein parkin, thought to be important to the health of certain neurons) have been found to cause Parkinson's disease. Pitt movement disorder fellow **Amber Van Laar** (MD '09, Neurology Resident '13) hopes to develop a way to protect neurons from damage by boosting PARK2's numbers. This summer—thanks to a competitive, three-year award she recently received from the American Brain Foundation and the Parkinson's Disease Foundation—she will probe the underlying mechanism of the disease and investigate whether gene therapy might prove a useful tool in safely boosting parkin levels. Van Laar, who has long dreamed of building a career as both a clinician and a scientist, is thrilled at the opportunity. "I feel tremendously grateful for this award," she says.

—Charles Huysman, Brett Murphy, and Elaine Vitone

COLLIN DIEDRICH

THINKS DIFFERENTLY

Diedrich (and, in the distance, a giraffe) on a safari in South Africa last year.

In grad school, Collin Diedrich (Molecular Virology and Microbiology PhD '12) was the guy who always sat in the front row with his recorder—the overachiever, classmates figured. "And I was like, *No, I have to go back and listen to them just to level the playing field*," he says.

Diedrich has struggled with reading and learning disorders since grade school. Now, as an emerging scientist, he's eager to help others facing the same uphill climb.

Diedrich started blogging about his experience as a PhD candidate with learning disorders while at Pitt. Getting there took years of extra elbow grease and a lot of support—which he happily reports he had the whole way through, including his time in the lab of Pitt professor of microbiology and molecular genetics JoAnne Flynn. He is on hiatus from posting to his blog, ldphd.org (LD stands for "learning disorder") while he focuses on research and grant applications. He plans to revive his blog—and eventually turn it into a book.

Now, as a postdoctoral fellow at the University of Cape Town in South Africa, Diedrich investigates HIV/TB coinfection immunology. About a third of the global population has TB, most of which are latent cases—however, those who also have HIV are far more susceptible to reactivation. The reasons why have proven elusive. Traditionally, groups around the world have studied these immune processes in human blood samples. At Pitt, Diedrich worked with Flynn and other collaborators to develop a novel non-human primate model. Now, Diedrich has added a helpful new piece to the puzzle: human tissue samples from the granulomas themselves—the nodules of immune cells in the lungs that attempt to wall in the infection. Granulomas, he says, are "right where the disease lives." Diedrich is gathering and analyzing these rare, coinfected specimens throughout Western Cape, South Africa, and developing a new hypothesis regarding how HIV changes granuloma functions.

Diedrich's learning disorders, though a hindrance in many ways, have also helped him as a scientist, he says—making him diligent and obsessive and teaching him that no one can know everything. Science has to be collaborative, he says.

"It does take me longer to process things. But because I'm able to think a lot about things, I feel like the end result is often that I can come up with a new idea or a new way to approach a problem." *—EV*

MAA SAYS, "ACT GLOBALLY"

Soriano in Lilongwe, Malawi, this February.

In the middle of a gynecological procedure this February at Kamuzu Central Hospital in Lilongwe, Malawi, the country's largest government hospital, the power went out. For 15 minutes, in the pitch black, the anesthesiologist manually pumped oxygen into the patient. The med student in the room was **Alex Soriano**, a fourth-year on a month-long global health elective funded by the **Medical Alumni Association (MAA)**, his third international rotation. Previously, he'd traveled to the Philippines and Honduras.

Resource scarcity, he's learned, is the biggest difference in health care between the United States and developing nations. "It was no longer about figuring out the cause of illnesses," he says of the 80-plus patients he saw daily in the women's ward, most of whom were HIV-positive. "You're just trying to make them comfortable and give them the best [treatment] you have."

Patients outnumber beds 3 to 1 in the corridors. Pain medication, blood, nurses, lab equipment, "and endless small things you wouldn't think of that a hospital needs to function" are in short supply.

"I realized how fortunate we [are in the United States]. . . . It was also comforting to know that I had it in me to make hard medical decisions in those circumstances," says Soriano, adding that he learned new methods in physical examination on his trip.

"For an American physician, there's so much value in going abroad," he says. "Our job is to be a resource or an outlet, not to tell them what to do."

Soriano was one of 10 students who received travel funding this past fall and winter—a proud tradition of the Medical Alumni Association. Students who wish to give something back are encouraged to volunteer at events like the annual phone-a-thon, Medical Alumni Weekend, and the White Coat Ceremony. For more details, contact Pat Carver at **cpat@pitt.edu**. *—BM*

MEDICAL ALUMNI ASSOCIATION WWW.MAA.PITT.EDU

MONTO HO

MARCH 18, 1927–DEC. 16, 2013

Ho

Monto Ho, whose father was an ambassador, started out at Harvard studying politics and philosophy. He turned to medicine, because "its sole purpose was to reduce human suffering," he writes in his memoir. The virologist left his mark on the fields of organ transplantation and HIV research.

Ho died on Dec. 16, 2013.

The physician scientist's early investigations provided seminal insight on interferons' inducers and mechanisms of action. For more than two decades, he studied herpesvirus infection following transplantation; he was the first to show that transplanted organs transmitted cytomegalovirus, which causes life-threatening pneumonia in these patients. Ho was one of the earliest supporters of serology testing of both the organ donor and recipient to reduce the risk of these infections, a standard of care that remains today.

Ho, former chief of the Division of Infectious Diseases at the University of Pittsburgh School of Medicine, attended schools in China, Austria, and Turkey before completing an MD and fellowship at Harvard, and then coming to Pitt. He chaired the Department of Infectious Diseases and Microbiology at Pitt Public Health from 1972 to 1997, when he was succeeded by Charles Rinaldo Jr., a PhD. In retirement, Ho advocated for measures to reduce antibiotic resistance in Taiwan, work that was recognized with the National Health Research Institutes' Excellence in Research Award.

In a forthcoming obituary in *Clinical Infectious Diseases*, Rinaldo states that Ho possessed "the exceptional human traits of intellectual excellence and refined gentility of true scholars," citing his final gift to his beloved profession: In 2006, Ho and his wife, Carol, established the Monto and Carol Ho Chair in Infectious Diseases and Microbiology at Pitt. *—CH*

DAVID H. RHODES

JAN. 16, 1927–FEB. 1, 2014

Rhodes

"Your dad treated mine like Jesus," a man said to Tom Rhodes at his father's funeral. In the sixties, David Rhodes (MD '53) had seen to it that the man's father got the urgent medical attention he needed.

Rhodes, a neuro-ophthalmologist, left lasting impressions on generations of patients. "I've gotten letters from people saying, 'He took care of me, my mom, and my daughter,'" Tom Rhodes says.

After serving in the navy, the elder Rhodes got his BA and MD from Pitt, following in his father's footsteps in ophthalmology. (Both completed residencies at Columbia University's Edward Harkness Eye Institute at NewYork–Presbyterian.)

In 1959, Rhodes was elected a fellow of the American Academy of Ophthalmology and Otolaryngology. He co-authored, along with anesthesiologist Deryck Duncalf, *Anesthesia in Clinical Ophthalmology* in 1964, one of the first primers on anesthesiology in eye operations.

Throughout his career, Rhodes, a clinical assistant professor of ophthalmology at Pitt, was on staff at what's now UPMC Mercy and UPMC St. Margaret. From 1980 to 1994, he was chief of ophthalmology at Mercy. His other passion, besides medicine, was sailing, the younger Rhodes says.

Rhodes spent the last season of his career before his retirement in 2008 at Everett & Hurite Ophthalmic Association in Pittsburgh, where he was surrounded by colleagues and friends, many of whom he taught over the years at Pitt. "They all remembered his lectures vividly," recalls his son. "He was old-school, but people learned so much from him." *—BM*

SARAH WOLFE

MARCH 14, 1975–FEB. 7, 2014

Sarah (left) and Susan Wolfe

"No animals were harmed in the making of these cookies," Sarah Wolfe often said of the vegan treats she routinely brought to work.

Wolfe (Combined Pediatrics/General Psychiatry/Child and Adolescent Psychiatry Resident '12), an assistant professor of psychiatry at Pitt, had a "marvelous, self-deprecating sense of humor and immense talent" as a pediatrician and a psychiatrist, says Dena Hofkosh, pediatric residency program director at Children's Hospital of Pittsburgh of UPMC.

Sarah and her sister, Susan Wolfe, were murdered in February in their Morningside home, news that stunned the School of Medicine and UPMC communities, and all of Pittsburgh. "At that point, so much of her career was potential," Hofkosh adds. "It was just a joy to work with her, because she was so competent and yet so humble. She had a deep connection with the kids and families she took care of."

In 2012, Wolfe completed the selective and rigorous triple-board program at the University of Pittsburgh and UPMC, a five-year residency that certifies its graduates in pediatrics, general psychiatry, and child and adolescent psychiatry. In homage to Wolfe's compassion and dedication, the "family" of physicians in the program coined themselves the "Wolfe Pack" years ago, with T-shirts and wristbands announcing their allegiance. Roberto Ortiz-Aguayo (Combined Pediatrics/General Psychiatry/Child and Adolescent Psychiatry Resident '07), an MD assistant professor of psychiatry and pediatrics, took note of her untiring attention to detail and flawless work as a pediatrician and child psychiatry fellow. "She made me want to be a better teacher and a better person," he says.

Wolfe consistently ranked in the top percentile of all psychiatry trainees in the national examinations, says Martin Lubetsky, an MD and chief of child and adolescent psychiatry services for Western Psychiatric Institute and Clinic and chief of pediatric behavioral health at Children's.

She grabbed the American Psychiatric Association Outstanding Performance Award for its Annual Mind Games Resident Competition, a national, *Jeopardy*-style joust. After residency, Wolfe joined Pitt's faculty.

She volunteered at animal shelters and civil liberties organizations. "Sarah was a friend to countless individuals," says Lubetsky. *—BM*

IN MEMORIAM

'30s

JACKSON S. POGUE
MD '38
JAN. 17, 2014

'40s

J. ALLEN MCAFOOS
MD '43
FEB. 5, 2014

WILLIAM M. MITRO
MD '44, RES '47
JAN. 4, 2014

JOHN BONO
MD '48
APR. 4, 2014

'50s

RICHARD E. HERSHEY
MD '50
FEB. 14, 2014

ROBERT E. WARNER
MD '51
DEC. 15, 2013

JAMES KENNEDY GREENBAUM
RES '58
MARCH 13, 2014

'60s

JOHN A. HODAK
MD '61
DEC. 22, 2013

'70s

PATRICIA B. JOZEFCZYK
MD '74
DEC. 6, 2013

'80s

ALAN M. NORBUT
RES '80
JAN. 20, 2014

ARTHUR P. CIACCHELLA
MD '85
DEC. 29, 2013

FACULTY

CARL R. PARTANEN
FEB. 4, 2014

EMANUEL KANAL IN THE MRI SAFETY ZONE

BY AMY WHIPPLE

COURTESY KANAL

Kanal created the most comprehensive MRI simulator in the world, which he routinely uses in his week-long CME courses on MRI. He often flies himself to his lectures and conferences.

Emanuel Kanal (MD '81, Res '85, Fel '86, Fel '92) is not about to let you give him credit—for just about anything. Like the time he saved his assistant's life.

In 2011, at Kanal's annual course in magnetic resonance imaging (MRI) education and safety in Vail, Colo., Robin DeAngelo arrived 10 minutes late—a first in 20 years—with a nagging headache. Noticing changes in her behavior, Kanal insisted she get checked out at the local ER. The hospital radiologist, seeing no red flags on her computed tomography (CT) scan, discharged her—with a copy of the scan on disk.

When Kanal reviewed the scan himself back at the hotel, he saw clots in blood vessels in DeAngelo's brain that the hospital radiologist had missed. He accompanied DeAngelo back to the hospital, where he personally conducted a second scan, an MRI, to confirm what was ultimately her diagnosis: a life-threatening and rapidly progressing central sinus thrombosis that demanded immediate care.

"Robin DeAngelo is alive today because she's absolutely never late," Kanal says.

See what he did there?

As an emergency neuroradiologist, Kanal, a Pitt professor of radiology and director of MRI Services in UPMC's radiology department, primarily sees victims of car accidents, drug overdoses, and strokes. His job, in a nutshell, is to figure out who needs what kind of help, and when. Additionally, Kanal, who is a fellow, founding member, and former safety committee chair of the American College of Radiology (ACR), has built a national reputation as a go-to guy for all things MRI safety—in government (he consults for the FDA), in industry, and in legal cases. He's been a lead author on every edition of the ACR's MRI safety guidelines to date.

Kanal began his training at Pitt as MRI was in its infancy. Kanal's wife asked whether what he was doing was safe, he recalls. His answer: *I don't know, but I'm going to find out.* "I'm still finding out," he says. In his own research, Kanal is best known for developing timed bolus contrast enhanced MRI angiography—basically, MRI for blood vessels—for safe clinical use.

Kanal has probably taught more health care providers about MRI safety than anyone else in the country. His annual CME course is the only course specifically designed to accredit MRI medical directors and safety officers.

He also created what is now the most detailed MRI simulator available, Kanal's MRI Simulator/Tutor. Kanal began writing the code for it as an MRI fellow at Pitt in the mid-'80s. He has since outsourced the programming but continues to use the software, which teaches the physics behind and clinical application of MRI technology. Throughout the last three decades, the simulator has benefited thousands of students.

In 1995, Kanal started the first MRI safety Web site for technologists, physicians, and nurses. "Then Google happened," he jokes. He started hearing from patients and their families. Eventually, he abandoned the site in favor of direct e-mail contact; he still answers between 50 and 75 questions per day.

Kanal sleeps three to four hours a night. With his bonus hours, we assume, he answers e-mails. He also flies airplanes (private pilot instrument rating) and enjoys archery and taking photographs. (Kanal is a member of the Associated Press.)

If you are impressed by any/all of this, he will chuckle kindly at you. If you tell Kanal you hear he's at the top of his field, he'll tell you it's not that big of a field. (See what he did there?) ■

WISH YOU WERE HERE

There must be 50 ways to leave your med school. You can go your own way, ride a horse with no name, or take a midnight train to Georgia. Tell us what you've been up to: career advancements, honors, appointments, volunteer work, publications. And we love old Pitt memories. Send us a message in a bottle (or via medmag@pitt.edu).


1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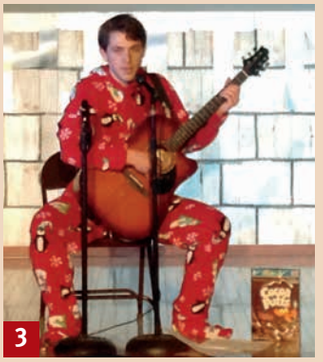
(1) Group dance. (2) Mr. Pitt Med 2014, Ben Rothrauff, with competition organizers, Carly Werner and Liny John. (3) Kyle Duff. (4 & 5) Rothrauff gets used to being center stage.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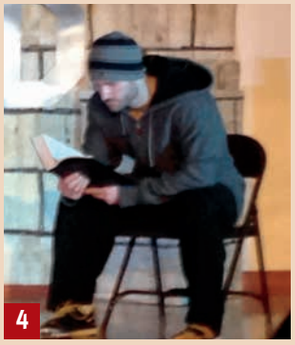
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5

DOCTORS AND DIADEMS

Some wore Speedos. Others wore more. G. Patrick, a second-year med student, was clad in a leotard and legwarmers as he danced across the stage in Scaife Hall's fourth-floor auditorium this February. At one point, in homage to the famous *Flashdance* moment, he dumped a bucket of water (well, blue confetti) on himself. We are speaking, of course, of the Swimsuit Competition.

Mr. Pitt Med, a beauty (cough-cough) pageant, has become the school's largest annual student-run fundraiser, says Liny John, a fourth-year who's long been involved with the event's organization. This year, the students pulled in $1,900; proceeds will go to the International Health Initiative to support global health organizations with med student ties.

The eight contestants tried—with brawn, brains, and bits—to win over the crowd (some 250 fellow students) and four panelists, School of Medicine profs with an eye for showmanship like Georgia Duker, PhD prof in the Department of Cell Biology. Her husband, MD professor of medicine Jamie Johnston, emceed the event.

So: Swimsuit portion. Eveningwear. Talent. (During which third-year Kyle Duff sang theme songs to Saturday morning cartoons in his pajamas.) Group dance. (Those who witnessed it will never hear Lady Gaga's "Applause" the same way again.) Q&A. (Which focused on contestant aspirations should they be named Mr. Pitt Med; fixing the broken coffee machine in the student lounge was a popular answer.)

West Mori, a first-year who put on a stunning rendition of Beyoncé's "Single Ladies," was named Mr. Congeniality after hauling in the most audience donations. But it was chiseled-jawed Ben Rothrauff, a fourth-year, who took home the title. His *Magic Mike* routine, garnished with backflips and push-ups, won the panel, and probably a couple of hearts.

Patrick walked away with some confetti in his hair but no crown. "I'm not salty," he says, sincerely. "I had fun and left it all on the stage. But maybe I'll wear shorts next time." *—Brett Murphy, Photos by Megan Wolf and Elizabeth Oczypok*

CALENDAR

FOR ALUMNI & FRIENDS

MEDICAL ALUMNI WEEKEND 2014
MAY 16–20
Reunion Classes:
2004, 1999, 1994, 1989, 1984, 1979, 1974, 1969, 1964, 1959, 1954

SENIOR CLASS LUNCHEON (ALUMNI WELCOME)
MAY 16, 11 a.m.
Campus View Club, Petersen Events Center

OPENING RECEPTION
MAY 16, 6 p.m.
Heinz History Center

SCOPE AND SCALPEL PRODUCTION
MAY 16, 7 p.m.
MAY 18, 2 p.m.
Carlow University, Antonian Theatre
www.scopeandscalpel.org

CHAMPAGNE BREAKFAST WITH THE DEAN AND PHILIP S. HENCH DISTINGUISHED ALUMNUS AWARD PRESENTATION
MAY 17, 9 a.m.
11th Floor Conference Center, Scaife Hall

THE WISER INSTITUTE 20TH ANNIVERSARY TOUR AND CME
MAY 17, 11:30 a.m.
WISER, 230 McKee Place

REUNION DINNER GALA
MAY 17, 6 p.m.
Fox Chapel Golf Club, 426 Fox Chapel Road

CLASS OF 2014 COMMENCEMENT
MAY 19, 4 p.m.
Soldiers & Sailors Memorial Hall & Museum

Unless otherwise noted, for more information: Pat Carver, 412-648-9059, cpat@pitt.edu. To find out what else is happening at the medical school, go to health.pitt.edu and maa.pitt.edu.

DOLLAR BILL: CORBIS; GIRL: SHUTTERSTOCK

FOR REAL! TWEEN SCIENCE.

Want to make an easy buck? Bet a friend that he can't catch a dollar bill. Have your buddy make a lobster claw out of one hand and hold it out toward you, knuckles pointing to the side. Hold the bill lengthwise from the top between your friend's fingers and thumb, with about half of the bill protruding above the claw before you let go. There's only one rule—your friend may only close his hand once you drop the bill. If played fairly, this trick works every time. That's because it takes a human longer to react than it takes for an object to fall 3 inches. Why are we so slow? Catching something is actually a pretty complicated maneuver: First your eyes must see the bill start to fall; then your brain must process this report and tell your motor neurons, "Close the hand"; and finally, your finger muscles must contract in a pinching motion. Really, getting all that done in about 0.18 seconds is pretty impressive. Reaction time comes down to the way our nervous systems are wired. It takes a certain amount of time for signals to travel from the sensory organs (eyes, skin, ears) to the brain, and a certain amount of time for instructions to travel from the brain to your muscles. If you can predict the appropriate response, you can decrease your reaction time, but only so much. And if you have to make a decision about how to react to a stimulus—like a goalie trying to block a shot—it takes longer to react than it would if you knew you just had to pinch your fingers together as soon as a bill starts to fall. But, as you now know, that takes long enough. *Cha-ching!*

—Jenifer Lienau Thompson

Thanks to Peter Strick, Pitt neuro-guru, for teaching us how to get our brains to play tricks on us. For more kids' stuff, **www.howscienceworks.pitt.edu**.

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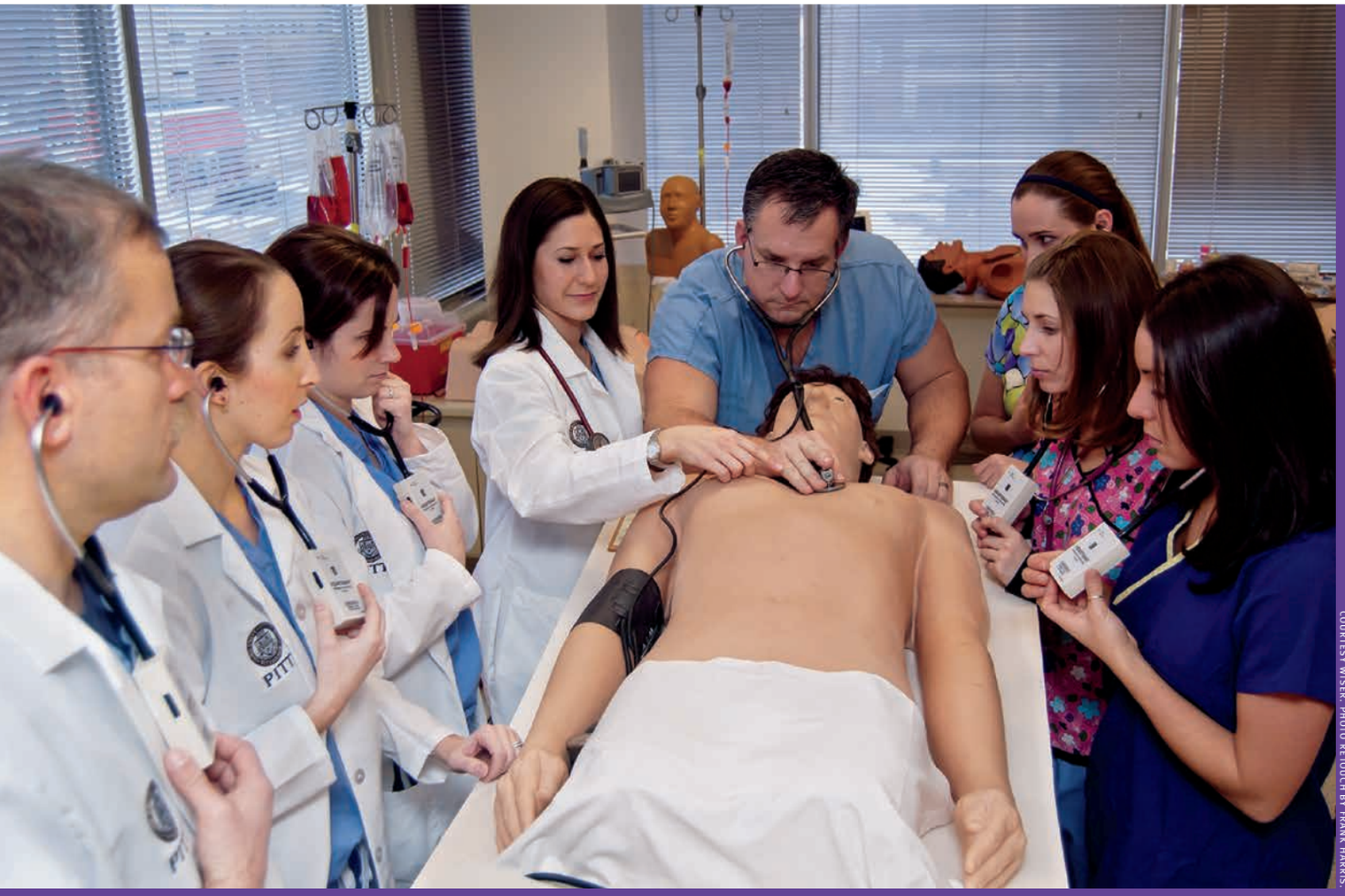

COURTESY WISER. PHOTO RETOUCH BY FRANK HARRIS.

WISE UP

Listen to your heart. Don't you want to join us for Medical Alumni Weekend this May 16–20, and get back to where it all began? Speaking of beginnings, the Peter M. Winter Institute for Simulation Education and Research (WISER)—which will be welcoming alumni to take a tour and participate in simulations, like the one pictured here—is celebrating its 20th anniversary this year. Come catch up with old pals, and pick up some CME credit while you're at it. You can learn a lot from a dummy.

The full Reunion schedule appears inside our back cover.

Reunion Classes:
2004, 1999, 1994, 1989, 1984,
1979, 1974, 1969, 1964, 1959, 1954

For more information, contact Pat Carver at 412-648-9059, cpat@pitt.edu.