UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | SPRING 2010

PITTMED



SCARY FOOD

BUT THERE'S AN ANTIDOTE

THAT FIRST WHITE COAT

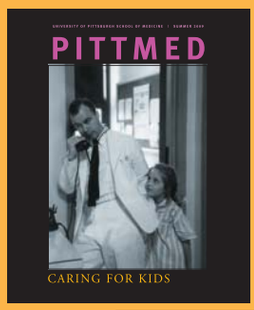
I sincerely hope that the University's newest medical students realize what a gift they were given in Sue Dunmire's address at their White Coat Ceremony, which was recently published in *Pitt Med* as "My First White Coat." Sue captures the real essence of what we do, day in and day out, in medicine. Much of this is easily lost and overlooked early on in medical education as students strive to learn and absorb what medical school throws at them. I suggest that all students preserve this piece and pull it out throughout their careers to remind them of the real reason that they practice medicine. I have been fortunate in my career to learn from the master, as Sue was a mentor to me in both medical school and in residency. The lessons that she teaches now are the same lessons she has taught throughout her career: Take care of yourself; take care of your patients; and take care of your family. Balance your medical education and your personal life—and laugh!

Thanks for the reminders, Sue. After almost 20 years, they still hold true.

William A. Jenkins
(BS '86, MD '90, Res '93)
Murrysville, Pa.

CARING FOR KIDS

I appreciate *Pitt Med* and enjoy it. Incidentally, I am the guy on the phone on the cover of the Summer 2008 issue [highlighting the Esther Bubley photo-essay covering Children's Hospital of Pittsburgh in 1951]. Also, incidentally, the same photo was used on the cover of a 1952 issue of the Children's Hospital bulletin. Also incidentally, the Alumni Association of Children's Hospital of Pittsburgh was "hatched" in June 1952 by the departing residents in the "relaxing room" in the quarters. Nothing official, just "we oughta get together in a year." No name for it. That came later. The hospital took it up and arranged for a reunion in '53 with a big turnout, which has continued every year since. The last "incidentally": I was "elected" president at that casual 1952 meeting.



Arthur Michael Coddington Jr.
(Res '52)
Johnson City, N.Y.

A FATHER REMEMBERED

I am a 1976 graduate of the University of Pittsburgh School of Medicine (as well as an anesthesiology resident and fellow for an additional four years).

My father, Henry W. Thomas, graduated from Pitt's School of Medicine in 1938 and died in 1994. His residency was interrupted by service in the Army Medical Corps during World War II, though he completed his residency in ob/gyn in 1948. He practiced at Magee-Womens Hospital, as well as South Side Hospital, all of his career, until he retired in 1980.

I'm sending a newspaper clipping you may find interesting. My father was just over 15 years old when he graduated from Pittsburgh's South High School. He entered Pitt the following autumn and graduated with an MD six years later, which made him just over 21 years of age upon graduation.


Youngest of Graduates

James J. Thomas
(MD '76, Res '79, Fel '80)
Shawnee Mission, Kan.

RECENT MAGAZINE HONORS

IABC Pittsburgh Golden Triangle
Award of Excellence, Magazines

IABC Award of Excellence, Feature Writing
(J. Miksch, "The Investigator's Path")

IABC Award of Honor, Publication Design
(E. Cerri)

Pittsburgh Black Media Federation
Robert L. Vann Media Award
Magazine Features, Third Place
(C. Zinchini, "Twins")

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

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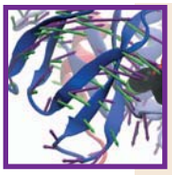
CORRECTION

In our Winter issue, we reversed the identifications of two first-year students and their alumni fathers—Katherine and Greg (MD '82) Hoyson and Julie and William (MD '74) Steinbrink—in a caption about the White Coat Ceremony. The fathers were still beaming, last we knew.

PITTMED

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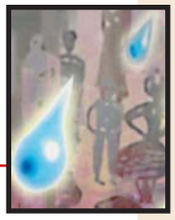


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CONTRIBUTORS

When she went to Africa in 1996, MARTHA RIAL ["A Hunka-Hunka Regenerating Starfish" and other stories] was simply following the storytelling reflex. Rial, then a photographer at the *Pittsburgh Post-Gazette*, spent a month in Africa documenting the work of her sister Amy Rial, a nurse working with refugees in Tanzania. The resulting images captured a Pulitzer Prize in 1998. This holiest of photojournalistic grails came as a surprise to Rial: "I always thought it was a very personal project. It was a way to honor Amy's work." After a three-year stint in Florida with *The St. Petersburg Times*, Rial is back in her hometown freelancing. The docs and other medical pros she meets on *Pitt Med* assignments keep her stimulated. "They have such a high energy level, such enthusiasm for what they do."

MIRAT SHAH (Class of '12) ["Why the World Needs Saving"] wanted to know what fellow med students thought was the most-neglected issue and what they would do about it. So she asked them to write to her. To her surprise, essays about roads, the environment, and social justice poured in. Selected essays from this collection appear in this issue's Attending section. Shah doesn't fancy herself a writer, but more of a reader. She decided on medicine while an undergrad at MIT, where she majored in materials science and engineering. A series of "little moments" led her to the big medical school decision. One of these included an experience following her advisor, an oncologist, on rounds with his patients.

COVER

Worldwide, billions eat aflatoxin, a fungal poison linked to liver cancer that's found in corn, tree nuts, and elsewhere. Pitt researchers are finding antidotes. (Cover: Juliette Borda © 2010.)



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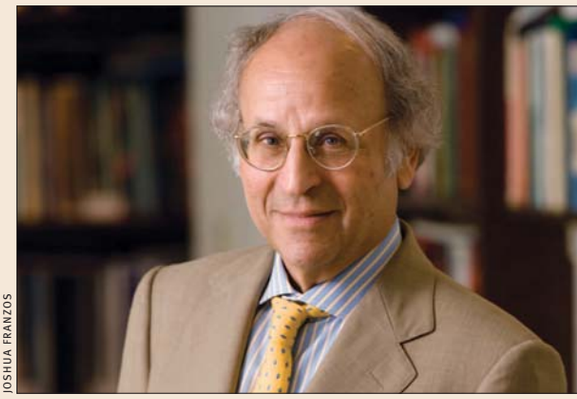
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JOSHUA FRANZOS

He that will not when he may,
When he will he shall have nay.
—Robert Burton

A few months ago, it seemed all but certain that some version of health care reform would become law this year. Now, if we are to believe the news coverage of the past few months, the possibility exists that reform in this country is dead. Those of us in academic medicine should be very concerned about this, and we cannot remain aloof from the political process unfolding around the issue of reform.

To consider the death of health care reform less than a tragedy is to discount the 45,000 Americans who die prematurely each year because of gaps in insurance coverage and the one million Americans in bankruptcy because of health care bills. We spend more on health care than any nation on Earth (now 17 percent of our total economy), and yet we lag far behind in many important metrics of health. We spend enormous amounts of money on unproven medicine and unnecessary interventions, some of which harm the patients they are supposed to help.

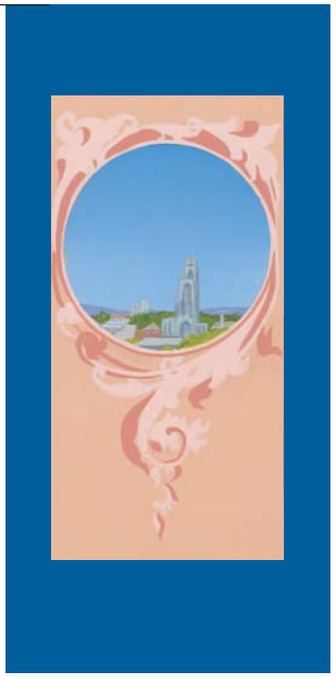
A dysfunctional health care system damages the entire country. It frustrates our competitiveness and our ability to take on new problems, such as investing in the science that could solve many problems that challenge all of humanity. If health care costs continue on their present course, every penny that Americans might gain in productivity or wages in the coming years is already spoken for.

Health care in America is marked by lack of access, high costs, and questionable quality. Access could be addressed by extending coverage to the 15 percent of Americans who have inadequate or nonexistent coverage. Addressing issues of cost and quality will require experimentation and analysis ("comparative effectiveness research"). This is where academic medicine excels. We must ask and answer questions. For example, won't patients benefit if their doctors are no longer paid for each individual service and test? Can we reduce cost and improve quality by paying doctors salaries and offering incentives for good outcomes? In fact, can't some primary care be offered by nurse-practitioners in drugstore clinics? Our faculty member Dr. Ateev Mehrotra has shown recently that for otitis media, pharyngitis, and urinary tract infections, quality of care in these retail clinics is as good as in emergency rooms and doctors' offices, and much cheaper.

As Atul Gawande pointed out last June in *The New Yorker*, these are empirical questions, not ideological. They are testable. Some medical centers, including ours, have explored these questions for years, but we must do better. Academic medicine has always been enthusiastic about the benefits of finding a new drug, discovering a new gene, or developing a new surgical procedure. We must become equally passionate about finding innovative ways to serve our patients.

Without it, I fear we will next year, and for years afterward, lament like Robert Browning: *This could but have happened once,—And we missed it, lost it forever.*

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



Devoted to noteworthy happenings

in the medical school

A New Home

Children's Hospital of Pittsburgh of UPMC prepared for the worst as it mobilized to receive 54 children uprooted from a Haitian orphanage as a result of the January earthquake. Yet when a team of nurses and physicians met the children at Pittsburgh International Airport, it found them in surprisingly good health. Mild dehydration was the most common ailment—no broken bones, even. Once medically cleared, the children were welcomed at a hospital comfort center outfitted with cots and, of course, plenty of toys.

The journey from the BRESMA orphanage in Port-au-Prince was fraught with logistical obstacles and required a coordinated effort by the children's caretakers (Pittsburgh natives Jamie and Ali McMutrie), UPMC, the U.S. Department of Homeland Security, the Allegheny County Department of Human Services, and several other agencies and nonprofits. The children have been adopted by families in the U.S., Canada, Spain, and elsewhere or taken in by the Holy Family Institute in Pittsburgh. ***—Ben Korman***

FOOTNOTE

Orthopaedic surgeon Victor Prisk's deepest cuts don't require a scalpel—just barbells and lots of protein. The Pitt prof and bodybuilder placed first in the welterweight division at the 2009 North American Bodybuilding Championships. A former competitive gymnast, he's been known to mix work and play. Among his research interests: musculoskeletal healing.



ILLUSTRATION: FRANK HARRIS. PHOTO: CAMI MESA

O'Toole

O'TOOLE ACCEPTS PRESIDENTIAL APPOINTMENT

President Barack Obama has appointed the University of Pittsburgh's Tara O'Toole to the position of under secretary for science and technology in the U.S. Department of Homeland Security (DHS). O'Toole, an MD whose appointment was confirmed by the U.S. Senate in November, was previously a professor of medicine in the School of Medicine and chief executive officer of the UPMC Center for Biosecurity.

The science and technology directorate is the primary research and development arm of DHS. It addresses the full range of homeland security issues, says O'Toole, from biometrics and digital identity to situational awareness of national borders. It supports research on detection of chemical and biological weapons and countermeasures against the effects of such weapons. For O'Toole, the appointment marks a return to government service; she was the U.S. assistant secretary of energy for environment, safety, and health from 1993–1997.

The biosecurity center is now under the leadership of former deputy director Thomas Inglesby, an MD associate professor of medicine at Pitt. O'Toole says the center has become "known as an expert source of information on a wide variety of biosecurity issues, from the specifics of medical care to issues associated with mass casualty care in hospitals."

—Chuck Staresinic



MARTHA RIAL

A&Q

Ryan Shugarman: Understanding Stalkers

Stalkers have made headlines for terrorizing stars such as Uma Thurman, Britney Spears, and Mel Gibson. But the majority of stalking victims aren't gracing the pages of *People*. Twelve percent of women and 4 percent of men have been stalked, says Ryan Shugarman (Fel '08). Shugarman, now a forensic psychiatrist at Saint Elizabeths Hospital in Washington, D.C., investigates these little-studied cases.

On the victims of stalking

No one is immune from stalkers. Victims can be young or old, but the average age is 28. It is a highly prevalent phenomenon. Women are three times more likely to be stalked than raped. ... The majority of stalking victims know their stalkers. In 30 percent of the cases, victims are stalked by former intimate partners. These victims are at the greatest risk of being harmed. Across all stalking cases, serious injury is infrequent, occurring in only 15 to 19 percent of the cases.

On people who stalk

You can't just look at someone and say, "He is high-functioning and doesn't have the potential for stalking." But some individuals are predisposed. They are often underemployed or unemployed, lack a history of successful relationships, and have concurrent substance abuse or psychiatric disorders. But the majority of stalkers are not psychotic, contrary to popular belief. The majority are male—68 to 87 percent. Eighty to 85 percent are unmarried at the time of the offense.

On treating stalkers

Typically they will not seek treatment on their own. Most who receive psychiatric evaluation are court-ordered to do so. Therapy involves [training the stalkers to empathize] with their victims, identifying motives, and showing how problematic this behavior is for their own lives. Often, stalkers don't initially experience remorse or shame about their conduct. Many don't see their behavior as problematic. Imprisonment may not deter stalkers. That is what makes it such an interesting phenomenon. They feel a strong desire to engage in this phenomenon, sometimes at any expense.

His question for us

With stalking so prevalent, why isn't there more research about it and training for clinicians about how to effectively treat these individuals? —*Interview by Cristina Rouvalis*

Faculty Snapshots

Scleroderma, characterized by a thickening of the skin and organs, is not the most fashionable of rheumatic diseases. Although it affects as many people as multiple sclerosis, it receives just 10 percent of the amount of federal research funding. In recognition of decades of much-needed work on scleroderma awareness and research, Thomas Medsger Jr., an MD, was recently awarded the Scleroderma Foundation's Lifetime Achievement Award. He is Pitt's Gerald P. Rodnan Professor of Medicine and director of the Scleroderma Research Program. Medsger's legacy extends to future generations of researchers. Six of his former mentees have developed scleroderma programs at other institutions.



Medsger

Killing cancer cells is relatively easy; killing cancer cells without also killing healthy cells is the challenge. Christopher Bakkenist is meeting this challenge head-on, thanks to a $50,000 Scientific Merit Award from the Lung Cancer Research Foundation. Bakkenist, a PhD assistant professor of radiation oncology, is searching for a less-destructive alternative to current cancer therapies.



Bakkenist

Jill Siegfried has been awarded a $1 million grant from the V Foundation for Cancer Research in support of clinical trials. The award comes as a result of promising lung cancer research from Siegfried, a PhD and coleader of the University of Pittsburgh Cancer Institute's Lung and Thoracic Malignancies Program, and Olivera Finn, a PhD, Distinguished Professor, and chair of Pitt's Department of Immunology. The grant will support one trial exploring the use of estrogen-blocking treatment in women to prevent lung cancer from occurring, recurring, or spreading. Another trial tests a vaccine shown to boost immunity against cancer. The V Foundation was established by former North Carolina State University basketball coach Jim Valvano, who died of cancer. —*Tiffani Emig*



Siegfried

GEORGIA SPORTS COMMUNICATIONS

Flashback

In 1796, English doctor Edward Jenner created history's first vaccine; it involved fluid from the cowpox pustules of bovines. This 1802 cartoon—rendered with cows emerging from Britons' faces, limbs, and rumps—satirizes a once-widespread fear that inoculation would induce bovine characteristics in people. Though perhaps for more nuanced and sophisticated reasons, many still fear vaccination. Pitt's Ernesto Marques, an MD/PhD in Pitt's Center for Vaccine Research, notes, "Two-hundred years later, we've got the same kind of story making headlines."



COURTESY LIBRARY OF CONGRESS/J. GILLRAY, 1802

HAVING A (SOFT) BALL

This is a community of high achievers. But it's unlikely that, aside from second-year med student Kellie Middleton, many have a .400 career batting average.

Middleton, a Georgia native, came to the School of Medicine after playing NCAA Division I softball at the University of Notre Dame and the University of Georgia. (She'd graduated from Notre Dame early and had a year of athletic eligibility remaining.) At Georgia, the starting center fielder earned a Master of Public Health degree. Then the Akron Racers of the National Pro Fastpitch softball league chose the speedy Middleton in the first round of the draft in 2007.

When she entered med school last year, Middleton decided to keep her body moving by teaching kickboxing, rather than remaining a softball pro.

Middleton would like to be a physician who concentrates on bringing a higher quality of care to underserved populations.

She credits her family for inspiring her to aim high. "My dad comes from a family of 14. He was taught to work hard, be the best, and express himself in whatever field he enjoyed most."

Middleton's brother, William, was a fifth-round draft pick for the NFL's Atlanta Falcons. Another brother, Wyatt, is in the U.S. Naval Academy, where he also plays football. His sister was in the stands when Pitt defeated the Midshipmen, 24–17, in September. "It was just before a huge exam, but I went anyway. Navy did not play well." *—Joe Miksch*



Middleton: big-league material

Starzl Given IOM Medal



Starzl

Thomas E. Starzl has won the Institute of Medicine's 2009 Gustav O. Lienhard Award. Starzl, MD/PhD Distinguished Service Professor of Surgery in the School of Medicine and director emeritus of the Thomas E. Starzl Transplantation Institute, earned a medal and a $25,000 prize with the award.

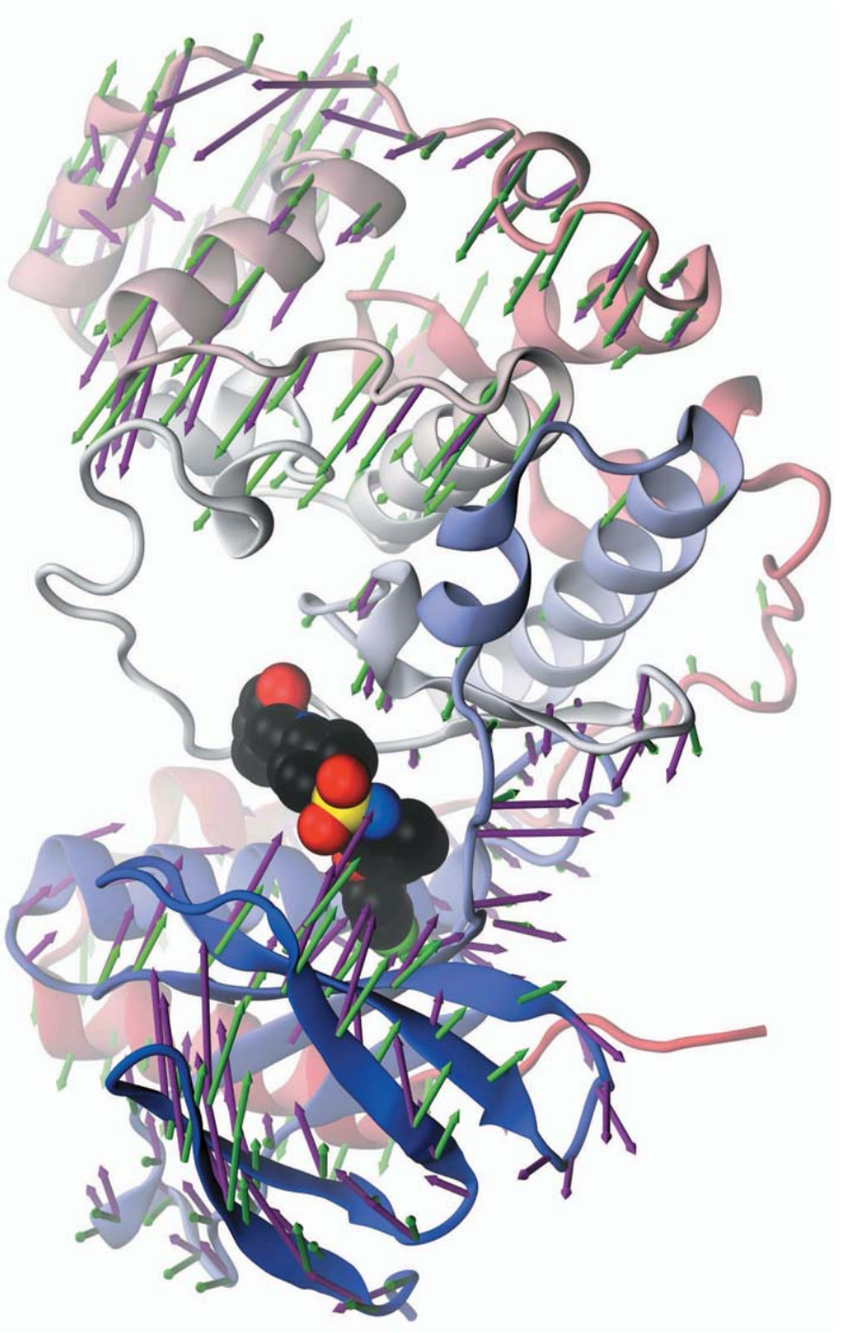
A household name in Pittsburgh and giant in modern medicine, Starzl is renowned for advancing the science and techniques of organ transplantation and immunology.

"Surgery and medicine have been profoundly affected by the transformative work of Dr. Tom Starzl and his clinical teams," says Harvey Fineberg, president of the Institute of Medicine. *—JM*

SHAPE-SHIFTERS

Though not an ideal procedure, it is possible to put a square peg into a round hole. But it's much better to match square with square and round with round. Ivet Bahar, John K. Vries Chair of the Department of Computational Biology in the School of Medicine, has made a discovery regarding the shape, or shapes, of proteins that may make it easier to design more effective drugs.

The theory was that drug binding causes a change in the target protein's structure. However, Bahar and her then-doctoral student, Ahmet Bakan (PhD '09), found—by computer modeling three common drug targets—that a protein has many different conformations and that the ligand, a binding molecule (shown right in black), attaches to the shape it fits best. This better fit, Bahar says, leads to more effective control of the protein's function. RIGHT: The shape-shifting of this kinase, which is of interest in inflammatory diseases, helped Bahar's lab rethink the fundamentals of protein binding. Arrows show which way key structural elements are likely to move, based on modeling (green) and experiments (purple). *—JM*



AHMET BAKAN, IVET BAHAR, 2009 PNAS USA 106, 14349-14354.

Name-Dropping

Science 2009, the University of Pittsburgh's annual science festival, brought these distinguished guests to town in October.

Victor Ambros, a PhD and the Lasker Award-winning Silverman Professor of Natural Sciences in the Molecular Medicine Program at the University of Massachusetts Medical School, gave the Dickson Prize in Medicine Lecture. Ambros was among the first to uncover the mysteries of microRNA, tiny RNA strands once thought to be junk, which turned out to be gene silencers and activators.

The Mellon Lecture was presented by **Cori Bargmann**, Torsten N. Wiesel Professor and head of the Laboratory of Neural Circuits and Behavior at Rockefeller University. Bargmann's expertise lies in the neurology of *C. elegans*, a roundworm that's proved to be highly valuable in biomedical research. (The worm is where Ambros first came across microRNA.) Bargmann, a PhD, discussed the genes that regulate how these nematodes recognize one another and how they interact socially.

Bruce Beutler, MD professor and chair of the Department of Genetics at the Scripps Research Institute, gave the Klaus Hofmann Lecture on how the innate immune system detects infections. Beutler, who is a member of the Institute of Medicine and the National Academy of Sciences, has dedicated his career to understanding molecular and genetic roles in inflammation as well as how organisms use inborn resistance to combat infectious diseases. *—JM*



A HUNKA-HUNKA REGENERATING STARFISH

An Elvis impersonator has been hired to inspire future generations in the fields of tissue engineering and regenerative medicine. Something about him is a little fishy, though.

This Elvis, whose real name is Seamore, is less a hunka-hunka burning love than a cartoon starfish with Presley's patented coif and shades. He explains regeneration from personal experience at the Carnegie Science Center's new exhibit, "If a Starfish Can Grow a New Arm, Why Can't I?"

The exhibit was funded by a Science Education Partnership Award from the National Center for Research Resources. Its creators gleaned much of the content from work at the University of Pittsburgh–UPMC McGowan Institute for Regenerative Medicine. One activity island helps visitors understand the basics of cell structure with a cell puzzle and twisting skin and bone cell matrices. Older students tend to gravitate toward another island with video games that simulate aspects of tissue engineering. Nearby are two monitors where visitors can learn about clinical applications, take an ethics quiz, or record opinions on stem cell research.

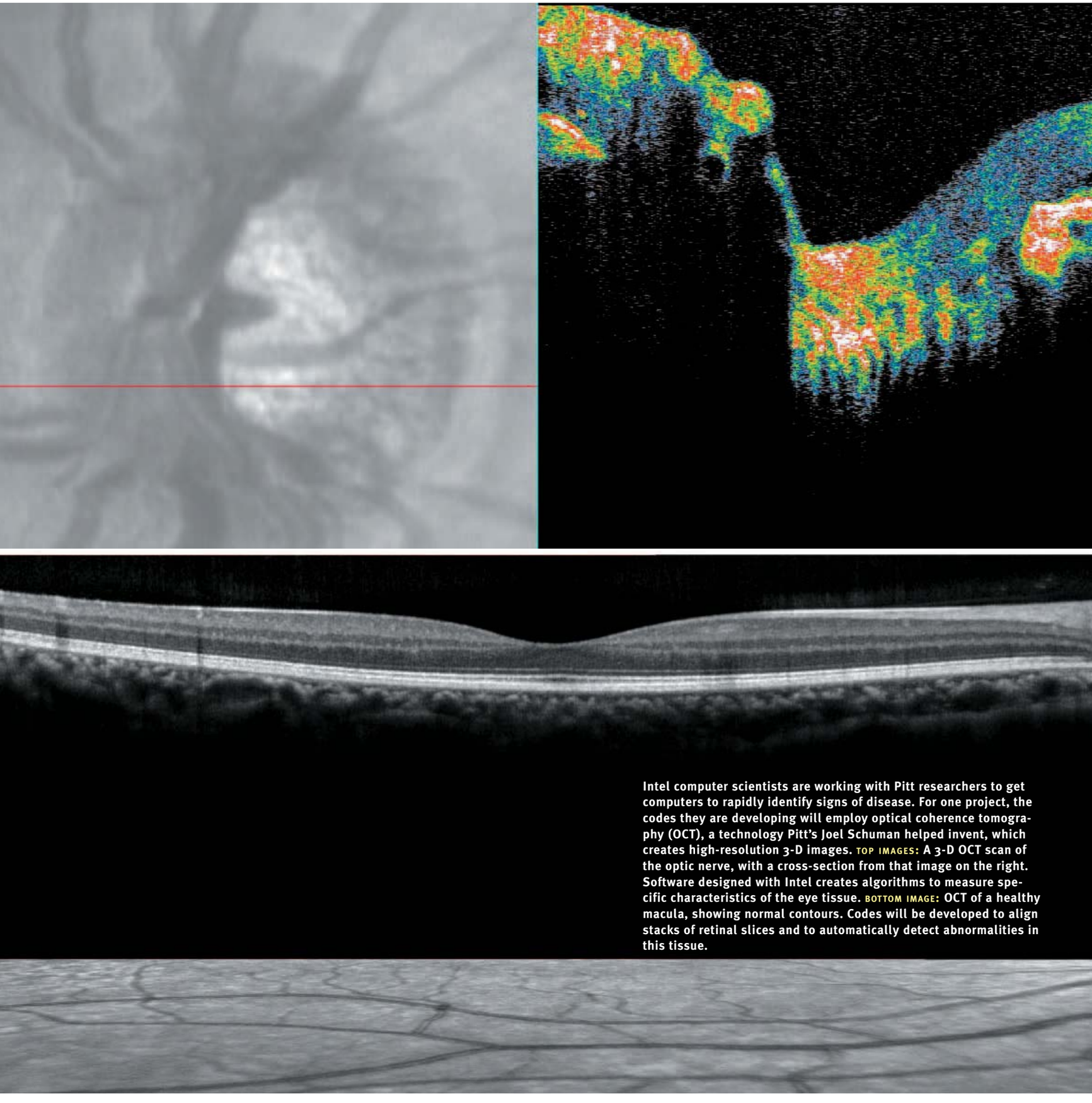
One Friday, a small group of elementary school students ran to touch-screen computers that offered Q&As from scientists, including Joon Sup Lee, an MD associate professor of medicine at Pitt and clinical director of the Cardiovascular Institute at UPMC. Though a surgical scene drew a wrinkled nose and an "Ew!" from an energetic girl in a Jonas Brothers T-shirt, her teacher remained fixated on the video through the end. He summarized: "You see how the starfish can grow a new arm? That's what they're trying to do with people's body parts."

Meanwhile, three boys stood at the zoetrope, a round drum with slats revealing progressive images of the regeneration of a newt's leg. "You're spinning it too fast," said one, as he slowed the drum to the proper speed to give the illusion of animation.

Seamore has a long career ahead of him: He is packing his sequined jumpsuit and heading on tour. A replica of the exhibit will appear in eight other science centers through 2013.

—Tiffani Emig

—Photo by Martha Rial



Intel computer scientists are working with Pitt researchers to get computers to rapidly identify signs of disease. For one project, the codes they are developing will employ optical coherence tomography (OCT), a technology Pitt's Joel Schuman helped invent, which creates high-resolution 3-D images. TOP IMAGES: A 3-D OCT scan of the optic nerve, with a cross-section from that image on the right. Software designed with Intel creates algorithms to measure specific characteristics of the eye tissue. BOTTOM IMAGE: OCT of a healthy macula, showing normal contours. Codes will be developed to align stacks of retinal slices and to automatically detect abnormalities in this tissue.

THE PIXELATED STETHOSCOPE

AT INTEL LABS PITTSBURGH, COMPUTERS CAN SEE WHAT DOCS CAN'T

BY REID R. FRAZIER

Among the many talents of Leonard H. "Bones" McCoy, *Star Trek*'s inimitable, sharp-tongued physician, were his capabilities with what looks like a medical ray gun. Pointing a saltshaker-like sensor at a patient, McCoy could detect brain waves, sense blood abnormalities, and identify pathogens like "Saurian virus."

It remains a far-fetched idea, this business of point-and-shoot diagnostics, but it turns out the technology needed for a McCoy-worthy medical sensor (or "medical tricorder," in Trekkie-speak) might arrive considerably sooner than the 23rd century if a group of Pittsburgh scientists has its way.

University of Pittsburgh researchers are working with computer scientists at Carnegie Mellon University and Intel, the world's largest maker of chips, to develop computers that will assist doctors in diagnosing and treating disease. In 2002, Intel established a foothold in Pittsburgh, on the CMU campus, building one of three such "lablets" to pull together top researchers in biomedicine, robotics, and computing.

The lab's unique collaborative arrangement allows scientists to put their heads together on some killer apps that would make McCoy proud.

"Everything we do is basic, 'far-out' research," says David O'Hallaron, Carnegie Mellon associate professor of computer science and electrical and computer engineering and director of Intel Labs Pittsburgh. Projects under way include developing catoms—tiny, programmable machines that may one day be able to glom onto one another to form 3-D objects that walk, talk, and do jobs we can't or won't do, as well as video recognition technology that can tell what a person is doing. A branch of the outfit is involved in "computational health"—harnessing the computer's incredible powers of organization, especially finding things that are like other things—to solve wide-ranging medical dilemmas.

Doug Weber and Wei Wang are hoping to read people's minds. The Pitt assistant professors of physical medicine and rehabilitation are sifting through magnetoencephalography (MEG) data with Intel and CMU computer scientists. MEG measures magnetic fields produced by brain activity The idea is to get a computer to recognize brain patterns when people think of specific words. This application could eventually help patients who have difficulty verbalizing—perhaps because of neurodegenerative disease, spinal cord injury, or stroke—to "talk" through a computer. The team can determine, with 80 percent accuracy, whether a person is thinking of, say, a hammer or a stalk of celery.

When analyzing images of patients, doctors already use a computer to form diagnoses—the one between their ears, that is. They compare a clinical scan—perhaps an X-ray or CT—to the hundreds of others they've already seen. But inevitably, unfamiliar shapes or shadows pop up on film or screen. What if docs could compare their referent image to millions or billions of other images? That's one possible use of Diamond, a program created by Intel scientists Rahul Sukthankar and Larry Huston with Mahadev Satyanarayanan, founding director of Intel Pittsburgh and Carnegie Group Professor of Computer Science at CMU.

A few years ago, Satyanarayanan wondered whether he could create an application that could search images in the same way that Google looks through reams of text on the Internet. When Pitt medical researchers heard about his idea, they quickly lined up to help create a version of Diamond for docs. "Imagine if, at the point of care, you have the world's fattest textbook, which can home in on the three or four most relevant cases," says Satyanarayanan.

Computers could also solve a glitch common to 3-D medical imaging. These systems require a computer to collate stacks of cross-sectional "slices" of organs and tissue. If the object moves (as when a retina shifts), the slices can become skewed. Mei Chen, an Intel computer scientist, has been keeping busy developing codes with a number of Pitt researchers that would allow a computer to reposition each slice after an imaged object has moved. Friedrich Knollmann, associate professor of radiology, and Athanassios Argiris, professor of medicine, want a code to follow blood flowing through a lung tumor (as they breathe, lungs don't really "sit still" for the camera). Joel Schuman, chair of ophthalmology, wants a similar program for optical coherence tomography (OCT), a 3-D eye-mapping system he helped invent. With Chen, his group is creating an automated diagnostic application, eye* (pronounced "eye star"), that would "proofread" the OCT image, compare it with a database of known eye diseases, and give a preliminary diagnosis. "If it sees tissue abnormalities, it will say, 'Oh, that's glaucoma,' or 'That's macular degeneration,' or 'That's diabetes,'" Schuman says.

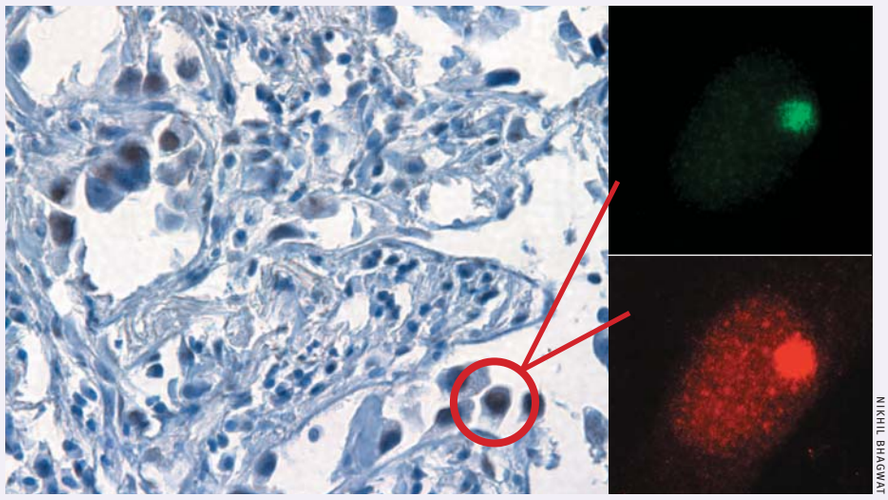
So, could a machine take a doctor's place one day? Probably not. But Schuman notes: "We have a technology that creates a 3-D image of the back of the eye. Wouldn't it be great if a computer could tell you if that eye is all right?" ■

COURTESY OCULAR IMAGING LABORATORY

ONE STEP CLOSER TO PERSONALIZED MEDICINE

A CHEMOTHERAPY BREAKTHROUGH

BY MELINDA WENNER



NIKHIL BHAGWAT

We may one day be able to predict drug response by testing tumors for a DNA-repair complex (green) that makes patients less likely to respond to chemotherapy. (The red stain shows an area of DNA damage in lung cancer cells.)

As if the devastating side effects of chemotherapy weren't enough, another problem cancer patients face is drug resistance. Nearly one-third of ovarian cancer patients fail to respond at all to platinum-based therapies, which form the cornerstone of many chemotherapy regimens. Those who do typically stop responding within several years, often causing their cancer to return. Although oncologists have long tried to understand and predict this resistance, a new study by Laura Niedernhofer, an associate professor of microbiology and molecular genetics at the University of Pittsburgh Cancer Institute, suggests that they may have been using the wrong tools to do it. Her study, published in September 2009 in *Cancer Research*, raises major questions about the way scientists have studied cancer drug resistance and presents a new method that may ultimately help save lives.

Platinum-based chemotherapies like cisplatin work by damaging the DNA inside cancer cells. If the injury is drastic enough, the cell dies, Niedernhofer explains. But our bodies also have built-in repair mechanisms to fix the minor DNA damage that we accrue over a lifetime. Some scientists have speculated, then, that the people who grow resistant to chemotherapy are those who have the strongest repair mechanisms.

One of the ways researchers have tested this idea is by assessing the activity of an innate cellular repair complex called ERCC1-XPF, the only enzyme complex known to be involved in addressing all of the types of damage that platinum drugs cause. If patients who do not respond to therapy have better repair mechanisms, they should, in theory, have higher levels of ERCC1-XPF in their tumor cells—so by measuring how much of the complex resides inside these cells, it might be possible to predict whether patients will respond to drugs.

For years, scientists have measured ERCC1-XPF levels by flooding cells with a fluorescently tagged antibody called 8F1 that is known to bind to the repair complex. But Niedernhofer and coauthor Richard Wood, formerly a University of Pittsburgh biologist now at the University of Texas M.D. Anderson Cancer Center, wondered whether 8F1 was actually specific to ERCC1-XPF. In other words, could it be binding to other cellular proteins, too? If so, then even if the antibody seemed to show high levels of ERCC1-XPF in tumor cells, the cells weren't necessarily chock full of it, because the antibody could be binding to something else instead.

Niedernhofer and Wood's hunch was correct. With the help of colleagues, including Pitt postdoc Nikhil Bhagwat, they showed that 8F1 binds to several proteins.

"There must be about 400 papers out there measuring ERCC1 levels. A lot of times [investigators were measuring levels] with an antibody that we demonstrated was not specific for ERCC1," Niedernhofer says. As a result, scientists who thought they were seeing evidence of ERCC1-XPF were sometimes seeing something else. This may have led "a lot of people in the wrong direction," she says.

Niedernhofer next checked whether any of the other 11 commercially available antibodies known to bind to ERCC1-XPF actually are specific to it—or if they, too, bind to other proteins. To do so, she and her colleagues looked for antibodies that got "hits" when added to cells that had ERCC1-XPF but did not when they were added to mutant cells that lacked the complex. In addition, Niedernhofer scouted for antibodies that bound only inside the nucleus, where ERCC1-XPF resides. Eventually, the researchers identified three antibodies that appear to be specific to ERCC1-XPF, and Niedernhofer showed it was possible to use these antibodies to identify the complex in fixed, paraffin-embedded tissue, which is how most doctors preserve tumor specimens after surgery.

Now, the researchers are using the three specific antibodies to test whether ERCC1-XPF levels do, in fact, correlate with drug response. But even if they do, there is still a long road ahead:

"All tumors are not created equal," Niedernhofer says. What predicts drug response in one type of tumor might not in another.

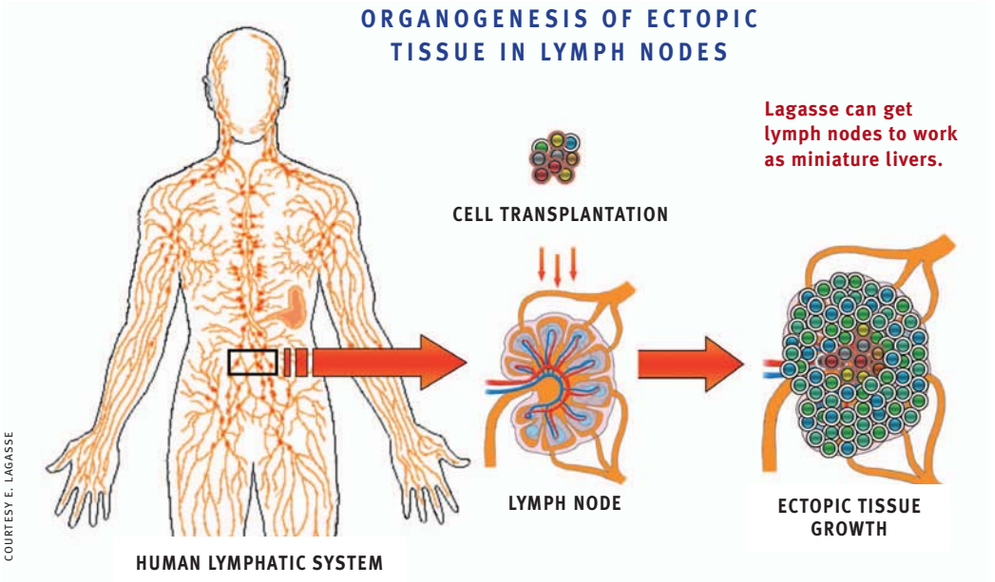
"It's not like you'll be able to go buy a kit to measure ERCC1 levels and that will predict, for every tumor type, whether or not they'll respond to cisplatin therapy," she says.

Still, Niedernhofer's findings bring doctors closer to being able to tailor cancer treatments to individual patient needs. It's a first step toward personalized medicine, she says. ■

LYMPH NODES

SPROUT LIVERS

BY MICHELE BAUM



WHERE THE WILD ORGAN GROWS

Eric Lagasse wants to fight liver disease by gaming the system—the lymphatic system, that is.

Lagasse, associate professor of pathology and director of the Cancer Stem Cell Center at the Pitt-UPMC McGowan Institute for Regenerative Medicine, is exploring a concept so revolutionary that, in September 2009, the National Institutes of Health (NIH) awarded him a five-year, $2.9 million Director's Transformative R01 grant. He is searching for ways to co-opt some of the body's 500 lymph nodes into doing double-duty as miniature livers. Different from standard R01 grants—R01 refers to "individual research project," and such grants are known as career-making benchmarks in themselves—transformative grants are designed "to fund high-risk research that will create new or challenge existing paradigms," according to the NIH. The Lagasse grant was one of 42 awarded in 2009.

The fact that the lymphatic system will host functioning colonies of hepatocytes "is a spectacular finding," says George Michalopoulos, Maud L. Menton Professor and chair of pathology at Pitt, who studies liver cancer and liver cell biology.

"Nobody had even thought about this before."

Lagasse foresees an alternative to transplantation, currently the only effective treatment for end-stage liver disease. Transplantation remains a costly option fraught with risks, not only from the surgical procedure, but also because of lifelong drug therapy to suppress the immune system.

"This is the first step of a complex idea that could lead to organogenesis," says Lagasse.

Among the can't-live-without-it major organs, the human liver is unique in that it regenerates. After a live-donor transplant, two complete organs will grow from the components of just one, typically within six months. Even with this quality, however, the organ can be so impaired by disease or injury that liver failure becomes inevitable.

Enter something Lagasse calls black magic.

"We have found that when you inject liver cells into the peritoneum [the abdominal lining] of a mouse, they will migrate to the lymph nodes.

"Large nodules then form in the stomach and gut region, and we found out that they were essentially mini-livers," explains Lagasse.

For the experiments submitted to NIH in support of his grant application, Lagasse used mice genetically engineered with liver defects as models of progressive liver failure. The animals' livers were endangered by tyrosinemia, a genetic enzyme deficiency. Yet the old black magic of that very failure appears to be a key component, Lagasse says, of his experiment's success, perhaps signaling the transplanted cells to take root, grow, and work.

"If you inject cells into an animal without liver failure, the cells die," he says.

"We want to give the cells an opportunity to find the right location and expand as needed, and we have found that they can expand dramatically," he says. Injecting mice with liver cells appears to result in localized migration of hepatocytes to lymph nodes without affecting the function of other, neighboring nodes. In the mice with tyrosinemia, transplanted liver cells functioned robustly—enough to rescue the animals from liver failure.

A healthy liver removes toxins and waste from the bloodstream and also works to aid digestion and regulate metabolism. There are many kinds of liver disease, yet the most common diagnosis leading to a transplant is cirrhosis, a scarring of the liver often related to long-term alcohol use. Cirrhosis may lead to liver cancer. Liver failure also can be tied to drug interactions, viral infections such as hepatitis C, or chemical poisoning.

"About 100,000 people in the United States have end-stage liver disease," notes Lagasse. "At least 20,000 are on a transplant waiting list."

"Every now and again there are really huge leaps of faith that occur in science, and this is one," says Alan Russell, director of the McGowan Institute as well as a Pitt University Professor of Surgery with appointments in chemical engineering, bioengineering, and rehabilitation sciences and technology. He names whole-organ transplantation as another leap-of-faith example.

"For decades, people have been injecting cells of one kind or another. But it's an extraordinary leap to think that you can take cells from one organ, inject them into another, and have [those cells] take on the characteristics of the first.

"Not only that—it works." ■



PATHOGENS ARE THE BEST TRAVELERS OF ALL

BY ELAINE VITONE

NO BORDERS

When Don Burke moves into a new space, he decorates the walls with maps. At Walter Reed Army Medical Center, where he trained as an infectious disease specialist and served for 22 years before retiring at the rank of colonel, he mounted maps of Thailand and Southeast Asia on his office wall. At Johns Hopkins University, where he directed the Center for Immunization Research for nine years, he hung maps of Cameroon and Africa.

But when Burke settled into his new digs at the University of Pittsburgh, where in 2006 he signed on as dean of the Graduate School of Public Health (GSPH); associate vice chancellor for global health, health sciences; and director of the Center for Vaccine Research (CVR); he had an idea for a slightly different conversation piece. It started with the round table he found just inside the door of his new office.

"You like that?" he says on a clear day in November 2009. He points to a photograph of Earth, enlarged to poster size and placed under a round sheet of glass on the tabletop. He laughs. "It's a subtle statement of my job. And speaking of 'no pressure,' here are some of our forebears at the University."

This puddle of rainwater in western Rio de Janeiro is a potential breeding ground for mosquitoes that carry dengue fever, also known as breakbone fever.

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Burke points to two framed *Time* magazine covers—a 1936 issue featuring then U.S. Surgeon General Thomas Parran Jr., who would later become the first dean of GSPH; and a 1954 rendering of Jonas Salk, the Pitt virologist who, with Pitt's Julius Youngner and others, developed the killed-virus vaccine that conquered polio. (Burke holds Salk's namesake chair in global health at the University of Pittsburgh Medical Center.)

Among his many responsibilities, Burke considers his directorship of the Center for Vaccine Research "the jewel in the crown." The CVR's mission: prevention, intervention, and therapy for infectious diseases, the leading cause of death worldwide.

No pressure, indeed.

Burke's codirector at the CVR, Pitt professor of microbiology and molecular genetics Ronald Montelaro, has a sobering take on the legacy they've inherited. For example, compare the poliovirus to the virus of the common cold.

"Worldwide, there are only three serotypes of polio—three to inactivate, combine, and put into a vaccine, and that's exactly what Jonas Salk did," says Montelaro. "But for the common cold, there are more than 130 different serotypes—and they're evolving."

Researchers in this field have a saying: All the easy vaccines have already been made.

Burke leads with what Montelaro calls a "bush-to-clinic mentality." He has conducted fieldwork in Thailand, India, China, and throughout Central Africa. He has used computational models to predict outbreak patterns and recommend vaccination strategies, establishing the University as a national center for disease-emergence work. Years ago, at Walter Reed, he was part of the team that produced the first hepatitis A vaccine, which has since been used to inoculate hundreds of millions of people. He was the fifth person in the world to receive it.

"These were the days when you volunteered to be your own test subject," Burke says.

The reason Burke has piled so much onto his plate is because he believes it will take a broad, all-encompassing vision to put resources to their best possible use in the years ahead. He's thinking big because he has to.

The Center for Vaccine Research is part of a network created by the National Institutes of Health (NIH) in the wake of 9/11 and the anthrax panic that followed. In those terrifying months, it became all too clear that there were a number of deadly pathogens in the world we didn't know much about and few laboratories that were properly equipped to study them.

Further, the federal government realized that this country could no longer afford to be so parochial as to limit research efforts to the pathogens that made themselves at home in our own subways, classrooms, office buildings, and shopping malls—nor could any other nation.

In this era of globalization, pathogens are the best travelers of all. For whatever microscopic saboteurs might float in the sneeze of a farm pig in Mexico, flow in the blood of an African bush-meat hunter's fresh kill, or flare up from the bite of a mosquito in Southeast Asia, each citizen of this borderless new world is just a plane ride away from becoming a potential new host.

10-minute Commute

In 2003, the NIH awarded the Center for Vaccine Research and 12 other institutions construction grants to build specialized labs called Regional Biocontainment Laboratories (RBLs). In summer 2008, Pitt's $33 million RBL became the second of these labs to begin studying live pathogens. The lab investigates more than a dozen highly infectious disease agents, with special focus on tuberculosis, influenza, and dengue fever.

Kelly Cole, associate director of the RBL and associate professor of immunology at Pitt, leads the RBL staff, a group of meticulous, detail-oriented types who are obsessive when it comes to pathogens. Plushy toy likenesses of bacteria and viruses decorate RBL staff member offices. They run contamination scenarios in their sleep.

"I dream of little bugs running after me at night and wake up wondering, *Did I do this today? Did I do that?*" Cole says with a self-deprecating laugh. "If you don't have those nightmares periodically, then you shouldn't be working in a BSL3 anymore."

BSL stands for biosafety level—that is, the level of biocontainment precautions required of a facility to safely study biological agents. The scale runs from BSL1—minimally hazardous bugs like the nonpathogenic strain of *E. coli*, which only call for a pair of gloves and maybe a surgical mask—to BSL4—the pathogens that cause fatal diseases for which we have no effective treatment, like Ebola.

As a BSL3, Pitt's Regional Biocontainment Lab is equipped for the class of airborne pathogens that can cause diseases that are fatal if left untreated (but they *are* treatable). Carefully screened and trained researchers wear facility-dedicated scrubs and shoes, face masks, respirators, double gloves, and disposable Tyvek suits. Showering-out is mandatory. Between the locker room and the lab suites just down the hall, it's a 10-minute commute.

When Cole accepted this job (she'd previously run her own research lab and two other BSL3 labs), she did so on the condition that she'd be able to hire full-time staff members for four areas of responsibility: research, biosafety, operations, and veterinary science.

The unprecedented RBL staff investment has paid off. Pitt runs a tight ship, and other labs have taken notice. Cole and her staff were invited to lead the inaugural national meeting of RBL staffers last May, and recently an NIH representative asked Cole to lead the meeting next year.

"She said, 'You guys are the model—let's be real here.' And I kept hearing that our management structure is the standard that all the RBLs are using. Everyone was calling us [for advice]."

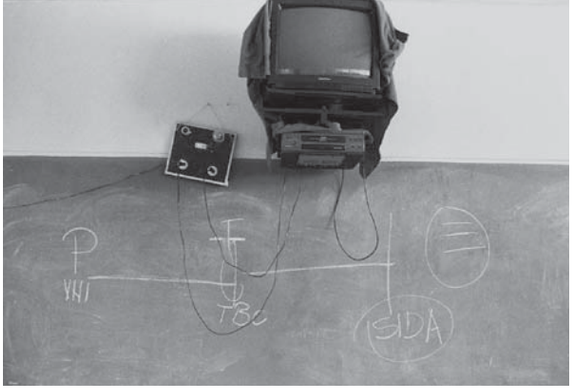
Bug Borne

Ernesto Marques, Pitt associate professor of infectious diseases and microbiology, moved from Johns Hopkins University to the CVR last August. In the past several years, he's conducted extensive field research in his native Brazil and built relationships between the country's government agencies and researchers here in the States. His goal: to get to the bottom of Brazil's recent outbreak of a debilitating mosquito-borne illness, dengue.

Dubbed breakbone fever, dengue causes joint and muscle pain, headaches, intestinal distress, and a bright-red skin rash. Once a disease of Southeast Asia, in recent years dengue has spread to more than 150 countries. Last fall, dengue returned to the United States for the first time in 50 years.

Climate changes and other factors have brought a reemergence of the disease's carriers. In Brazil, mosquitoes were all but eliminated in the 1950s in response to a yellow fever epidemic. But in the mid-'80s, a new government dropped the mosquito eradication program, giving the pesky pathogen-passers free rein over a totally unprotected population. Cases









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TOP LEFT: **Former mosquito control workers in Brazil protest a slow government response to a recent dengue fever outbreak.** BOTTOM LEFT: **The *Aedes aegypti* mosquito carries dengue.** TOP RIGHT: **Teaching about AIDS in a classroom in Peru.** BOTTOM RIGHT: **Center for Vaccine Research faculty are studying avian flu among other influenzas, including H1N1.**

in Brazil have grown steadily since then, with major upticks in 1998 and 2002.

Marques' first step was to establish a cohort of patients for the study in the city of Recife, the densely populated epicenter of the outbreak, but that was a lot easier said than done. His team couldn't find enough children to represent the range of ages that dengue has been known to affect in other parts of the world. Figuring there must be a lot of undiagnosed pediatric cases, Marques and his colleagues at Hopkins launched an effort to increase pediatricians' awareness of childhood dengue and to train them in using appropriate diagnostic tools.

They got their childhood cohort, all right. And they also got their work published for addressing this pediatric health concern. But their efforts were just beginning.

Next, Marques' team used NIH funding to design a centralized, open-source database that streamlined record-keeping in area hospitals and made data collection much easier for the study. This effort made ink in a few journals, too. It also won the support and cooperation of local doctors, who were grateful to Marques' team for significantly reducing their paperwork.

The cohort of 450 patients in place, Marques' team began mapping immune responses to dengue. The resulting knowledge base has provided a solid foundation for vaccine development.

There are four types of dengue virus. Once you develop the response against one, your immune system wants to respond the same way to the next type it encounters. Consequently, dengue tends to be far more severe the second time you're infected. (Credit Burke's epidemiological research in Southeast Asia for this discovery.)

Marques' data have shown that, as people age, they're more likely to be exposed to a second strain of the virus and fall ill. It follows that the inverse is true for the young—no wonder it was so hard to find children for his cohort.

However, he realized that as each of the four strains continue to spread, exposures won't be so scattershot anymore. Secondary infections are likely to occur in younger and younger people. (Note: Before we went to press, Marques checked back with his colleagues abroad; so far, it appears he was right.)

Husband-and-wife team William Klimstra and Kate Ryman, Pitt associate professors of microbiology and molecular genetics, also specialize in mosquito-borne diseases. They joined the CVR in December 2009.

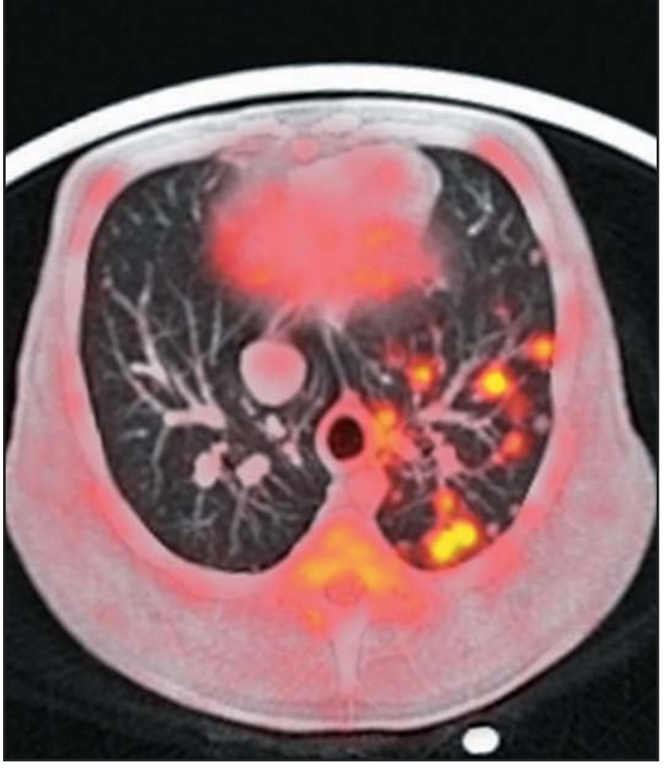
Ryman was recently awarded NIH funding for her work with chikungunya, a disease very similar to dengue that's pandemic in nations along the shores of the Indian Ocean. Originally, chikungunya was a disease of monkeys, but an adaptation enabled the virus to be carried by another species of mosquito—one that feeds on humans.

The possibility that the same could happen with other viruses worries Klimstra and Ryman. They've been monitoring, for instance, eastern equine encephalitis. Though for now human cases of this horse disease are still rare, they are on the rise. The Centers for Disease Control and Prevention estimates the fatality rate in humans to be 33 percent; others estimate it as high as 70 percent.

In their studies, Klimstra and Ryman are examining what happens right after a virus enters a host, hoping to identify steps in the infection cycle that might be blocked by antiviral drugs. They're also exploring ways of better targeting antigen-presenting cells—the immune cells that initially bind to the virus and haul it into lymph nodes, enabling the immune system to recognize it and sound the alarm.

Model Behavior

Tuberculosis (TB) infects about one-third of people on the planet. Pitt professor of microbiology and molecular genetics JoAnne Flynn explains that 90 percent of people infected with TB have the latent, or asymptomatic, form of the disease. Although they remain TB-positive for the rest of their lives, they're







LEFT: RECONSTRUCTION OF PET/CT IMAGES BY M. TERESA COLEMAN. TOP AND BOTTOM RIGHT: © GETTY IMAGES

LEFT: Pitt researchers came up with a new way to image TB over time, showing both the structure and metabolic activity of granulomas (see red and yellow spots in lungs). TOP RIGHT: TB has always been difficult to study in the clinic. In 1957, people of Glasgow, Scotland, line up for chest X-rays during an epidemic. BOTTOM RIGHT: Work at Pitt may help produce more-effective TB vaccines.

totally unbothered by the bacteria in their lungs, which their bodies contain in ball-like masses of immune cells called granulomas—the hallmark of TB.

But for the unlucky 10 percent of those infected, at some point their TB will progress to active disease, causing chest pain, bloody coughs, fever, chills, fatigue, and shrinking appetite and weight. Worldwide, nearly two million die of TB each year.

For 30 years, the standard treatment for TB has remained the same: a combination of four antibiotics taken over six months. Particularly in the developing world, the expense of this unusually long course of treatment is a problem. Many people stop treatment before it's complete, which gives rise to drug-resistant TB.

No one knows why this particular drug combination works, why it takes so long, or what exactly happens inside the lungs to cause latent infections to become active. Clinical data are virtually nonexistent because people with latent TB live healthy, normal lives and are not too keen on signing up for trials. Animal data, too, have been sorely lacking. Traditionally, the only way to study granulomas in the lab has been to sacrifice the animal.

"Not only is that a humane issue, but then you're also stuck with one time frame," says Flynn. "You don't really know what happened before or after that."

The thinking has always been that different drugs in the TB treatment regimen must target different subtypes of granulomas—and there are a lot of them. In the same set of infected lungs, you might find granulomas both large and small, that are "hot"—meaning metabolically active—or "cold." And what's more, every one of these types of granulomas is common among both latent and active TB cases.

With diligent work over the past decade, Flynn has developed a model that mimics the huge spectrum of TB found in humans. And with a new imaging tool, she has struck a gold mine of data. In 2008, she was awarded a two-year, $11.4 million grant from the Bill & Melinda Gates Foundation's Drug Accelerator Program to create a unique TB imaging system. (She's just been renewed for a third year.)

Flynn teamed up with Pitt's Jonathan "Eoin" Carney, assistant professor of radiology, and Brian Lopresti, research instructor in radiology and head of preclinical research at the University's PET Facility. Carney and Lopresti devised a way to make two separate scanners work with one another and overlay two types of scanning technologies in the same image. In one layer, a CT (computed tomography) scan paints a clear picture of the structure of a granuloma. In the other, a microPET scan (the small-scale version of a PET scan, or positron emission tomography) shows the metabolic activity in the animal's granulomas.

Now, her team can follow each granuloma over time. They're starting to ask the really nagging questions: Which kinds of granulomas does a given drug target, and how fast? What kinds of vaccines might prevent the bacteria from spreading from person to person or latent TB from turning active? And what causes latent TB to activate, anyway?

Flynn's team is finding what appears to be a huge spectrum of latent disease. Though it's too early to say for sure, she suspects that different types of latency may have different triggers, and latent people with the most metabolically active and widespread granulomas could well be the most prone to reactivation. She's just beginning to sort it all out, though, working with collaborators around the world—among them Clifton Barry, chief of the Tuberculosis Research Section at the NIH, who is conducting a PET study based in South Korea on people with drug-resistant TB.

AIDS is another disease for which the model studied could make all the difference. Consider the work of Cristian Apetrei, Pitt associate professor of microbiology and molecular genetics, and his wife, Ivona Pandrea, Pitt associate professor of pathology. They joined the CVR last summer after having worked in Gabon and at Tulane University.

Macaques infected with simian immunodeficiency viruses (SIV) are often used to simulate HIV infection in preclinical studies. In the wild, SIVs naturally infect more than 40 African monkey species, each carrying a specific SIV. Interestingly, although up to 60 percent of the monkeys in Africa are infected with

SIVs, they generally do not end up with AIDS. When these viruses are transmitted to non-natural hosts, however, the new host may end up with an infection that progresses to AIDS. By comparing nonprogressive to pathogenic and controlled infections, Apetrei and Pandrea hope to understand how some species are able to fend off AIDS and what cues humans might take from the ones who stay healthy.

The First Test

On the day the H1N1 story broke last April, Ted Ross—Pitt associate professor of microbiology and molecular genetics and a CVR faculty member—was in France, at an influenza conference full of vaccine manufacturers and researchers.

"People started fleeing the meeting to fly back home," he says.

Ross was immediately telephoning, Skyping, talking with Burke and others at the CVR. The Centers for Disease Control and Prevention had contacted the CVR and other labs like it, and they wanted to know: Could they ship out samples of this virus for testing the next week? Could these labs help government officials get a sense of what we were up against?

"I told Don and the others that there was bound to be an outbreak of something, be it man-made or natural," says Ross. "I said, 'This is our first test. Better that it's flu than an anthrax outbreak.'"

Ross pulled his entire team off of what they were working on to study swine flu. After six weeks of intensive preclinical studies, they were able to tell the CDC that H1N1 would spread a lot faster and further than the typical seasonal flu; however, this new disease, in its current incarnation, wouldn't be nearly as deadly as other influenza outbreaks—not like avian flu, which has a 75 percent mortality rate; not like Spanish flu, which killed upwards of 50 million people in the pandemic of 1918-19. Knowing this, the government could begin to form a vaccination plan.

H1N1 highlighted problems that Ross and his colleagues have worried about for decades: the cost, time, and uncertainty associated with the current, antiquated vaccine-production process of cultivating live virus in chicken eggs. Ross' team is using novel technologies that might alleviate the problem, including virus-like particles (VLPs)—man-made structures that mimic the outer shells of viruses, minus the genetic innards.

His team is currently working on vaccines for five different pathogens: HIV, influenza, West Nile virus, Rift Valley fever, and dengue virus. He has an NIH grant to study highly pathogenic (i.e. highly infectious) avian flu. He also shares with several other CVR faculty members a Department of Defense grant for a dengue-vaccine candidate, among other grants and contracts.

More than half of Ross' team is devoted to influenza because there's a lot to do: high-path influenza, low-path influenza, avian flu, and now H1N1.

"I think if, back in April [2009], the only places the government had to do this work were the CDC and the NIH, they wouldn't have been able to handle it. They were just dealing with a flood of samples coming in and needed to outsource to the network that had been established. This is exactly what this containment facility was built for." ■

THE SCIENCE OF SNEEZING

As we've all become keenly aware in the wake of H1N1, the most common means of passing an airborne pathogen is in the fine particles of a cough or a sneeze. However, most research has used animal models infected intravenously or via nasal drops, simply because the science of simulated sneezing—dubbed aerobiology—is so difficult to master.

To date, the University of Pittsburgh's biocontainment facility is one of only a few with dedicated aerobiology faculty members. The team is led by assistant professor of immunology Doug Reed.

His bosses like to brag that he's one of only two academic infectious disease aerobiologists in the country with his level of training. For nearly a decade before he joined the University, Reed was a principal investigator at the United States Army Medical Research Institute of Infectious Diseases (USAMRIID), the historical home of aerobiology research.

Appreciation for the discipline has come and gone over the decades, Reed says. The Persian Gulf War of the early '90s saw a resurgence as biological weapons became a very real concern—a concern that has heightened in the past decade.

"When I first got to USAMRIID in '99, we were using 40-year-old technology," says Reed. "It was all manually driven and very prone to operator error."

His close friend and ex-officemate at USAMRIID, a physicist named Justin Hartings, took the human out of the equation and put a computer in her place, making it easier to reproduce all the variables that can make or break an experiment: temperature, air pressure, and humidity, to name a few. Hartings has since founded his own aerobiology-device company—Biaera Technologies, based in Frederick, Md. Reed often beta tests these devices.

On his computer monitor, Reed pulls up photos of the aerobiology equipment. A large, sealed cabinet keeps contaminated air separate from the air in the room. The cabinet is topped by a large metal hood, which directs the air outside via a series of sanitizing HEPA filters.

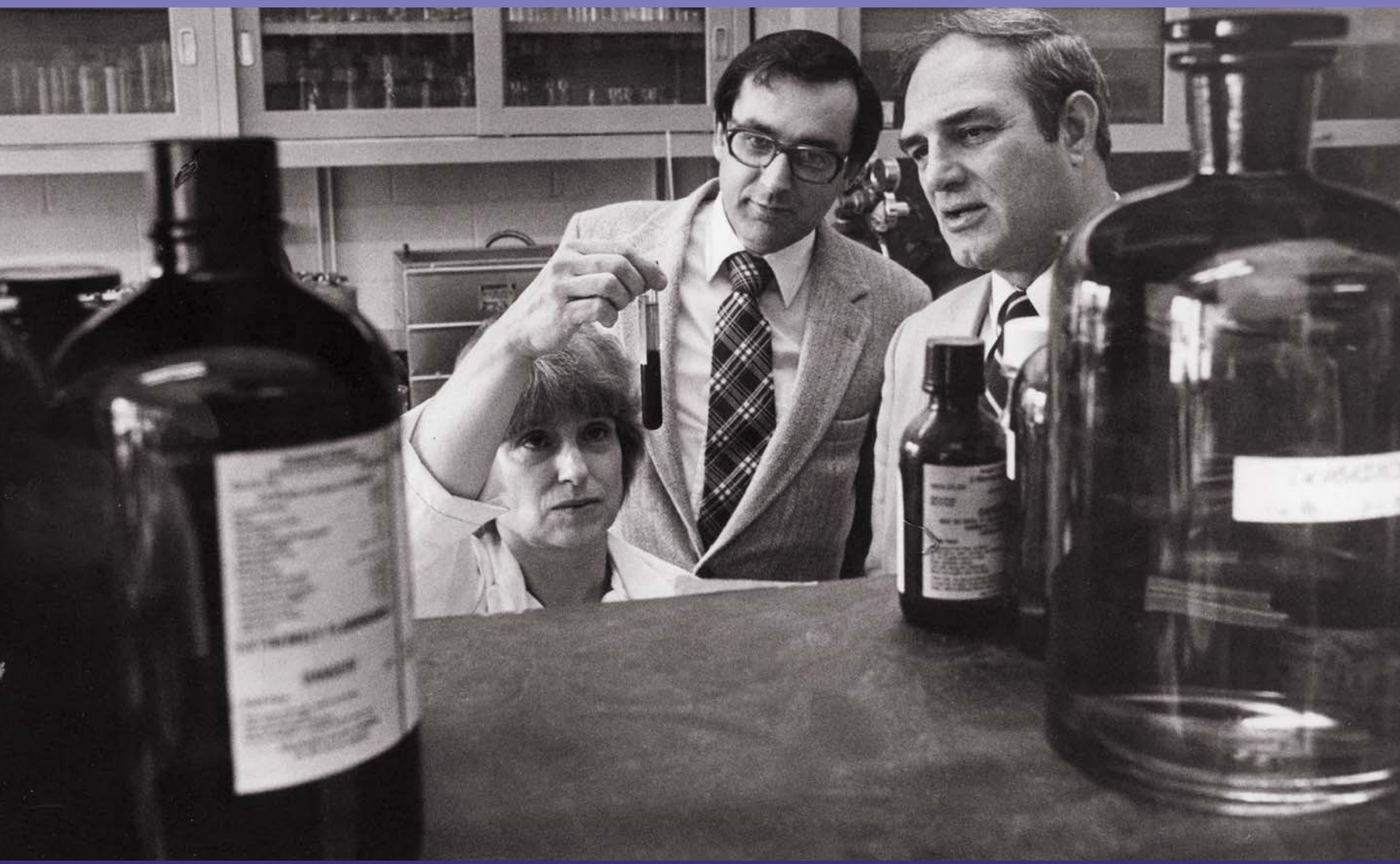
"There's nothing getting out of that sucker," Reed says. "Viruses can do a lot of things, but they can't defeat physics."

The synthetic sneezer of choice for both the RBL and the Army is known as the three-jet collision nebulizer, a device that vaguely resembles a bicycle-tire pump with a glass base. Air is forced down to the bottom of the tank, into a pool of liquid, and through three jets. The jets shoot the liquid back out, and when the liquid hits the glass, it becomes aerosol.

This device generates particles of just one micron—the ideal size, says Reed. Any larger, and it won't penetrate the deep lung, as more severe disease tends to. Any smaller, and it could float right back out.

Reed is excited to be working at the CVR, a research facility with a grand scope that's not limited by what the military intelligence of the moment says might someday become a tool for bioterrorists.

"Take seasonal flu," Reed says. "The military doesn't consider it a threat. But it kills 36,000 people a year in this country alone. To me it's a more real-world disease." *—EV*



Children in Western Pennsylvania and around the world benefited from the diabetes treatment advances that started here and spread. Allan Drash led much of that work. He's shown here (right) in 1985 with colleagues Trevor Orchard and Eileen LaRocca.

THE DOC WHO BUILT A DIABETES TREATMENT AND RESEARCH CENTER WITHOUT PEER | BY CHUCK STARESINIC

"WE HAD DR. DRASH"

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A slight 6-year-old girl from Pittsburgh's North Side became ill with a virus one day. Her sickness was not all that unusual—she developed a fever and was vomiting. But when she failed to bounce back after several days, her parents took her to the pediatrician, who said, "She has a virus," and sent her home with instructions to rest and wait it out.

This was in the early 1970s. She may have had a run-of-the-mill viral infection initially, but something else was happening now. She lost weight. She urinated a lot, and she was always thirsty. The parents bypassed their pediatrician and brought her straight to Children's Hospital of Pittsburgh. It seemed like they had been in the hospital only moments when someone said, "This looks like diabetes."

Those were scary words. Diabetes may be manageable, but much less was known about how to manage it back then. All the parents knew was that their child was no longer just sick; she had an incurable disease. Some children entered the hospital in her state, continued to deteriorate, and died. Some came home less than whole. They were frail or had damaged minds. Others survived but lost something of their childhood.

At Children's, the physicians and nurses saw it a bit differently. There was an acute crisis to overcome in that the girl's blood was becoming increasingly acidic. This was life-threatening, but if she overcame it, the family could manage her disease.

Ketoacidosis, as the condition is called, is the most common, acute, and serious complication resulting from diabetes in childhood. The crisis often leads to the initial diagnosis. The problem begins, many experts believe, when the immune system reacts to a common virus in an uncommon way. Rather than fighting off the virus, then ramping down the attack, the immune system continues its assault, attacking cells in the pancreas.

Tucked into pearly clusters in the pancreas called islets of Langerhans, these cells produce insulin, a hormone that metabolizes glucose to fuel the body. When the body experiences a glucose shortage, it begins to metabolize fat instead, causing sudden weight loss and a buildup of acidic byproducts in the blood called ketones. Uncontrolled, it can lead to swelling in the brain, kidney failure, death of bowel tissue, and heart attack.

Through happenstance, the girl's family had arrived at what was arguably the best place in the world for a diabetic child to go. What is now Children's Hospital of Pittsburgh of UPMC and the University of Pittsburgh were building a diabetes research center without peer. Children in Western Pennsylvania benefited from the treatment advances that started here and spread around the world.

"Diabetes will become part of your life," he said, "but do not give up on your dreams for your child."

The physician who walked into the room that day and talked with the family about their daughter's diagnosis was the one most responsible for the bustling hive of diabetes-related research in Pittsburgh: Allan Drash, a pediatric endocrinologist and professor of pediatrics in the University of Pittsburgh School of Medicine. He and others had created a multifaceted center that simultaneously advanced the treatment of diabetic patients and probed the underlying epidemiology—who gets the disease, and why?

The girl in our story not only recovered from her bout with ketoacidosis, but she also went on to become a nurse and a diabetes educator. For decades afterward, she and her parents remembered the words of Dr. Drash.

He told them the disease could be managed. "Diabetes will become a part of your life," he said, "but do not give up on your dreams for your child. She can achieve anything she puts her mind to."

Allan Drash was a Tennessee native who stayed close to home for college (Vanderbilt University), then went to medical school at the University of Virginia, trained at Johns Hopkins Hospital, and later accepted a position with Children's Hospital of Pittsburgh. He was a pediatric endocrinologist who set about perfecting a clinic to treat children suffering from diabetes.

The year was 1966, and, compared to what we know now, physicians had an incomplete understanding of the disease. They knew that many people experienced adult-onset diabetes in their 40s or later. These people showed insulin resistance, meaning their insulin didn't process glucose as well as it should have. Other people developed diabetes in childhood or early adulthood. Both of these groups experienced hyperglycemia—excess sugar in the blood. But it wasn't clear whether there were major differences between the two types of diabetes aside from the age of onset.

In 1967, one year after arriving in Pittsburgh, Drash published a study confirming that most children with diabetes were not insulin resistant like most adults with diabetes. The children were insulin deficient. They had no insulin, or they had not nearly enough. The study contributed to a new understanding that there were two types of diabetes: Type 1 usually came to light in childhood and was marked by a deficiency of insulin. Type 2 usually appeared in adulthood and was marked by the body's resistance to the insulin it produced.

Drash's motivation was to find the best treatment for diabetic children. Aggressive treatment with insulin injections eventually became the unquestioned standard of care for type 1—hence the moniker insulin-dependent diabetes. Drash was instrumental in pushing for federal funding of the Diabetes Control and Complication Trial, which eventually grew to 29 sites. It demonstrated that metabolic control was critically important in the development and rate of progression of vascular complications in people with diabetes. And it showed that an aggressive regimen that included multiple daily injections of insulin was the most important element of treatment.

He quietly fomented a revolution in endocrinology at a time when pediatric endocrinology was a rather neglected field. At professional conferences, he and other endocrinologists who treated children typically had a session or two devoted to their interests. His work on diabetes illustrated his point that children were not just smaller in size than adult patients: Diabetes, like many other endocrine disorders, was fundamentally different in children than it was in adults. Drash lobbied for pediatric endocrinology to be taken more seriously. And, over the course of his career, it was.

In Pittsburgh, Drash employed a unique team approach to treating diabetes. He believed in treating the family, not just the child. He enlisted nutritionists, nurses, social workers, educators, and psychologists. Physicians in his clinic were just one part of a team that strived to educate the family and manage the disease with aggressive monitoring and intervention.

With philanthropic help, Children's Hospital provided funding so that families who could not otherwise afford care could receive the same treatment.

The epidemiology of diabetes intrigued Drash. There were hints that genetics played a role—siblings and other relatives of diabetic children seemed to be at higher risk of developing the disease. Because early diagnosis and intervention were important elements of successful treatment, Drash believed that epidemiology was a natural extension of the clinic. In the early 1970s, Drash and epidemiologist Lewis Kuller developed a registry that aimed to include every child in Allegheny County diagnosed with type 1 diabetes.

"Allan focused very much on developing an unusual, multidisciplinary clinic that gave quality care for children," says Kuller, who is now a Distinguished Professor of Public Health at Pitt. "And that helped in developing the registry and getting families and patients into research programs. The research program just blossomed dramatically."

Epidemiologists who trained in Pittsburgh include Ronald LaPorte, a Pitt professor of epidemiology who led the diabetes project for years, and Trevor Orchard, currently the interim chair of epidemiology at Pitt.

The diabetes epidemiology group in Pittsburgh exported the model worldwide, with Drash as its principal ambassador. In 1990, Drash calculated that he had averaged 100 days of travel per year for the preceding eight years. "We were married 38 years," says Diane Drash. "There were no real holidays.

We would travel for meetings, or when he would lecture or give a keynote address at a conference."

She recalls her husband, who died on August 3, 2009, visiting clinics around the world: "I loved to watch him interact with parents and children. His whole life was built around trying to help children with diabetes and to reassure parents."

His travel and years of professional duties led to one memorable argument with his then-teenage daughter, one of two Drash children. A few days later, Drash wrote a long, thoughtful letter to his daughter about his reasons for being dedicated to his profession and his love for her.

He wrote, "There is nothing more important than to be consumed by a sense of dedication and responsibility to a profession, a calling, that takes one out of one's own self and into the service of others. It is not the job of medicine that is demanding, but that we are demanding of ourselves."

About his dreams for her, he wrote, "Despite what the U.S. Constitution says… Happiness should not be pursued. It is the byproduct of a meaningful, contributing life. I hope for you such a life."

At Children's Hospital of Pittsburgh, Drash trained a long line of stellar pediatric endocrinologists. Dorothy Becker is a Pitt professor of pediatrics who now occupies Drash's former position as chief of pediatric endocrinology and diabetes. She also is the director of the diabetes program at Children's and is principal investigator on a multicenter trial funded by the NIH to determine whether a cow's-milk infant formula can keep children from later developing type 2 diabetes. She "continues to carry forward [Drash's] investigative prowess," notes Orchard. Ingrid Libman is another Drash trainee, an MD/PhD assistant professor of pediatrics who works in prevention and treatment of type 2 diabetes in children. Silva Arslanian, the Richard L. Day Professor of Pediatrics, is an internationally recognized endocrinologist and authority on the long-term consequences of type 2 diabetes and racial disparities in its prevalence.

Pitt's diabetes epidemiology project was probably the largest such project in the world, Kuller says. "In our international project, we had 155 centers in 70 countries across the world. For a while, we were publishing 35 to 40 papers a year at a time when we were probably responsible for 20 to 30 percent of the world's literature in that area." To offer evidence, Kuller walks to a bookshelf across the hall from his office. He pulls down a few bound sets of scientific papers, each roughly as thick as the Pittsburgh telephone book.

"This is [from] the early days," he says, paging through the bibliography in the front of one volume. "It's almost all Drash. It's Drash and epidemiology group. It was a broad project, from the basic immunology all the way up to the global work."

Pitt's reputation has attracted expertise throughout the health sciences schools. Linda Siminerio—a diabetes educator, faculty member in the schools of medicine and nursing, and executive director of the University of Pittsburgh Diabetes Institute—was the national spokesperson for World Diabetes Day in 2009.

Andrew Stewart, Pitt professor of medicine and chief of the Division of Endocrinology and Metabolism, left Yale University to join the Pitt faculty in 1997. Stewart's lab has identified the genes and proteins involved in the creation of new insulin-producing cells. Stewart is exploring the possibility that we might stimulate the production of new cells in patients with diabetes, restoring their ability to manufacture insulin.

In the mid-'80s, Drash and his colleagues recruited Massimo Trucco, an MD immunologist and geneticist who was prepared to take the expertise in Pittsburgh and build on it to create a new understanding of the basic immunology and genetics behind type 1 diabetes. Today, Pitt's Trucco is the Hillman Professor of Pediatric Immunology, a professor of pathology, human genetics, and epidemiology, as well as director of the Division of Immunogenetics.

Simply put, Trucco is on the trail of a cure for diabetes. He has uncovered genes that confer susceptibility to type 1 diabetes and described some of the molecular activities in the immune system that cause the destruction of insulin-producing cells. Trucco and his colleagues—notably Nick Giannoukakis, an associate professor of pathology and immunology—have developed cell and microparticle vaccines that reverse or prevent type 1 diabetes in mice. The group is wrapping up a safety trial of a vaccine in recently diagnosed children.

"Allan had this phenomenal commitment to taking care of the people," says Kuller. "It wasn't just screening these kids to do an interesting genetic study. He was actually saying, 'Hey, what are we going to do about it?'"

For much of four decades, until his death last year, Drash was the doctor leading the way for families in Pittsburgh with diabetic children. One former patient says it's impossible to overstate the significance of his words and actions on her family. Drash told her parents not to let their child be defined by a diagnosis:

"We all know what that diagnosis means. It's this overwhelming shadow of darkness. But we never had that. We had Dr. Drash." ■

Children's Hospital is establishing the Allan Drash Diabetes Scholarship to further the careers of pediatric diabetes trainees and perpetuate Dr. Drash's work. To contribute contact Chip Eagle, 412-586-6317 chip.eagle@chp.edu

To protect patient privacy, some details were changed in this story.

DIABETES INVESTMENTS

When he was 35 years old, Allan Drash received an offer to relocate from Johns Hopkins University to Children's Hospital of Pittsburgh and the University of Pittsburgh. One of the attractions for Drash was that, at Children's, the diabetes clinic had long been a priority. A $1 million fund had been established in 1937 by Emilie Renziehausen to support the care of diabetic children and honor the memory of her two brothers, one of whom had diabetes. The interest from that fund has contributed to clinical care at Children's for more than 70 years. The fund allows for aggressive outreach to families coping with diabetes, regardless of the family's financial situation. Additional gifts from the Renziehausen family through the years have created an additional trust fund at Children's to support laboratory research and education. These deep roots have nourished an extraordinary breadth and depth of diabetes research at Pitt. —*CS



Tea made with broccoli sprouts holds promise as an antidote to a toxin linked to liver cancer.

WORLDWIDE, BILLIONS EAT AFLATOXIN, A FUNGAL POISON THAT KILLS. SO HOW TO KEEP IT AT BAY?

BY REID R. FRAZIER

THE OTHER GREEN TEA

TURKEY X DISEASE

In the spring of 1960, a plague descended on the turkeys of Southeastern England. More than 100,000 turkey poults, partridges, and pheasants fell prey to an ailment that rendered them lethargic, unable or unwilling to eat, and dead within a week of the first symptoms. When they died, they assumed a characteristic arched position with their neck, legs, and head all drawn backward. Autopsies showed tissue death and lesions on the liver, as well as swollen kidneys. At about the same time, a similar liver-affecting illness broke out in trout farms in the Western United States.

There were no indications of a viral or bacterial vector—all signs pointed to some type of poisoning. At first, scientists could find no toxin—at least none that was known. They suspected the poison was a plant-produced alkaloid, or perhaps something from a fungus. The condition was given a name befitting its mysterious etiology: "Turkey X Disease."

ILLUSTRATION | JULIETTE BORDA

Veterinary epidemiologists soon located a commonality among the affected turkey farms. They all bought feed processed at a pair of mills in and around London. Both processed Brazilian peanut meal brought over on the freighter *Rosetti*. After analyzing the *Rosetti* peanuts with paper chromatography, scientists found a high prevalence of an unknown material that appeared bright blue under UV light.

An analysis of the toxic nuts later showed high levels of hyphae, the filament-like branches of a fungus. The suspect was a mold that liked heat and humidity and often grew in the tropics: *Aspergillus flavus*. The fungus gave science a name for the strange poison that killed 100,000 English turkeys—aflatoxin.

Since Biblical times, people had long suspected that eating moldy foods could make them and their animals sick. Then, with the discovery of aflatoxin, there was definitive proof. Scientists scrambled to identify the mechanisms behind this new class of fungal poisons, or mycotoxins.

Samples of the bright blue material ended up in the lab of Gerald Wogan, an MIT toxicologist. Wogan regrew the fungus responsible for the poisoning, and, along with MIT chemist George Büchi, characterized the chemical's structure. After feeding the chemical to ducks and rats, Wogan found the substance was not only toxic, but highly carcinogenic. In ducks and rats, it could induce liver cancer with a mere parts per billion dose, a level most of the world's food supply would likely exceed.

The bright blue substance, it soon became clear, posed a major public health problem. If tiny doses of this poison could kill turkeys and trout, what would it do to the billions of people who were probably eating it every day? At the time, UNICEF was considering using peanut meal as a high-protein component of infant formula.

One of Wogan's PhD students in the early 1970s was a young scientist named Thomas Kensler. He remembers those times. "We were really just beginning to understand that carcinogens interact with DNA," says Kensler, who recently joined the Pitt faculty as professor of pharmacology and chemical biology. Kensler researched the compound's mechanisms of action—why it was such a biological hand grenade. By the end of the decade, one of Kensler's MIT colleagues, John Essigmann, found that an aflatoxin metabolite formed an irreversible bond with DNA inside the liver, keeping the cell's genetic message from correctly transcribing. By the time Kensler earned his PhD, the question of how aflatoxin worked was largely answered. Now it was time to address the problems aflatoxin created. This, as it turned out, would be the hard part.

CAST OUT MOLDY STONES

The earliest recorded public health advice concerning fungus is set down in Leviticus, in a dictum from God to Aaron and Moses. "On the seventh day, the priest shall return. If he sees that the mold has spread on the walls of the house, the priest shall order the stones with the affection in them to be pulled out and cast outside the city into an unclean place."

During the Middle Ages, a mycotoxin was responsible for the disease known as St. Anthony's fire, a common ailment that caused convulsions and hallucinations and led to gangrenous blisters on victims' hands and feet. The poison was ergot, a product of *Claviceps purpurea*, a mold that grows on rye grass.

Ergotism made people more susceptible to the Black Plague and has been linked to events like the Salem Witch Trials and the religious movement known as the Great Awakening of 1741, during which "thousands experienced fits, trances, and visions," according to the historian Mary Matossian. Other mycotoxins have proved dangerous, even lethal—fumonisin, ochratoxin, the aptly named vomitoxin (it's linked with gastrointestinal disorders, in case you were wondering), to name a few.

It isn't entirely clear why fungi produce such powerful chemicals. Mycotoxins aren't necessary for the lifecycle or growth of a fungus, but scientists believe they may give the mold a competitive advantage against other microorganisms. "Is it part of a chemical warfare battle that the mold fights with bacteria or other organisms? Almost certainly," Kensler says. "I suspect it was the acute toxicity of aflatoxin that led to its selection and elaboration by the fungi."

(Their potent antibacterial qualities, of course, led scientists to harness fungi for antibiotics like erythromycin and penicillin.)

The sharpest sword in the fungal arsenal is aflatoxin, so powerful it's been produced as a biological weapon. (Saddam Hussein reportedly produced 2,200 liters of the stuff in the early 1990s.) When ingested in high doses, it causes aflatoxicosis, a severe abdominal ailment that carries a 40 percent mortality rate. In low doses, chronic exposure can cause liver cancer, especially in those with hepatitis B virus, of which 350 million people are carriers.

The aspergillus fungus that produces aflatoxin was first described in 1729 by the Italian priest and biologist Pier Antonio Micheli. (Under a microscope, the mold looked like a holy water sprinkler, or aspergillum.) It's a widespread mold that eats organic matter, especially carbon-rich plant sugars. *A. flavus* and its other toxin-producing relatives, like *A. parasiticus*, are prevalent in the tropics, growing best in humid, warm temperatures, between 25 and 40 degrees Centigrade. It thrives on several important crops—corn, peanuts, and cottonseed. It tends to infect plants already weakened by drought or insect damage, and damp storage conditions accelerate the spread of its colonies. Aflatoxin is heat stable—you can't destroy it in cooking. All of this suits it perfectly to thrive in the fields and huts where much of the world's food originates.

Although feed and food are subjected to other contaminants here, aflatoxin is not a major problem in the United States. Part of the reason is climate—most corn grown in the United States falls outside the fungus' preferred habitat. Southern-grown cotton and peanuts, however, are susceptible to aspergillus. Yet irrigation, insecticides, and other modern agricultural practices keep mold away from many crops in the United States. The FDA also limits the amount of aflatoxin allowed in the food supply.

But none of these methods are feasible in large swaths of the developing world like Africa and East Asia, says Felicia Wu, Pitt assistant professor of environmental and occupational health in the Graduate School of Public Health who also holds an appointment in the School of Medicine.

"When we run across these problems in the United States, we throw out infected crops," Wu says. "You can't really afford to do that in Africa or Southeast Asia, where their choice is to either eat moldy foods or go hungry."



MIKE DRAZDZINSKI / CIDDE

Thomas Kensler notes that aflatoxin is "perfectly engineered as a carcinogen."



JOSH FRANZOS

Felicia Wu is looking for aflatoxin solutions that cost almost nothing.

Wu is studying ways to get aflatoxin out of the world's food supply. She codirects a pilot study on dampening the effects of aflatoxin in Africa that is supported by a $2.7 million Bill & Melinda Gates Foundation grant.

As a doctoral student in engineering and public policy at Carnegie Mellon University in the early 2000s, Wu found that genetically modified corn harbored very little mycotoxin. Corn engineered with a gene from the insecticidal bacterium *Bacillus thuringiensis* (Bt) was remarkably resistant to aspergillus infection because the mold capitalizes on plants compromised by pest damage. "Insect damage exposes the sugars of the plant to the environment, and the fungi just love that," Wu says.

Wu is an affable and energetic young scholar (a finalist in the 1994 *Jeopardy!* Teen Tournament). Last fall, she spent time in Kenya, learning how farmers grow, process, and store their corn. She hopes that her team will soon conduct bioassays to determine how much aflatoxin the farmers have in their blood.

"We're looking at where the maize is being planted in the field, when it's being harvested, the conditions in which it's being stored, the conditions in which it's being sold," Wu says. Her team is searching for the most promising and cost-effective point to control for aflatoxin.

One of the interventions she has studied is administering the hepatitis B vaccine, which greatly reduces cancer risk in individuals exposed to aflatoxin. Another measure is biocontrol, in which farmers intentionally spread nontoxigenic (friendly) strains of *A. flavus* to keep poisonous strains out. If done properly, biocontrol can reduce aflatoxin exposure by 50 to 90 percent. (Using transgenic crops like Bt corn would not work well in Africa, Wu says. There are laws against genetically modified organisms there. Also, African farmers save their seeds, and transgenic crops lose their efficacy after a generation or two.)

Wu and Kensler have taken on an ambitious task. More than 4.5 billion are exposed to aflatoxin through their food, the vast majority of whom live in the developing world. In portions of sub-Saharan Africa, almost everyone is exposed to aflatoxin. Where liver cancer is common, as many as 50 percent of the tumors carry a mutation linked to aflatoxin exposure. Liver cancer, the third-leading cause of cancer death worldwide, kills 600,000 people a year. Its five-year survival rate is 2 percent, and the average age of diagnosis is 47.

But cancer might be just part of the problem. Studies have found that aflatoxin stunts childhood growth and suppresses the immune system. "We've seen a striking association between exposure to aflatoxin early in life—post-weaning—and impaired growth in the child in West Africa," says Chris Wild, director of the World Health Organization's International Agency for Research on Cancer. Though he cautions these findings are preliminary, Wild says the trends are alarming, especially if exposed children are more susceptible to the bacterial and viral vectors that contribute to the developing world's staggering childhood mortality rates.

Could aflatoxin have an effect on other major public health issues, like the HIV pandemic? It appears so. One study found HIV carriers with high exposure to aflatoxin have a more-severe disease course than those with lower exposure. Another found HIV patients with high aflatoxin exposure in Ghana had lower levels of immunoprotective T and B cells, critical to the body's reaction to HIV.

A RIDDLE

There are no obvious solutions to the worldwide aflatoxin problem. Getting rid of aspergillus in the field as we do in the West costs more than many farmers can afford. Hepatitis B vaccine is a priority, yet wouldn't protect the 350 million already infected by hepatitis. And hardly anyone has heard of the poison you're trying to eradicate.

Solving the riddle means finding solutions that could work anywhere and cost almost nothing. Wu is looking at a variety of interventions, each of which centers on educating farmers. Once they learn about the poison, Wu says, "the farmers ask to be tested for aflatoxin. They say, 'We'd like to know if we are exposed to this toxin.'"

One solution could be an approach Wild and his collaborators tested on farmers in Guinea. The scientists educated the farmers about aflatoxin, then taught them simple ways to dry and store their peanuts properly—making sure they dried harvested crops in the sun, for instance, and stored the peanuts in natural fiber bags, as opposed to plastic ones. Aflatoxin exposure dropped by 60 percent.

Wu says solutions like these are probably going to have the greatest impact.

"What I like so much about this package is that it's low technology," she says.

Even with these types of interventions, it's unlikely aflatoxin will be eliminated from the world's food supply anytime soon, Kensler says. "In these high-risk regions, we have no short-term prospect of getting aflatoxin out of foods. Our fundamental thought is, 'Well, given this unavoidable exposure to aflatoxin, can we make the host more resistant to that unavoidable dose?'" Kensler says.

He believes that one solution may lie in the bottom of your refrigerator.

QIDONG

It is twilight in Qidong, an agricultural peninsula along the northern lip of the Yangtze River Delta. A group of about a dozen factory workers and farmers mill around a concrete-floored kitchen. Tom Kensler stands, binder in hand, making sure everyone drinks the plastic bottle full of brownish liquid he's brought for them.

The brown beverage is a tea made from broccoli sprouts. This cruciferous vegetable is full of a chemical that seems to detoxify aflatoxin. (It appears your mother was right: Broccoli is good for you.)

The next day, at about 5 or 6 a.m., the dozen or so participants will return the liquid favor, in the form of urine samples taken overnight. The samples will be waiting for Kensler when he gets to his lab at 8. He'll then have the unenviable job of measuring them. "It's a great way to start your day," Kensler says. In a few months, Kensler will fill several rolling suitcases with bags of frozen urine and cart them back to the United States as checked baggage. ("It makes for some interesting conversations with customs agents," Kensler says.)

Qidong is relatively close to the mega-city of Shanghai, 50 kilometers to the south, across

the yawning mouth of the Yangtze. Though it's growing rapidly, Qidong remains largely rural, and many there still rely on locally grown crops for food, especially maize, served as a filling porridge. The hot and humid climate makes the peninsula a haven for the aspergillus mold. In the 1970s, the Chinese government mapped the prevalence of liver cancer around Shanghai. On a gradient map the government produced—with dark brown being the highest prevalence, and white being the lowest—Qidong's district looks like a piece of chocolate dropped into the froth of a cappuccino. The people of Qidong were 50 times more likely to contract liver cancer than their counterparts 150 miles away.

This map eventually made it into the hands of Kensler, who by then was a professor of toxicology at Johns Hopkins University. With John Groopman, a collaborator at both MIT and Hopkins, Kensler had isolated a key biomarker for aflatoxin and was using the biomarker to test ways to keep aflatoxin from binding to DNA in animals. He'd made a breakthrough with the drug oltipraz, which cut the carcinogenic effect of aflatoxin by 55 percent.

"After 10 years of working in animals, I could protect any number of rats and mice from liver cancer," Kensler says. "John Groopman came up to me one day and said, 'What do you think about putting this in people?'"

It wasn't long before Kensler and Groopman were on a flight to China.

Among the first projects the Hopkins group undertook was an epidemiological study of liver cancer in Shanghai. The group collected urine and blood from 18,244 men, then waited five years to see how many of them developed liver cancer. Men with aflatoxin exposure were 3.5 times more likely than nonexposed participants to contract liver cancer. Those with hepatitis B virus were seven times more likely. If they had both hep B and aflatoxin exposure, the men were 59 times more likely.

This was astounding—"an explosion of risk," Kensler says.

The two factors formed "a perfect storm" for carcinogenesis, says Groopman, the study's lead author. "There's an infection with hepatitis B, so there's a lot of cell proliferation, and at the same time there's a lot of DNA damage caused by the aflatoxin. The effect is on the order of magnitude of, say, asbestos exposure and cigarette smoking as risk factors for developing lung cancer."

BERMUDA TRIANGLES

Kensler came to broccoli sprout tea through the aflatoxin molecule's potentially troublesome chemical structure. When metabolized by a liver enzyme, aflatoxin forms an epoxide—a flat molecule with a short dogleg off one end. The dogleg consists of a three-sided chemical bond between a single oxygen atom and two carbons. Triangular shapes in chemistry are generally suspect—the acute angles apply more pressure on chemical bonds. (With their obtuse angles, hexagons are much more stable shapes, chemically speaking.) Those acute angles create what Kensler calls the "Bermuda Triangle" of toxicology. Add to that instability the fact that the aflatoxin epoxide is an elecrophile—a positively charged substance seeking a negative charge. "It's a lovelorn molecule that's looking for an electron," Kensler says.

In the liver, the epoxide finds an electron on a negatively charged nitrogen in a specific location within the DNA. The epoxide slides snugly inside the double helix structure and forms an irreversible bond with the nucleotide. It binds 10 times better to DNA than any other bulky carcinogen.

"It's perfectly engineered as a carcinogen—and that's why it's so potent," Kensler says. (He, by the way, is married to another recent Hopkins recruit, Nancy Davidson, who directs the University of Pittsburgh Cancer Institute.)

Once the epoxide binds, it cannot unbind. This is where the cancer starts. "Perhaps that stretch of DNA can no longer be copied or transcribed, or it gets falsely transcribed," Kensler says.

"Mistakes are made, and you have errors in the progeny. It's a subtle chemical change that can have a profound impact in that cell or, more importantly, its daughter cells."

Since the 1970s, researchers had been looking at an enzyme group that could modify this chain of events. These enzymes, GSTs (glutathione-S transferases), produce the antioxidant glutathione, which acts like a sponge. Rather than binding to DNA, the aflatoxin epoxide bonds to a negatively charged sulfur atom in the glutathione molecule. The newly conjugated aflatoxin-glutathione is excreted, with no harm to the body. It's the body's natural way to rid itself of toxins.

Kensler wanted to amplify this effect, to shuttle aflatoxin off with an alternate "dance partner" before it latched on to the DNA. So he started looking for chemicals that could elevate GST expression, like oltipraz. It reduced DNA damage caused by aflatoxin, but there was a drawback. Oltipraz was expensive and in limited supply. To boot, Chinese are skeptical of Western-style pills. So Kensler began looking for another approach.

Around that time, a colleague, Hopkins pharmacologist Paul Talalay, had found that sulforaphane, a metabolite of broccoli, present in even greater quantities in broccoli sprouts, was 100 times better than oltipraz at upregulating GST. The key to its success, Kensler and others believe, is sulfur. Many of the target molecules Kensler used to amp up glutathione and GST production in the liver are "decorated" with sulfur-based cysteine amino acids. Kensler thinks these amino acids act like antennae, looking for distress signals. If they "hear" a call for help, they send out a clean-up crew of transcription factors and other proteins to mop up the insulter. (Not everyone is convinced of the safety of this pathway. Kensler's convinced it's safe to target with foods like broccoli for disease prevention.)

Because tea drinking is part of Chinese culture, Kensler decided to see whether a broccoli sprout tea would lessen aflatoxin binding to the DNA. His team built a sprout-growing lab in Qidong, brewed tea in cauldrons, and filled hundreds of plastic bottles with the brew and a control liquid. (A little mango juice cuts the bitterness.) The results so far are encouraging—the aflatoxin biomarker is lower in those who drank the sprouts tea.

Kensler says he's had no problem finding volunteers for the study—everyone in Qidong knows someone who has died of liver cancer.

If the GST pathway works on aflatoxin in the liver, what about other organs or diseases?

"We think this is a very central protective mechanism of a cell," Kensler says. "We're working in a little sidebar relevant to a half-million people, but in fact, this pathway is going to touch the way we think about prevention and even treatment [for many diseases]." Kensler and others are testing broccoli sprouts on breast cancer, asthma, and degenerative diseases like chronic obstructive pulmonary disease.

This spring, Kensler moves from Johns Hopkins to a space in Pitt's Biomedical Science Tower. On his first day at Pitt in December, he surveyed the soon-to-be lab as a crew installed wiring in the room's bare aluminum studs. Kensler ordered a single architectural flourish to the layout—a glass splash guard next to a sink, which will hold a laminated satellite image. The photo shows a green peninsula, Qidong, above the cyan-tinted Yangtze. Aflatoxin country. The people of Qidong will remain in Kensler's thoughts here at Pitt. ■



Rocky Tuan uses nanofibers, which mimic a cell's natural environment, as a structure to encourage and support the growth of adult stem cells into tissue like cartilage.

COURTESY R. TUAN

"LOOK AT IT FROM THE CELL'S POINT OF VIEW"

ROCKY TUAN PERSUADES JOINTS TO FIX THEMSELVES

BY JOE MIKSCH

Children are naturally inquisitive. "Mom. Mom. Mom. Why is the sky blue?" and all that sort of stuff.

Sung Chi Tuan was no different. As a tyke growing up in Hong Kong, he was full of questions. Often he'd take it upon himself to find the answers.

His father had a few wristwatches. On each was engraved the number of jewels contained in each timepiece. In watch parlance, a jewel is a little pivot used to reduce friction between all the moving parts that help keep time.

Young Master Tuan did not know this.

"So I would take the watches apart to find the jewels," Tuan says with a hint of decades-long disappointment tinting his words.

Although he found no multicarat diamonds or deep red rubies, Tuan admits that he did learn something about watches and, in retrospect, something about science: You don't get the right answers without asking the right questions, and, at times, desired outcomes can elude even the most prepared inquisitor.

But the most important lesson, Tuan says, is to keep asking questions.

Today, Tuan—now known as Rocky—is the founding director of the University of Pittsburgh School of Medicine's newly established Center for Cellular and Molecular Engineering in the Department of Orthopaedic Surgery. He is also professor and executive vice chair for orthopaedic research.

He and his wife, Cecilia Lo, both left positions at the National Institutes of Health (NIH)—he as chief of the Cartilage Biology and Orthopaedics Branch at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and she as principal investigator in the Laboratory of Developmental Biology at the National Heart, Lung, and Blood Institute—to come to Pitt.

Lo, a PhD, is the founding chair of the new Department of Developmental Biology in the School of Medicine.

She says that her husband's move from the NIH to Pitt was predicated on his desire to have a closer set of clinical collaborators. "The NIH is huge and has a lot of scientists, of course, but not as many tissue engineering personnel, and they don't have an orthopaedics department. He had collaborators at Georgetown and George Washington University, but in terms of having close contact with clinicians, that wasn't there."

Tuan's boss at NIAMS, director Stephen Katz, wasn't glad to see him go, of course, but believes that Pitt orthopaedics did pretty well for itself in recruiting Tuan. "Rocky is a tremendously enthusiastic scientist. He really has a 'can do' attitude," Katz says. "He is one of those rare individuals who makes the biology and engineering come together."

Tuan, as of fall 2009, was still getting situated in his brand-new digs at 450 Technology Drive, across the Monongahela River from the South Side. After making coffee—a process that led to a brief digression on the explosive potential of some kinds of nondairy creamer—and a pause to advise a couple of physical plant workers on where to hang a paper-towel dispenser, Tuan retired to his undecorated and mostly empty office, evidence of his recent arrival at Pitt. As construction workers banged about in the as-yet-unfinished building—the sound would be a companion throughout the conversation—Tuan put his 30-plus-year career in perspective.

After studying at Swarthmore College, Berea College, and Rockefeller University (where he earned his PhD in biochemistry and cell biology), Tuan has established himself as a premier tissue engineer cum stem cell biologist. He brings with him from the NIH a research portfolio with one major thrust: Use the body's own regenerative power—augmented with biomaterials, nanomaterials, and/or stem cells—to make musculoskeletal tissue exactly as the body would.

"The ultimate goal is cell-based therapy or cell-based tissue regeneration," Tuan says. "But in order to regenerate tissue, you need to understand the building blocks, the cells—they're the real tissue engineers. We're not; we're cheerleaders." He pauses and adds, "You've got to look at it from the cell's point of view."

Getting to a cell's eye view of things started at Rockefeller and required two catalysts: Aristotle and a chicken.

Tuan recalls arriving at Rockefeller not entirely sure of what he intended to study, a fact that made the program and him well suited for one another. As he describes it, Rockefeller wasn't a traditional pedagogical situation: "It was very unconventional. There were 400 faculty and only 20 students per class," during Tuan's time, the early 1970s. "There really weren't classes—we would go around to laboratories, and they'd challenge us to come up with something."

After a time, Tuan opted for Zanvil Cohn's lab. Cohn, a cell biologist and immunologist, who died in 1993, was expert in the function of T cells and macrophages, using his knowledge to investigate leprosy, tuberculosis, and AIDS. Yet, even after choosing the broad area in which he would apply himself, Tuan still wasn't sure of his scientific niche:

"So [Cohn] said, 'Why don't you disappear and come back and talk to me after a month?'"

Tuan holed up in the Rockefeller library—"It was open 24 hours; you could sleep there"—and just read.

"I read a lot," Tuan says. "Old stuff, new stuff, some Greek literature … whatever. In a sense, I was looking for a topic that related to improving quality of life but could be approached using modern technology."

Though he can't remember the title, Tuan says he came across a tome whose author argued that Aristotle was the world's first embryologist. Aristotle, the writer says, wrote a treatise on the egg. How, the grand old philosopher asked, could something with an oblate spheroid shape and hard shell give rise to something feathery, fleshy, bony, and beaky? The question, then, was not, "Which came first, the chicken or the egg?" but, "How the heck did an egg make a chicken?"

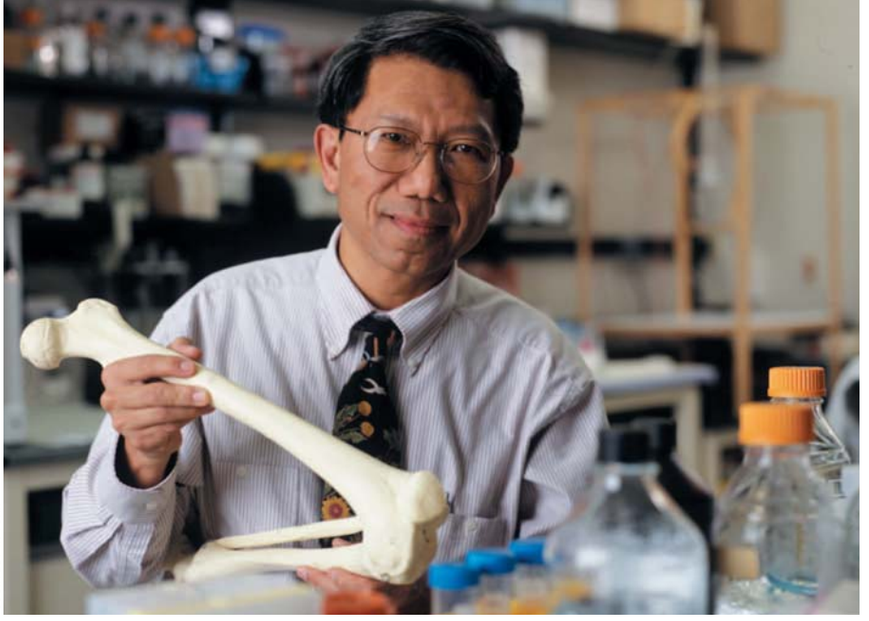
Aristotle didn't get all that far in answering the question, but he did note that all the matter that became a chicken had to be present in the egg. Tuan took it upon himself to move the ball forward; upon returning to Cohn's lab, he had decided to pursue how the calcium that makes up an eggshell becomes chicken bone.

"My boss said, 'What?,'" Tuan recalls. Cohn then thought of his med student days when he worked with eggs and viruses and told Tuan, "Sure, go ahead." (Apparently, chickens aren't the only things that spring forth from eggs—inspiration does, as well.)

In his resulting PhD thesis, Tuan established the manner in which calcium is transported from the shell to the embryo. He was the first to do so, which, naturally, was exciting and prompted a whole new series of questions centered on bone.

"I realized that the skeleton has to repair itself, that it's constantly undergoing turnover. Ossification is an active process. I asked myself, 'How is this happening and why?' I started thinking about stem cells, precursor cells, progenitor cells," Tuan says. "That's how I got into [orthopaedics]. I don't think I ever set out with any sort of business plan—year one, do this; year two, do that—I've just followed my nose pretty much.

"Remember early attempts at building airplanes? They tried to make them look like birds, but mechanically it didn't work. When the Wright Brothers built their airplane, it was totally different from the way a bird flies. It's got wings, but it's nothing like a bird."



COURTESY R. TUAN



CIDDE

Tuan hopes to use biology and engineering to save joints, like the knee above, from the ravages of osteoarthritis. He also studied the skeletal development of chickens with an eye toward understanding how the process is biologically regulated.

"I've become very interested in repairing, regenerating, and engineering new tissues, particularly [those] related to the skeleton, and it all started with looking at how this calcium business works," he says.

Lo says her husband's tendency to yield easily to curiosity and grasp opportunity—as manifested in the Aristotle, egg, chicken, and calcium transport equation—was evident even when he was an undergrad. "He loves music, which he didn't have the opportunity to study when he was growing up," she says. "When he went to Berea College, he was in work study at the music library and listened to all kinds of music. He got his own musical education. His taking advantage of chances is a character trait."

That spell as a musical autodidact led to Tuan performing with the Tanglewood Festival Chorus in Boston. "He has a nice baritone voice," Lo says. Will he do the same with the Pittsburgh Symphony's Mendelssohn Choir? "Maybe. He hasn't exactly had a lot of time as of late," she notes.

As Tuan gets his Pittsburgh lab up to speed, he's no longer particularly interested in chickens; he's more concerned with how to create cartilage, tendon, and ligament tissues to replace those ravaged by injury or age. When these tissues are injured or worn by overuse, the result is often osteoarthritis—a painful, chronic, and difficult-to-treat condition that affects some 27 million Americans, according to the NIAMS.

At present, osteoarthritis is managed through pain medication, physical therapy, and, in severe cases, surgery to repair the damaged tissue or replace joints. The problem with surgery is that the mended tissue—scar tissue, essentially—cannot bear the same weight as the native, healthy tissue. Further, it has a tendency to erode over time, necessitating follow-up procedures. Replacement joints, as sophisticated as they have become, don't hold up well over time.

Tuan says we can do better, and we can do so by mimicking nature.

Making man-made, or rather, "man-assisted" tissue in vitro from adult stem cells, particularly mesenchymal stem cells that are drawn from bone marrow, muscle, or fat, is the easy part—not that it's particularly easy. The real difficulty arises, Tuan says, in making something that looks like muscle, cartilage, or a spinal disc function like muscle, cartilage, or a spinal disc.

"The mechanical properties are lousy, but it's a beginning," Tuan told *Wired* magazine in 2008 of his earlier efforts.

To improve function and make the new tissue as good as the old, Tuan has decided to give these stem cells something of a kick-start. With knowledge about how cells differentiate during embryonic development—what growth factors play which roles at what times—Tuan is capable of turning mesenchymal stem cells into what he wants, or at least a fair simulacrum of it. But this is clearly not enough.

"This is a little different from the classical engineering approach of 'Oh, something's missing, I'll just build something that looks like it,'" he says. "In the body, it doesn't quite work that way. Remember early attempts at building airplanes? They tried to make them look like birds, but mechanically it didn't work. When the Wright Brothers built their airplane, it was totally different from the way a bird flies. It's got wings, but it's nothing like a bird."

Tuan's challenge, however, is a bit different from what Orville and Wilbur Wright faced as they, in effect, cheated their way around the avian model to achieve flight. Tuan has got to build tissue that not only looks like what it's intended to replace but also essentially *is* what it's intended to replace.

To ease the transition from stem cell to tissue, Tuan decided to build a template. In normal human development, embryonic stem cells, as they differentiate, assemble themselves into heart, bone, muscle, cartilage, etc. This is easier for them because, as Tuan says, embryonic stem cells are much more adept at becoming whatever they need to become. Adult stem cells are less malleable, but still open to influence and less likely to proliferate out of control.

"An embryonic stem cell is like a kindergartner—it doesn't know very much, but it can become anybody as long as it's taught the right things," Tuan says. "Adult stem cells are more like high school graduates. They've already learned a few things but have developed some bad habits. Still, though, you can influence them by putting them with the right friends."

Their best friend, in Tuan's metaphor, is a scaffold matrix. Without a space-filling guide the mesenchymal stem cells can glom onto, there's a high risk that they'll be swept away before they can become tissue. "Unless you can make cells happy," Tuan adds, "you're not going to have the right kind of tissue in the end. What do cells like? Well, they live in a matrix that they make themselves." Logic then dictated to Tuan that he try to make a matrix as close in appearance, structure, and function to the original matrix as he could.

In high-resolution microscopy, an "original matrix" appears as a bunch of nanometer-

scale fibers. Tuan takes a liquid polymer and, using a technique borrowed from the textile industry, spins the stuff rapidly in the presence of a strong electrical field. As the polymer attempts to diffuse the charge, it forms into—you guessed it—a bunch of nanometer-scale fibers.

"The cells love this!" Tuan says. "They think they're at home. It's assisted development. Otherwise it might take them a while to put all that stuff [the matrix] together. Now that we gave them the stuff, they can decorate it with their own molecules."

The scaffold can also be treated with other molecules that help attract mesenchymal stem cells and induce them into turning into what Tuan wants them to become. "We can attach those [biologically active] reactive groups to the fibers according to whatever we want," Tuan says. "What we have done now is load these fibers with very small molecules, and we can add hormones or growth factors. Let's say you have osteoarthritis; you can add drugs to treat it. The goal is to use these fibers for structural tissue regeneration and for therapeutic applications."

Tuan recently completed a trial of the scaffolding involving injured pigs. In the trial, researchers sutured cell-laden scaffolds over damaged cartilage in the pigs' knees. Within six months, new cartilage had formed. What's most encouraging to Tuan is that the new growth not only looked like what it replaced but had mechanical properties similar to the native cartilage. Tests on goats are on the horizon and will probably be completed within two years. After that, Tuan says—human clinical trials.

As this work progresses, Tuan is also looking to learn a bit about regeneration from soldiers with blast injuries that necessitate amputation. The muscle at the end of the injured limb—where a prosthesis would attach—often becomes bone as it heals. This unwanted transformation can occur in the time it takes for a soldier to be transported from the battlefield, to a U.S. military hospital in Germany, to Walter Reed Army Medical Center in Washington, D.C.

It turns out that the wound site attracts stem cells at up to 4,000 times the density found in bone marrow and much, much higher than found in normal muscle tissue. This overzealous attempt at healing is likely what causes bone to form, but Tuan has yet to sort out why the stem cells make this error in differentiation.

Some good, though, has come out of this problem. These extra stem cells, Tuan found, also have the ability to induce nerve growth. He suggests that perhaps these cells can be harnessed to induce peripheral nerve repair. "We're not too far along on this," Tuan says, "but it's a work in progress for sure."

Tuan's not alone in Pitt orthopaedics when it comes to regenerating tissue, particularly cartilage. His colleague Constance Chu mines a similar vein. Chu, the Albert Ferguson Associate Professor of Orthopaedic Surgery and director of the Cartilage Restoration Center at Pitt, is preparing to test her work on horses.

An MD, Chu recently received a $1.7 million Grand Opportunities grant from the NIH for her project "Multicenter Cartilage Repair Preclinical Trial in Horses." She's collaborating with investigators from Cornell University, Colorado State University, and the University of California at San Diego.

Chu also works with bioactive scaffolding and bone marrow stem cells, but her Grand Opportunities grant takes another approach: "What I'm doing I call 'back-table tissue engineering.' Basically, we're aspirating bone marrow from horses and concentrating stem cells and clotting factors by centrifuge in the operating room." This material can lead to tissue regeneration once implanted in the knee.

While Chu admires, and shares, Tuan's approach, she thinks lab-engineered cartilage may take longer to reach the clinic than her "back-table" work. "With gene therapy or nanotechnology or synthetic polymers, there are major hurdles regarding proving safety and efficacy," she says.

If the horse trial goes well, Chu plans to pursue clinical trials in humans within two years.

Tuan sees a lot of promise in Chu's work. In the meantime, he's going to keep busy with his scaffolds. "When you're dealing with tissues whose main function is to bear weight, I think it's good to have a scaffold that can take care of that aspect of it," he says.

Questions remain, of course. Tuan thinks it's vital to develop a deeper understanding of how cells communicate with one another while they construct new cartilage or tendon as well as how a cell's environment in the body influences its function.

"This goes to a very fundamental question about the niche of a cell. This is a very hot topic right now in the stem cell field. 'Niche' is just a fancy French word for microenvironment," he adds, digressing to say, "Although 'environment' is of French origin as well … the French know everything!"

Becoming serious, he continues, "The niche is defined as the environment that maintains the stem cell in a stem cell state while allowing it to differentiate upon induction. We need to know what all the environments the cell deals with are and tease them apart to understand what cells do when stretched or subjected to the pressures that go along with being in a ligament or tendon."

"An embryonic stem cell is like a kindergartner—it doesn't know very much, but it can become anybody as long as it's taught the right things," Tuan says. "Adult stem cells are more like high school graduates. They've already learned a few things but have developed some bad habits."

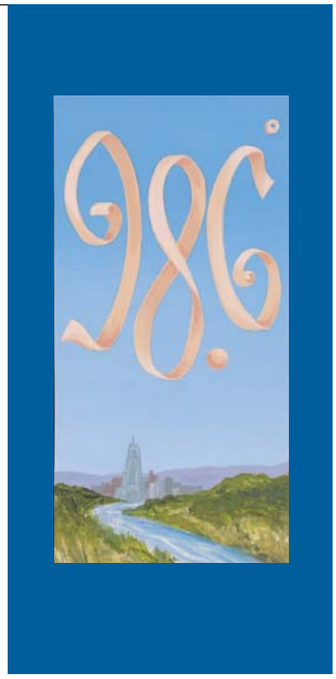
Freddie Fu, David Silver Professor and chair of the Department of Orthopaedic Surgery at Pitt is confident his new recruit will find the answers he seeks. "I've been following his career for 20 or 25 years now, even before he was at the NIH, and I think he's leading the world in this biological approach to the problem," Fu says. "It's a solvable problem, and I think he's going to find a solution."

Tuan says he's glad to be at Pitt to pursue this stage of his work.

"For the kind of work I am interested in, Pittsburgh is a powerhouse," Tuan says. "I don't have to come in here and build anything, which is actually nice. Here, science is truly multidisciplinary, and I think it's a lot more fun when you have different kinds of people thinking about these problems. It's great to be in a place with that kind of interaction."

Well, Tuan concedes (as construction workers drill and hammer nearby), he *does* have to build something—cartilage, muscle, tendon. After all, that's why he uprooted his lab and came to the banks of the Monongahela River. ■

People and programs that keep the school healthy and vibrant



GAMING FOR GLORY AND THERAPY, TOO

BY BRANDON ELLIS

The suspense is palpable as Dorothy Ionadi, a stroke patient at UPMC Mercy's Institute for Rehabilitation and Research (IRR), readies her mind and body for competition. She dazzles the crowd by collecting rain droplets in a cup, washing a window at lightning speed, and felling airborne turkeys with deadly accuracy. And she does it all using her left arm.

Ionadi is sitting in the same chair that she occupied months ago, when she had trouble with her left visual field because of a condition known as homonymous hemianopia and couldn't move her left arm. She had suffered a stroke in late August and arrived at Mercy on Sept. 5. Her introduction to video game therapy came soon after, and her occupational therapist, Jackie Glosser, remembers when Ionadi showed the first signs of healing:

"She was sitting in this chair playing the game, and I saw that she was moving her eyes in response to movement on her left side."

Her vision was returning to normal. Ionadi's video game regimen involved 45 minutes of gaming per day with her arm in a robotic sling. She regained full control over the arm and left Mercy on Sept. 22, earlier than the most hopeful predictions.

Now, she shows off her skills as doctors, reporters, and other patients watch. She tightens her grip around the joystick, and a turkey on the screen disappears in a mess of blown feathers.

The digital carnage is part of a fund-raiser called Gridiron Gaming, conceived by Michael Boninger, professor and chair in the University of Pittsburgh School of Medicine's Department of Physical Medicine and Rehabilitation and director of IRR. Pittsburgh Steelers offensive lineman Max Starks brought 10 of his teammates to the event. After paying guests lined up for autographs, they got the chance to challenge one of the Steelers on the Nintendo Wii—a key element of IRR's innovative approach.

"We enjoy video games," Starks says of himself and his teammates. "We're big kids."

Although they can't replace traditional therapy, video games offer distinct advantages. The screen gives feedback so patients see that they are moving. The robotic sling de-weights the arm, so patients can work their muscles without working too hard.

"When you're having fun, your heart rate goes up, and you release those endorphins," Boninger says. He hopes to use the money from Gridiron Gaming ($27,000 was raised) to promote existing programs. Boninger also introduced guests to the GameCycle—a combination exercise bicycle and video game invented and developed by Boninger and Rory Cooper, a PhD professor in Pitt's School of Health and Rehabilitation Sciences with an appointment in orthopaedic surgery. Rehabilitation centers across the country are buying it and mimicking IRR's approach.

Video games are serious therapy for Ionadi, but they can be simple fun, too. She played with her grandson, now 23, when he was younger.

Back then, she couldn't keep up. He always told her, "Grandma, you never win," she reports with a triumphant smile. ■

JOHN MCCAULLEY



Rehabilitation patients who use video games as physical therapy meet the Steelers'. Shown here, ready for competition: Max Starks (left) and Deshea Townsend with the IRR's Tiffany Calloway (Res '04), who is Starks' wife.

BOOSTER SHOTS

As cofounder of a group of hospitalists in metro Atlanta, **Vaughn Clagette** (MD '93) believes hospitalists help patients heal faster and leave the hospital sooner. In a world of increasing specialization, hospitalists are generalists who focus on the care of the hospitalized patient. The benefits, including earlier diagnosis and fewer medical errors, should make hospitalists mandatory worldwide, Clagette says. (Most American hospitals now use hospitalists, whose numbers increased from around 1,000 in 1996 to 28,000 in 2007.)

Speaking of measurable results, Clagette feels a debt to Pitt. When he enrolled in medical school, he was offered role models and mentors through programs that introduced him to faculty and alumni. In support of such programs and scholarships to disadvantaged students, Clagette has made a major gift commitment to the Office of Diversity Affairs in the School of Medicine. —*Jamar Thrasher*

Growing up in Pittsburgh, **Charles E. Reel** (MD '89) always felt that many of the finer things in life were wrapped up in the University and its environs. He and his siblings swam at Pitt's Trees Hall pool as children. His father and namesake, ophthalmologist **Charles M. Reel** (MD '51), had met his future wife at Montefiore Hospital when he was an intern and she, **Ann Reel**, was a nurse anesthetist.

After the death of Charles M. Reel in 2008 and Ann Reel in 2009, the Reel family established a scholarship in their names for a Pitt med student. Charles E. Reel, a neurologist in private practice in Maryland, says his parents were always thankful for the training and education they received at Pitt, believing it enabled them to lead rewarding and happy lives. —*Chuck Staresinic*

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WHY THE WORLD NEEDS SAVING

MED STUDENTS SPEAK

COMPILED BY MIRAT SHAH

What follows are excerpts from the booklet Why the World Needs Saving, *edited in 2009 by University of Pittsburgh med student Mirat Shah (Class of 2012). Reprinted with permission.*

The idea for a publication grew out of conversations I had with my classmates during the 2008 presidential election. The national focus on the state of the country and the world led my peers to think about what issues were important to them and also what kinds of contributions they hoped to make as physicians. I wanted to record this dialogue. Moreover, I wished to capture what it felt like to be a medical student at this point of personal development, against a backdrop of national transition.

This publication asked medical students across all years to answer the following question: What is the most-neglected issue in the United States or the world, and what will you do as a physician to address this? The choice of the word "neglected" was deliberate. Ask what the most important issue is, and people will try to be objective. They will think about what affects the most people, or costs the most money, or causes the most destruction. They may quote statistics and provide fact-based arguments. Ask about the most neglected issue, and the responses change. They undoubtedly will be colored by personal experiences, beliefs, and values. And they will be more passionate.

The topics students chose to write about ran the gamut from health care to roads, water, and social justice. Some proposals focus on broad systemic changes while others describe specific interventions. All of the essays show us that medical students are both pragmatists and optimists. They also illustrate the importance of thinking about why we do what we do and what we hope to accomplish. The only way to achieve change is by remembering what we'd like to do. —*Mirat Shah*

NOT ENOUGH TIME TO CARE

As medicine continues to evolve, the profession will have to reconcile the doctor-patient relationship. The growing need to lessen costs will detract from how doctors engage with patients. Current reimbursement practices could lead to fewer physicians providing treatment to underserved populations—especially in primary care. The economic dilemma could also force doctors to overburden themselves with unmanageable caseloads, impacting patient outcomes and quality of care.

The patient is not a consumer but a person, with needs existing beyond the doctor's appointment that day. The real challenge will be to negotiate humanism in medicine with the more objective measurement of medicine's economics. Physicians must resolve the tension of what is most time-efficient (e.g., prescribing another drug) with what is best for the person (e.g., unearthing the psychosocial issues that may account for the "ailment's" presentation).

Physicians and physicians-to-be must remain vocal in the health care debate and find their voices in outlining the future construct of the doctor-patient relationship. —*Peter Asante Jr.*

Peter Asante Jr. is a first-year medical student originally from Pawtucket, R.I. He graduated from Harvard University in 2007 with a Bachelor of Arts degree in biological anthropology. After college, he moved to Bronx, N.Y., where he helped families with children with developmental disabilities access the public insurance system.

VEER

A feeling of voicelessness,

SCHIZOPHRENIA: A BURDEN FOR THE AGES

Schizophrenia has a long history of being misunderstood and is still shockingly neglected in our society. Approximately one in 100 Americans will develop this devastating illness, with symptomatic onset typically occurring in the late teens to mid-20s. The disease robs people of their formative years and leaves them trapped on psychological islands of desolation.

While the most dramatic and typical features of schizophrenia—hallucinations, delusions, and loose associations—are common knowledge because of movies like *A Beautiful Mind* and *The Soloist*, early prepsychotic cognitive dysfunction is more pervasive and debilitating on a daily basis. One of my goals as a physician-scientist will be to raise awareness and generate enthusiasm about the real potential to identify early markers and pursue novel treatment strategies for schizophrenia. As we learn more about core features of this syndrome, we will be better equipped to identify and treat various subtypes of schizophrenia based on biological insights. Equally importantly, I will fight for the rights of each of my patients and battle the stigmatization of the illness. —*Gil Hoftman*

Gil Hoftman is from Calabasas, Calif., and a first-year graduate student in the MD/PhD program. He is interested in the clinical neurosciences.

A NEED FOR COMMUNITY

The paradox of our age: As population density increases, our communities become more dispersed. Those of us living within the Western gospel of individualism are especially likely to forget that we are a collective organism: Individual circumstances—be they financial or medical—have widespread effects on our neighbors and ourselves.

When our communities fall into disarray, the fabric of our collective health disintegrates (as we see with the influx of illicit drugs or in the Gulf Coast post-Katrina). Indicatively, our family and friends are often more aware of our poor health and the toll it takes than anyone else. And they are our strongest motivators, speaking to our most intimate values.

Not coincidentally, the largest gaps in our current health care system concern matters best addressed by interpersonal dialogue outside the clinic and in the community: preventative medicine, stigmatization of mental health issues, and end-of-life care. At the same time, examples as disparate as cystic fibrosis and drug abuse demonstrate that communal support makes an immense difference in prognosis, even in the face of daunting biological challenges.

As a physician, I will seek to implement treatments that create and reinforce positive social relationships. Support groups, walking/running clubs, interest groups, information forums, home visits, and community health workers are all variations of the same idea. Still, we must expand our repertoire further, capitalizing on tools like social networking that are not limited by geography. Most importantly, we must limit our tendency to deconstruct multifactorial diseases. We should begin thinking more like community organizers and less like mechanics.

—*Benjamin Meza*

Benjamin Meza is a second-year student from Arlington, Va. He has worked with refugees and juvenile offenders and intends to be a primary care physician who serves children and adolescents.

THE REINVENTION OF PREVENTION

Few people argue against the potential benefit of better preventative health care in the United States. The challenge is how to achieve this in a culture that endorses and rewards excess and instant gratification. We are a reactive society that thrives on and is concurrently plagued by insatiable appetites—for all kinds of things.

For health care providers, this mentality is difficult to approach. We are up against insidious chronic diseases that lull their hosts into a comfortable lifestyle for decades without apparent consequence. Our task then so often is to convince patients to change behaviors (perhaps lose weight or quit smoking), which requires considerable effort and, often, discomfort to accomplish.

The earlier we help establish healthy behaviors, the more successful we'll be. We especially need more aggressive and creative strategies aimed at our nation's kids. But to craft effective preventative strategies for patients of any age, we must first understand the social constructs that shape their health—like education/literacy, family support structures, and financial resources.

To better understand these factors that define barriers to care for so many, I propose that U.S. medical schools require a year of postgraduation practice in a medically underserved area, as many other countries do. Such a program could foster or reestablish trust between young physicians and depressed communities in this country and would be a sustainable way to facilitate access to health care and health education. It would reenergize our efforts to address prevention. —*Jaime Moore*

Jaime Moore is a third-year medical student originally from Rockville, Md. She plans to go into primary care.

We should begin thinking more like community organizers and

or of invisibility, seeps into all aspects of life, and it is damaging to health.

HEALTH IN AN ILLITERATE WORLD

It's easy to forget that much of the world never has been and never will be part of the "information age" in which many of us unthinkingly live our lives. They are excluded by illiteracy, which is as repressive of individual autonomy as any dictatorship. In the broadest sense, literacy connotes more than being able to read. It also means access to unbiased information, the ability to understand this information, and the freedom to discuss it. Literacy creates the chance to learn, to question, to decide, to escape—in sum, to engage. Having the ability to participate actively in one's own life is what differentiates those who feel they have a voice from those who feel unheard.

A feeling of voicelessness, or of invisibility, seeps into all aspects of life, and it is damaging to health. Without literacy, health care can be one-sided and, in a sense, foisted onto the patient. For too many, there is no choice but to accept that this is the standard of care—and to accept that this is life.

The key to better health is literacy: having the knowledge to take care of one's own health and that of one's family. We as physicians must strive to understand the frameworks that shape our patients' understanding of their health so they can participate in their own care.

Literacy matters not just for health care but also for personal dignity. —*Emily Rosenberger*

Emily Rosenberger is a first-year medical student in the MD/PhD program. She graduated from Wesleyan University in Connecticut, where she studied history, sociology, and anthropology of science and health.

NOT A DROP TO DRINK

Ninety-nine percent of the water on earth is unsafe or unavailable to drink. Consequently, one-third of the world has limited or no access to clean water, and millions die each year as a result. This essential, natural resource engenders unnatural war, and the hunt for safe water creates a constant struggle between humans and their environment.

For everyone to have clean water will require collaboration between diverse groups of professionals and nonprofessionals. Engineers, for example, should continue inventing effective, portable, high-volume, long-lasting filtration devices that clean water from the dirtiest of sources. Distributing these devices requires infrastructure and the support of government and nongovernmental organizations. Conservationists must work with industrialists to ensure that populations have access to water without crippling the environment. At all times, the public must sit at the decision-making table and have a voice in executing solutions.

Physicians can fill many roles to help these groups succeed. They can treat those suffering from dehydration or consumption of unclean water. On a broader scale, they can use their knowledge and good standing in the community to coordinate sanitation education campaigns. And as advocates for patients' well-being, physicians should press governments to meet the water needs of their people.

Can we work together to equitably use the 1 percent of water available to us? We must try. —*Jason Sanders*

Jason Sanders, from Framingham, Mass., is a second-year medical student in the MD/PhD program. His professional and research interests include medical education, outcomes research, and the biology of aging. He hopes to become a surgeon.

TAP TAP: A NARRATIVE ON CATARACTS, THE NUMBER ONE CAUSE OF BLINDNESS WORLDWIDE

Tap. Tap. Tap. Tap. A long, thick wooden stick hits the rocks on the remote, dusty Honduran road. The stick is worn smooth underneath a woman's darkly pigmented hand; her skin sinks in between the muscles, ligaments, and joints. Her world is veiled in a thick fog. People appear as shadows. Familiar obscured images guide her along the path to the community clinic. She is met by a group of nurses who lead her into a room to shower and to change into a strange dress that leaves her backside exposed. After a few moments of rest in the clinic, she hears a gentle voice and feels a soft, warm hand on her forearm.

"Bienvenida a la clínica de oftalmología señora Martínez. Yo soy la doctora Allison Ungar y hoy voy a operarle su catarata." *Welcome to the ophthalmology clinic, Mrs. Martínez. I am Dr. Allison Ungar. I will be taking out your cataract today.* Mrs. Martínez reaches out for the doctor's hands to say a prayer with her.

The following day, her eye shield is peeled away to reveal a bright vision. She is surrounded by family—her children with faces decades older than she remembers and beautiful grandchildren seen clearly for the first time. She stands up inches taller than before and walks down the same dusty road. Her walking stick is missing, but she is too distracted by the colors to notice. —*Allison Ungar*

Allison Ungar is the 2009-10 UPMC Department of Ophthalmology Research Fellow and will be graduating with the Class of 2011. She is interested in combining her passions for underserved and international medicine with a career in ophthalmology. She volunteers with a mobile free eye clinic, the Guerilla Eye Service, which serves the Greater Pittsburgh area.

less like mechanics.



CLASS NOTES

'60s

Bert O'Malley (MD '63), professor and chair of molecular and cellular biology at the Baylor College of Medicine in Houston, spent a decade on Pitt's campus as a young man. He's now at the top of his profession, and he's going to be hanging around Pittsburgh permanently. O'Malley earned his bachelor's degree at Pitt in 1953. A decade later, he received his MD here, as well. Since then, he has blazed a path in science, becoming what many call "the father of molecular endocrinology."

Now he has been immortalized in oil paint. His portrait will hang with other Pitt med luminaries—including Thomas E. Starzl, Julius Youngner, and Jonas Salk—in the Gallery of Scientists in the Thomas E. Starzl Biomedical Science Tower lobby.

"It looks great!" O'Malley said at the unveiling ceremony. "In fact, it looks better than me." Turning serious, O'Malley added, "This is wonderful. This is where I grew up, and this is where my life changed."



MARY JANE BENT / CIDDE

Bert and Sally O'Malley with Dean Levine at the portrait unveiling.

Sheldon Weinstein (MD '63, Obstetrics and Gynecology Resident '67) was awarded the 2009 Patricia Kovac Vaginal Surgeons Award. Weinstein is a clinical professor of obstetrics and gynecology at the University of Texas Southwestern Medical Center in Dallas. He is the vice chair of the pelvic surgery fellowship and director of the obstetrics residency program at Texas Health Presbyterian Hospital Dallas. Among Weinstein's accomplishments is his invention of the loop electrosurgical excision procedure, commonly known as LEEP, which uses an electrical current to remove diseased cervical tissue.



Weinstein (right) invented LEEP to remove diseased cervical tissue.

'70s

David Bahnson's (MD '73, Orthopaedic Surgery Resident '78) medical aspirations were cultivated as a child and, later, as a medical student, by regularly seeing his father, the late Henry Bahnson, return from work with a sense of elation. The elder Bahnson was a cardiothoracic surgeon and chair of Pitt's Department of Surgery from 1963 to 1987. David Bahnson is now a surgeon at Vermont Orthopaedic Clinic, in Rutland, where he sees a lot of injuries related to skiing. In his spare time, he indulges in his hobby, aviation. As a boy, he was always fascinated by the early history of flight, and his special interest is wooden propellers. His web site, www.woodenpropeller.com, lists some 40 examples in his collection, including the 8-foot mahogany prop from a Sopwith Camel, circa 1917. Bahnson also owns and flies two planes, a Piper J-3 and a Cessna 206.

'80s

Joseph Strayhorn (Child/Adolescent Psychiatry Fellow '83) is a psychiatrist teaching behavioral and psychological skills that help children with issues like self-discipline and anxiety management. To refine and expand his learning-based approach to mental health, he founded Psychological Skills Press, through which he publishes books and electronic media for parents, educators, and youth. A homeschooling father, Strayhorn recently published an article with his daughter Jillian in *Reproductive Health*. Using data from the U.S. Census, the Centers for Disease Control and Prevention, and the Pew Forum on Religion and Public Life, the Strayhorns found strong correlations between teen birth rates and the degree of religiousness. The more religious states had higher teen birth rates. Strayhorn speculates that conservative religious communities may be better at discouraging use of contraception than they are at discouraging sexual intercourse. But he cautions that the findings by themselves do not permit causal inferences.

'90s

It was the third inning of a game between the Pittsburgh Pirates and Cincinnati Reds when a 60-year-old man in the stands at Pittsburgh's PNC Park became short of breath. Fans sitting in front of him turned to ask if he was okay, but he slumped in his seat and turned ashen. Sitting 40 feet away, **James Christopher Post** (Pediatric Otolaryngology Fellow '91, Pediatric Otolaryngology Research Fellow '92) saw the commotion and didn't hesitate to react. As a former Army Green Beret medic with a Combat Medical Badge and a Bronze Star, Post is a good person to have around in a medical emergency. He administered CPR for a few minutes. When he saw the man grimace, he knew it was a good sign. Paramedics took over and transported him to a hospital. Several days later, the lifelong Reds fan was sitting up in bed, thanking his lucky stars, and wearing a Pirates cap.

Post, who earned a PhD in human genetics from Pitt's Graduate School of Public Health in 1999, is president and scientific director of the Allegheny-Singer Research Institute; medical director for its Center for Genomic Sciences; professor of otolaryngology, microbiology, and immunology at Drexel University; and a member of the Pitt-UPMC McGowan Institute for Regenerative Medicine. Post conducts research on bacterial biofilms.

There was a time when **Rick Ganzi** (Anesthesiology Resident '94) couldn't even run a mile. After being disappointed at the amount of weight he gained while in



Ultramarathoner Ganzi finishes first among Americans in Durban.

residency, Ganzi began running with an old friend who said it was a sure way to shed pounds.

Ganzi started out running modest distances and not very fast, but somewhere along the line, he picked up a great deal of momentum. That's putting it mildly. Since turning 40, he has finished seven marathons in less than three hours. Last year, he was the first American to cross the finish line at the 2009 Comrades Marathon in South Africa. And this is no ordinary marathon. Ganzi describes it as the "Boston Marathon of Ultramarathons." Covering 56 miles between the inland city of Pietermaritzburg and Durban on the coast, the race is the oldest and largest ultramarathon in the world. Ganzi was the third American to finish in 2008, and he returned in 2009 to be the first of 61 Americans. His finishing time of seven hours and 28 minutes earned him a silver medal.

In addition to managing his own training, Ganzi helps to design customized training programs for other runners. In Grand Rapids, Mich., where Ganzi and his wife, Lois Ganzi (Anesthesiology Resident '94), practice, he is the pace team director of the Metro Health Grand Rapids Marathon.

—Brandon Ellis, Joe Miksch, Chuck Staresinic, and Jamar Thrasher



CIDDE

LOUIS SULLIVAN VISITS

During Homecoming in October, the University of Pittsburgh again held a Health Sciences Diversity Alumni Reunion Banquet for all the schools of the health sciences. Hosted by Paula Davis, assistant vice chancellor for health sciences diversity, the program included a keynote address by Louis Sullivan, an MD, the former secretary of the Department of Health and Human Services, and first dean of the Morehouse University School of Medicine. The banquet offered a chance for far-flung alumni to reconnect, as well as inspiration for all to work to increase diversity in the health sciences professions. Vaughn Clagette (MD '93) returned from Atlanta for the chance to chat with Sullivan and others. (See p. 31 for more on Clagette.) Pictured above with Sullivan (center) are Clagette and Margaret Larkins-Pettigrew (MD '94, Res '98), Pitt assistant professor of obstetrics, gynecology, and reproductive sciences.

THE WAY WE ARE

CLASS OF '89

From inside the cafeteria at UPMC Presbyterian, a group of third-year medical students on an intensive care rotation heard the code. They put down their sandwiches and raced to the ICU.

David Gerber (MD '89, Fel '98), now the chief of the abdominal transplant division and associate professor of surgery at the University of North Carolina at Chapel Hill, was one of the first to arrive. The patient had been on cardiac service for several weeks, and now he was in cardiac arrest. His once-rosy cheeks had faded to gray. Gerber was called to assist, and he administered chest compressions for several minutes. An upperclassman noticed the sweat building up around his neck and said, "Hey Gerber, take your shirt off. It'll make you more comfortable."

So Gerber, who didn't realize the suggestion was a joke, continued the resuscitation—without his shirt. A defibrillator was brought in, and the students eventually stepped back to realize that, for the first time, they had helped save a life.

"I assumed it would be an extension of my college years," says Gerber of medical school at Pitt, "but it was a quantum leap." In Chapel Hill, Gerber's clinical work includes liver and kidney transplantation. The surgeon, who went to Emory University for residency but returned to Pittsburgh for a fellowship at the Thomas E. Starzl Transplantation Institute, conducts research on liver and islet stem cells, with an eye toward the development of bio-artificial organs to treat patients with diabetes and liver failure.

Jill Baren (MD '89) was one of those third-year students called to the ICU at Presby. Baren fondly remembers the camaraderie among the class of more than 100 Pitt med students. When she arrived at Harbor-UCLA for her emergency medicine residency, she felt like medical school had prepared her well. "I had been exposed to the demand and rigor of top-notch physicians," she says, pointing out that when a med student walks the same halls as Thomas E. Starzl and other Pitt mentors, it can lead to high aspirations.

Baren is an associate professor of emergency medicine and pediatrics at the University of Pennsylvania. In 2009, she was named president of the Society for Academic Emergency Medicine. In her new role, she hopes to boost federal funding for emergency medicine research and enhance the development of young academic researchers in the field.



Gerber

Bruce Pollock (MD '89, Res '96) says that inspiration was everywhere when he was a med student, to the extent that he wrestled with indecision when it came to choosing a specialty. He became fascinated with brain surgery when he attended a lecture by Pitt's Peter Jannetta, then chair of neurological surgery.



Baren

"I was thinking about pursuing a PhD in molecular biology, but then I saw the lecture," he says. In his final year of medical school, Pollock was invited to be a Pitt neurological surgery resident. He stayed in Pittsburgh for a fellowship in stereotactic and functional neurosurgery. Today, he is a professor of neurosurgery at the Mayo Clinic in Rochester, Minn. He has become an authority on the use of stereotactic radiosurgery in which focused beams of radiation are used to treat tumors and other malformations without incisions.



Pollock

This past summer, Pollock and Gerber vacationed together with their families in the Outer Banks of North Carolina.



Deune

When **E. Gene Deune** (MD '89) left Pittsburgh, he took with him the Pittsburgh Surgical Society Scholarship, which is given annually to the top graduating med student going into surgery. For the next seven years, Deune, now a hand surgeon, trained at Washington University in St. Louis.

Today, he is an associate professor of orthopedic and plastic surgery at Johns Hopkins University and codirector of the Division of Hand Surgery, performing a wide range of procedures. As a reconstructive microsurgeon, he is nationally known for his work restoring soft tissue defects and function in upper and lower extremities affected by sarcoma surgery.

Deune, thinking back to his med student days, notes that he was well prepared to meet the challenges of internships and residency.

—Chuck Staresinic and Jamar Thrasher



Gitlin

DAVID GITLIN

AUG. 7, 1921–JAN. 4, 2010

In the 1950s, David Gitlin and Harvard University colleague Charles Janeway solved the riddle of agammaglobulinemia, a syndrome that causes repeated, severe, and often fatal infections in children. This work led to gamma globulin replacement therapy, which continues to save lives.

Gitlin also elucidated the metabolism of plasma proteins in children with kidney disease, discovered the mechanisms of iron absorption in the intestine, identified ceruloplasmin deficiency as a biochemical marker of Wilson disease, and found that alpha fetoprotein is a biomarker for various life-threatening birth defects.

The MD was heralded internationally for his work and suitably proud of his achievements. Yet his son, Jonathan Gitlin (MD '78), who chairs the Department of Pediatrics at Vanderbilt University and is physician-in-chief at Monroe Carell Jr. Children's Hospital of Vanderbilt, says his father was most proud of being a professor. The elder Giltin was a professor of pediatrics at the University of Pittsburgh from 1963 until his retirement, after which he held emeritus status.

"If you met him on a plane, he'd say that he was a professor, not a doctor or a scientist," Gitlin says. "He loved being part of the University of Pittsburgh." *—Joe Miksch*



Hoy

RONALD J. HOY

SEPT. 30, 1916–SEPT. 21, 2009

Ronald Hoy taught a generation of budding radiologists to remember that behind every image, there is a person.

Hoy, 92, longtime Pitt professor of radiology, died at his home in Sydney, Australia, in September. Hoy came to Pitt from Yale University in 1971 and retired from the department in 1992. During his 20-plus years here, Hoy was instrumental in implementing the med school's radiology curriculum. He imparted the need for critical thinking when using new imaging technologies in diagnosis and treatment.

"Nowadays, we have evidence-based medicine," says former colleague Carl Fuhrman, chief of thoracic radiology and Pitt professor of radiology. "Ron was 30 years ahead of his time in understanding the question, 'Is this test I'm about to give a patient really valuable?'"

A captain in the Australian Army Medical Corps during World War II, Hoy became one of the first dedicated radiologists in Australia in the 1950s. He was also among the first clinicians to use angiography and ultrasound in his home country, and he taught radiology to medical students in Malaysia and Vietnam.

In 1991, his contributions to radiology medical education were recognized by Pitt with the naming of the Ronald J. Hoy Excellence in Teaching Award, given each year by radiology residents to an outstanding faculty educator. *—Reid R. Frazier*



Kahler Hench

PHILIP KAHLER HENCH

SEPT. 19, 1930–OCT. 28, 2009

Philip Kahler Hench (MD '58) was born with one famous name in Rochester, Minn. His mother, Mary Genevieve Kahler, was the daughter of the founder of the Kahler Hotel adjacent to the Mayo Clinic. (The hotel included a hospital wing with operating suites when it opened in 1921.)

Before he graduated from the University of Pittsburgh School of Medicine in 1958, Hench would have two famous names. Hench's father was rheumatologist Philip S. Hench (MD '20). In 1950, the elder Hench was awarded the Nobel Prize in Physiology or Medicine for the discovery of cortisone and its ability to relieve the symptoms of rheumatoid arthritis.

When he was 20, P. Kahler Hench accompanied his father to Stockholm to accept the prize. After medical school, he completed training in rheumatology at the Mayo Clinic, where his father was on the faculty until his death in 1965.

The younger Hench was head of the rheumatology division at Scripps Research Institute and Clinic in California from 1974 to 1982. He retired from Scripps in 1998 and continued to live in La Jolla until his death last fall. Hench published widely on nonarticular rheumatism and coined the term fibromyalgia to describe it. *—Chuck Staresinic*



Shogan

JEFFREY SHOGAN

OCT. 12, 1953–JAN. 9, 2010

Jeffrey Shogan (MD '82, Res '86) spent his life searching for a better way to fight cancer, and in the process, he helped create one of the world's largest cancer networks. He died Jan. 9, of cardiac arrest. He was 56.

Shogan was director and chief business officer of the UPMC Cancer Centers and "a driving force" in streamlining and expanding the network, says Stanley Marks, director of clinical services and chief medical officer of UPMC Cancer Centers. In 1989, Marks recruited Shogan to Pittsburgh to start a bone marrow transplant center at Allegheny General Hospital. Then UPMC recruited the pair in 2000; the doctors brought with them one of the country's largest oncology practices. Under Shogan and Marks, the network expanded into dozens of sites throughout the region and internationally.

Shogan received his MD from Pitt in 1982, was chief resident at UPMC Presbyterian, and completed a fellowship in oncology at Duke University Medical Center. He had recently begun steps to open a charitable medical clinic for Burmese refugees in Thailand, where he had spent two years in the Peace Corps.

"When he died, I picked up a lot of his patients the next week," Marks says. "Many of them felt like they lost their best friend." *—RRF*

IN MEMORIAM

'40s

DAVID FLOM
MD '42
DEC. 8, 2009

THOMAS EVANS
MD '43A
OCT. 20, 2009

'50s

JOHN DAVIS
MD '55
NOV. 17, 2009

FRANK BEGG
MD '56
DEC. 5, 2009

'60s

LAWRENCE MULHERN
MD '60
NOV. 19, 2009

EUGENE HERRON
MD '62
NOV. 30, 2009

'70s

FRANCIS PLUNKETT
MD '75
OCT. 26, 2009

'80s

STEPHEN ESTNER
MD '84
OCT. 17, 2009

FACULTY

FRANK LUPARELLO
JAN. 5, 2010

ON THE MOVE
ENDOCRINOLOGIST THERESA GUISE

BY SHARON TREGASKIS



JOE KAPELEWSKI / CIDDE

Guise was honored as a Pitt Legacy Laureate in fall 2009. She's shown here with Chancellor Mark A. Nordenberg.

Theresa Guise (MD '85, Res '88) ran her first marathon in 1989. A few months later—inspired by the mentorship of pituitary expert Joseph Verbalis (MD '75), an attending during her residency at Pitt—she headed for an endocrinology and metabolism fellowship at the University of Texas Health Science Center at San Antonio. There she would garner a young investigator award in mineral metabolism and eventually build a world-class reputation for her work on the site-specific chain of molecular processes that brings about bone metastasis, the leading cause of cancer deaths.

"He made us think a lot about mechanisms," says Guise of her training under Verbalis. "I think that helped drive my interest in understanding how disease works."

In the intervening 15 years, Guise ran 25 more marathons—in New York, San Diego, and Boston. "Theresa has tremendous energy," says David Roodman, formerly associate chair of research at San Antonio and now director of the University of Pittsburgh Cancer Institute's Hematologic Malignancies Program. "She is also one of the nicest people you'd ever want to deal with. She's civil, rational. Her intellect and knowledge of the literature and of her own work make her an outstanding collaborator."

Despite her current post—as the Jerry W. and Peg S. Throgmartin Professor of Oncology at Indiana University's Melvin and Bren Simon Cancer Center—and the fact that her research investigates the mechanisms of bone metastasis, Guise is no oncologist. Rather, she brings the sensibility of an endocrinologist to her investigations of how cancer of the breast, prostate, and lung affects both uncontrolled cell growth and destruction in the skeleton.

"Tumors are like little endocrine organs," she says, describing how the growth factors they secrete work both locally and at distant sites to prepare for metastasis. In the process, cancer can so weaken the skeleton that merely rolling over in a hospital bed can induce a hip fracture, as with a San Antonio man whose case inspired her inquiry into the field. In addition to pursuing research and clinical care for people with bone metastasis, Guise investigates and treats osteoporosis precipitated by the hormone-blocking drugs used to fight breast and prostate cancer.

These days, the sustained pounding of the marathon circuit doesn't suit Guise's joints; she runs fewer than 15 miles a week. Instead, she cycles, practices yoga, and combines underwater photography with scuba diving.

She also trots the globe. This past December, Guise traveled to South Korea to lecture at Seoul National University and give two talks at the Korean National Osteoporosis Meeting. Earlier in 2009 she spoke at the Chinese Metastases Society Meeting in Beijing; at a research seminar at the University of Leuven, in Belgium; and on pathology grand rounds at the University of Queensland Centre for Clinical Research in Brisbane, Australia. "She's invited to every meeting in the world," says Roodman, who credits Guise with a capacity to inspire interest in the field among scientists with a wide array of expertise. "She's a champion of bone research."

Guise was elected to the American Society for Clinical Investigation in 2004, and in 2007 she was appointed to a two-year term as chair of the National Institutes of Health's Skeletal Biology Structure and Regeneration Study Section. Last fall, the University of Pittsburgh honored her by naming her a Legacy Laureate. Ultimately, says the physician-scientist, it is the synergy of bench and bedside that has proved most satisfying.

"There's long-term gratification when you do make discoveries that have clinical meaning," she says, noting that molecular discoveries she published in the '90s are currently being tested in clinical trials. "And in the clinic, there's a lot of reward and immediate gratification in taking care of patients." ■

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NOT JUST A DAY IN THE PARK

Pitt's annual Science festival would soon be upon them, and Donna Beer Stolz, associate director of the University's Center for Biologic Imaging, and her team wanted to once again wow the crowds. They had in previous years supplied the festival with eye candy like *The Periodic Table of Electron Microscopy* (see our Spring 2009 issue). For fall 2009, they decided to bring new life to old art, creating mosaic replicas of paintings of the masters.

Using the free program Andrea Mosaic, Stolz and her crew drew from the millions of biologic images they had on hand to build their own masterpieces. In Stolz and Co.'s version, the woman's bustle in Seurat's *Sunday Afternoon on the Island of La Grande Jatte* (shown here), for example, includes images of a trachea (hematoxylin and eosin stain), and a dust mite (scanning electron microscopy), and fat tissue (fluorescence).

You can access a gallery of the works on our Web site (pittmed.health.pitt.edu). Don't miss the Center's take on Wood's *American Gothic* (oddly, scans of mistakenly delivered boxes of breast implants ended up in Pa's shirt) and, of course, Coolidge's timeless *Dogs Playing Poker*. —*Erica Lloyd*

IMAGE COURTESY CENTER FOR BIOLOGIC IMAGING

CALENDAR

OF SPECIAL INTEREST TO ALUMNI AND FRIENDS

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

FISHER LECTURE
FEBRUARY 24
3:30 p.m.
Lecture Room 6, Scaife Hall
Max S. Wicha, MD, Speaker
For information:
www.surgery.upmc.edu

HEALTH SCIENCES ALUMNI RECEPTION
MARCH 8
New York, N.Y.
For information:
Pat Carver
412-647-5307
cpat@pitt.edu

HEALTH SCIENCES ALUMNI RECEPTION
MARCH 31
South Hills Country Club
Pittsburgh
For information:
Pat Carver
412-647-5307
cpat@pitt.edu

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

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

PITT MED GOLF OUTING
APRIL 24
8:30 a.m.
Quicksilver Golf Club
Midway, Pa.
For information:
prodromo.john@medstudent.pitt.edu

SIMMONS RESEARCH DAY
MAY 12
8 a.m.–1 p.m.
University Club
For information:
www.surgery.upmc.edu

MEDICAL ALUMNI WEEKEND 2010
MAY 21–24
Reunion Classes:

2000	1995
1990	1985
1980	1975
1970	1965
1960	1955
1950	

SENIOR CLASS LUNCHEON
MAY 21
11 a.m.
Soldiers & Sailors
Memorial Hall & Museum

ALUMNI WEEKEND WELCOMING RECEPTION
MAY 21
5:30 p.m.
Alumni Hall, Connolly Ballroom

SCOPE AND SCALPEL'S "MALPRACTICE IN BLUNDERLAND"
MAY 21
7 p.m.
MAY 23
2 p.m.
Hillman Center for Performing Arts
Shady Side Academy
For information:
www.scopeandscalpel.org

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

REUNION GALA
MAY 22
6 p.m.
LeMont Restaurant

CLASS OF 2010 COMMENCEMENT
MAY 24
10 a.m.
Carnegie Music Hall

UPCOMING HEALTH SCIENCES ALUMNI RECEPTIONS
Boston, Mass.
Other cities, TBA
For information:
Pat Carver
412-647-5307
cpat@pitt.edu

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MARTHA RIAL

THE VIEW FROM HERE

When you were in med school, you probably tried to peer into your future. Would you become an internist, a cardiologist, a pediatrician? Would you work in a big-city practice? A rural town? A major university medical center? Join us this May 21–24 to reflect on your past and all the effort that got you to where you are today.

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

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

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