UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | SPRING 2012

PITTMED



WHY IT HURTS

THE BIOLOGY OF CHRONIC PAIN

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2012 AAMC Robert G. Fenley Writing Award
Award of Excellence, Basic Science
(E. Vitone, "Mars and Venus Revisited")

2011 CASE, District II
Gold, Covers
("None of My Memories Are My Own," design by E. Cerri)

2011 CASE, District II
Silver, Staff Writing

2011 IABC Golden Triangle
Award of Excellence, Feature Writing
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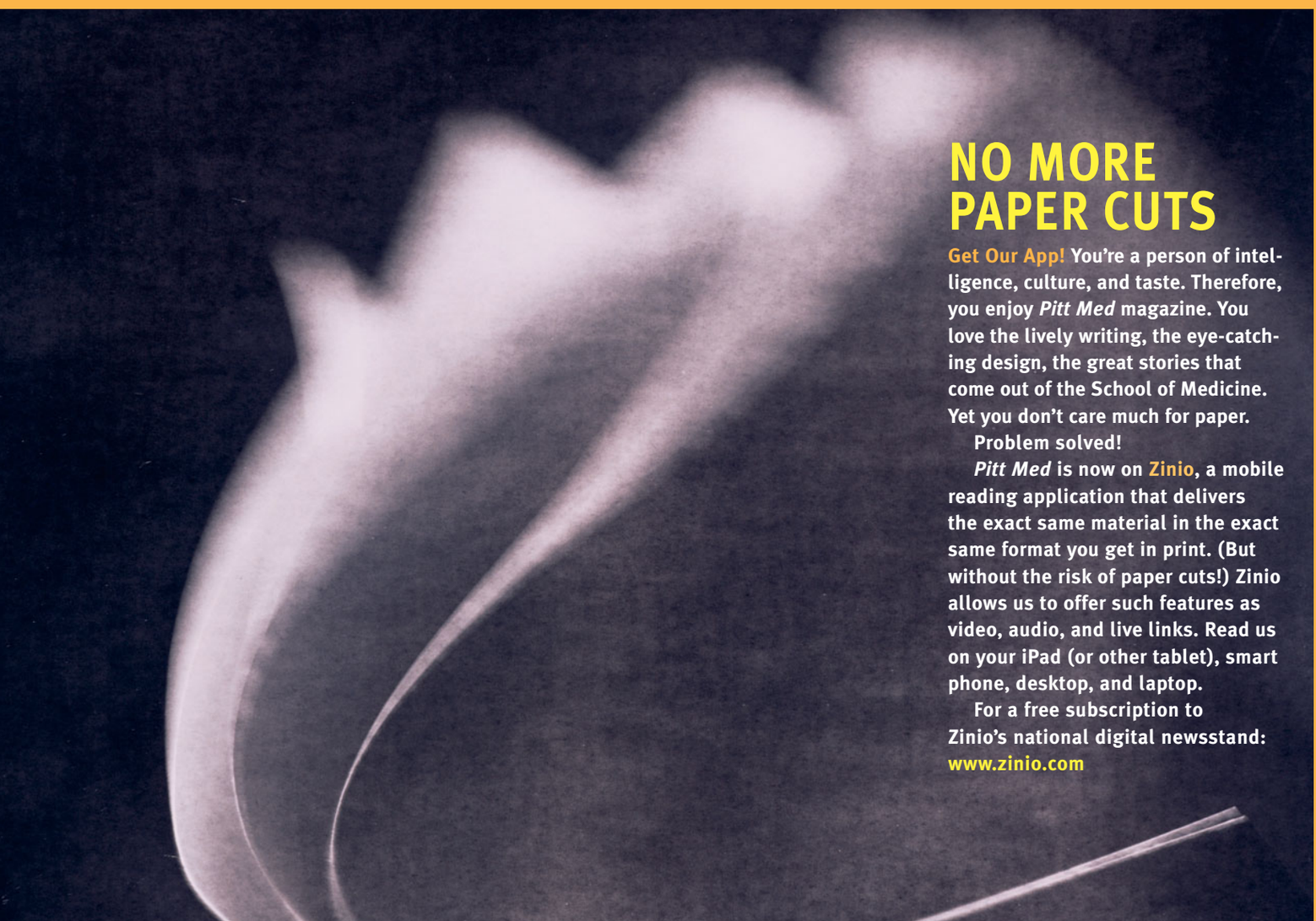
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PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, SPRING 2012

VOL. 14, ISSUE 1



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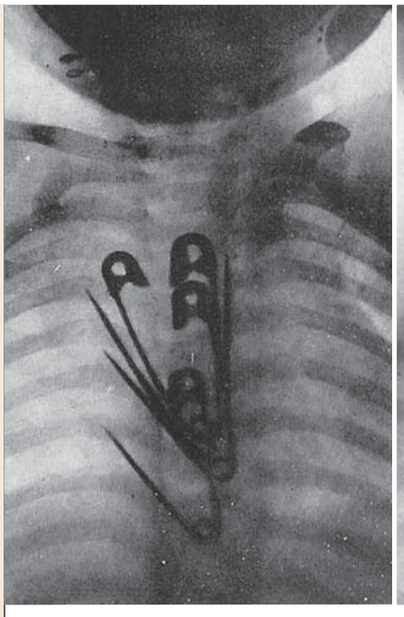


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People with schizophrenia struggle profoundly with certain cognitive tasks. David Lewis thinks that understanding related brain processes is the road to promising new treatments.

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Chronic pain: Why is it so implacable and unyielding? Pitt investigators are finding their way to answers and, with that, perhaps to a brighter future for millions.

COVER STORY BY JOE MIKSCH

The Evangelist of Bronchoscopy 26

Chevalier Jackson was appointed head of laryngology at Pitt in 1900, then went on to other medical schools to spread "the gospel of safe bronchoscopy." The astonishing doctor removed safety pins, keys, and coins from his often very young patients, holding onto 2,000 such objects as keepsakes.

FOREWORD BY CHUCK STARESINIC
STORY BY AMANDA SCHAFFER

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TIM GROEN ["Cover and "It's Not Just in Your Head"] gets his artistic sense from '70s magazines. As a kid in the Netherlands, he pored over periodicals about antiques, pop culture, and fashion. Over time, "I became aware of the aesthetics and design history involved," says Groen, who now works as an illustrator and art director in New York City and Amsterdam. He's had work published in *Interview*, *The New York Times Magazine*, and *Marie Claire*, among others. For *Pitt Med*, Groen used his signature style—which he says is "a little bit psychedelic"—to capture pain in a serious and broadly relatable way.

JUSTIN HOPPER ["Good, Old-Fashioned Interventions" and other stories] was music editor for the *Pittsburgh City Paper*. Then he began covering contemporary art, science, and the intersection of the two for the weekly. Today he labors on *Public Record*, a multimedia art project involving poetry based on 19th-century Pittsburgh crime reports. And for this issue of *Pitt Med*, he wrote about Temple Grandin and evolutionary biology. Of this new endeavor, Hopper says, "Scientific research is so inseparable from everything we do in the 21st century yet is often portrayed as beyond the ken of many people. And that's just not true—if you tell the stories the right way."

COVER

With new understanding of biology, including the pain genome, Pitt researchers are imagining a world without chronic pain. (Illustration: Tim Groen, © 2012.)

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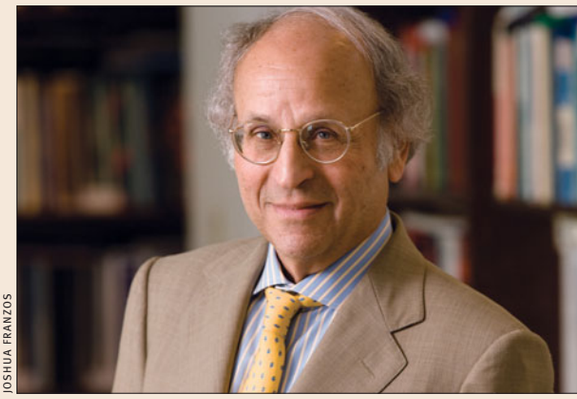
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The theorist's world is a world of the best people and the worst of possible results.
—Ted Taylor, American physicist


JOSHUA FRANZOS

Recently, the world heard that Dutch researchers had mutated the bird flu virus, H5N1, so that lab ferrets became sickened as the virus traveled through the air. (Ferrets are considered a good model for influenza infections in humans.) The public health, science, and government issues this raised were profound. H5N1 had not been transmitted through the air between mammals before; but when humans did contract it by handling infected birds, more than half of those known to have become infected had died. A swirling controversy has ensued about whether these studies should be published. Our own D.A. Henderson has been featured in the press on the subject. (See p. 4.) And now adding to the confusion, the Dutch researcher who led the study has stated that the mutated virus was not as virulent nor as contagious as those first reports suggested.

The issue illustrates how complex science can be, technically, logistically, and ethically. Of course there is good to come from understanding the nature of H5N1. It could help us to prepare for a naturally occurring mutation and to develop effective vaccines and antivirals for this and related viruses. The reconstruction of the extinct 1918 influenza strain in 2005 was a similar case. That synthesis helped scientists understand which genes conferred heightened transmissibility of the virus in ferrets. It allowed researchers to begin to design novel agents to better prepare for future pandemics.

But many observers raised similar concerns then: What if someone with access to the virus or the information used to synthesize or mutate it were to develop it into a weapon? What if the new virus accidentally leaked out of the lab? The original 1918 influenza, one of the most virulent pathogens in human history, killed up to 50 million worldwide.

Ted Taylor, quoted above about "the worst of possible results," designed small atomic weapons during the Cold War. Looking back on his career, he said his belief in deterrent nuclear military postures had eroded to zero. "I thought I was contributing to a permanent state of peace. I no longer feel that way. I wish I hadn't done it."

The H5N1 case is highly nuanced. How virulent would the mutation be in humans? Who should have access to the information gleaned from these studies? What other precautions should be taken? And who decides? A recent *New York Times* editorial pointed out that the first international group charged with determining how to proceed was full of stakeholders (those interested in quickly publishing the results and the researchers who created the virus, among others). Decisions about the uses of science should be weighed carefully by independent, informed, and wise observers. Knowledge confers great power and responsibility.

This H5N1 mutation study reminds us that science and its fruits (nuclear technology, genetically modified food, antibiotics ...) can reap consequences that are unintentional. Moreover, science *qua* science is neither good nor evil, but its uses can be either. (For instance, mustard gas was used as a weapon in WWI; later, scientists noting its inhibition of cell division developed nitrogen mustard as a very successful cancer chemotherapy.)

These notions are at least as old as the myth of Pandora.

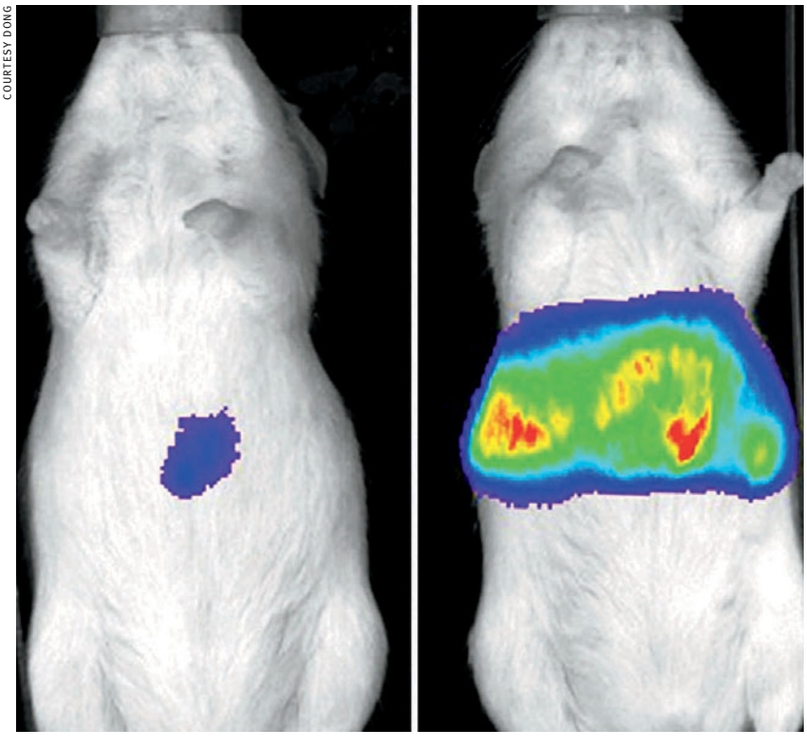
Arthur S. Levine, MD
Senior Vice Chancellor for the Health Sciences
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Devoted to noteworthy happenings

at the medical school

COURTESY DONG



The mouse on the right, genetically engineered for elevated FOXo6 activity, shows higher glucose production compared to a control rodent.

FOOTNOTE

A medical school seeking reaccreditation from the Liaison Committee on Medical Education is judged by more than 100 criteria every eight years. Pitt med did so well in 2011 that the school's John Mahoney, an MD and associate dean for medical education, and Chenits Pettigrew, PhD assistant dean of student affairs and director of diversity programs, were invited to tell the story of the school's success at the Association of American Medical Colleges' annual meeting in Denver.

DIABETES: TARGET ACQUIRED

When you think type 2 diabetes, you probably think of the insulin-producing pancreas. But the liver, it turns out, offers another target for fighting the common disease. New research at Pitt's School of Medicine shows that a protein called forkhead box o6 (FOXo6) plays a vital role in the management of the liver's production of glucose, which, in excess, causes diabetes.

In a healthy body, the liver stores blood sugar as glucose, releasing it during sleep and other periods of fasting to keep glucose levels within a normal range. In diabetes, though, the liver continues to pump out glucose even when insulin is provided as a treatment to manage high glucose levels.

"In type 2 diabetes, this [FOXo6] pathway is broken," says H. Henry Dong, PhD associate professor of pediatrics and a researcher on the project. "Insulin doesn't check the liver, so it continually pumps out glucose."

Dong and his colleagues discovered that when mice with excessive amounts of FOXo6 had those levels suppressed, glucose production returned to normal.

"There's never been a single target in the liver" to control glucose production, Dong says. "We've said that FOXo6 is the pathway controlling glucose in the liver. And if you can suppress that, you can win the battle against diabetes." At least you can in mice. —*Justin Hopper*



CAMI MESA

A&Q

D.A. Henderson: When Not to Publish

Dutch researchers announced last year they had effectively eased the transmission of the H5N1 virus, the cause of what's called bird flu. This winter, news organizations reported that investigators at Erasmus Medical Center had created a strain of the virus that passed through the air from ferret to ferret in a lab. Fear that the mutant virus could escape from a lab or be transformed into a weapon has led to a debate over safety and censorship. The leader of the Dutch team, however, recently said that the altered virus is not as contagious or virulent as first reported. Others contend that the mutant virus may be more easily transmissible and life threatening in humans, as compared to ferrets. As we went to press, federal and international panels were still weighing the merits and risks of publishing the results in whole or modified form. Coming out on the side of suppression and caution is D.A. Henderson, a Distinguished Scholar at UPMC's Center for Biosecurity and professor of public health and medicine at Pitt and Johns Hopkins University, who led the smallpox eradication effort for WHO. Henderson's views and those of others are featured in the Feb. 17 issue of *Science*.

Why an airborne H5N1 could be be hard to stop

Based on our considerable experience with new pandemic strains of influenza, the virus spreads so rapidly that no efforts to date have yet succeeded in stopping it. Closing of schools, screening of incoming passengers from infected areas, quarantining of patients have all failed, however rigid the measures.

On the merits of the discussion

The outcome of the controversy is that a great many scientists and administrators now appreciate more fully that a mutant H5N1 virus capable of killing some 50 percent of its victims and with a capability of pandemic spread [if airborne] would be the most dangerous biological agent ever known.

On containing scientific knowledge

We've already undergone the process of confining smallpox to two laboratories, and the scientists there can only perform protocols that have gotten international approval. It has been followed very effectively.

His question for us

How comfortable would you be to work with H5N1 in your laboratory? —*Interview by Nick Keppler*

Faculty Snapshots

The Institute of Medicine has awarded Ellen Frank the 2011 Rhoda and Bernard Sarnat International Prize in Mental Health. She shares the prize with William Bunney of the University of California, Irvine. Frank is a Pitt Distinguished Professor of Psychiatry. Among her contributions to the field is her discovery that patients prescribed lower doses of antidepressant drugs after their depression subsides are prone to relapse. Full-dose therapy, thanks to her work, is now standard practice even after depression symptoms are alleviated.



Frank

Pitt's Etienne Sibille is helping to unravel the intricacies of the biological basis of major depression. Sibille, Pitt associate professor of psychiatry and principal investigator in Pitt's Center for Neuroscience and a member of Pitt and Carnegie Mellon University's Center for the Neural Basis of Cognition, has demonstrated that when genes responsible for the maintenance of neurons and for spurring the production of a neurotransmitter called GABA don't do the job well, major depression can result. Neuroscientists had suspected this to be the case, but Sibille and his team were the first to pin down the genetic culprits.



Sibille

President Kareem Abu-Elmagd has a nice ring to it. Abu-Elmagd, an MD/PhD professor of surgery in Pitt's School of Medicine, recently assumed the presidency of the Intestinal Transplant Association. Abu-Elmagd helped develop surgical techniques and postsurgical management methods that have increased the success rate of intestinal transplant. He also had a significant role, with Thomas Starzl and others at Pitt, in studying the efficacy of using the drug FK506 (tacrolimus) for immunosuppression.



Abu-Elmagd

Short bowel syndrome, in which the body is unable to absorb food after a significant loss of functioning intestine, can cause death in a variety of ways. David Hackam, an MD/PhD Pitt professor of surgery and of cell biology and physiology, is working to help those with the disorder by developing an artificial intestine. His project, undertaken in collaboration with John March of Cornell University, got a boost, to the tune of $543,000 over three years, thanks to a Hartwell Biomedical Research Collaboration Award. —*Joe Miksch*



Hackam



CATHERINE LAZURE

Worms in Space!

N. Armstrong, B. Aldrin, *C. elegans*. Second-year Pitt Medical Scientist Training Program student Elizabeth Oczypok helped send 4,000 *C. elegans* worms—millimeter-long, 959-cell nematodes—to the International Space Station in 2007 in an attempt to understand how the microgravity and radiation that are part of long-term space travel affect organisms.

A 2010 Pitt University Honors College graduate with a Bachelor of Science degree in molecular biology, Oczypok became part of the project when she earned a position working with Nate Szewczyk in the Pitt lab of Lew Jacobson. Szewczyk, who was then a research assistant professor, is now an associate professor of medicine and health sciences in the University of Nottingham School of Graduate Entry Medicine and Health in England; he earned his PhD in molecular, cellular, and developmental biology at Pitt in 2002.

The results of the six-month, 12-generations-of-worms study, published in the UK's *Journal of The Royal Society Interface* showed that the nematodes fared quite well. Being that *C. elegans* shares many of its 20,000 genes with humans, indications are that we might be able to fly to Mars or hang out on the Moon for a while without our bodies falling apart. —*JM*

COLD COMFORT

The *New England Journal of Medicine* pegs the survival rate of cardiac arrest patients who have been given CPR at 18 percent. Samuel Tisherman says he finds this figure "disheartening." He and colleagues are planning a clinical trial that uses extreme hypothermia to try to buy more time for cardiac patients. Tisherman, professor of critical care medicine and of surgery and associate director of the Safar Center for Resuscitation Research at the University of Pittsburgh, sees the trial of EPR-CAT (Emergency Prevention and Resuscitation for Cardiac Arrest from Trauma) as a potential lifesaver. At its normal temperature, the body cannot tolerate a lack of blood flow for long periods of time. Earlier studies suggest that a cold body temperature successfully slows bleeding and reduces a body's dependence on oxygen.

Here's the tricky part: How do you get consent for a study from someone who has just been rushed to the hospital and is unconscious? The clock is ticking, and no family members have arrived yet to agree to an experimental treatment.

Pitt's Institutional Review Board, which helps protect rights of study subjects, has given the clinical trial the go-ahead, with the caveat that the doctors "actively participate in community consultation." So in November 2011, the team kicked off a campaign to educate the public about the hypothermia trial. The trial organizers created bus posters, an informational Web site, and a YouTube video detailing the procedure. In December 2011, Tisherman appeared at two town-hall meetings to address issues and possible complications with the trial. UPMC posted videos from these meetings on its Web site. And most recently, Tisherman visited the Center for Health Equity to discuss details of the study.

Tisherman expects the trial to begin this spring.

—Shermi Sivaji

FOOTNOTE

Doing science is both an end unto itself and a possible starting point for new treatments, new technology, and big business. Since Pitt's Office of Technology Management was established in 1996, the University's researchers have launched 80 start-up companies. (And in 2011 alone, Pitt licensed 105 technologies to industry, claimed 37 U.S. patents, and filed 257 new invention disclosures.)



JIM JUDKIS

MOVIN' ON UP

The people who might take the guilt out of eating salami (nitrates may actually be good for you in some respects, but sorry, the fat still isn't) are moving up. Such findings are the kind of meaty results we have come to expect from members of the Vascular Medicine Institute, who worked with faculty from the Department of Pharmacology and Chemical Biology on the nitrate studies. And now they can keep mixing things up in their new digs, including the Collaboration Room, shown left. In October 2011, the Institute relocated from its temporary home on the third floor of the Thomas E. Starzl Biomedical Science Tower to the 12th. Fifteen million dollars, in the form of a National Institutes of Health grant, refurbished 44,530 square feet of lab space.

The Institute seeks to find new therapies for pulmonary hypertension, sickle cell vasculopathy, atherosclerosis, hypertension, and heart disease. The highly functional new space, says Institute director Mark Gladwin, an MD, will make achieving these complex goals a bit easier. "The new open layout and glass construction will encourage interaction and collaboration," he says. *—SS*

IOM Picks from Pitt

The Institute of Medicine of the National Academies (IOM) has recently grown stronger with the election of four new members with ties to Pitt's School of Medicine: Nancy Davidson, Jeannette South-Paul (MD '79), Jonathan Gitlin (MD '78), and Paul Offit (Res '80). One of the highest honors in the field of health, election to the IOM requires contributing to studies that help guide health-related decisions made in government and the private sector.

Renowned for her research on the role of hormones on gene expression and breast cancer cell growth, Davidson, an MD, came to Pitt from Johns Hopkins University in 2009 to serve as professor of medicine, Hillman Professor of Oncology, associate vice chancellor for cancer research, and director of the University of Pittsburgh Cancer Institute and UPMC Cancer Centers.

South-Paul studies maternal and child health while staying actively engaged in her family practice. After receiving her Pitt MD, she spent more than 20 years as a family physician with the U.S. Army before returning to the School of Medicine, where she is the Andrew W. Mathieson Professor and chair of the Department of Family Medicine.

Gitlin, senior scientist at the Marine Biological Laboratory in Woods Hole, Mass., earned his MD at Pitt and now serves on the medical school's Board of Visitors. His work includes the exploration of Menkes syndrome, a fatal disease caused by a defective gene that regulates copper metabolism.

Offit's residency at Children's Hospital of Pittsburgh of UPMC helped to launch a successful career in virology and immunology that led to his current position as chief of the Division of Infectious Diseases and director of the Vaccine Education Center at Children's Hospital of Philadelphia.

Current IOM members selected the new crop based on professional achievement and ability to assist in future IOM research for the advancement of public health. *—Tiffani Emig*



THE LEAKS OF LIFE

In the study of evolution, there are few questions as immense as the origins of life's spectacular diversity. In the microscopic peculiarities of a tiny fly, Mark Rebeiz, a PhD assistant professor in the Department of Biological Sciences at the University of Pittsburgh and faculty member in the computational biology PhD program run by Pitt's School of Medicine and Carnegie Mellon University, may have found an important new clue to this mystery.

The mystery started to unravel as Rebeiz wondered how genes evolve new ways to be expressed.

"One of the big ideas that came out of the human genome [sequencing project] is that it's not new genes that made something as complex as us, but the rearrangement of existing genes," says Rebeiz.

In 2011, Rebeiz began peering into the developmental mechanisms of fruit fly vision. Studying relatively recent evolutionary developments in the fly's optic lobe, Rebeiz realized that sometimes the DNA's transcriptional switches—stretches of DNA that activate genes—which are meant to trigger a gene in one location on the body, can "leak," causing activation elsewhere.

"The evolution of development is all about these switches. Once one starts to leak, an old switch is modified to generate a second expression pattern," says Rebeiz, who was awarded a 2011 Alfred P. Sloan Foundation Fellowship.

What he'd really like to understand now, Rebeiz says, is how whole networks consisting of multiple switches evolve to generate complex animals.

"Science is all about finding the biggest unanswered questions you can sink your teeth into. It makes it a joy to come into the lab every day."

—Justin Hopper

—Photo by David Scharf/Photo Researchers

Explorations and revelations taking place in the medical school



For the first time in seven years, Tim Hemmes touches his girlfriend's hand; to do so, Hemmes uses a robotic arm he controls with his thoughts.

MEANINGFUL MOVEMENT

BRAIN INJURY PATIENT ABLE TO MOVE ROBOTIC ARM WITH THOUGHTS

BY ANITA SRIKAMESWARAN

Like a bashful but determined suitor, 30-year-old Tim Hemmes cautiously maneuvered an unsure hand toward his girlfriend. As their palms touched, tears spilled over onto Katie Schaffer's cheeks, while Hemmes' shined with joy and hope.

The moment was a reminder to the researchers and physicians watching the unfolding drama of why they had been working so hard for so long. Since a motorcycle accident snapped his neck seven years ago, Hemmes hasn't been able to move his body below his shoulders, nor has he had feeling there. Using technology and fundamental understanding of neurobiology advanced by researchers in the University of Pittsburgh School of Medicine, Hemmes guided with his thoughts a robotic arm made by Johns Hopkins University's Applied Physics Laboratory, managing a high five that was a profound illustration of the emotional power, often taken for granted, of touching a loved one.

"We're not just trying to generate movement," says Pitt's Andrew Schwartz, a PhD professor of neurobiology whose experiments in monkeys helped inform the algorithms that were used in this trial of brain-computer interfaces in patients with spinal cord injury.

The ultimate goal is to develop a device that gives paralyzed people the ability to make purposeful movements. The Pitt researchers imagine it would help immobile people perform activities of daily living—like handling a cup and fork or opening doors—and express themselves through gesture—perhaps a welcoming handshake, a jubilant high five, or a tender hug.

Schwartz's monkeys learned to manipulate a robotic arm while their arms were restrained. The monkeys came to see the mechanical arm as their own, licking remaining bits of marshmallow from the grabber after the test tasks were completed, using the grabber to nudge food around in the mouth, and even grooming the metal as they would their own fur.

Schwartz notes that when Hemmes reached out with the prosthetic arm, "you really did start to sense that, for instance, his girlfriend had taken this as an embodied hand of Tim's, and was actually feeling the extension of Tim's body scheme to that hand."

Michael Boninger, an MD professor and chair of Pitt's Department of Physical Medicine and Rehabilitation, describes a brain-computer interface as a device that taps into thoughts so they can be translated into action. The grid being used in the trial grew out of electrocortigraphy (ECoG), a technique in which electrodes are placed directly on the brain to study brain signals (often to help doctors pinpoint cortical areas in the brain that set off seizures). The grid sits on the surface of the brain, gathering neuronal signals from the motor cortex mapped to where Hemmes imagined and observed arm movement. In a Pitt pilot study led by Elizabeth Tyler-Kabara, an MD/PhD assistant professor of neurological surgery, and Wei Wang, MD/PhD assistant professor of physical medicine and rehabilitation, epilepsy patients admitted for seizure-mapping tested the grid. In that study, volunteer patients raised their eyebrows, flexed their elbows, or made other specific movements to send signals through the grid to a computer processor, enabling them to move a cursor on a computer screen or take Super Mario through an adventure. The results of this pilot project paved the way for techniques in patients with spinal cord injury.

Hemmes, the high-fiving patient, was first charged with the task of moving one ball to touch another on a computer screen. Soon, his commitment to the project and his own desire to best his previous "score" had him quickly progressing from two-dimensional movements of up-down and right-left to moving the ball "in and out" on a 3D TV screen. He worked with the arm only a few times during the 28-day study protocol. The high five with Schaffer happened after he'd done the same thing with lead researcher Wang—in part, to celebrate the end of nearly daily data collection.

"When you plan an experiment, you always picture it," Boninger said. "What you can't picture really is the human factor. Seeing [Hemmes'] face light up as well as those of the amazing team of investigators that were working with him was quite a spectacular sight."

This year, more participants will be enrolled in the ECoG-based protocol. In tandem, the team will start a yearlong trial to test another kind of brain-computer interface, a 10-by-10 microelectrode array that barely penetrates the brain to pick up signals from hundreds of neurons in the motor cortex; it's the same type of interface that Schwartz has been using in the monkey experiments. Tyler-Kabara will implant two grids in each participant: one in the area mapped for arm movement and the other for the hand. The higher-signal resolution could allow greater control of the arm, including the fingers, and a full exploration of its potential.

Then, they hope to make the device wireless and add sensors to the arm to deliver signals to the brain and recreate sensation.

Hemmes' achievement has validated conclusions reached after 20 years of studying neural signaling and motion, Schwartz says. And, he notes, now hundreds of people are working toward moving the technology forward from what his small group started.

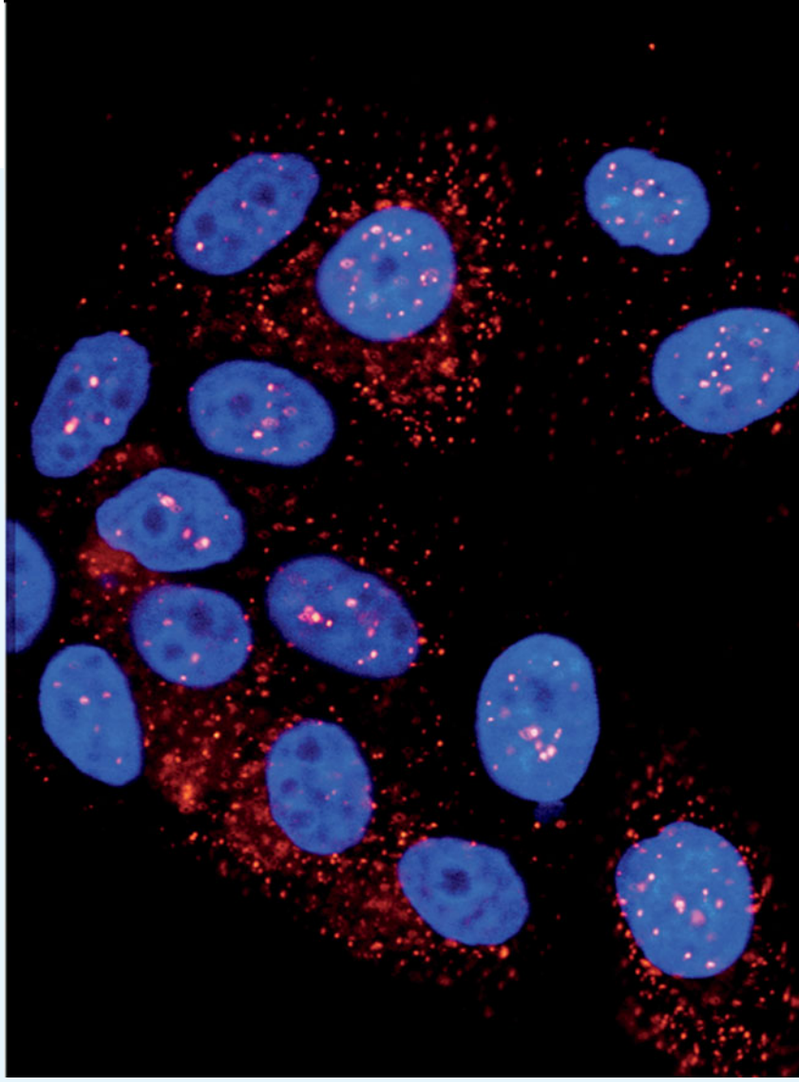
"That's really satisfying," Schwartz adds. ■

ILLUSTRATION: JESSE LENZ (BASED ON PHOTO COURTESY UPMC NEWS BUREAU)

RUNNING A MUC1

ANOTHER REASON TO DETECT CANCER SOONER

BY DANA YATES



The protein MUC1 helps cancer spread. Here, MUC1 within cellular nuclei (magenta dots in the blue) and surrounding the nuclei (red dots) in breast cancer cells.

Within healthy cells, the protein MUC1 (pronounced "muck one") is normally found in low levels, and that's all well and good. But in the cells of adenocarcinomas—epithelial cancers, which include breast, colon, and prostate cancers—MUC1 is found in higher amounts, and its presence has been known to aid the spread of tumors. How and why exactly MUC1 mucks things up, however, has never been clear.

Sandra Cascio, a native of Italy, is a postdoctoral associate who has received a fellowship from the Ri.MED Foundation—a partnership between the Italian government, the Presidency of the Region of Sicily, the Italian National Research Council, the University of Pittsburgh, and UPMC—to conduct biomedical research in Pitt's Department of Immunology. In her work here at Pitt, Cascio may have figured out the mechanisms that send MUC1 running amok, and her paper on the topic was published—without revision—in the December 2011 issue of the *Journal of Biological Chemistry*. The paper was coauthored by Pitt visiting scholar Lixin Zhang and the chair of Pitt's Department of Immunology, Distinguished Professor Olivera Finn, Cascio's mentor. It was selected by Faculty of 1000, a global panel of more than 10,000 expert scientists and clinical researchers, as among the top 2 percent of published articles in the fields of biology and medicine.

"Some inflammatory cells within tumors act to kill [the tumor] while others help it to grow," says Cascio. "One molecule can make a difference."

The molecule the team zeroed in on is a cytokine. In normal cells, cytokines are produced to signal the immune system to fight bacteria, viruses, allergens, and toxins in the body. In response, the immune system battles those harmful agents with inflammation. Within cancer cells, however, there are far more cytokines, and their upsurge promotes inflammation throughout the body—a circumstance that enables the cancer to spread even faster.

The researchers knew that a specific cell-communication pathway known as nuclear factor-κB p65 played a critical role in inflammation. And by using human breast cancer cells that contained abnormal MUC1 proteins, the Pitt team made an important discovery: The MUC1 protein connected with the nuclear factor-κB p65 pathway. Together, the two formed a new and special unit—one that controls cytokine production.

The team also explored the genetic material that repeats itself in the MUC1 protein. This replicated material, known as tandem repeats, varies in number among individuals. The number of tandem repeats makes no difference in normal cells, but the researchers wondered whether the same was true in cancer cells.

The team developed two MUC1 proteins—one with two tandem repeats and another with 22—and then inserted them into mouse lymphoma cells and human melanoma cells that otherwise lacked any MUC1 protein.

The goal: to determine whether the amount of cytokine produced varied according to the number of tandem repeats.

The researchers discovered that the MUC1 protein with the higher number of tandem repeats stimulated the production of more cytokines. This finding implied that tandem repeats in the MUC1 protein are vital to the formation of the MUC1-p65 complex.

"It's best to nip cancer in the bud. Otherwise we have a harder time controlling its growth," says Finn. "Eighty percent of tumors come from carcinomas. So if all those cancers have the same molecule in common, we can figure out how to target that. And if we can interfere with the formation of the MUC1-p65 complex from the beginning, we can inhibit tumor growth." ■

A LIFE WELL LIVED

ADAPTIVE IMMUNE CELLS KEY TO HEALTHY GOLDEN YEARS | BY DANA YATES

GETTY IMAGES



A new understanding of the immune system of older adults.

COURTESY SANDRA CASCIO

The outward signs of healthy aging are easy to see. Consider, for example, an elderly person who is active, independent, and involved in the community. So what, then, is happening inside seniors who age well? At least part of the answer, according to researcher Abbe de Vallejo, is found within the immune system.

An associate professor in the University of Pittsburgh's Departments of Pediatrics and Immunology, de Vallejo is also a member of the Division of Pediatric Rheumatology at Children's Hospital of Pittsburgh of UPMC, the Cancer Immunology Program at the University of Pittsburgh Cancer Institute, and the Pitt-UPMC McGowan Institute for Regenerative Medicine. His research on the immunological side of exceptional aging, funded by the National Institutes of Health, was published in the October 2011 issue of the online journal *PLoS ONE*. The study also involved Anne Newman, professor and chair in the Department of Epidemiology in the University of Pittsburgh Graduate School of Public Health (GSPH) and director of Pitt's Center for Aging and Population Health, as well as others from GSPH and the School of Medicine.

Why would a scientist who is based at a children's hospital study the immunological profile of seniors? "Aging is part of development," says de Vallejo. "It's a process, not a series of stages. And what we learn from older people can help us better understand children."

That said, just as kids aren't miniature grown-ups, it's inaccurate to view seniors as "only defective versions of young or middle-age adults," he notes. There are key differences between the groups, including how their immune systems work.

Until age 50, for instance, the body regularly produces T-cells, the soldiers of the immune system that kill invaders. During the later years, however, the T-cells' ranks are depleted, forcing the body to make do with the limited number that are left. So what does the immune system do to compensate for the decreased supply? It adapts.

With age, T-cells start behaving like natural killer (NK) cells, another component of the immune system that typically attacks tumors and viruses. Normally, a T-cell is sent into battle only when its surface T-cell receptor is activated—or "tickled," as de Vallejo says. Although that trigger can also occur when a T-cell assumes an NK receptor, the Pitt researchers discovered a distinct pattern of T-cell activity among seniors with higher levels of physical and cognitive function compared to those with mild health impairment.

To start, the researchers gathered blood samples from 140 participants whose average age was 86; the research volunteers had been tracked for nearly two decades in the Cardiovascular Health Study (CHS). Funded by the National Heart, Lung, and Blood Institute, the CHS explored the risk factors for cardiovascular disease in adults 65 years or older.

The Pitt team collected additional details about the CHS participants' health, including their hospitalization and medical history. They also used quantitative tests to evaluate participants' physical and cognitive function.

The researchers found the cells of the higher-functioning participants had more stimulatory NK receptors on the surface of their T-cells. In addition, these elders had an ideal balance and quantity of cytokines, which mediate immune responses. Both features suggest an increased ability to fight illness. "[The results] show beneficial adaptation or remodeling in our immune system," says de Vallejo.

On the other hand, the group with mild health impairment had more inhibitory NK receptors and a less-than-ideal arrangement of cytokines. This situation could help disease take hold in the body.

De Vallejo hopes his research will contribute to a philosophical shift in medicine—from replacing deteriorating body parts (e.g., knees) to improving what remains (e.g., immune cells). It's an idea that will take on greater importance in the future. By 2050, in fact, the global population of people 60 or older is expected to reach nearly two billion, according to the United Nations.

"The versatility of T-cells is astounding," says de Vallejo. "We need to find ways to enhance what we have." ■


HE SEEMED TO
BE TRAPPED
IN A WORLD
HE DIDN'T LIKE

SCHIZOPHRENIA EMERGES OUT OF THE GRAVEYARD OF NEUROPATHOLOGISTS

BY KRISTEN COSBY

At the International Congress of Neuropathology in 1972, the famed neurologist Fred Plum summarized the pervading attitude towards schizophrenia in a now-infamous phrase: "Schizophrenia is the graveyard of neuropathologists." Plum thought that not only had nothing been learned about schizophrenia from the study of the brain, but that nothing could be learned. The human brain was still largely considered an unknowable organ. Plum's remark may seem counterintuitive from our current perspective—in the past two decades neuroscience has experienced a sort of renaissance. In vivo neuroimaging, neurophysiology, and postmortem neurochemical studies have allowed researchers to gather data on the activities of brain cells in normal and afflicted tissue as never before. What was once considered unknowable—the causes of human behavior, emotion, and motivation—now seems within our grasp. And the field of neuroscience is now a vast landscape, with seemingly endless possibilities for investigation.

David Lewis's approach to understanding and treating schizophrenia starts with the cognitive impairments associated with the disease.

ILLUSTRATION | NICOLE FICHERA

So where do you begin to try to understand schizophrenia? Historically, the study of schizophrenia has been problematic because of its evasive, heterogeneous nature. Different people contract the illness for different combinations of reasons (both genetic and environmental), and there is no diagnostic test for schizophrenia. Patients are diagnosed with the disease after the onset of the severest of symptoms: psychosis. In other words, treatment can only begin after the disease has significantly altered brain function.

Researchers eventually realized that the antipsychotic effects of chlorpromazine stemmed from its ability to block type 2 dopamine receptors.

Today, more than half a century after its introduction, psychiatrists still treat schizophrenia with derivatives of chlorpromazine.

But if the University of Pittsburgh's David Lewis—an MD, chair of Pitt's Department of Psychiatry, and UPMC Professor of Translational Neuroscience—is correct, the route to the next generation of therapies for schizophrenia will appear from looking elsewhere. Decades of research have convinced Lewis that we can identify and treat the disease better by understanding aspects of the disease you don't hear much about—people with schizophrenia struggle profoundly with working memory and certain other cognitive tasks. Patients with schizophrenia typically score 1 to 1.5 standard deviations below the mean on cognitive tests. They are likely to have trouble absorbing or manipulating the information needed to perform daily functions. Even something as basic as remembering and dialing a phone number is challenging when your working memory is impaired.

And unlike psychotic episodes, which can be treated, the cognitive impairments are considered permanent and constant.

Lewis has been hailed as one of the most innovative and creative contributors to the field of psychiatric illness by many of his peers, mentors, and even the director of the National Institute of Mental Health. Now a lot of people are watching to see how his approach unfolds. An alternative method of treatment based on Lewis's work is already in phase II trials.

"One of the things that really struck me about the cost of the illness for him was that although his hallucinations and delusions were suppressed with medication, he was still very impaired by his inability to engage in actions."

If a patient experiences delusions, hallucinations, and speech or cognitive impairments, has been ill for more than six months, and *cannot be diagnosed with any other condition*, a psychiatrist will give the diagnosis of schizophrenia. So the diagnosis is one of exclusion. It's uttered when nothing else can explain these symptoms.

In the early 1950s, a French pharmaceutical company developed and distributed chlorpromazine—the first effective treatment for schizophrenia and the first marketed (under the trademarked name Thorazine) antipsychotic—but its champions had no idea how the drug worked to reduce the effects of psychosis.



Lewis

In the past two decades, tissue studies have revealed a common neurochemical characteristic of schizophrenia: increased activity of the neurotransmitter dopamine at the basal ganglia (a group of interconnected nuclei near the upper brain stem and deep in the cerebral hemispheres that allow us to make voluntary body movements and to control speech and other social behaviors). The dopamine receptors control the neural signaling that influences important behaviors and certain kinds of memory.

When he was a psychiatry resident at the University of Iowa, Lewis encountered a number of patients who experienced hallucinations and delusions. His encounters with one young patient, an 18-year-old who suffered from schizophrenia, has remained with him.

"One of the things that really struck me about the cost of the illness for him was that although his hallucinations and delusions were suppressed with medication, he was still very impaired by his inability to engage in actions," Lewis recalls.

"There was this disconnection between his stated desires and his ability to make decisions, to take initiative, and to think through a course of actions that would be required to achieve his goals. My impression at the time was that he seemed to be trapped in a world that he didn't like, but unable to plan or take actions to get into a different world.

"That experience with him gave me an appreciation for the complexities and the burden of the illness." It also turned Lewis's attention to the study of psychotic disorders and how executive processes, like cognition and working memory, become disrupted.

Although schizophrenia is not diagnosed and, therefore, not treated until the onset of psychosis, many studies indicate the impairments in cognition are present much earlier in life—though not all people who demonstrate the cognitive challenges associated with the disorder are later diagnosed with it. According to Lewis, the opportunity to treat schizophrenia before the onset of psychosis lies in our ability to understand which neurocircuits malfunction in the brains of people with schizophrenia and in our ability to understand how healthy circuits and diseased circuits develop differently in adolescence. (To learn what Lewis and a number of researchers at Pitt are discovering about the effects of cannabis use during this vulnerable time, see p. 17.)

He is interested in the interactions of two kinds of cells in the dorsolateral prefrontal cortex, which is, not surprisingly, a region of the brain associated with cognition and working memory. The two types of neurons, pyramidal cells and chandelier cells, communicate using GABA neurotransmitters. (GABA is a molecule that determines when neurons are active and their level of activity.) The long, tree-like pyramidal cells span several layers of

the cortex. The chandelier cells talk only with pyramidal cells and powerfully control their activity. The pyramidal cells are responsible for much of the electrical signaling in the prefrontal cortex and are essential for cognition. Over the years, postmortem tissue studies (several of which Lewis's lab completed) have revealed that pyramidal cells in the brains of adults with schizophrenia are stunted. Lewis thinks that in adolescents likely to develop schizophrenia, the pyramidal cells and the chandelier cells fail to cultivate the kind of "relationship" necessary to create the strong, organized neural firing that produces healthy cognition. It's not clear whether this is caused by excessive synaptic pruning during adolescence or whether children born with a predisposition toward schizophrenia have fewer synapses to begin with.

The drug in a phase II clinical trial targets GABA transmissions from chandelier cells to pyramidal cells. The treatment has demonstrated an ability to improve synchronicity in the electrical activity of the prefrontal cortex and shown signs of improving working memory in patients with schizophrenia. Though the conceptualization of the precise role of chandelier cells in the circuitry of the prefrontal cortex has changed since the trials of the drug began two years ago, Lewis believes those cells remain a proper target for new drug therapies. "It turns out we think the drug should have the same beneficial effects, but perhaps for a different reason," says Lewis.

For Lewis, new information about synaptic activity that complicates a drug study is an advancement, not the source of a headache; it illuminates something new about the disease process. "The pursuit of drug development in psychiatry is rapidly changing because of our growing understanding of what's happening in the brain, in the illness, and how the brain normally functions," notes Lewis.

"This is an incredibly exciting time to be in psychiatry because of the advances that are being made in the basic sciences that are critical to our field," he adds. "We have the opportunity to consider novel linkages and relationships between different areas of investigation and with a level of resolution that is unprecedented."

Lewis's line of research into chandelier cells was featured in the Nov. 10, 2010, edition of *Nature*, which was well received by many of his colleagues. John Morrison, dean of basic sciences and the Graduate School of Biological Sciences at Mount Sinai, and a mentor of Lewis's during his days as a postdoc, says, "The therapy that's been used for schizophrenia for years has been dopamine based and that's … still useful in many ways, but I think [Lewis's] work will open up other therapeutic strategies for schizophrenia." These avenues could include both new drugs and cognitive behavioral therapies, which, Lewis speculates, might help strengthen and maintain healthy synaptic processes through, for instance, repetitive computer training.

Lewis is fond of sayings. His favorite was acquired from one of his mentors, Floyd Bloom, an MD, former editor-in-chief of *Science*, and former chair of the Department of Neuropharmacology at the Scripps Research Institute, who often asked his mentees, *Now that you know what you know, what do you know?*

Lewis uses this phrase so often that, three years ago, his graduate students gave him a bobblehead doll of himself with a voice recording that could be heard when a button on the doll is pressed. The recording is a chorus of his students repeating the line.

Now that you know what you know, what do you know? The question might seem redundant or simple, but Lewis's lab is all at once attempting to figure out schizophrenia's toll on cognition and working memory, as well as mapping the development of neurocircuitry in the prefrontal cortex during adolescence. And when you are taking on all that complexity, knowing what you know isn't always clear.

But the science is crystallizing. "When I entered the field of schizophrenia research," says Lewis, "there were lots of different opinions about the core clinical features of the illness and about the nature and location of the brain disturbances that resulted in those features. In the past two decades, the field has moved substantially to a more unified view of the core feature [cognitive deficits] and the underlying cortical circuits." Although less dramatic than delusions or hallucinations, cognitive deficits may provide avenues for earlier intervention.

When Lewis started his education as an undergraduate student of psychology and then a med student at Ohio State in the mid-70s, he intended to become a psychotherapist. But he was disappointed to find that practitioners working with patients suffering from psychiatric disorders concerned themselves primarily with theories of personality and human behavior rather than empirical studies of the brain.



WIKIPEDIA

Thorazine (aka, chlorpromazine) helped people with psychosis decades before anyone knew how the drug worked.

"The idea of using a solid empirical basis, a set of facts from experiments, using that to intervene therapeutically with someone, it just didn't exist then. Or at least I wasn't exposed to it," says Lewis, who also serves as director of both Pitt's Translational Neuroscience Program and of its NIMH Conte Research Center. He found that to be extremely problematic and limiting. He says, "I was disenchanted … People seemed to have abandoned a key principle of medicine, which is that you have to look at the organ that's diseased.

"You have to look at … the level at which it's organized, which, with the brain, is the circuits, the cells that form the circuits, the molecules that determine the functions of those cells. That kind of physiological basis wasn't there [when I was a student].

"That concept [of starting with the diseased organ] is not innovative at all. It just

hadn't been directly applied or completely applied to psychiatry," says Lewis.

After completing his internal medicine and psychiatry residencies at the University of Iowa, Lewis went on to (what's now called) the Scripps Research Institute as a visiting investigator in neuroscience and endocrinology. In December 1984, just after starting at Scripps, Lewis attended the annual meeting of the American College of Neuropsychopharmacology in San Juan, Puerto Rico. At the conference, he heard two talks. The first demonstrated, using the first positron emission tomography (PET) imaging studies, that the prefrontal cortex of individuals with schizophrenia was clearly disturbed when they were conducting a task that involved working memory. The second, given by the late Patricia Goldman-Rakic, a PhD, was on the essential role of dopamine in working memory function in nonhuman primate studies.

When Lewis returned to his hotel room the night after the second talk, his mind was abuzz. He sat at his hotel desk scrawling notes, synthesizing what he saw as two clearly related studies of working memory. "It was a real lightbulb moment. … This was the strategy that would help me understand … the normal circuitry that contributes to working memory and how that circuitry is disturbed in schizophrenia."

Ten years of meticulous research passed between his lightbulb moment at the conference in San Juan and the publication of his first integrated study of postmortem tissue of people with schizophrenia and nonhuman-primate tissue. In 1991, he published his first paper on chandelier cells in the nonhuman primate cortex, the same cell type that his lab targeted in its development of the drug now in clinical trials. In 1998, he published his first paper on how chandelier cells are altered during schizophrenia.

When Lewis's predecessor, David Kupfer, now Pitt's Thomas Detre Professor of Psychiatry and professor of neuroscience and of clinical and translational science, became chair of the Department of Psychiatry at Pitt in 1983, he set out to build an "academic powerhouse." He recalls, "We really wanted to recruit some young people who, while being psychiatrists with MDs or MD/PhDs, would bring an element of strong basic science so that we could figure out better interventions, better drugs, better ways of thinking about prognosis, better understanding of genetics of all these disorders."

Lewis was his first recruit. While attending a series of talks at Floyd Bloom's lab at Scripps, Kupfer encountered the young man and was immediately struck by his proficiency with tissue studies.

After listening to Lewis's lecture, a colleague of Kupfer's who had accompanied him to the lab, turned to him and said, "He's the one!" From that moment on, Kupfer conspired to bring Lewis to Pitt. "Sometimes you can identify a star before he becomes a star. We were lucky to get him. He's what you call a productive Midwesterner!" Kupfer says, laughing.

Morrison, who was Lewis's mentor at the time of Kupfer's visit, agrees. "Perhaps as much as anyone who's ever trained with me, David took that training [in neurochemistry] and expanded it beautifully into all the approaches that he now takes into understanding human neurologic and psychiatric disorders. Twenty-five years later, he is still one of the leading figures who is bouncing between what he can use from the nonhuman primate and the diseased human brain. What he's been able to do is to show precisely what is disrupted in schizophrenia," says Morrison, referring to Lewis's stubborn pursuit of chandelier and pyramidal cells.

In the past 25 years, Lewis has published more than 250 papers, 65 book chapters, and two books. In the process, he has amassed a number of awards and acknowledgments of his work, including being chosen as the president-elect of the American College of Neuropsychopharmacology and a member of the Institute of Medicine. He is the only investigator in the United States to have simultaneously held a Senior Scientist award, a MERIT award, and a Conte Center Directorship from the National Institute of Mental Health.

Now he has his own saying that his graduate students repeat: *When a disease process is at issue, the answer is in the tissue.*

Every year since 1987, Pitt's psychiatry program has garnered more National Institutes of Health funding than any other psychiatry program in the country. It certainly has become a research powerhouse. What attracted Lewis to Pitt in the first place, and continues to impress him, is the strength of the faculty's research and the amount of collaboration that occurs within the department and with other members of Pittsburgh's neuroscience community.

"I think we've contributed to changing the mind-set about the importance of looking at tissue from people with psychiatric illnesses, schizophrenia in particular. And I think we helped contribute to raising the bar on the standard of how the work was done," says Lewis, who assumed the position of department chair in 2009.

"I see my role as chair now to stimulate people to find linkages and the points of intersection across their different strategies and approaches. Ultimately we need to have a fundamental understanding of brain circuits and their dysfunction, but we have to take that knowledge all the way through to applications in the real world of clinical care. We can know a lot about the illness, but if we don't bring the capacity to bear in the real world where our patients live and under the challenges that they face in society, we won't have accomplished the goal.

"We're trying to move the field into preemptive interventions. This is particularly important in psychiatry because many of the targets we treat are pretty far along in the disease process. In a sense, the treatment of schizophrenia today is the heart-disease equivalent to treatment after a patient has had a myocardial infarction. What we desire to do is to push the field so we are making interventions before the disease has a major functional impact."

In the case of schizophrenia, treating patients earlier in the disease process would allow doctors to assist patients in salvaging more of the neurocircuits necessary for completing cognitive tasks and preserving working memory. With a greater variety of targeted drug and cognitive therapies, we can hope that patients will be able to lead happier, more productive lives—and not be trapped in worlds they don't like. ■



WHAT WERE WE TALKING ABOUT?

DOES ADOLESCENT USE OF MARIJUANA STUNT BRAIN DEVELOPMENT AND OPEN THE DOOR FOR PSYCHOSIS?

BY DAVID R. ELTZ

Let's say you're starting your first day as an intern at a software company. In 20 minutes your boss meets with the senior partner, and he's just finished polishing a product proposal that could earn the company millions … and put him in line for the division vice president position.

He e-mails the proposal to you, with directions to print 10 copies and staple and deliver them to his desk in five minutes.

ILLUSTRATION | NICOLE FICHERA

Excited, you send the document to the printer, jump from your chair, and rush to retrieve the printouts, running the instructions through your brain. Oh. And you've recently been diagnosed with schizophrenia and can't help but think you need this internship amid the daily struggle to keep your mind focused, away from your occasional debilitating delusions, hallucinations, and depression.

You take with you all your hope for a normal life and normal thoughts along with your boss' instructions. But when you grab the printouts from the tray, you suddenly freeze, thinking, *Now what was I supposed to do with these?* The rest of the instructions are gone, wiped from your brain.

What's happened to you, a failure of a brain process called working memory, is similar to what occurs when someone high on marijuana says, *Dude. What were we talking about?*

Your brain is an orchestra, with highly specialized subsections playing in tune, under the direction of a conductor delivering a central timing signal. In schizophrenia, and in people who smoke pot, the timing is "off." Specifically off: working memory, the core cognitive process that allows you to keep a limited amount of information in your head and follow a logical path—like a set of instructions—without having to, say, stop and wonder what you were supposed to do after printing a document.

Researchers have known for a while that people with schizophrenia and marijuana users share working memory impairments. But they've always measured those impairments after smokers and schizophrenia patients had already exhibited problems with working memory. So how did they get the impairments?

David Lewis, UPMC Endowed Professor of Translational Neuroscience and chair of Pitt's Department of Psychiatry, and colleagues aim to find out by testing the brains of adolescents before they start using marijuana.

They wonder: Does using marijuana early in adolescence cause some kids to eventually develop schizophrenia, the most common psychosis in the world? Did the kids who have impaired working memory have those problems before they started smoking marijuana? If marijuana is a catalyst, does it change something in the brain, or is the change an indirect consequence of something else?

"Maybe it's starting to use marijuana early, and then the kids get unmotivated," says Lewis. "They don't go to school. They don't engage in cognitively challenging activities. And the absence of practice means that their neural circuits don't develop properly."

In other words, if you don't use it, you might lose it, and then maybe your brain becomes susceptible to psychoses like schizophrenia.

When people smoke marijuana, their lungs quickly absorb the psychoactive chemical THC. Just as fast, THC infiltrates the bloodstream and races to the brain, attaching to cannabinoid receptors, throttling the regions of the brain that control sensory perception, motor control, pleasure, and memory.

They are high within minutes because their brains stop working the way they should.

During that high, marijuana disrupts neurotransmitter paths essential for memory and decision making. What results is uncoordinated and inaccurate brain activity, similar to what goes on in the brain of someone with schizophrenia.

The use of marijuana or other forms of cannabis has been linked with a significantly increased probability of developing schizophrenia in multiple studies. Many of the studies suggest the risk is higher when adolescents use marijuana while their brains are still developing, particularly before the age of 16. In the United States, about 6,000 people start smoking pot every day, or about 2.1 million every year. Most are under the age of 18.

Many researchers believe that using pot while the brain is still developing boosts levels of the chemical dopamine in the brain, which may directly lead to schizophrenia—although moderate amounts of the chemical are essential for brain health. Others believe that kids who smoke pot and harbor the variant of a gene called COMT are at risk for developing the disease.

Lewis has already discovered that one neurochemical system of the brain affected by pot, the endocannabinoid system, is altered in people with schizophrenia.

Studies have also found that people with schizophrenia are about twice as likely to smoke pot as those who don't have the disease. (In people with schizophrenia, cannabis can enhance mood while dulling hallucinations and delusions before eventually making these symptoms worse.) Meanwhile, those who smoke pot seem to be two or three times as likely to develop psychosis as people who don't.

In work funded by the National Institute on Drug Abuse, Lewis has already discovered that one neurochemical system of the brain affected by pot, the endocannabinoid system, is altered in people with schizophrenia. The change happens in the prefrontal cortex (the gray matter behind the forehead) and contributes to changes in the transmission of GABA, an important molecule that determines not only how active brain neurons are but also when they are active. If GABA production is disrupted, and either too much or too little is in your brain, the timing of your brain function is off.

"Lots of things don't work right," Lewis says. "And in the prefrontal cortex, if the timing is off, then abilities like cognitive control and working memory are disrupted."

That is, in the orchestra inside your brain, the horns play out of sync. The cellists come in too soon. The violins hold their notes too long. The orchestra dissolves into cacophony,

and the conductor, GABA, can't bring the musicians under control.

In animal studies, Lewis found that the cannabinoid 1 (CB1) receptor, the principal target of both THC in marijuana and the brain's own endocannabinoids, was present in lower amounts in mice that had less GAD67, the enzyme that makes GABA. Activation of CB1 receptors supresses GABA release. These findings suggest that the lower levels of CB1 receptors in schizophrenia were compensating for deficient GABA in the illness. This could mean that when people with schizophrenia smoke pot, they essentially flood the brain with THC, which binds to the CB1 receptor and robs the brain of this compensatory mechanism.

"This may explain why when people who have schizophrenia are hospitalized, they get better, they're discharged; then they start using marijuana, and they get worse," says Lewis.

Adolescence is a key period in which the brain undergoes extensive remodeling. Our neural networks receive an upgrade then that we continue to depend on throughout our lives. To try to determine whether marijuana short-circuits that network and leaves kids susceptible to psychoses like schizophrenia, Pitt researchers are studying kids at 12—before they start using marijuana—and again when they are 16. (In case you're wondering: No, the researchers won't be giving the kids pot. In fact, they're also embarking on a pilot project to reduce teenage marijuana use.)

For the study, currently funded by a tobacco settlement grant from the Commonwealth of Pennsylvania, Nancy Day, Pitt professor of psychiatry and epidemiology, is recruiting 100 kids. Day's earlier work found that adolescents born of women who smoked pot during pregnancy have problems with attention, impulsivity, depression, and school achievement. Based on previous research, she expects as many as 50 percent of the kids will start using marijuana during the new study.

Pitt researchers plan to follow the kids throughout four years, initially measuring baseline cognitive performance while they play spatial delayed-response games that require working memory, like trying to remember where a circle should be on a computer screen after seeing it disappear 30 seconds earlier.

While the kids perform the tasks, Beatriz Luna, Pitt professor of psychiatry and of psychology and director of the Laboratory for Neurocognitive Development at the Western Psychiatric Institute and Clinic, will measure brain function using functional MRI (fMRI). Luna, whose work explores the role an adolescent's developing frontal cortex plays in executing cognitive tasks, will take baseline neuroimaging snapshots of the kids' working memory.

Raymond Cho, Pitt assistant professor of psychiatry and of psychology, will use electroencephalography (EEG) to measure rhythmic brain waves called gamma oscillations, which are highly dependent on GABA, the brain's primary inhibitory neurotransmitter.

After four years, the kids are to perform the tasks again, during fMRI and EEG tests. And the researchers will look for changes between the earlier, baseline measurements and the second set of images that indicate slow and uneven development or disrupted brain waves.

"First we determine [how their working memory is] when they're young," says Luna. "Then, when they come back at an older age, some of them would have had exposure to cannabis, some would not, and then we can very nicely start to see if there has been a toll on working memory."

Lewis will mirror his colleagues' work with kids in a study of adolescent monkeys, some given intravenous THC daily. The monkeys will perform spatial delayed-response tasks similar to those undertaken by the kids while also having working memory measured by EEG.

Will the kids and young monkeys exposed to THC both develop deficiencies in working memory? If so, it will lend credence to the hypothesis that THC in pot disrupts adolescent development of orchestral neural circuits, leading to cognitive impairment. ■

WHAT YOU DON'T KNOW CAN HURT HIM

Peter Tosh urged, "Don't criticize it." And Black Sabbath sang of the "sweet leaf." Yet what might have once seemed like merely a playful indiscretion—toking up—may have debilitating repercussions in youth. Scientists at Pitt and elsewhere are investigating apparent links of cannabis use in teens with cognitive impairments, and even with schizophrenia.

So how does a parent or pediatrician intervene? Teenagers, by nature, are secretive when it comes to telling parents about experimenting with risky behaviors. And pediatricians don't have much time during an office visit to gauge the risk for marijuana use and intervene.

Duncan Clark, Pitt associate professor of psychiatry, hopes to change that. Clark is researching the best way to build an intervention program. He envisions teens and their parents, while in a doctor's waiting room, answering questions on a tablet computer about risk factors for later experimentation with pot. The software would immediately generate an assessment for the pediatrician before the teen walks into the examination room, so the doctor would know if the adolescent is likely to try smoking pot. Whether the adolescent is at risk—or probably already smokes marijuana—the doctor could take steps to help the child stop smoking pot. The pediatrician would also give parents pamphlets from the National Institute on Drug Abuse (www.drugabuse.gov/marijbroch/parents) that can help them talk to their son or daughter about the dangers of marijuana.

Clark says he'll be using focus groups in the next few years to develop the program. He has already tested similar software that assesses teenage alcohol use, which happens to be a risk factor for later smoking pot. *—DE*


MILD
THROBBING
RADIATING
INTENSE
EXCRUCIATING
NAGGING
MODERATE
HEAVY
SHARP
DULL
NUMB
TAUT
SORE

EVIDENCE SUGGESTS DOCTORS WILL ONE DAY BE ABLE TO END CHRONIC PAIN | BY JOE MIKSCH

IT'S NOT JUST IN YOUR HEAD

On Dec. 8, 2011, a Cleveland Browns defender rolls up on the leg of Pittsburgh Steelers quarterback Ben Roethlisberger. The weight of the assailant forces the quarterback's ankle to do things ankles shouldn't do. Yet Roethlisberger finishes the game and—with the exception of one missed start—finishes the season despite a clearly painful injury diagnosed as a high-ankle sprain.

As he limped around the pocket in those last few games, pain was telling Roethlisberger that perhaps he shouldn't be out there trying to run away from 300-pound men with bad intentions.

Pain was reminding Roethlisberger that he had an injury and saying that putting his 250-pounds of heft on that damaged ankle probably wasn't doing the joint much good. *Come on, man, this isn't helping you heal.* Through the offseason, though, Roethlisberger's ankle will get better, the pain will go away, and in 2013 the Steelers will dismantle their opponent in Super Bowl XLVII by a score of 118 to -45 and all will be right with the world.

Emily Dickinson said of pain, "It has no future but itself." But the shadows may be lifting. There's much to figure out still, yet the work of Pitt researchers offers new inroads, and new optimism, for treating seemingly intractable pain.

ILLUSTRATIONS | TIM GROEN

But sometimes pain is just pain. It doesn't help anything. (Not in any way that we know of. Oddly, in some cases—and we'll learn more about this later—an intolerance of pain may be associated with a resistance to the ravages of cancer.) It doesn't tell you to not let your body do certain things. It doesn't protect you from reinjury. And it may never stop. Ever. Chronic pain—the kind associated with cancer, arthritis, fibromyalgia, diabetes, postsurgical agony that continues after the wound has healed, and phantom pain, among other conditions—can ruin lives and is difficult, if not impossible in some cases, to treat.

What do you do when it seems there's nothing but pain? You've fallen into a pit of depression, and you can barely hold the pill that's supposed to confer relief. You wake up crying because it hurts so much. Getting up and going to the bathroom is so excruciating that there are times you don't. You've become a hermit trapped by agony.

Poet Emily Dickinson had a pretty good grasp on chronic pain when she wrote, "It has no future but itself."

"It's been a longstanding argument in the field—some people believe that [chronic] pain is centrally driven [caused by malfunctions in the brain], and that flies in the face of all the evidence," says Gerald Gebhart, Pitt professor of anesthesiology, medicine, neurobiology, and pharmacology and chemical biology, as well as director of the University's Pittsburgh Center for Pain Research. "Basically, if you don't have peripheral input, you don't have pain. While it's true that pain is in the brain in the sense that you interpret peripheral events there, our progress has been on the afferent side, the pain fiber side. And we're identifying genes, mediators, and growth factors that contribute to pain. If you could identify two or three [such] things that are involved, you might be able to block pain selectively. That's the key for treating pain."

A key that can open the lock of chronic pain has yet to be made. Still, we've been allowed a glimpse behind the door. The work going on in Pitt labs—and some optimism—makes it possible to imagine a world where gene therapy can help a pain-wracked body produce more of its natural painkillers, where doctors can predict who will respond to a certain treatment and who requires another approach, where stopping nerves from going haywire can put a bedridden sufferer back out on the golf course. Pitt researchers are working toward a world where chronic pain sufferers are not thought of as malingerers, and no one says, "There's nothing 'wrong.' It's just in your head."

If these efforts are successful, the 25 percent of American adults who suffer from chronic pain will be grateful, as will the U.S. economy. The Institute of Medicine estimates that chronic pain costs us $560 billion to $635 billion annually in terms of lost productivity and health care costs.

One nearly foolproof way to treat pain—acute or chronic—is flooding the body with an opiate like morphine. The drug can even bring relief to most terminal cancer patients who are in extreme agony.

How sensible is that approach for people with arthritis, for example, or diabetes? There's really no practical treatment for their pain. Non-narcotic nonsteroidal anti-inflammatory drugs such as aspirin and ibuprofen can help, but not much, says Joseph Glorioso III, PhD professor of microbiology and molecular genetics in the University of Pittsburgh School of Medicine. "You give them narcotics, and they can become tolerant and/or addicted," or the narcotics can render a patient relatively pain-free but in a mental fog, he adds.

And, he continues, "The problem with any systemic [drug] application to treat pain is that it goes everywhere, and it affects the brain and so on. Morphine is not a very nice drug from the standpoint that it makes you half-aware of what's going on. It doesn't block pain, though, it just blocks the perception of pain." If that's not enough of a problem, Glorioso concludes, narcotic-related side effects—dulling of perception, constipation, the need to dose every few hours—can stop pain sufferers from taking narcotics. And a pain drug not taken is no pain drug at all.

Since 1999, Glorioso has been working to find a new way, a more precise way, to calm or even eliminate chronic pain. And it looks like he might be getting close. His work, conducted in concert with, among others, David Fink of the University of Michigan and Michael Gold, professor of anesthesiology at Pitt, has come far enough that phase I and phase II clinical trials have ended successfully, and a phase III trial will begin soon.

"… we're identifying genes, mediators, and growth factors that contribute to pain. If you could identify two or three [such] things that are involved, you might be able to block pain selectively."

In essence, Glorioso hopes to curtail pain by stuffing a herpes simplex virus (most of us carry the dormant virus anyway), engineered so it can't reproduce, with the gene for enkephalin, one of the body's self-made pain relievers. The virus, with its payload, is injected into the skin, and then the herpes virus does what herpes viruses do: It follows the nerves to the nuclei of the sensory nerves off the spinal cord. Then the gene product is released inside the spinal cord.

"Now the thing that's interesting about enkephalin is that it's a protein that's processed into small peptides that are just five amino acids long," Glorioso says. "And the peptides bind to a specific receptor. When they bind, they block the release of neurotransmitters, and so the pain signals are lost or inhibited. The beauty of it is that the receptors are only on the right neurons for silencing."

This gambit had proven successful in rats on numerous occasions. It was time to see whether it worked in people. A company called Diamyd Medical, of which Glorioso's a stakeholder (Glorioso will also earn royal-

ties from the gene-therapy technology under a University licensing agreement), conducted the trials, recruiting and treating 10 adults with intractable cancer-related pain. The results of the phase I trial, published in the *Annals of Neurology* in 2011, seem promising.

"Pain is usually measured on a self-reporting scale of 1-to-10," Glorioso says. "One is nothing, and 10 is bad news. Well, these patients had scores of eight or nine that went to almost zero.

"So far, it has worked extremely well!"

Glorioso's optimism is not dampened by the fact that the phase I trial was very small—some of the 10 patients succumbed to their cancer, as well. After all, he says, the trial was intended to test the safety of the treatment and the ability of patients to tolerate it. Yet it also showed a measurable, and significant, decrease in reported pain.

Phase II, using a similar patient population, is not only larger, but it is randomized, double-blind, and placebo-controlled. Phase I participants were also given morphine during the four-week trial. Phase II (which has ended, with results pending) assesses the efficacy of the gene therapy minus morphine. Thirty patients are enrolled.

"We've already found that gene therapy is longer-lasting and doesn't induce tolerance like opiates do," Glorioso says. "And we've found that it complements morphine, enhancing its effects so you can lower the dose substantially. In phase II, the real boon for patients is the possibility that we'll be able to withdraw morphine completely." To be able to do so, he says, would mean that patients would not only be relieved of their pain, they would not have to endure any of morphine's unpleasant side effects.

"Joe's stuff has been tested, and it's quite interesting, and it works," Gebhart says. "The results are being evaluated. They've found a way to increase enkephalin, an opioid made by the body. But there's another side of the spectrum—finding the genetic differences, the genetic contributions that lead to chronic pain or total pain insensitivity. If you find out what [the issues are] genetically, you can find out what the underlying ion channel or molecule is." Then scientists can imagine new treatments taking advantage of the body's natural painkillers or those tailored to the individual, he says.

Pitt's Inna Belfer, an MD/PhD associate professor of anesthesiology and human genetics, calls what Gebhart is referring to "the pain genome." Thus far, more than 10 genes have been proven to play a role in human perception of pain and pain tolerance. More are being sought.

From Belfer's perspective, to know the pain genome is to pave the way to pain relief, personalized-medicine-style. She offers an example: A genetic variation causes some women who have never experienced chronic pain to experience perpetual agony after giving birth. Small doses of pain medication provide relief for some. Others can't get any relief, no matter how high the dose. Redheads feel pain more acutely. And a genetic variation shared by some breast cancer victims—recently pinpointed by Belfer and her colleagues—makes them almost untouchable to pain medications but four times as likely to survive. Finding a way to manipulate the responsible gene or genes is a distant but, to Belfer, attainable goal.

"All of this started with animal work in 1999," says Belfer, who also directs the molecular epidemiology of pain program at Pittsburgh Center for Pain Research. "We found that, when you control very tightly for environmental factors, you see that 40 to 60 percent of variability [in how mice experience pain and respond to treatment] is genetic. We see something very similar in humans. Twin studies show that there is a very pronounced genetic contribution to variability in pain and analgesia. Not only are these genes statistically associated with pain modalities, we have functional data."

The process of finding pain genes in humans begins with a suspicion (termed the "candidate gene approach") or a genome-wide association study. The researcher takes one group of people with a certain trait—as in the aforementioned case of breast cancer victims who are extremely susceptible to pain but more likely to beat the disease—and a control group of similar women who have breast cancer but don't exhibit a tendency to be resistant to pain-relief drugs.

Belfer suspected that the gene (OPRM1) that codes for a particular opioid receptor might play a role.

"It's an obvious candidate in that [the receptor] binds to opioids," she says.

It turned out that the women who tended to suffer pain more and survive longer were found to have a variation in OPRM1 not shared by the control group. (The variation is a single nucleotide polymorphism, or SNP, in which one form of a gene, called an allele, differs from the other form of that gene.)

The fact that this SNP (people say "snip") relates to pain wasn't much of a surprise (since it is an opioid receptor), but its association with cancer survival sure was.

"All we have now is a statistical association between this particular allele and survival, but the sample size was over 2,000, and we think it was a well-designed study. So this leads us to the conclusion that Mother Nature is doing something balanced," Belfer says. "These women are poor responders to opiates throughout their lives, but when it comes to breast cancer, the same polymorphism makes them better survivors. This was absolutely unexpected."

This kind of discovery, and this is a conclusion that applies to the pain genome project as a whole, Belfer says, will do two things: It will provide new drug targets for the treatment of pain, and it will predict outcomes for already-established treatments.

"We will know whether to give this patient opiates, or we will know that opiates don't work," she says. "We will know whether we should give a patient bigger doses of opiates or whether dosage is not a factor, and they simply won't respond."

As is often the case, though, it's not as simple as all that. Identifying a pain gene is one thing. Understanding all the factors that influence the expression of such a gene is another, much more complex matter entirely.

In October, Belfer and colleagues at McGill University in Montreal and the University of Florida in Gainesville published a paper in *Nature Neuroscience* showing that the activation of the vasopressin receptor pathway (vasopressin is an antidiuretic hormone) can relieve inflammatory pain caused, in this study, by capsaicin, the stuff that makes hot peppers hot. Well it did so in some cases. Once in a while.

Mice lacking a certain gene (AVPR1A),

which encodes for the vasopressin receptor, bit and licked at their hind paws, which were irritated by capsaicin. Pain-resistant mice had significantly higher numbers of the receptors and didn't gnaw and lick. But something curious happened when Belfer et al. tried to replicate these findings in people. Subjects who were given a vasopressin-like drug on their first day of testing experienced no pain relief. Those who received the drug on the second day did.

So, why? Well, Belfer and her team theorized that because it's something new, an experience fraught with novelty and maybe a sense of anxiety, the first day of testing might be stressful for participants. Examining the data, the team found that stress activates the natural production of vasopressin. Administering it as a drug, it turns out, only works if the pathway hasn't already been activated by stress, explaining why those who received the vasopressin analog on day two, when they felt more comfortable, experienced pain relief.

(When the researchers looked back at their mouse data, they discovered that the mice that had been in the testing environment longer were the ones who responded best to the vasopressin drug. They'd fared much better than the newbies who were freaking out before becoming acclimated. The group can't yet be certain that stress is what skewed their results, but the correlation, Belfer says, is there.)

"And there are other factors, too. The interplay between genes and environment is really everything," Belfer says. She notes that a patient's anxiety level, sex, sleep patterns, and so on, all make a difference. "Finding the gene, understanding the molecular pathway—that's vital, of course. But we must not only identify and understand genetic factors, we must also identify and understand risk factors [for pain] that may be demographic, clinical, or psychosocial that influence genetic expression," she says.

What of the nerves themselves? They are, after all, responsible for sensing pain and telling the brain, *That hurts!* This is the bailiwick of Brian Davis, who, with Gebhart and others, is searching to understand and find ways to treat the primary reason for doctor visits in the United States: ongoing somatic and visceral pain (particular flavors of pain detected by specialized nerves in the skin and organs).

Pathological changes to these pain sensors can cause sufferers of irritable bowel syndrome and pancreatitis—among other diseases—to continue to suffer after the underlying cause of their agony is treated. Davis wants to understand what causes this damage and how it can be reversed.

How he came to want to do so is a bit unusual.

"I started out as a developmental neuroscientist with a background in anatomy, physiology, and neurophysiology. And my wife [PhD Kathryn Albers, Pitt professor of medicine in the Division of Gastroenterology, Hepatology, and Nutrition] was two doors down. She's a molecular biologist, and back in the '90s, when transgenic technology was just taking off, she developed a transgenic mouse that overexpressed a developmentally important growth factor—nerve growth factor (NGF)—in the skin."

Neat-o, thought Davis—who is also a PhD professor of medicine in the Division of Gastroenterology, Hepatology, and Nutrition, as well as a professor of neurobiology. But nerve growth factors weren't in his line of study, and he wasn't particularly interested in the model. "So I begrudgingly looked at [Albers' mice]—and they had this incredible phenotype where the sensory nervous system was really [ramped up]."

A pain drug not taken is no pain drug at all.

Suddenly Davis found Albers' mouse model interesting. And soon it became the genesis for a new line of scientific inquiry. "We had very disparate interests, but we came together because of this tool she made. I went from having a developmental lab to … a pain lab."

NGF is vital. Without it and other growth factors, the nervous system doesn't develop. In adults, NGF modulates pain sensitivity and the development of pain fibers. That's helpful. But, when it's overactive, it can cause hypersensitivity to pain. (Hypersensitivity is one symptom that makes some people wonder whether a patient's pain is real or imagined.)

"In a lot of disease states like rheumatoid arthritis, inflammatory bowel disease, or cystitis, NGF goes up, and things get hypersensitive," Davis says.

But further study proved that NGF isn't the only player.

"As important as NGF is, there's actually another growth factor called artemin that's maybe more important, and, in fact, it may work synergistically with NGF to produce chronic pain states not only in the gut, but in the skin and musculature as well."

The Davis/Albers group has found that a population of sensory neurons has receptors for both NGF and artemin. These neurons also have certain channels that are known to play a role in inflammatory pain. That's part of the puzzle.

In 1997, when Michael Caterina (now a professor at Johns Hopkins University) was a postdoc in David Julius' lab at the University of California, San Francisco, he identified the receptor for capsaicin. At first scientists thought the receptor, called TRPV1, only sensed heat, but it turns out that TRPV1 is present in many pain-sensing neurons. Why is it so prevalent?

"It's actually probably more important for inflammatory pain than detecting heat," Davis explains. "Originally it was thought to be a thermal detector, but it turns out that you can use genetic engineering and get rid of it, and animals are still relatively normal in being able to detect heat—but they don't develop inflammatory pain."

Drilling down deeper, Davis and colleagues found that sensory neurons that express TRPV1 also express the receptors for NGF and artemin. A series of experiments then showed that if such sensory neurons are exposed to NGF and artemin alone, pain lasts for about four hours. If TRPV1 is thrown into the mix, pain lasts for six days.

Then add in TRPA1, which responds to mustard oil. When TRPA1 and TRPV1 exist in cells along with NGF and artemin receptors, Davis says, "You have this really evil population of sensory neurons that express TRPA1 and TRPV1—both of which, if you knock them out, decrease inflammatory pain—and these cells also express the receptors for the growth factors, which increase inflammation. It's like the perfect storm converging on one type of neuron." This perfect storm doesn't exist in all of us, just, it seems, those of us who experience this kind of ongoing nerve-related pain.

These growth factors are among those primarily responsible for wiring organs with nerves. In cases of visceral pain—such as colon, bladder, stomach, and pancreatic cancer—70 to 80 percent of the cells that innervate those organs express TPRV1 and

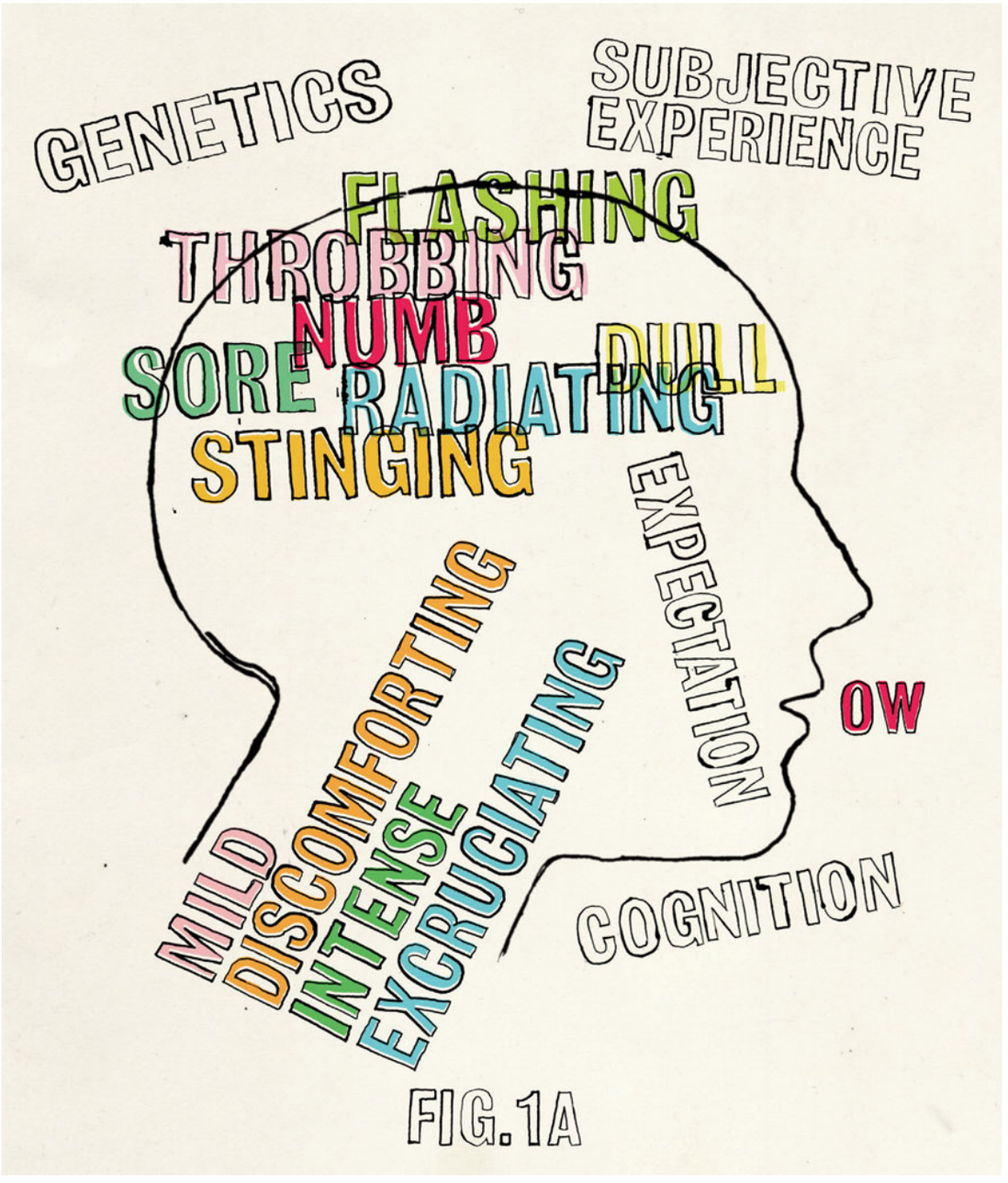


FIG. 1A

TRPA1. So, it's pretty obvious why finding a way to block these bad actors (which are also good actors, to an extent) might be a way to alleviate pain.

"One of our postdocs, Erica Schwartz, used drugs that blocked TRPV1 and TRPA1 in [Albers'] model for pancreatitis," Davis says. "She not only blocked the inflammation, but blocked the pain. If you can block the sensory neurons from releasing their peptides [known as CGRP and substance P], you not only can block the pain, but you can block the inflammation, block the disease itself."

Blocking TRPV1 and TRPA1, though, can't yet be done without a cost. The good things that TRPV1, TRPA1, NGF, and artemin do—help us perceive heat, regulate vasculature—can be blocked this way, as well. Some experimental TRPV1 blockers, for example, caused some participants in a drug company clinical trial to develop fevers and burn themselves with hot liquids. An anti-NGF drug may have caused the death of blood vessels in participants' hips. (The drug company contends that people felt so free of pain that overexertion caused the injury.)

There still is a lot to sort out, Gebhart says. "There are physiological differences (between individuals), plus there are emotional, cognitive, and affective contributions that influence the way you interpret pain." But not delving into such complexities, he concludes, means no new targets and no new therapies. It means that chronic pain will continue to have no future but itself. ■

THE EVANGELIST OF BRONCHOSCOPY

FOREWORD BY CHUCK STARESINIC

PHOTOS COURTESY THE MÜTTER MUSEUM OF THE COLLEGE OF PHYSICIANS OF PHILADELPHIA

Chevalier Jackson was born in 1865 in a plain, three-story brick building on Fourth Avenue in downtown Pittsburgh. The city was a bustling manufacturing center, and the air was frequently filled with smoke and coal dust. He would spend his boyhood just a few miles downriver at the family home on a steep hillside overlooking the Ohio River.

It was coal country, and back then the stuff was mined by hand, loaded onto wagons, and hauled by horses to the iron mills. It was hard, dirty living for a great many in the region, and Jackson was a sensitive boy. In his autobiography, he describes his childhood as a time of terror, tears, and torment at the hands of bullying children. He recounts vivid memories of mothers grieving for their children killed in accidents involving wagons and horses. He describes his anguish at the brutal and unnecessarily cruel treatment of working animals such as horses, mules, and dogs.

Jackson was a tinkerer, perhaps even a bit of a mechanical prodigy, and he was good at drawing. From age 4, he was never without workspace where he could build and experiment. He describes one experience when he was about 12 years old that is oddly prescient of his later career as a pioneering bronchoscopist. Because the family was located just 25 miles from oil-producing territory, a prospector put down a test well on his father's property. When a great length of rope came loose several hundred feet deep in the well, the driller declared the well a lost cause owing to the immovable plug of old line. Jackson conceived of and designed a barbed probe that would screw onto the drilling rig in place of the bit. He took the drawing and a wooden model to a forge, where a toolmaker fabricated it. This harpoon was lowered into the well at the end of a new rope. When it was pulled out, the old rope was firmly attached to the barbs. Jackson described it as his "first foreign body case" and declared it typical of hundreds of his later successful bronchoscopic cases.

Jackson studied at the Western University of Pennsylvania (the forerunner of the University of Pittsburgh) and decided he was ready for medical school in 1884. However, Pittsburgh's medical school wasn't yet ready for him. (The Western Pennsylvania Medical College admitted its first class in 1886.) A skilled artist and illustrator, Jackson earned cash for his medical education by painting glass lamps and china at Fort Pitt Glass Works. When he had earned enough, he took the train to Philadelphia and enrolled at Jefferson Medical College.

After medical school, Jackson made a visit to London—"the cradle of laryngology," he called it—to learn what he could from the most highly regarded physicians in his chosen specialty. When he returned to Pittsburgh, he set up practice in a newly vacated tailor's shop near Penn and Sixth Avenues.

While in London, he'd seen a device for inspecting the esophagus. He deemed this particular device impractical and began working on his own version. He developed his prototypes and his skill at manipulating them to remove foreign objects from the throats of children, usually for no fee. And he ventured farther into the bronchi to remove objects such as safety pins. By the turn of the 20th century, the first bronchoscopes were in use for peering into the lungs and even extracting foreign bodies, and Jackson had set up his own bronchoscopy clinic in Pittsburgh. A meticulous and fastidious recorder of case histories, Jackson published some of the first bronchoscopy texts.

At the age of 35, Jackson was surprised by an offer to chair the Department of Laryngology at the Western Pennsylvania Medical College (now the University of Pittsburgh School of Medicine). "The great honor carried with it additional expenses but no salary," he noted in his autobiography, adding, "Everything had to be financed out of a practice that was 95 percent charity."

Far from complaining of the limitations, Jackson seemed to relish his role as the evangelist of bronchoscopy. His appointment in Pittsburgh launched a segment of his career during which he would join the faculty of a series of medical schools in succession, always moving on when he deemed the bronchoscopy clinic able to stand on its own. He left Pittsburgh for Jefferson Medical College in 1916. In

(continued on next page)





TOP RIGHT: Chevalier Jackson shows a diagram of a foreign object in the digestive tract. ABOVE: Some of the many pins and other items that are part of the Chevalier Jackson Collection of Swallowed Objects.

(continued from previous page)
Philadelphia, his prestige grew so great that no institution wanted to remove his name from the faculty roster. At one time, he held chairs in all five medical colleges there.

"[H]aving spread the gospel of safe bronchoscopy...," he wrote, "it is necessary that I move on to where doubters and heretics abound."

What follows is an article on Jackson that appeared last year in The New York Times. *It is reprinted here with permission. Copyright January 11, 2011.*

DOWN THE HATCH AND STRAIGHT INTO MEDICAL HISTORY

BY AMANDA SCHAFFER

From brain tissue to gallstones, doctors have long preserved specimens from their patients—sometimes as trophies, sometimes as teaching tools, sometimes as curiosities or even art. But Dr. Chevalier Jackson went much further than most.

A laryngologist who worked in the late 19th and early 20th centuries, he preserved more than 2,000 objects that people had swallowed or inhaled: nails and bolts, miniature binoculars, a radiator key, a child's perfect-attendance pin, a medallion that says "Carry me for good luck."

Jackson retrieved these objects from people's upper torsos, generally with little or no anesthesia. He was so intent on assembling his collection that he once refused to return a swallowed quarter, even when its owner threatened his life.

"He was a fetishist, no question," said Mary Cappello, the author of *Swallow* (New Press), a new book about Jackson and his bizarre collection. "But his obsession had the effect of saving lives. That's kind of amazing, and lucky for us that his madness made possible forms of rescue."

Jackson was an artisan and a mechanical prodigy, a humanist and an ascetic whom colleagues sometimes described as aloof or cold. He spent hundreds of hours crushing peanuts with forceps to learn exactly how much pressure to exert. He experimented extensively on mannequins and dogs.

In those days surgery was associated with high mortality, and few physicians were willing or able to peer into the air and food passages, let alone remove objects like open safety pins. Yet Cappello writes that the survival rate among patients from whom he removed objects was better than 95 percent.

"If Jackson could tell us how he wished to be remembered, I'm certain he would do so by assemblage, or meaningful collage," said Cappello, an English professor at the University of Rhode Island. For him, collecting was a form of self-portraiture as well as a clinical and scientific pursuit.

Jackson viewed the world as a precarious place. Small and bookish as a child, he endured intense torment and bullying; at one point other children blindfolded him and threw him into a coal pit, and he was rescued only after a dog happened to find him unconscious.

So in a sense, Cappello said, when Jackson became a physician—first in Pittsburgh, then Philadelphia—he "was saving lives, yes, but he was also saving himself." He grew to be a pioneer of the upper body, developing new endoscopic techniques for peering into dark recesses.

He attached a tiny light called a mignon lamp to the end of a rod that he inserted into his scopes. (Previously, physicians who used endoscopes had worked mainly with light held outside the body.)

And he was an early and outspoken safety advocate, particularly when it came to children. As one of his assistants put it, his quest was to make the public and the medical profession "foreign-body-conscious" about swallowing.

If it had been up to him, Cappello said, "parents who fed peanuts to children without molars would be drawn and quartered." Chew everything thoroughly, he exhorted the public: "Chew your milk!"

And he lobbied for passage of the Federal Caustic Poison Act of 1927, which required manufacturers to place warning labels on poisonous substances like lye, which burns the esophagus and causes severe scarring that can make it impossible to swallow.



Rigid bronchoscopes like the ones pictured above are used to retrieve foreign objects from the bronchi. Jackson refined their design in the 1920s.

Children often ingested lye because it was present in many households (where it was used to make soap) and because it looked like sugar. A 7-year-old girl who could not swallow even a drop of water was taken to Jackson, who fed an endoscope into her esophagus and removed a grayish mass—perhaps food, perhaps dead tissue—with a forceps. Afterward, one of his assistants gave the child a glass of water.

"She took a small sip expecting it to choke her and come back up," Jackson recalled in his 1938 autobiography. "It went slowly down; she took another sip, and it went down. Then she gently moved aside the glass of water in the nurse's hand, took hold of my hand and kissed it."

Jackson also developed a technique for dilating the esophagus in children with scarring. He taught them to swallow a long tube and to do so regularly for an extended period. He suggested they might think of themselves as sword swallowers and imagine that the feat "inspires awe in other children." This eventually helped many of them to eat and drink again normally.

To remove objects like keys and coins and pins, Jackson would insert a long, rigid tube into his patients—usually children, and usually awake, though his assistants did help to hold them still. "He must have had an exquisite gentleness and ability to calm people," Cappello said. He also treated many poor children without pay.

Still, his eccentricities marked him. "Some people might have painted him as a socially phobic, friendless loner," she added. "He was not a warm and fuzzy doctor."

Nor would he compromise when it came to his collection. In the case of that swallowed quarter, he told the patient's infuriated father that "all foreign bodies removed from the air and food passages were put into a scientific collection where they would be available to physicians working on the problems of relieving little children."

The father had beaten the boy as punishment, and when he didn't get the coin back he apparently beat him again, so viciously he broke his son's arm.

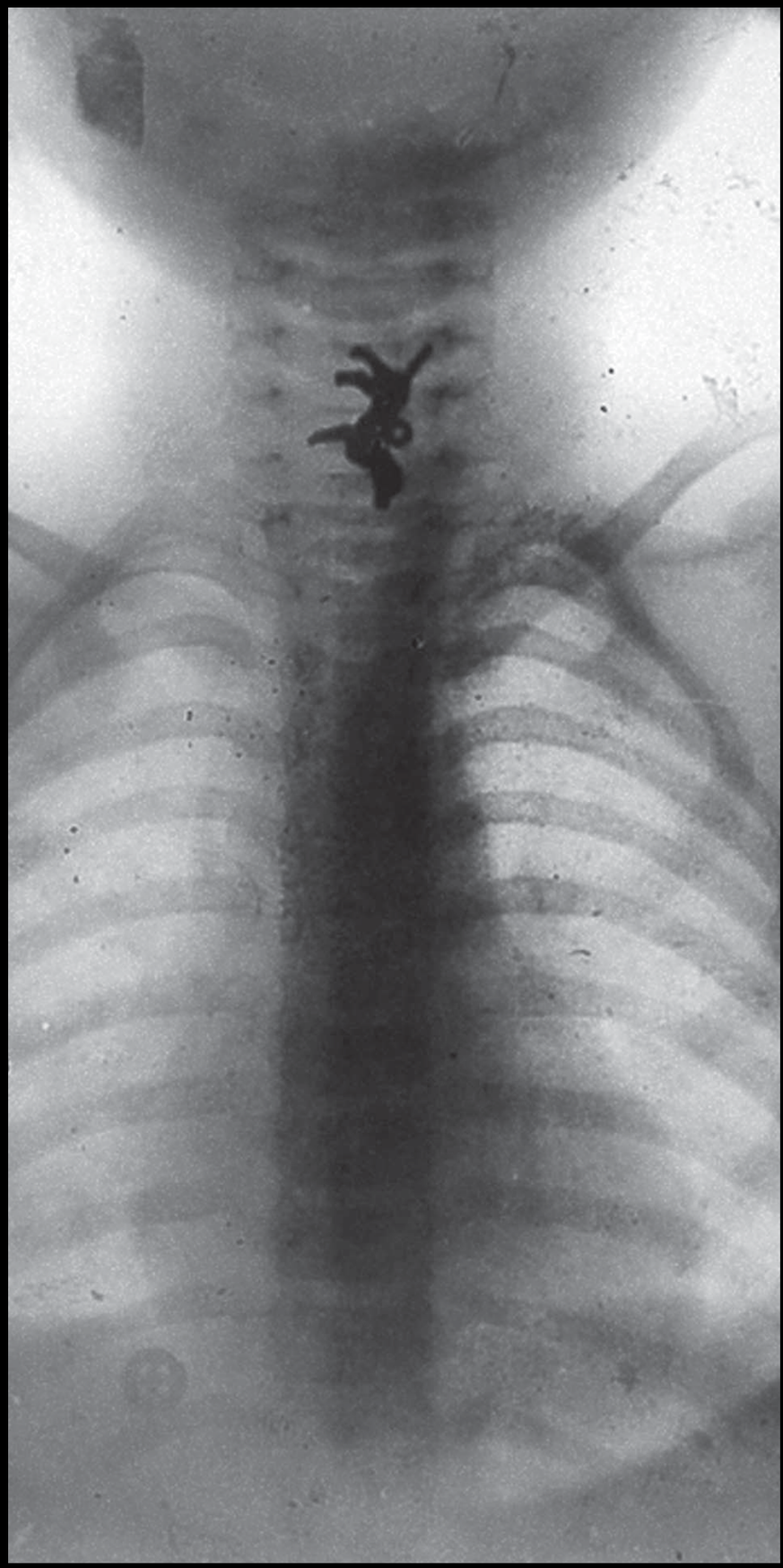
At that point Jackson gave the family a half dollar. But he did not return the swallowed coin.

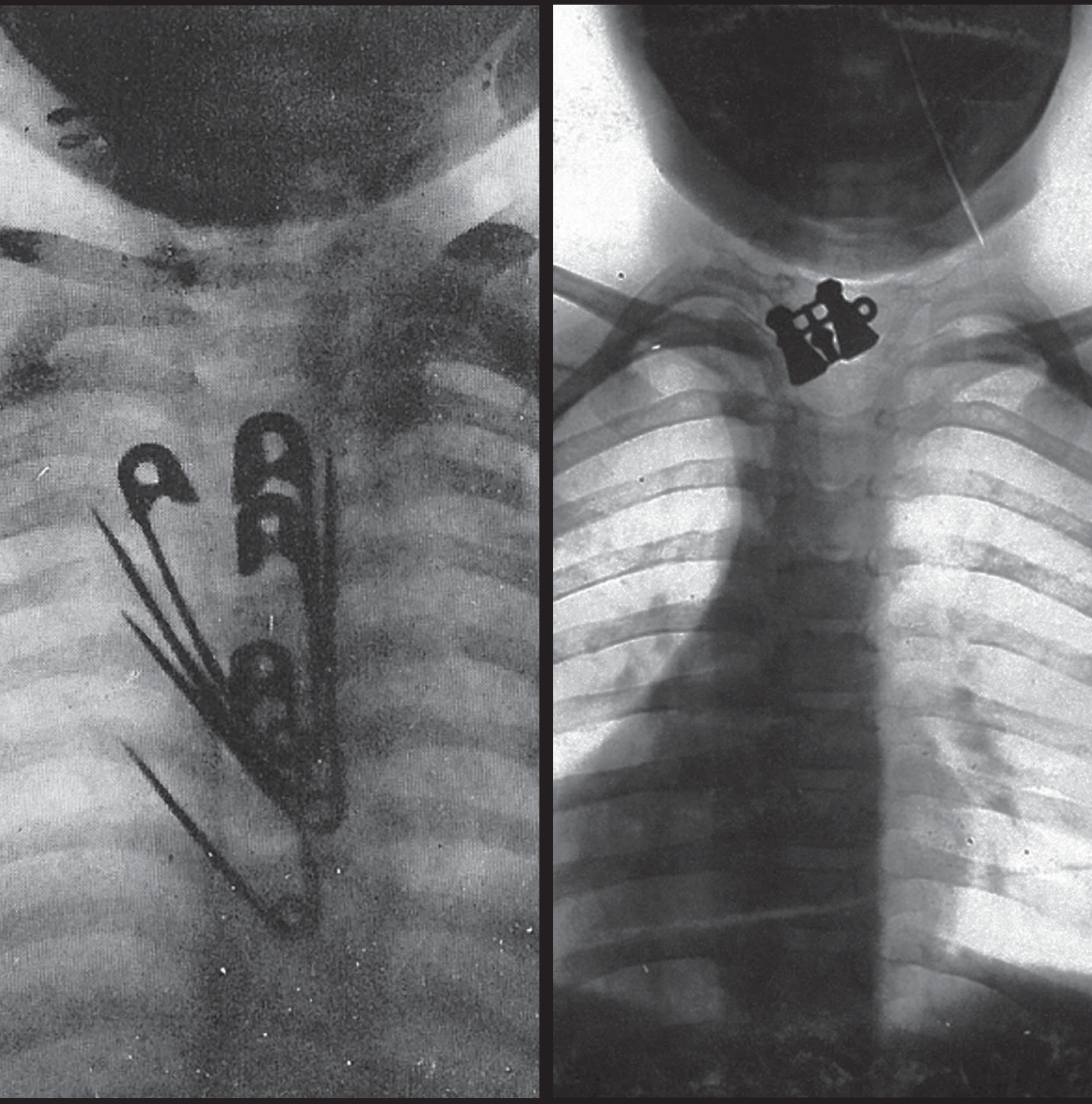
The Jackson collection is now owned by the Mütter Museum of the College of Physicians of Philadelphia, which is refurbishing it for an exhibition. ... Cappello will help curate the exhibition; Anna Dhody, the museum's curator, called her work a substantial contribution that "we're very lucky to have."

V. Alin Botoman, a gastroenterologist at the University of Miami who has also done scholarly work on Jackson, called him "truly a renaissance man who made so many contributions to medicine and has been all but forgotten." Until now. In October, Cappello gave a lecture on Jackson at the Observatory, an art and events space in Brooklyn. She also presented black-and-white films from Jackson's family that had never been seen in public.

In a series of clips, Jackson is shown on a small boat, looking out at the sky. He is riding in the back of a pickup truck, writing intently.

His granddaughter, then a toddler, wobbles across a lawn holding a stuffed animal and a flower. She looks at the camera, shakes the flower and puts it in her mouth. ■





Skiagraphs (positive prints made from X rays) showing foreign bodies, including metal charms and safety pins, swallowed by children before Jackson successfully extracted them.



As a teenager, Grandin didn't want to visit her aunt's ranch. But her mother insisted, and that visit awakened her fascination with animals.

GOOD, OLD-FASHIONED INTERVENTIONS

AT PITT, TEMPLE GRANDIN'S WISHES ARE COMING TRUE

BY JUSTIN HOPPER

In her black embroidered cowboy shirt and white scarf looped like a bolo tie, Temple Grandin's onstage appearance matches her speech: Equal parts severity and unadorned approachableness, all couched in an almost impossible confidence. Introduced to the standing-room-only audience at Western Psychiatric Institute and Clinic's auditorium this winter, Grandin doesn't acknowledge the gathered crowd before launching into her subject matter.

"I've got some real concerns" about autism care in America, says Grandin. "I travel all around the country, and it's a *wasteland*. You get down to the Southeastern United States, they've got kids zapped up on so many drugs, it's disgusting…"

In her trademark gruff, straight-to-the-point address, Grandin makes a point that most scientists would agree with: that early diagnosis of autism and caregivers educated in the disorder are worth more than a cabinet full of medication.

Grandin, who has a PhD in animal sciences, is arguably the world's best-known advocate for people with autism. She is the author of more than a half-dozen books on the subject; in 2010, Grandin was named one of the 100 most influential people in the world by *Time*. She thinks there's a problem with the way the disorder is diagnosed and treated in the United States.

"A lot of mild Asperger's [syndrome] cases are going to get shunted off into these other disorders" under potential new diagnostic guidelines, says Grandin. She believes that will put many at risk of being further distanced from the kinds of therapeutic interventions that seem to work.

Grandin, herself, was a child with autism at a time when diagnosis and treatment were rudimentary at best. She is 64. As late as the 1970s, autism was regularly associated with—and frequently misdiagnosed as—schizophrenia. And yet she has risen to the top of her profession as a designer and consultant to the American animal industry. Half the cattle sent to processing plants in North America are handled with equipment Grandin designed.

Grandin has no doubt as to what allowed her to thrive: the early intervention of her persevering mother and a series of other mentors. Research at the University of Pittsburgh is helping to build an intervention model that sounds a lot like Grandin's story.

As late as the 1970s, autism was regularly associated with—and frequently misdiagnosed as—schizophrenia.

As a child growing up in the 1950s, Grandin was reared in an environment that she thinks was just what a kid with autism needs. And there's still a bit of the '50s left in her. Speaking to the Western Psychiatric Institute and Clinic's audience of autism specialists, psychiatrists, scientists, and educators, Grandin peppers her talk with *Leave It to Beaver*-isms, referring to people who talk a lot as "yak-yaks" and visibly perking up when she brings up childhood shenanigans with her cousin or her participation in a model-rocket club.

But to Grandin, the stricter, more manners-based culture of the Eisenhower era is more than just nostalgia. It's therapy.

"This is where my 1950s up-bringing helped me" as a child with autism in Massachusetts, says Grandin, noting that her mother wouldn't allow her to shy away from conventional New England life. "Turn-taking games and conversational board games. Having to be on time and do activities I didn't particularly like, like going to church—sitting there, squirming. Saying please and thank you … and consistent discipline between home and school.

"I had extremely good early intervention. And by the time I was 2-and-a-half years old, I was in intensive speech therapy. When I was 3, my mother hired a nanny who spent hours playing turn-taking games. You've gotta teach these kids how to take turns. And one of the things about being autistic is you've got to

MATT SLABY/LUCEO IMAGES

stretch the kid to learn new skills. … When I was 15, I was afraid to go to my aunt's ranch, but my mother wasn't going to let me *not* go: The choice was one week or all summer."

That trip to the ranch turned out to be a turning point, sparking Grandin's lifelong fascination with animals (she is a professor of animal sciences at Colorado State University), her involvement in advocacy for the humane treatment of animals, and an extraordinary career in the cattle industry. To Grandin, such very basic interventions—which stretch autistic children to give them a broad range of experiences and teach them the social skills necessary for community and workplace communication—are vital. They allow children a chance to find a calling.

Nancy Minshew, an MD and Pitt professor of psychiatry and neurology, is program director of the Center for Excellence in Autism Research (CeFAR) at the University of Pittsburgh. Minshew has been a prolific investigator of the neurobiological roots of autism. She's also been instrumental in contributing to our understanding of how people with autism see the world and why they see it that way.

By scanning the brains of people with and without autism disorders (including Grandin's) while they are given a variety of questions to process, Minshew and colleagues—notably CMU professors Marcel Just and Marlene Behrmann, who, like Minshew, are members of Pitt and Carnegie Mellon University's Center for the Neural Basis of Cognition—have shown that in people with autism spectrum disorders similar to Grandin's, thought is driven from what Grandin calls the "bottom up." In other words, rather than starting with broad concepts, Grandin's thinking begins with visual imagery and specific examples. In her Pitt talk, Grandin explained this thought process with her own specific example.

"I realized my thinking was different when I asked people to think about a church steeple," says Grandin. "I was shocked to find out that most people had this vague, generalized image of a church steeple. I only see specific ones. They flash up like a Google [image search]—there is no generic steeple."

Minshew's research also shows that people with autism have difficulty with another form of generalization, categorizing objects. Knowing these two things, explains Minshew, sheds light on how best to help people with autism learn and communicate more effectively in our society.

"You can't think other people understand what you do just because they have all the same facts," says Minshew. "We know that people with autism have problems with automatic processing. There's a lot we learn without realizing we're learning it. [Most of us] know that it's not polite to say to a fat person, 'Why are you so fat?' Or that you don't have to tell the blind person he's blind—because he already knows."

Grandin underscores that this kind of learning isn't automatic in the autistic mind: Just because you don't cross against the light at *this* street corner doesn't necessarily mean that you don't do so at *another* corner.

This sort of basic socialization and understanding of how the world works is a lot like what Grandin gained from her mother's early efforts. And it's similar to the experience that CeFAR is creating for people with autism in the Perspectives Program, an experimental intervention effort based on decades of research and led by Pitt's Shaun Eack, PhD assistant professor of social work and psychiatry.

In the National Institutes of Health–funded program, people 16 to 40 years old with autism begin by working in pairs on activities that develop skills such as paying attention and taking turns. After six months, the groups are expanded to four pairs each and the participants engage in a curriculum based on social wisdom and those difficult automatic-learning issues.

The goal, Minshew says, is to create an intervention method that can be used in the everyday classroom. And not just for students with autism.

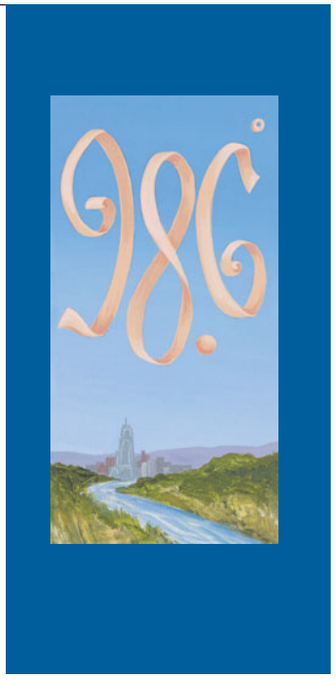
"How many people can benefit from being more socially skilled?" asks Minshew. "From being a better communicator, a better problem solver, from being more flexible—able to look at things in different ways? Who's *not* going to benefit? There's a spectrum [of social abilities] amongst the nonautistic population as well, and 50 to 70 percent of kids can benefit from this type of interaction. If we can train people to [conduct this intervention method] outside of this institution, any teacher who's trained in it will automatically begin to do this in [the] classroom. And perhaps they'll notice that student who isn't quite as able."

"I was shocked to find out that most people had this vague, generalized image of a church steeple. I only see specific ones."

The heart of Grandin's talk is simple: People with autism can make important contributions to society if only they are given the opportunity to discover their potential. And that means helping them to engage in the world, rather than hide behind their disorder.

"Too many autistic kids are getting fixated on their own autism," says Grandin. "I don't like it when I'm at a book signing, and a 9-year-old wants to talk about his autism. I'd rather have him talk to me about a science project or that he likes history. People ask me, *If I could snap my fingers, would I want to not be autistic?* No, I like the way I think. But on the other hand, being a college professor and a cattle specialist, that comes first. Autism comes second. I don't let autism take over." ■

People and programs that keep the school healthy and vibrant



A FAMILY MATTER

THE KITCHEN FOUNDATION TAKES ON CYSTIC FIBROSIS

Robert Kitchen laughs warmly at the thought of his sister, Gloria, wide-eyed and nervous, walking into a hometown business and pleading her case. At 18, Gloria Kitchen spent much of her time visiting shops, restaurants, and beauty parlors in search of donations for the Cystic Fibrosis Foundation. And despite her youth—or perhaps because of it—Gloria was very, very good at raising money. By that time, in 1996, Gloria's life had already been turned upside down by cystic fibrosis. Her brother, Thomas, died from the disease that year, and in 1995, Gloria herself had received a lung transplant as part of her own battle with the disease. But neither grief nor illness slowed her ceaseless fundraising for the search for a cure.

"The amazing thing about Gloria is that she was doing all of this fundraising while maintaining her own health," says Robert Kitchen.

In the years after her brother's death, Gloria Kitchen raised more than half a million dollars for the Cystic Fibrosis Foundation. Then, in 2010, Gloria launched the Thomas Kitchen Memorial Foundation, which raises funds to be donated directly to cystic fibrosis researchers.

Sadly, not long after starting the foundation, Gloria's health worsened.

"She pushed herself," says Robert Kitchen. "And right after the foundation got going, deep-set rejection [of her lung transplant] set in."

Late in 2010, Gloria was scheduled to travel from her native Michigan to receive a second lung transplant at UPMC Presbyterian. Just days before the operation would have taken place, had she been strong enough for it, Gloria died. In December 2010, the renamed Gloria and Thomas Kitchen Memorial Foundation made its first major donation: $49,000 raised through two fundraising events that year was given to the University of Pittsburgh's Cystic Fibrosis Research Center, headed by Raymond Frizzell, PhD professor of cell biology and physiology.

In accordance with Gloria's wishes, the foundation's gift went directly to Frizzell's research.

"The Kitchen Foundation's funding has provided seed money to pursue two new endeavors related to finding treatments for cystic fibrosis," says Frizzell. "First, we were able to identify and manipulate the activity of a receptor on the cilia of surface airway cells." This receptor, according to Frizzell, helps moderate the cilia—the tiny hair-like structures that help keep the lungs and airway clear. "Defects in airway clearance are a major issue in cystic fibrosis lung disease, and we hope to be able to manipulate this receptor to improve this process."

In people with the most common cystic fibrosis gene mutation, the mutant protein cannot reach the surface of cells where it should function, leading to severe disease. In a second research front funded by the Kitchen Foundation gift, Frizzell and colleagues have developed a new strategy to be used to discover and validate drugs that can rescue the mutant to the cell surface.

"We sincerely believe [Frizzell] is making important strides in research to treat cystic fibrosis and is committed to improving the longevity and quality of life of those afflicted with this genetic killer," says Robert Kitchen, who is now president of the Kitchen Foundation. He is driven by the memory of his brother and sister; he also has a living reason to raise money for CF research: "It's really important to us as a family that a cure will be found in my parents' lifetime."

—Shermi Sivaji and Justin Hopper



Gloria Kitchen

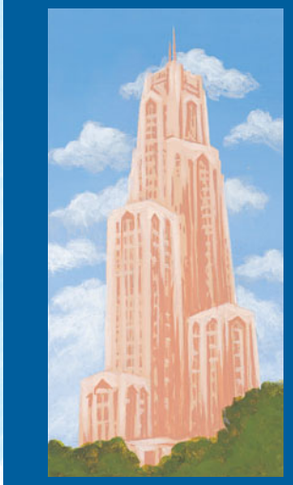
BOOSTER SHOTS

In spring of 2010, Nadine Champsi stood in front of her graduating class with tears in her eyes as **Larry Nichols**, an MD associate professor of pathology, handed her a check for $20,000, the Larry Nichols Family Medicine Scholarship Award. Champsi is among a steadily decreasing number of medical school graduates nationally who pursue a career in family medicine. (Specialists tend to make more money; and considering the heft of student loans, money must be on a young doc's mind.)

Nichols hoped that his generosity would inspire others, which it has to some degree. But he wants more people to come to the aid of those who'd rather practice family medicine but opt not to for financial reasons. So, again, he has put his money where his hopes are and made another $20,000 donation. Perhaps that will provide added inspiration.

Even if its influence is small, Nichols is happy. "If [my gift] resulted in even one more student going into family medicine, my $20,000 would help thousands of patients over many years," he says. *—SS*

FOR MORE INFORMATION ON GIVING TO THE SCHOOL:
Eric White, emw61@pitt.edu



CLASS NOTES

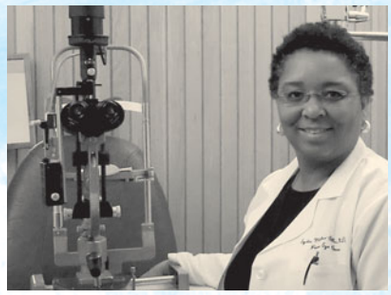
'60s

Donald Malkoff (MD '60) majored in physics at Harvard University, studied medicine at the University of Pittsburgh, and trained to become a neurologist at the University of Michigan. He was a researcher in the fields of electron microscopy and biology at the Marine Biological Laboratory in Woods Hole, Mass., and at the National Institutes of Health in their Gerontology Branch. He ran his own neurology practice for several years and then got into the oil business, which required him to travel extensively throughout Europe and the Middle East (becoming "embroiled" in many adventures, he reports).

On his return to the States, Malkoff obtained a master's degree in computer science at the University of California, San Diego. He ended up serving as an expert in artificial intelligence for the U.S. Navy and as chief scientist for a number of defense corporations before retiring.

'80s

As a committee member for the American Academy of Ophthalmology, **Eydie Miller-Ellis** (MD '85) gives junior researchers a chance to gain exposure by inviting them to speak at national meetings; she also regularly organizes discussion panels where at least half of the members are women. Even so, Miller-Ellis says she was "pretty shocked" to be the recipient of Women in Ophthalmology's Suzanne Veronneau Troutman Award for championing women in her field. Miller-Ellis, professor of ophthalmology at the University of Pennsylvania and director of the Glaucoma Division for the Scheie Eye Institute, says that too often she sees doctors inviting their established colleagues to speak at events, leaving out capable up-and-comers who are eager to progress academically. "In order to advance and excel you need to have a recognized and national reputation," she says. "I try to make sure women who are clearly talented, but who people just haven't invited, get on the national stage."



Miller-Ellis keeps an eye out for up-and-comers.

As a professor and practitioner of emergency medicine at the University of Pennsylvania, **Jill Baren** (MD '89) faces ethical dilemmas on a daily basis. There are bedside decisions, like resolving when to terminate resuscitation and making choices for unconscious patients, among other difficulties. Her desire to enhance her knowledge in these complicated situations led Baren to pursue a mid-career master's degree in bioethics. Her particular interest in studying federal regulations gave her niche expertise in clinical trials where informed consent isn't possible.

Baren was recently named chair of the Department of Emergency Medicine in Penn's Perelman School of Medicine. In this new role, she plans to develop an emergency department with a strong patient- and family-centered position. "I think when you have that kind of outlook on clinical care," she says, "you're able to incorporate a lot of the principles that we learn in clinical ethics and ethical decision-making."



Baren heads emergency medicine at Penn.

'90s

William Kuzon (Microvascular and Hand Surgery Fellow '92) likes to think of plastic surgery as the house band. There's no set list of procedures; it's more of an approach to surgical problems, a practice of reshaping the patient's own tissues for better function and aesthetics. "You've gotta be able to play whatever the crowd wants to hear," he says. Kuzon is section head of plastic surgery at the University of Michigan. In his research, he's been known to riff on abdominal-wall reconstruction, "one of the major surgical problems of our day," he says. He also studies the basic science of why muscles fail to regain function after nerve injury. His group's observations were among the many that supported a shift in peripheral-nerve-injury treatment: In some situations, especially nerve injuries in the proximal arm, surgeons now favor nerve transfers (which borrow an intact nerve to substitute for the function of a divided one) over nerve grafts or repairs (which fix the original nerve). Kuzon's clinical repertoire runs the gamut, including treatment of facial paralysis, weight loss, various cancer or traumatic defects, and gender identity disorder. He directs surgical services for University of Michigan's Comprehensive Gender Services Program, a multidisciplinary outfit founded in 1993 that he helped organize.

'00s

With the advent of antiretroviral therapy, HIV patients are living decades longer, but they are developing new complications, such as cardiovascular disease, renal disease, and bone disease, says **Allison Ross** (MD '02), assistant professor of pediatrics at Emory University and attending physician at the Ponce Family and Youth HIV Clinic in Atlanta, Ga. Many patients battling the virus have low levels of vitamin D, which only makes things worse—even healthy people are at greater risk for immune dysfunction and other complications when their vitamin D levels decline. Ross has been conducting preliminary studies on the effects of high doses of vitamin D on children and young adults

with HIV, with encouraging results. Recently, she was awarded two five-year grants from NIH (an R01 and a K23) to continue her work, which she hopes will lead to better preventive measures for these patients. "I'd like to find simple measures like vitamin D supplementation that may allow children with HIV to live not only longer lives, but also live with less morbidity."

Anda Vlad (PhD '02, Immunology Fellow '04), MD/PhD assistant professor of obstetrics, gynecology, and reproductive sciences at Pitt, had a very merry Christmas, indeed. At the end of December, she received word that her R01 grant application was accepted. Her $1.4 million from the National Cancer Institute will fund her research on ovarian cancer and vaccine candidates against it, using a first-of-its-kind animal model that she developed. Vlad's triple-transgenic mice generate ovarian tumors that closely mirror those of humans, developing and spreading through the abdomen in the same insidious way ours do. But more importantly, ovarian tumors in these mice express the very same antigen as we do. "It's a very savvy tool," she says. "We're able to identify the influence of a human molecule—and one that's very well studied—in the biology of the disease."

Brian Zuckerbraun (Surgery Fellow '03, General Surgery Resident '05), associate professor of surgery at Pitt, is giving the veggie-haters of the world another reason to hold their noses and swallow their spinach. This nitrate-rich veggie triggers the release of nitric oxide (NO), an important signaling molecule in the blood vessels that helps maintain cellular communication and vascular health. Recently, Zuckerbraun discovered an alternative method of NO production in the body. During injury, the nitric oxide synthase pathway is ineffective; therefore, the body's response is to open another gate in order to bring extra nitric oxide to the site of the wound. Further, Zuckerbraun found, supplementing rats with nitrite before inducing vessel injury protected them, whereas a diet low in nitrate and nitrite made matters worse. Zuckerbraun's study was published in the *Journal of Clinical Investigation* last year.

Alexis Colvin (Sports Medicine Fellow '08), an assistant professor of sports medicine at Mount Sinai Hospital in New York City, has worked with a long list of professional athletes (including members of the Pittsburgh Steelers and Penguins while a fellow). For the past three years, she has helped care for professional tennis players at the U.S. Open in Flushing, Queens, N.Y. Colvin specializes in the surgical treatment of knee, shoulder, and hip disorders. This spring, she'll be presented with the 2012 Women on the Move award by the Arthritis Foundation, New York Chapter.

—Dennis Funk, Shermi Sivaji, Elaine Vitone

ISMENE PETRAKIS

A TRIPLE THREAT TO DUAL DIAGNOSIS



PHOTO ILLUSTRATION BY JESSE LENZ (BASED ON A PHOTO COURTESY I. PETRAKIS)

Veterans with both psychiatric and substance-abuse disorders need help on multiple fronts, says Petrakis.

When Ismene Petrakis (MD '87) completed her residency in psychiatry at Yale, she wasn't ready to hang up her stethoscope. "I didn't want to forgo my medical training after graduating from Pitt," she says, adding that she could see herself continuing to treat both bodies and minds because "the faculty there was so well-grounded in both." Now a professor of psychiatry at Yale and chief of psychiatry at the Veterans Administration Connecticut Healthcare System, Petrakis calls on her skills as a physician, educator/researcher, and administrator in caring for U.S. veterans of the wars in Afghanistan and Iraq, many of whom suffer from a combination of substance abuse and psychological disorders.

"There's plenty of evidence to show that combat veterans with post-traumatic stress disorder are more likely to develop substance abuse problems," she says. "But, historically, the two issues were kept at arm's length. People trained to treat psychiatric disorders were uncomfortable dealing with substance abuse. And people treating addictions didn't focus on psychiatric issues. Because of increased awareness and interest in these issues, we've developed an understanding that these issues do co-occur and that we can't isolate them from each other and adequately serve the client."

With nearly 25 years of experience with these comorbid patients and intensive clinical research on the problem in the past decade, Petrakis has found that various medications can be used to simultaneously treat mental disorders and substance abuse, and with encouraging results. Still, there is no magic bullet. Since 1949, when the FDA approved disulfiram, the first drug to treat alcoholism, just three additional medications have received the agency's approval.

That means more work needs to be done, says Petrakis, and "[primary care] physicians must be better trained to spot the issues when they occur and know how to treat them."

Fortunately for the vets under her watch, Petrakis will continue to hold on to her stethoscope. *—John Altdorfer*

MICHAEL STANG

A PROCEDURE INSPIRED BY TABOO

Traditionally, to remove the thyroid, the butterfly-shaped gland near the trachea, an endocrine surgeon parts the muscle bands, dissects the surrounding tissue, and excises the organ. This method is "extremely reliable," says Pitt's Michael Stang (General Surgery Resident '08, Endocrine Surgery Fellow '09). But it leaves a scar, about two inches long, on the front of the neck.

In 2010, Stang, assistant professor of surgery, started performing the procedure using robotic tools to remove a patient's thyroid—through the armpit. "Anatomically, it makes perfect sense," Stang says. If you raise your arm in the air,

he explains, your clavicle also extends upward, and your underarm is just a few inches from your thyroid.

The robotic technique is still used experimentally in America—only a handful of surgeons, Stang included, perform the surgery regularly. (An FDA review is pending.) But in South Korea, the robotic procedure is the norm. "In Korean culture, the display of a scar nonverbally displays a history of illness, which is not acceptable from a cultural standpoint," Stang



PHOTO ILLUSTRATION BY JESSE LENZ (BASED ON A PHOTO COURTESY M. STANG)

Stang makes his mark with a new procedure that leaves no visible scars.

says. The Korean scar taboo is particularly strong for women, who are also about five times more likely to be affected by thyroid disease than men worldwide.

To learn the technique, Stang spent nearly a month in South Korea shadowing Woong Youn Chung, the surgeon who pioneered the practice. Today, Stang is the most experienced robotic thyroid surgeon in the Northeast and has performed the procedure nearly 90 times.

For Stang, the technique is a perfect example of the kind of innovation surgeons can achieve through robotics. "The uses are going to expand," he says. "We're just at the beginning."

—Jenelle Pifer

MOREY S. MORELAND

MARCH 20, 1939—OCT. 2, 2011

In 2003, after almost three decades as a practicing orthopaedic surgeon, Morey S. Moreland—the William F. and Jean W. Donaldson Professor of Orthopaedic Surgery at Pitt since shortly after his arrival in Pittsburgh in 1989—became the department's executive vice chair of research. His new job was helping researchers set up labs rather than seeing to the health of children with orthopaedic issues. So Moreland decided to retire his collection of more than 50 Mickey Mouse ties he wore to help put his young patients at ease.



Moreland

"He told me to get rid of them," his wife, Marilyn Moreland, says, "but I put them in a box." When she had her husband's colleagues and friends over shortly before his funeral, "I put [the ties] in a bowl by the front door and asked everyone to take one. I think people really enjoyed having something to remember him by."

Moreland published more than 60 papers in peer-reviewed journals on such topics as scoliosis and hip dysplasia. He is remembered as an excellent instructor, earning a Golden Apple teaching award in 2000, generous with his time and expertise. He frequently visited Honduras with Marilyn as a member of CURE International, an organization dedicated to bringing medical care to underserved children.

Outside of work, Moreland skied, swam, and sailed. "He was always active, and he loved his work," Marilyn Moreland says. "He was a wonderful person to be around."

—Joe Miksch

OSCAR M. REINMUTH

OCT. 23, 1927–SEPT. 23, 2011



Reinmuth

Oscar Reinmuth, who chaired Pitt's Department of Neurology for more than a decade and influenced the careers of a great many clinicians and scientists in the field, died in September.

Known to one and all as "Mack," Reinmuth helped to pilot stroke research into a new era, according to Lawrence Wechsler, professor and chair of neurology. Reinmuth received his MD from Duke University in 1952 and completed a residency in internal medicine at Yale. He then completed a second residency in neurology under Derek Denny-Brown, an influential physician-scientist at Boston City Hospital and Reinmuth's most important mentor.

As one of the early stroke specialists, Reinmuth made important contributions to the study of cerebral blood flow and stroke, says Wechsler. "The fact that he was editor of the journal *Stroke* for four years [1987-1991] also demonstrates that he was at the very top of his profession."

A collegial and highly social man, Reinmuth inspired loyalty in his patients. He was known for both his bedside manner and his bedside teaching. After leaving Pittsburgh in 1993, Reinmuth became a clinical professor of neurology at the University of Arizona and enjoyed many years of caring for patients and teaching in Tucson. His family asks that donations be made on his behalf to the long-standing Reinmuth Resident Graduation Award in Pitt's Department of Neurology. (For more information on the award, contact Jim Olsen at jao28@pitt.edu or 412-647-7781.)

—Chuck Staresinic

IN MEMORIAM

'40s

CARL W. HOCH
MD '43B
JAN. 11, 2012

FRANK P. CLEVELAND
MD '44
NOV. 28, 2011

WILLIAM E. PALIN
MD '44, RES '51
DEC. 22, 2011

'50s

EDWARD LOREN FARRELL
MD '51
NOV. 29, 2011

ROBERT LEWINE
MD '53
JAN. 26, 2012

'70s

JUDITH ELLEN ORIE
MD '78, RES '79, FEL '84
NOV. 5, 2011

'80s

DAVID LEE WULKAN
MD '80
NOV. 22, 2011

'90s

DAVID A. COFFEY
MD '91
JAN. 17, 2012

FACULTY

ANN LOUISE BUCK
NOV. 17, 2011

KODI AZARI
A SURGEON'S HANDIWORK

BY SHARON TREGASKIS



COURTESY AZARI

Azari (right) arm wrestles U.S. Marine Corporal Josh Maloney, UPMC's first hand-transplant recipient.

As a Persian immigrant, 13-year-old Kodi Azari was expected to choose a career in medicine, engineering, or law. He told his relatives he'd study medicine, "just to get them off my back." Soon after, a family friend in Pittsburgh began sending newspaper clippings about the pioneering liver-transplantation surgeon and Pitt professor of surgery Thomas Starzl. Azari was hooked.

Today, the 43-year-old is chief of reconstructive transplantation and founding surgical director of the UCLA Hand Transplant Program and associate professor of orthopaedic surgery and plastic surgery in the David Geffen School of Medicine at the University of California, Los Angeles. He keeps a pair of Starzl's scissors in his desk drawer and a copy of Starzl's autobiography, *The Puzzle People*, on his bedside table, rereading it annually. "I live in L.A., so I get to meet a lot of my heroes," he says. "Inevitably, they let you down. But, boy, did Dr. Starzl live up to expectations."

That fateful meeting came when Azari (General Surgery Resident '00, Plastic Surgery Resident '03) came to Pitt in the late '90s. The human hand had captured Azari's imagination in 1993, during his first-year gross anatomy class at East Carolina University School of Medicine. "I am not a religious man," he says, "but if there is an argument for creation, it is the hand." He started dreaming of marrying his interest in transplantation with his awe of the hand.

Azari was convinced that training at the academic medical center that had welcomed Starzl would speed his dream to reality, and in 1998, he began his general surgery residency at UPMC. In the operating room, he begged Chester Gist, Starzl's one-time scrub tech, for tales of the early days. He completed a research fellowship in bone tissue engineering at Carnegie Mellon University, then a plastic surgery residency at UPMC. After a hand and microsurgery fellowship at UCLA, he joined the UPMC faculty team committed to launching a hand-transplant program. Starzl was among the team's advisors. "Despite all of the self-doubts we had, he was the one who said, 'No, you have to do it.'"

The first hand transplant—by Ecuadorian surgeons in 1964—lasted just two weeks before profound rejection set in. The second attempt came in 1998, a year after Azari began training at Pitt. Doctors in Lyon, France, employed the trifecta of developments that would prove critical: binocular operating microscopes, reliable microsurgical equipment, and the sophisticated drug cocktails—many of them developed at Pitt—that stave off rejection.

On May 14, 2009, Azari was one of 40 physicians and nurses in UPMC Montefiore's OR No. 40 who first performed the procedure at UPMC. Over the course of 11 hours, they attached a donor hand to U.S. Marine Corporal Josh Maloney's right arm; he'd lost his hand in a munitions accident on base at Quantico, Va. Since then, Azari has performed the surgery three times at UPMC and once at UCLA. Each patient commits to a regimen of three to six hours a day of physical therapy, six days a week, for the first year with the new hand, as well as a lifetime of immunosuppressants that carry a litany of risks, from diabetes to cancer. Known as "life-enhancing," the procedure is elective because of the dangers of immunosuppression.

Azari, who promises patients his technical best, can't say what decision he'd make if he were faced with the choice they confront.

"When there are self-doubts, and I'm lying there in bed, Dr. Starzl comes to mind," he says, recalling the uncertainty that plagued his hero in the early, experimental days of liver transplants.

"I don't know what it means not to have a hand. I have an idea, because I get a paper cut and don't use it for a day. But I truly don't know what it means not to have a hand." ■

To hear Azari tell his story, run these Internet search keywords: Moth Kodi Azari

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JAN MADISON (MD '85)
JOHN F. MAHONEY (MD '90)
VAISHALI DIXIT SCHUCHERT (MD '94)
ADAM GORDON (MD '95)
CHARISSA B. PACELLA (MD '98)
HEATHER HEINRICHS WALKER (MD '99)
BRETT PERRICELLI (MD '02)
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medalum@medschool.pitt.edu



INSIDE OUTSIDERS

William Kurelek was born in 1927 to a Ukrainian farm family who'd immigrated to Canada's prairie. Kurelek developed a passion for art early on but was discouraged by his father from pursuing it. While living in England in the early 1950s, he was institutionalized for depression and schizophrenia. It was during this stay at psychiatric hospitals in London and the vicinity that Kurelek created his best-known early works—*The Maze* and *Where Am I? Who Am I? Why Am I?* (shown here).

Kurelek went on to have a full psychiatric recovery. At the time of his death from cancer at the age of 50, he was considered Canada's greatest painter. He is one of the 20th century's best-known "outsider" or "visionary" artists—artists from positions beyond the mainstream of both the art world and everyday life, who perhaps are institutionalized, driven by religious zeal, or are simply great but untrained talent. Which is not to say that their work doesn't impact the mainstream. Art-world superstars from the turn of the last century (Paul Klee) to some of today's hottest names (David Shrigley) have been influenced by creations of those plagued by schizophrenia, in particular.

Pittsburgh will soon discover the influence of these outsiders, if tangentially so. Daniel Baumann, a curator of the prestigious 2013 Carnegie International at the Carnegie Museum of Art, is also the curator of the oeuvre of another important artist with schizophrenia, Adolf Wölfli; that collection is housed at the Museum of Fine Arts in Bern, Switzerland. With the hand of the psychiatric patient and other outsiders so prevalent in today's art world, it seems unlikely that Baumann would let these voices remain quiet. *—Justin Hopper*

WILLIAM KURELEK, *WHERE AM I? WHO AM I? WHY AM I?* PHOTO BY DAN MEYER, COURTESY AMERICAN VISIONARY ART MUSEUM

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

HEALTH SCIENCES ALUMNI RECEPTION
APRIL 21
6 p.m.
Los Angeles, Calif.
For information:
Pat Carver
412-647-5307
cpat@pitt.edu

PITT MED GOLF OUTING
APRIL 28
8:30 a.m.
Quicksilver Golf Club
Midway, Pa.
For information:
www.pittmedgolfouting.org

MEDICAL ALUMNI WEEKEND 2012
MAY 18-21
Reunion Classes:

2002	1997
1992	1987
1982	1977
1972	1967
1962	1957

SENIOR CLASS LUNCHEON
MAY 18
11 a.m.
Alumni Hall, Connolly Ballroom

CLASS OF 1962 DINNER
MAY 18
6 p.m.
Fairmont Hotel, Pittsburgh

ALUMNI WEEKEND OPENING RECEPTION, BUFFET, WINE TASTING, AND SILENT AUCTION
MAY 18
6 p.m.
Bigelow Conference and Reception Center

SCOPE AND SCALPEL'S "BAT MED: THE DARK KNIGHT MATCHES"
MAY 18, 7:30 p.m.
MAY 20, 2 p.m.
Carlow College
Pittsburgh
For tickets and information:
www.scopeandscalpel.org

ALUMNI CHAMPAGNE BREAKFAST AND AWARDS PRESENTATION
MAY 19
9 a.m.
Scaife Hall

REUNION GALA
MAY 19
6 p.m.
Le Mont
Pittsburgh

ALUMNI FAREWELL BREAKFAST
MAY 20
10 a.m.
Holiday Inn Select, University Center
Pittsburgh

CLASS OF 2002 10 YEAR REUNION FAREWELL BREAKFAST
MAY 20
11 a.m.
Pittsburgh

CLASS OF 2012 COMMENCEMENT
MAY 21
10 a.m.
Carnegie Music Hall
Pittsburgh

UPCOMING HEALTH SCIENCES ALUMNI RECEPTION
DATE TBA
San Francisco, Calif.
For information:
Pat Carver
412-647-5307
cpat@pitt.edu

TO FIND OUT WHAT ELSE IS HAPPENING AT THE MEDICAL SCHOOL, GO TO www.health.pitt.edu

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DON'T PLAY THE GOAT COME BACK FOR REUNION

Billy, here, and his white-clad friend were best buddies at the School of Medicine in the mid-1930s, but they lost touch. Never attended any of their Pitt med reunions—don't that bleat all?

Don't mutton to yourself over missed opportunities. Take time—Friday, May 18 to Monday, May 21, 2012—to reconnect with the people and places that made your medical education special. It'll be fun.

Classes whose years end in 2 and 7 will be recognized throughout the weekend. Figuring out if your cohort is one is so easy a kid can do it. (Or you can just look at the calendar list on the other side of this cover.)

So goat for it, and join your classmates at Medical Alumni Weekend 2012.

Register at www.maa.pitt.edu/reunionweekend/

PHOTO COURTESY FAMILY OF EDWARD J. CARROLL JR. (MD '34)