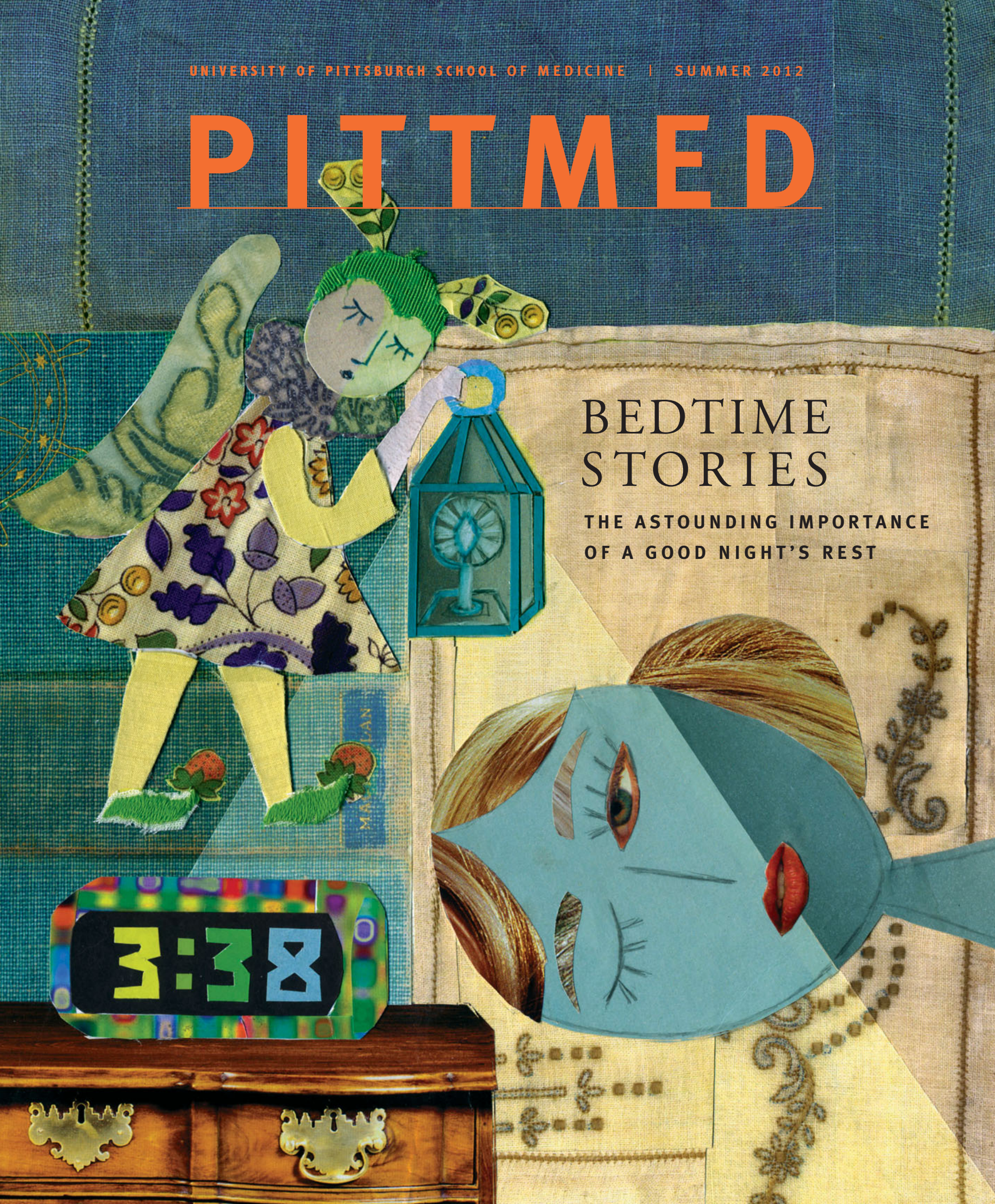
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | SUMMER 2012

PITTMED



BEDTIME STORIES

THE ASTOUNDING IMPORTANCE OF A GOOD NIGHT'S REST

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RECENT MAGAZINE HONORS

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

2011 IABC Golden Triangle
Award of Honor, Magazines

STEP RIGHT UP

Okay, maybe your life feels like a three-ring circus. But you can spare a minute to catch us up on your doings, right? Tell us about your career advancements, honors you've received, appointments, volunteer work, publications, and other death-defying acts. And we love to hear old Pitt memories. For instance, what's the story with this uni-doc we found in Pitt's 1970 *Hippocratean*? Quit clowning around and drop us a line at the contact info listed above, or friend us on Facebook at www.pittmedfb.pitt.edu/.

PITTMED

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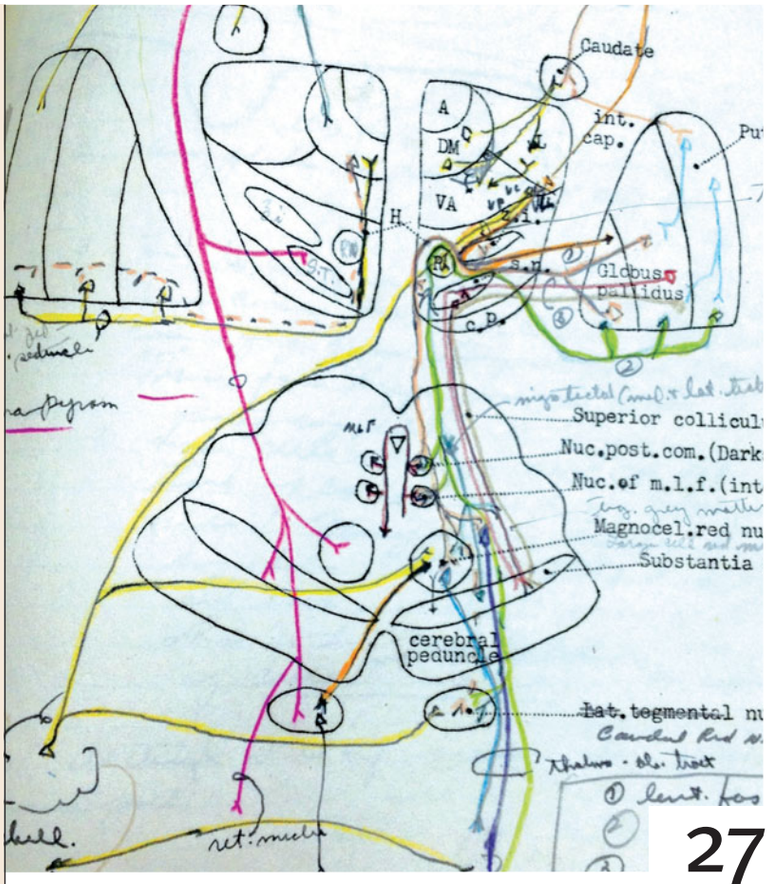
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In the spring of 1923, Davenport Hooker began to change the way medical students learned anatomy.
BY JENELLE PIFER

CONTRIBUTORS

JENELLE PIFER ["The Great Equalizer" and other stories] served as assistant editor at the literary magazine *Creative Nonfiction* before turning her attention to public radio. She now tells stories about science and the environment for *The Allegheny Front* and reports daily news for Pittsburgh's Essential Public Radio. She likes to combine voice, music, and the occasional goofy sound effect to make science stories approachable to a general audience. Pifer won the Press Club of Western Pennsylvania's 2012 Ed King Memorial Award for Radio. She says she values a good character and a juicy narrative—and found both while writing her feature story on Davenport Hooker's visionary leadership of the anatomy department. In addition to writing the Hooker feature, Pifer ably filled in for Associate Editor Elaine Vitone during Vitone's maternity leave. (Elaine and her husband, Dylan, and new daughter, Lena, are happy and thriving.)

Artist SHEILA ADVENTO ["Hard Bear Woman"] took up painting just last year—that wasn't long after she'd had a double hand transplant. She has always loved to draw, preferring Sharpies and other pens over pencils or chalk. "I draw whatever pops into my head. I'll draw faces . . . and sometimes, people will ask, *Who is that?* I'll say, *I don't know. It just came to me*." Advento also writes poetry and is considering pursuing studies in international business one day.

COVER

Sleep has the power to make or break health. (Cover: Catherine Lazure © 2012)

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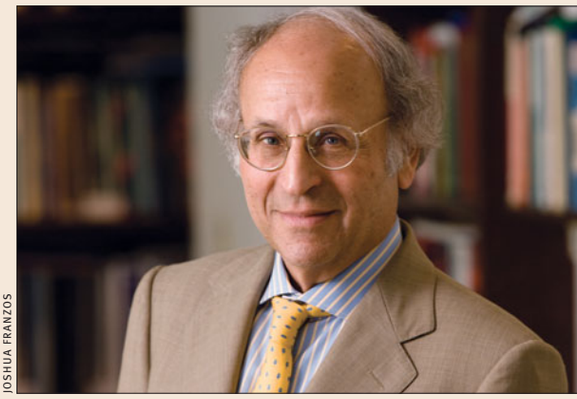
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JOSHUA FRANZOS

If you get to thinking you're a person of some influence, try ordering somebody else's dog around. —Will Rogers

This spring, my wife became enamored with a breed of dog with which I was unfamiliar, the Havanese. She suggested getting one, and I suggested that we dog sit for a weekend for a friend's Havanese, to get a sense of the breed, before making any decisions. A weekend was arranged with the Havanese guest; to protect his privacy, I'll call him Che. Che's owners warned us that the dog was quite affable except that he was insistent about sleeping with his owners in their bed. *Fine,* I thought to myself. *But that isn't going to happen in my house. This dog just needs discipline.* Well, I must have pushed Che out of bed 21 times before he surrendered and curled up on the dog pillow in the corner. Finally, we could rest soundly—until 2 a.m., when we found ourselves sitting bolt upright to earsplitting howling. The dog had rushed downstairs to the front door. *Someone's breaking in!* I rushed downstairs, but as I reached the bottom step, Che rushed up the steps. Having found no one breaking in, I returned upstairs, only to find the dog in my place in the bed. He'd taken advantage of my interest in preserving my territory just as he was attempting to expand his own.

Che exploited opportunities available to him; in an evolutionary sense, so do all organisms—and so do tumors. Case in point: A March 8 paper from British researchers in the *New England Journal of Medicine* shows us, in fine detail, using DNA and RNA sequencing and other methods, the genomic landscape of four primary renal carcinomas. In each case, the investigators found scores of varied and different mutations across spatially separated regions of the same tumor. Pathologists had a sense for some time that this was happening in cancer, but seeing intratumor heterogeneity in this detail is "somewhat frightening," admits Pitt's Adrian Lee, a renowned breast cancer specialist. "When you look at the complexity, it's hard to imagine a targeted therapy working." Gene expression patterns associated with good and poor prognoses were seen in different areas of the same tumor!

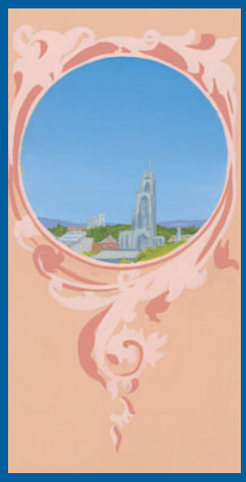
The researchers also found convergent evolution taking place—entirely different mutations ended up having the same effect (just as bats and birds independently developed wings)—notably, a loss of function of multiple tumor suppressor genes. "Obviously these genes have a very important function normally," notes Adrian, but "the tumor was going to select for mutations that would delete that function somehow and allow the tumor to survive and grow." Those mutations might have been selected in response to a lack of nutrients in particular areas of the tumor.

Though the challenges it reveals seem daunting, in the end, such research (similar molecular-level studies of tumor cells are going on at Pitt) and a deeper understanding of tumor biology will tell us how to approach personalized medicine. It probably makes sense, for example, to re-biopsy patients after targeted treatments. The group Adrian leads has already found that this may be a useful therapeutic strategy. It may also make sense to biopsy multiple sites in a tumor (and its metastases), given what we now appreciate about tumor adaptation and consequent therapeutic failure.

For the most part, the human species has excelled at adapting to our environment, but it appears the same is true of many tumors. Yet the evolutionary timescale for mutations in tumors is probably months rather than millions of years. This makes the work of Adrian and his colleagues all the more urgent.

A postscript: The affable traits and intelligence shared by the Havanese as a consequence of their Darwinian selection won out. We adopted Sasha, our delightful puppy, in April.

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



Devoted to noteworthy happenings

at the medical school

JOINING THE PARTY OF LINCOLN

Abraham Lincoln established the National Academy of Sciences (NAS) in 1863 to provide counsel to the government on matters scientific. In May 2012, three University of Pittsburgh School of Medicine faculty members joined the roll call of luminaries.

Among the 84 new members inducted this year are Yuan Chang, Patrick Moore, and Peter Strick. Chang, an MD Distinguished Professor and American Cancer Society Research Professor of Pathology, and Moore, an MD/MPH Distinguished Professor and American Cancer Society Research Professor of Microbiology and Medical Genetics, are husband and wife. He is also director of Pitt's Cancer Virology Program. They have identified two of the seven viruses known to cause cancer in humans. (For the latest one they identified—the Merkel cell virus, which causes a rare skin cancer—they also quickly found potential therapeutic agents.) Strick's work has illuminated the way in which neural circuitry controls voluntary movement. He is a PhD, Distinguished Professor of Neurobiology, director of the Systems Neuroscience Institute, codirector of the Center for the Neural Basis of Cognition, and a senior research career scientist in the VA Pittsburgh Healthcare System.

Chang, Moore, and Strick join Susan Amara, Thomas Detre Professor and chair of neurobiology, and Angela Gronenborn, UPMC Rosalind Franklin Professor and chair of structural biology, as active School of Medicine faculty in the NAS. *—Joe Miksch*



COURTESY DARREN SMITH

About Face

Although all transplants are complex, a face transplant offers additional challenges, notably aesthetics and the fact that several kinds of tissues are involved rather than just a single organ. But thanks to plastic surgery resident Darren Smith, Pitt surgeons have a new tool to help them prepare for their first patient. (The University of Pittsburgh and UPMC's plastic and reconstructive surgery program was given the go-ahead to do face transplants in 2010 and has since screened potential patients.)

Before coming to Pittsburgh, Smith (Res '14) was spending his summers in New York City as an undergrad and then a medical student working with Court Cutting, professor and surgeon in the Departments of Plastic Surgery and Surgery at New York University. In the program, Smith learned how to build computer-based models of craniofacial anatomy for teaching purposes.

Shortly after arriving in Pittsburgh, Smith began to experiment more with his interest: "[Pittsburgh's] transplant program was huge. It was an opportunity. . . . In Cutting's lab, we built generic models of anatomy from image data to teach surgical techniques. Now, we are using similar principles to build anatomical models of specific patients to plan face transplants." *—Shermi Sivaji*



CAMI MESA

A&Q

Darlene Zellers: Improving the lot of postdocs

It's hard out there for a postdoc. You're not quite a student any longer, and you're not faculty. You have some idea where you want your career to go, but you might not know how to get there. To help sketch out the career road map, Pitt's schools of the health sciences recently established the Center for Postdoctoral Affairs in the Health Sciences, which is led by Darlene Zellers (shown above, center, flanked by staff members Tammy Dennis and Steve Wendell), associate dean of postdoctoral affairs in the School of Medicine. The office will help postdocs—there are about 650 of them in the health sciences at Pitt, 90 percent of these in the School of Medicine—form concrete career goals by pairing them with faculty supervisors and requiring that these mentors and postdocs work together.

Why Pitt chose to formalize the postdoc experience

There are guidelines for postdocs that the provost established in 2003. If you're going to say, "What kind of progress are postdocs making on their research?" you have to understand what they were supposed to accomplish. This is where the career development plan comes into play. It's a preliminary document that then later serves as the baseline for the individual being evaluated. We are among a handful of institutions to require a career development plan. Our process is unique in that there is so much structure to our template.

On expected results

A national survey of postdocs called "Doctors Without Orders" found that structured oversight of postdoc training correlated with increased trainee satisfaction, increased number of publications, higher rating of faculty-mentor relationships, and decreased conflicts between faculty and postdocs. So they found a very positive correlation between degree of structure and those positive outcomes.

Her question for us

I would be interested in other faculties' reactions to putting a similar process in place. How adaptable do they think our process is to other academic cultures? *—Interview by Joe Miksch*

Next Generation

The School of Medicine's scholarly project requirement, an integral part of the curriculum since 2004, has given students a taste of the research world while they learn the physician's arts.

The Bert and Sally O'Malley Awards for Outstanding Medical Student Research recognize especially notable scholarly project efforts with $500 prizes. (Bert and Sally O'Malley got their bachelor's degrees at Pitt in 1959; he went on to obtain his MD here in 1963 and then enjoy a career as an innovative endocrinologist. Bert O'Malley, a National Medal of Science winner, is chair of molecular and cellular biology at Baylor College of Medicine.) The Class of 2012's O'Malley winners are Naomi Pitskel, Sameed Khatana, Adam Christopher, and the team of Hyun Kim and Mark Bernard. Pitskel's work (performed under the tutelage of Kevin Pelphrey of Yale University) used functional imaging and neurogenetics to study atypical gaze processing in people with autism. Khatana (working with Wen-Chih Wu at Brown University) examined the association between certain antipsychotics and metabolic syndrome in patients with mood and psychotic disorders. Christopher was recognized for his project studying the role of cilia in complex congenital heart disease. (He was mentored by Cecilia Lo, a PhD, Dr. F. Sargent Cheevers Professor, and chair of developmental biology at Pitt.) And Kim and Bernard looked into ways to protect cells from radiation damage. (The two worked with Pitt's Michael Epperly, a PhD and associate professor of radiation oncology, and Joel Greenberger, MD professor and chair of radiation oncology at Pitt.) *—JM*

Partners with J&J

Money is tight. Federal funding of basic science is lagging. The state has cut support for Pitt's School of Medicine and the University as a whole. So, the medical school is looking for additional partners. It's embarked on a new venture with the New Jersey–based Johnson & Johnson Corporate Office of Science and Technology, hoping that this symbiotic relationship will benefit research here and provide new commercial prospects for J&J.

D. Lansing Taylor, director of the University of Pittsburgh Drug Discovery Institute and Allegheny Foundation Professor of Computational and Systems Biology in the School of Medicine, is leading the effort on this end. J&J will fund four research projects, expected to take 12 to 18 months to complete, to the tune of $100,000 each. "The idea is that while science is imperfect, out of the four, one or two may look really promising, and J&J will want to invest more," Taylor says. The grants will be awarded in July. (The University's Clinical and Translational Science Institute will also contribute funding.)

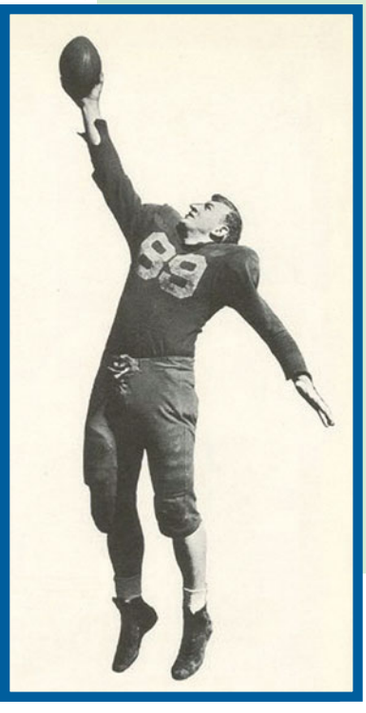
"Hopefully this is just the first [partnership]," Taylor says. "We're going to be aggressive in going after industry and getting our name out there." *—JM*



CATHERINE LAZURE

FLASHBACK

His patients remember the late Richard Deitrick (BS '54/MD '59) as the man who helped care for them and their babies (he served as head of ob/gyn at UPMC Mercy). Pitt football fans remember him as the man who, in 1952, helped the Panthers beat the Ohio State Buckeyes on their home field for the first time since 1936. Quoth the *Pittsburgh Press*: "Deitrick, a 215-pound end, caught the ball on Ohio State's 35-yard-line and stormed the rest of the way to the goal like an irritated bucking bronco, with several shifts of piggy-back riders having no success whatever at reining him in." After Deitrick's death in August 2011, we learned that the good doctor (who also played on Pitt's basketball and baseball teams) was drafted by the LA Rams, but instead chose to go to med school.



THE OWL, 1954

Deitrick captained the Panthers as a Pitt senior.

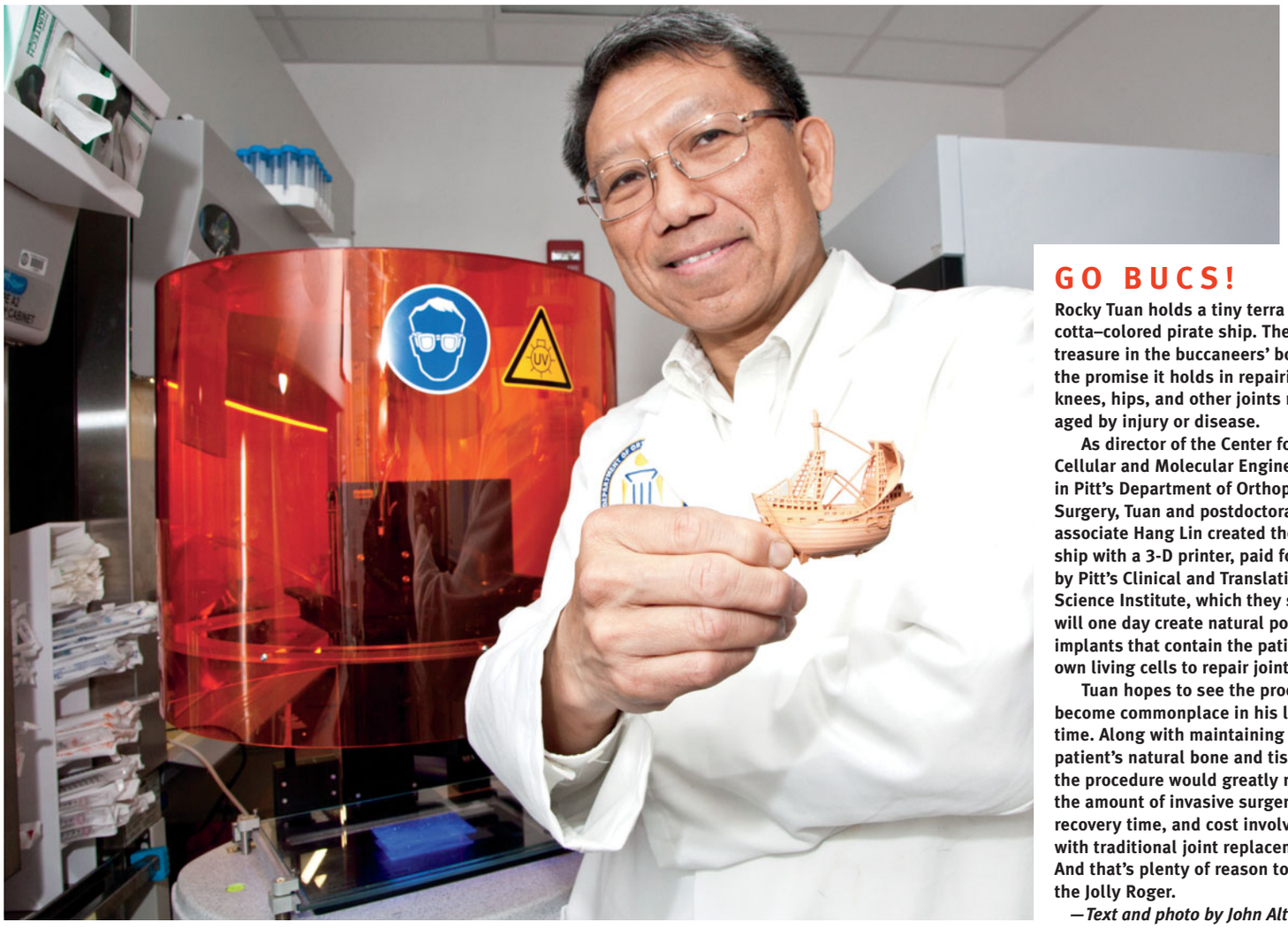
LONG LIVE MICE!

It seemed like a simple proposition. The stem cells in mice bred to age rapidly (mimicking the rare disease progeria) show signs of degeneration like those of naturally old mice. So Pitt's Johnny Huard, a PhD and professor in the Departments of Orthopaedic Surgery and of Microbiology and Molecular Genetics in the School of Medicine and director of its Stem Cell Research Center, and Laura Niedernhofer, an MD/PhD associate professor in Pitt's Department of Microbiology and Molecular Genetics and a member of the University of Pittsburgh Cancer Institute, wondered how an injection of stem cells derived from the muscles of a young mouse might affect the rapid aging process.

The results were beyond their wildest dreams. Not only did the mice injected with stem and progenitor cells display healthier, more active behavior, but they also lived two or three times longer than expected (sometimes as long as 66 days, instead of the 20- or 21-day lifespan seen in other mice bred to inherit progeria). Three sets of control groups demonstrated no change in life span.

Further experimentation showed that the new cells had spread out beyond the abdominal injection site to reside throughout the body, "but even that doesn't explain the benefit we're getting," says Huard. By placing aging and healthy stem cells side by side, Huard and Niedernhofer discovered that an as-of-yet unknown secretion of the healthy cells actually rescues the aging cells.

"We really believe that, down the road, we can help to improve aging and delay aging-related disorders in people," says Huard. "This is what scientists dream about." *—Justin Hopper*



GO BUCS!

Rocky Tuan holds a tiny terra cotta–colored pirate ship. The real treasure in the buccaneers' boat is the promise it holds in repairing knees, hips, and other joints ravaged by injury or disease.

As director of the Center for Cellular and Molecular Engineering in Pitt's Department of Orthopaedic Surgery, Tuan and postdoctoral associate Hang Lin created the ship with a 3-D printer, paid for by Pitt's Clinical and Translational Science Institute, which they say will one day create natural polymer implants that contain the patient's own living cells to repair joints.

Tuan hopes to see the process become commonplace in his lifetime. Along with maintaining the patient's natural bone and tissue, the procedure would greatly reduce the amount of invasive surgery, recovery time, and cost involved with traditional joint replacement. And that's plenty of reason to raise the Jolly Roger.

—Text and photo by John Altdorfer

Appointments

Jian-Min Yuan, an MD/PhD, will lead the Cancer Epidemiology, Prevention, and Control Program in the University of Pittsburgh Cancer Institute. He will also serve as professor of epidemiology in Pitt's Graduate School of Public Health (GSPH) and associate director of cancer prevention and population science at the University of Pittsburgh Cancer Institute.

Yuan is interested in how environment, diet, behavior, and genetics influence cancer. His investigations have included the potential roles that green tea, incense, and volatiles released by Chinese home cooking might play in the disease. Yuan is a principal investigator on four National Institutes of Health–funded projects; he comes to Pittsburgh from the University of Minnesota.



Yuan

One of the U.K.'s foremost ophthalmic surgeons is now chief of the Division of Pediatric Ophthalmology at Children's Hospital of Pittsburgh of UPMC, director of Pediatric Program Development at UPMC Eye Center, and visiting professor of ophthalmology at Pitt. **Kanwal "Ken" Nischal** came to Pittsburgh last fall from Great Ormond Street Hospital for Children in London. In addition to his experience as a pediatric eye surgeon, Nischal has developed treatment algorithms that include innovative surgical techniques for children born with opaque corneas.



Nischal

Nathan Yates, a PhD, has been named associate professor of cell biology in the School of Medicine and scientific director of Pitt's Biomedical Mass Spectrometry Center. As codirector of the University of Pittsburgh Cancer Institute's Cancer Biomarkers Facility, Yates will pursue research on the discovery and measurement of protein biomarkers that may be used to detect disease early and help doctors select the best treatments. Prior to joining Pitt, Yates was scientific director for the Department of Exploratory and Translational Science at Merck & Co., where he codeveloped differential mass spectrometry. At Pitt, Yates plans to collaborate with scientists from leading academic institutions to develop a groundbreaking cloud computing platform for the storage and analysis of proteomics data.



Yates

As of April, the McGowan Institute for Regenerative Medicine has a new director and associate director. Professor of Surgery **William Wagner**, a PhD who takes over as director, is one of the institute's founders. Wagner's research into cardiovascular engineering, focusing both on the monitoring of existing equipment and the development of new technologies, involves graduate and postdoctoral researchers from a broad range of specialties and has resulted in numerous patent filings and awards for innovation. McGowan's new associate director is **Rocky Tuan** (shown with miniature ship above), a PhD and the Arthur J. Rooney Sr. Professor of Sports Medicine in the Department of Orthopaedic Surgery. Before coming to Pittsburgh in 2009, Tuan served as chief of the Cartilage Biology and Orthopaedics Branch of the National Institute of Arthritis and Musculoskeletal and Skin Diseases. Tuan's research has run the gamut from the development of the musculoskeletal system, to cell biochemistry, nanotechnology, and tissue-regeneration technology. *—JH*



Wagner



RUB MY BELLY 101

Nola, a muscular and squirmy Staffordshire terrier of an almost metallic gray hue, was lounging in the Cathedral of Learning on a winter Tuesday evening. The wind blew cold outside, and as University of Pittsburgh students made their way in from the chill Nola leapt into action—okay, lounged into action. As hand after hand petted her short, soft coat, she smiled, kissed, and wiggled.

Aaah . . . that'll take the edge off a stressful day.

It really does, too, says Dawn Marcus, an MD professor in the Department of Anesthesiology at the University of Pittsburgh. Marcus is a pain researcher and author of *The Power of Wagging Tails: A Doctor's Guide to Dog Therapy and Healing* (Demos Health, 2011). "[Therapy dogs] lower heart rate, blood pressure, and respiratory rate. Endorphins go up. There are substantial and long-lasting physiological changes," she says.

So how do dogs get schooled for the clinic and other therapy environments? Here's one way: Top off a rigorous certification program by allowing hundreds of students to canoodle with the pooches. The College Canines have been visiting the Cathedral every Tuesday evening when class is in session for years now. Nola and her cohort of about 10 other beasties are accompanied by volunteers from the Western Pennsylvania Humane Society, which sponsors the program. Students stop to kiss and pet and coo and snap photos to share with family. Some say they miss their own hounds, and the College Canines help alleviate some homesickness.

Marsha Robbins, an educator with the Humane Society, therapy dog trainer, and all-around pooch pusher, says, "The students seem to find this a very relaxing time. The dogs love it, too. They start to wiggle their tails when they know they're coming here." *—Joe Miksch*

—Photo by Martha Rial

Explorations and revelations taking place in the medical school



The U.S. Department of Agriculture recommends that about 66 percent of dietary fat should be unsaturated. But don't overdo it. An excess accumulation of these fats seems to be harmful in obese patients with pancreatitis.

UNSATURATED SOLUTION

RESEARCH INTO PANCREATITIS DEATHS YIELDS AN UNEXPECTED CULPRIT

BY MELINDA WENNER MOYER

Vijay Singh was perplexed. The assistant professor in the University of Pittsburgh's Division of Gastroenterology, Hepatology, and Nutrition was using rodents to study acute pancreatitis, a rapid-onset illness in which the pancreas becomes swollen and inflamed. But time and time again, what Singh learned from his average-weight animals didn't explain what happened to people when the condition was severe: They often died within days. The consensus based on animal studies was that pancreatitis was caused by malfunctioning proteins that ate up the organ; yet researchers had developed drugs to tame these vicious proteins, and all had failed miserably in clinical trials.

"After being in the field for 10 years, one starts thinking, 'What is going on?'" Singh says. To find out, he teamed up with his wife, Pitt's Sarah Navina, an assistant professor of pathology, who had access to the postmortem bodies of pancreatitis victims. Seventy-four autopsies and a handful of lab experiments later, Singh and Navina published a paper in *Science Translational Medicine* uncovering a shocking new cause for deadly pancreatitis: unsaturated fat.

Obese people with pancreatitis are much more likely than lean people to succumb to multi-organ failure. When Singh and Navina compared the pancreases of lean and obese people who had died, they began to see why. Whenever Singh asked his wife to point out a pancreatic region that was necrotic—that is, where cells had died a particularly violent death—"it would be around a chunk of necrosed fat," Singh recalls. In other words, fat and dead pancreatic cells seemed to go hand in hand. They also found that those with severe pancreatitis were more likely to be obese and have considerably more pancreatic fat than were healthy subjects.

Singh still didn't know whether fat cells caused pancreatic cell death. Their juxtaposition might be a coincidence. When the pancreas' pyramid-shaped acinar cells become damaged, as they do in pancreatitis, their normal processing fails and the cells begin spilling their powerful enzymes everywhere. Back in his lab, Singh placed acinar and fat cells side by side so that everything the acinar cells secreted came into contact with the fat cells and vice versa. The acinar cells soon died. Inside the shared liquid in which the cells were cultured, Singh found high levels of unsaturated fatty acids—essential fats that we get through our food. But the cells survived when Singh added a molecule called orlistat, which inhibits lipases that break down triglycerides. (Orlistat prevents the body from absorbing the fats and is sometimes prescribed for patients so they don't regain lost weight.)

Singh surmised that the spilled digestive proteins prompted the fat cells to release their stored unsaturated acids. Then, lipases (also part of the cocktail of digestive proteins) broke down the unsaturated fats. But what he still didn't know was how the unsaturated fats' byproducts were harming the pancreatic cells. When he looked inside dying acinar cells, he saw that the byproducts were blocking two key steps in the cells' energy-production pathway. Unsaturated fat was literally starving pancreatic cells of energy and killing them.

This discovery explains how unsaturated fats harm pancreatic cells. But how do they cause multi-organ failure? Because blood travels from the pancreas directly to other organs, including the kidneys and lungs, Singh believes that unsaturated acids reach those organs and damage them, too. As the final piece of his puzzle, Singh gave orlistat to obese mice with pancreatitis. They did not develop multi-organ failure and die. "I was very, very, very surprised," says Singh.

The U.S. Department of Agriculture recommends that 66 percent of dietary fat should be unsaturated. Singh speculates that unsaturated fats are only dangerous when we eat too many of them and they are stored. In smaller quantities, these fats are used up rapidly.

"The secret lies in the excess accumulation," he says.

Singh's work was funded by the National Center for Research Resources, Pitt's Clinical and Translational Science Institute, and others. His next goal is to determine which pancreatic lipases break down unsaturated fats and attempt to inhibit them with drugs to protect obese pancreatitis patients. (When taken as a pill, orlistat doesn't get absorbed enought to inhibit pancreatic lipases, says Singh.) But this work could apply to other acute conditions, too: For example, burn victims have higher-than-normal blood levels of unsaturated fats.

There are far more questions than answers at this point, but one thing seems certain: Unsaturated fats aren't harmless. "What is chanted about unsaturated fats being very good—we have to take that with a pinch of salt," Singh says.

GETTY IMAGES

SCHOOL OF FISH

A NEW DIRECTION IN PARKINSON'S RESEARCH

BY JUSTIN HOPPER



COURTESY E. BURTON

A 7-day-old zebra fish larva used to study neurodegenerative disease swims in the well of a plate in Burton's laboratory.

Edward Burton, an MD, looks forward to the day when the two sides of his work coalesce. As a practicing clinician in UPMC's Department of Neurology, Burton spends a few days each week seeing patients suffering from Parkinson's and other neurodegenerative diseases. As a research scientist in the University's Pittsburgh Institute for Neurodegenerative Diseases (PIND) and assistant professor of neurology and of microbiology and molecular genetics, Burton spends the balance of his time with an unlikely subject—zebra fish.

Unlikely, that is, for a practicing MD. Besides being home-aquarium favorites, zebra fish have long been found in labs studying developmental biology. In the early days of their lives, zebra fish are transparent—a state made permanent in the human-engineered species called Casper zebra fish. This gives researchers the opportunity to view physiological changes in a living, growing vertebrate. But in 2004, Burton looked at Pitt's world-class zebra fish facilities—aquarium tanks stacked 10 feet high filling a football-field-sized room—and began to think, "What could these animals tell us about Parkinson's disease?"

"You can do things with zebra fish you can't do with other animals," says Burton. "If we had a zebra fish model for Parkinson's, because they're transparent we could look at the biochemistry [of the disease and potential treatments] in a living animal."

Before zebra fish can be effectively used to study Parkinson's, someone needs to create a model—to understand how the disease affects a zebra fish's behavior and biochemistry in ways that can be correlated with the same effects in a human. (Since 2004, several other labs around the world have begun working on creating this model, often using Burton's publications as groundwork.)

Behavior is relatively easy: Zebra fish are active critters with fast-paced lives, and Burton can tell a Parkinsonian fish within two hours (that makes it possible to do quick, large-sample tests for drug effectiveness). In fact, Burton and others at PIND showed that scientists could make a zebra fish observably Parkinsonian by knocking out its dopamine system.

The biochemistry is tougher to sort out but has come a long way recently, as evidenced by a paper Burton and colleagues published late in 2011 in *The Journal of Biological Chemistry* titled "Hypokinesia and Reduced Dopamine Levels in Zebrafish Lacking β- and γ1-Synucleins." This research has made an important advance towards establishing Burton's zebra fish model for Parkinson's by mapping zebra fish synucleins—proteins present in neural tissue that are heavily implicated in Parkinson's research.

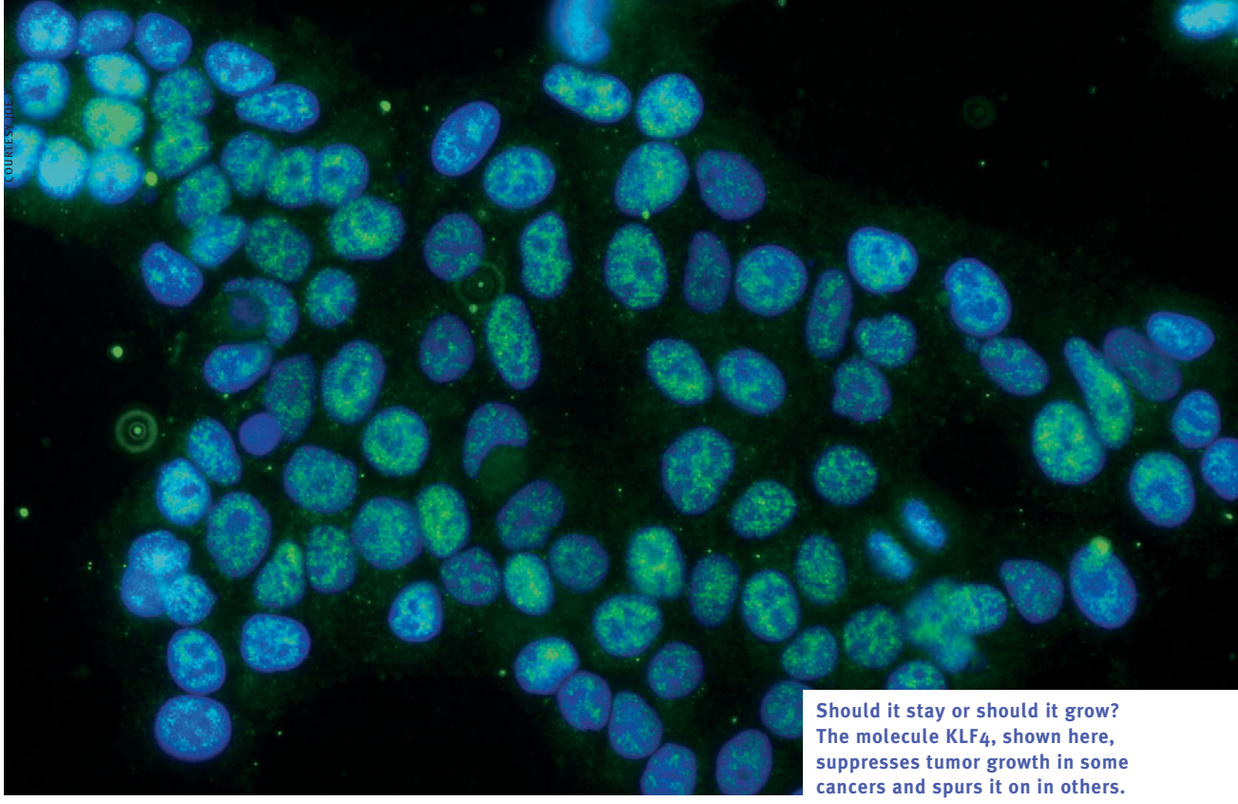
"Synucleins are important in Parkinson's. For example, rats lacking α-synuclein become resistant to toxins commonly used to model Parkinson's," says Burton. "We wanted to know, 'Do zebra fish have α-synuclein?'"

The answer, it turned out, was no. Which makes it somewhat more complicated, but by no means impossible, to create the model. His lab will attempt to genetically engineer a fish with α-synuclein.

That fish is next on Burton's to-do list. He believes there will be a big payoff in terms of the ability of scientists to witness Parkinsonian biochemistry and degeneration in a transparent model. "It's a long road, because we've got to invent everything ourselves [in terms of techniques and reagents]," says Burton. "Creating an effective treatment for human patients is a multidecade process." ■

ONE MOLECULE, TWO EFFECTS ON CANCER

BY DANA YATES



COURTESY YONG WAN

Should it stay or should it grow? The molecule KLF4, shown here, suppresses tumor growth in some cancers and spurs it on in others.

QUITE A RANGE

The human body can work in contradictory ways. Take, for instance, Kruppel-like factor 4 (KLF4)—a molecule that suppresses tumor growth in colon cancer but spurs it on in breast cancer. So what drives these different responses? According to a University of Pittsburgh researcher, it could all come down to one protein.

Yong Wan, an associate professor in the Department of Cell Biology and Physiology and a member of the University of Pittsburgh Cancer Institute, has studied KLF4 for several years. The molecule is of great importance to current cell research: In 2006, researcher Shinya Yamanaka at Kyoto University discovered that KLF4, in combination with three other molecules, could be used to turn mature cells into a type of cell very similar to embryonic stem cells. Because stem cells are a possible starting point for cancer, KLF4—and its flip-flopping effects on cancerous cells—is of particular interest to researchers such as Wan.

"It was an exciting development, and I wanted to know what triggered the switch and how the process worked," says Wan. His research on the subject, which was funded by the National Institutes of Health and the American Cancer Society, was published earlier this year in *Molecular Cell*.

To solve the KLF4 conundrum, Wan and his research team grew cancer cells in the laboratory. From there, the researchers separated proteins produced by the cancer cells from the larger groups in which they normally work. Using sophisticated techniques to examine the interactions of individual proteins, Wan's team began to focus on a protein made by the von Hippel-Lindau gene. Called pVHL, this protein binds to KLF4, activating a process that ultimately causes KLF4 to lose function.

KLF4 affects the fate of cells by stimulating or inhibiting a network of genes that are involved in a variety of cellular functions. Those tasks include everything from cell-cycle regulation and metabolism to stem-cell renewal and cell death. Essentially, KLF4 is akin to an actor with an impressive range. In some cases, KLF4 acts as a villain, increasing cell numbers and encouraging them to transform into stem cells—two scenarios that lead to cancer. But, as the researchers found, KLF4 can also play the role of a superhero. In fact, in some cells it prompts the production of proteins that stop new cells from forming.

Enter pVHL stage right. When pVHL is high, the lifespan of KLF4 is cut short; if it is low, KLF4 lasts longer and cell numbers multiply. But there's more to the story. Cancer cells are abnormal, and as such, they produce atypical proteins. Wan believes these unusual proteins could also influence the interaction between pVHL and KLF4. And for that reason, Wan's work to better understand these processes is ongoing. Down the road, Wan's research could contribute to a number of important outcomes. Among them, a new way to predict a future cancer diagnosis and a novel target for drug therapy.

Additionally, Wan's work may one day change how doctors treat estrogen-receptor-positive breast cancer. Currently, some women with this type of cancer take tamoxifen to interfere with the activity of estrogen, the naturally occurring and tightly controlled female hormone that can be hijacked to promote tumor growth. Tamoxifen, however, can have serious side effects, such as blood clots, strokes, uterine cancer, and cataracts. Moreover, many women develop resistance to the drug. Wan's research could lead to a new endocrine therapy for hormone-sensitive breast cancer.

"It all starts with knowing how KLF4 is regulated," he says. ■


3:38

THE POWER TO MAKE OR BREAK OUR HEALTH, FROM BIRTH TO ADULTHOOD AND EVER AFTER | BY ELAINE VITONE

SLEEPING'S BEAUTY

Pick a piece of your physiology, any piece. Heart health, lung health, kidney health. Appetite and metabolism. Or consider memory, learning, and emotion. Pain. Aging. The immune system. Neurological development. Fetal development. Heck, any cellular-level kick-starting or daily humming-along, period. Every single aspect of our health that's been measured so far has been directly linked to sleep. There are "clock genes" in every cell of our bodies. How we operate in our 24-hour rhythms is central not only to the quality of our lives but also how long we get to live. That could make for a pretty scary bedtime story, given that we live in a culture that tends to squeeze in shut-eye between the 11 o'clock news and breakfast.

"Measuring sleep is like measuring temperature and blood pressure," says David Kupfer, an MD and the Thomas Detre Professor of Psychiatry and a professor of neuroscience and of clinical and translational science in the University of Pittsburgh School of Medicine. (Kupfer served as chair of psychiatry when that department, with Western Psychiatric Institute and Clinic of UPMC, or WPIC, first became known as a preeminent research center.)

A sleep schedule gone askew can have devastating effects throughout the life cycle. Fortunately, sleep is a modifiable behavior.

ILLUSTRATIONS | CATHERINE LAZURE

When we lose step in our 24-hour rhythms and feel the inevitable effects, it's an outward sign that something's wrong, Kupfer says—or, many times, if sleep problems are left untreated, something will be.

A couple years ago, for the first time in its 30-plus-year history, *Healthy People*—the marching orders the U.S. Department of Health and Human Services (HHS) issues as benchmarks for better health—included an entire chapter on sleep. But the integral role of sleep in every aspect of medicine has been a mantra at Pitt for decades now.

It all started once upon a … okay, in 1973, when Kupfer came here from Yale as the first recruit of the late, great head of WPIC, Thomas Detre, to set up a chronobiology lab—one of the first four or five clinics of its kind in the country. Kupfer was among the first to look at sleep as a biological marker of depression, and those observations were among a few that prompted the biological revolution in psychiatry.

Sleep research at Pitt helped bring psychiatry into the realm of the biological science of the body. And ever since, Kupfer and Co. have urged Pitt's medical community to (so sorry) wake up to sleep.

"Now we have a third generation of sleep researchers here," says Kupfer, adding that Pitt has probably had more federal funding in this area than just about any other institution—and is beginning to train more people.

About five years ago, the 50-some-odd sleep researchers scattered across the University began to organize more formally under what's now called the Sleep Medicine Institute, which is based on the 11th floor of WPIC. It's a veritable Who's Who of sleep peeps: former presidents of the American Academy of Sleep Medicine and the Sleep Research Society, and authors of the sleep-disorders section of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM). (Kupfer mentee Charles Reynolds, UPMC Endowed Professor of Geriatric Psychiatry and director of the Pitt/UPMC Aging Institute, chairs the sleep-disorder group for the forthcoming DSM-5. Kupfer himself chairs the overall DSM-5 task force.)

At sleep-medicine conferences, it's hard not to notice Pitt people; their colleagues call Pittsburgh a "sleep mecca." On these pages is a sampling of what these scientists—with support from the National Institutes of Health, the Commonwealth of Pennsylvania, the Department of Defense, and Pitt's Clinical and Translational Science Institute, among others—are uncovering about sleep and human health.

They're finding that a sleep schedule gone askew can have devastating effects throughout the life cycle—but, fortunately, sleep is a modifiable human behavior. When we sleep better, we drift back to health, both in body and mind. Our zzz's can become the stuff of a Disney happy ending rather than a grizzly Grimm fairy tale.

DOWN WILL COME BABY

"There is absolutely no excuse for watching the 11 o'clock news," says Pitt's Timothy H. Monk, PhD, DSc professor of psychiatry. "I always say that when I'm interviewed on TV programs, and it ends up on the cutting room floor."

Monk, who has a sense of humor about just about everything except the importance of a healthy sleep rhythm, has been studying the body clock since 1974, back when people wouldn't even use the term *circadian rhythm* without putting quotes around it. He investigates what happens to sleep, performance, and mood when the biological clock is disrupted—by jet lag, space travel, depression, age, what have you. Monk wrote some of the first studies showing disruptions in circadian rhythms experienced by night nurses, astronauts, depressed patients, and octogenarians. He also developed widely used tools for measuring sleep rhythmicity.

Most of Monk's work has focused on late adulthood, but in recent years, he has learned that a botched circadian cycle can be detrimental even in infancy ("something a million miles from your thoughts," he says with a laugh, gesturing to this writer's then-very-pregnant belly).

Collaborating with researchers at the University of Wisconsin in the early '90s, Monk enlisted new parents in a study of their 1-month-old babies' daily routines, charting out their sleep times as well as their time spent feeding, playing, diaper-changing, and cuddling-up for comfort. Monk's Wisconsin colleagues then revisited these families several times throughout the tykes' school-age years.



A bad night's sleep can turn even the most amiable among us into monsters the next day. Can poor sleep patterns impair the ability to regulate our emotions in the longer term?

The team found that the babies with irregular sleep and lifestyle routines were significantly more likely to grow up to have anxiety in early adolescence.

Monk believes that, among other factors, more regular routines for Baby make for a more predictable set of demands on Mom and Dad, which in turn makes the parents more cued into their kids' cues. When these things line up, parents are all the more confident in their parenting skills. And a confident parent who's attuned to a baby's needs is exactly the sort of parent to turn out children who can regulate their emotions.

So what's his advice for new parents? Is there anything we can do? Are the circadian rhythms of kiddos set by nature or nurture? "Both. So you help it along," says Monk, adding that letting the sun shine into the room during the daytime and darkening the bedroom at night certainly help. But mostly, it's about tending to an infant differently at night than you do the rest of the day. "At night, you're talking quietly, you're soothing her. But in the morning, it's, *Hey, Baby!*"

MONSTER UNDER THE BEDHEAD

Sleep and emotion have all sorts of interesting intersections (which David Kupfer, Charles Reynolds, and others at Pitt have helped to uncover, by the way): People with insomnia often have problems with emotion regulation. Depression is more severe and resistant to treatment in people who have poor sleep, and it's often preceded by poor sleep. And then, of course, even for those of us who don't suffer from either malady, an all-nighter—or even a bad night's sleep—can turn the most amiable among us into monsters.

So, Peter Franzen, Pitt assistant professor of psychiatry, wondered: Is this more than just coincidence? We all have our own anecdotal evidence along these lines, but is this something you can measure in a lab? And what is the cumulative effect? Over time, can poor sleep actually

sabotage our emotional health?

Franzen did a pilot study of teens in their all-too-typical state—way more sleep deprived than their still-developing brains ought to be. He showed them photographs of emotionally charged scenes and played for them recordings of disturbing verbal exchanges, then asked the teens to control their emotional reactions to these stimuli. Meanwhile, Franzen's team measured the teens' pupil-dilation responses: "It's sort of an old-school measure [of emotional regulation]," he says, "but it's cheap and easy to do, and it's noninvasive." (Pupil dilation also coincides with cognitive function. So, just to be sure that wasn't what was behind any changes in their peepers, Franzen also observed the kids discussing conflict with their friends and measured signs of emotional regulation or lack thereof.)

Sure enough, when Franzen compared the sleep-deprived adolescents to controls, pupils were about twice as big when the sleepy kids were exposed to negative stimuli. (Their interactions with their friends hinted at a similar pattern—dominance, aggression, general short-fusedness.)

With a new National Institutes of Health Research Project Grant (a.k.a. R01 grant) in hand, this summer Franzen is launching a full investigation of these pilot-study results, hoping to finally arrive at the first objective measures of impaired emotional control related to sleep deprivation. He's comparing the results of the teen studies to his previous work with young adults, probing the question of whether or not adolescents are more vulnerable to the ill effects of sleep loss. And further down the road, he plans to tease out how exactly neural circuitry changes when people, especially adolescents, don't get enough sleep.

Even as kids are waking up early for the 8 a.m. school bell, they're burning the midnight oil—because that's what they're hardwired to do, says Franzen. "At puberty, the desire to stay awake at night is not just social—there are biological influences, too."

The teen years are such a vulnerable time—"when kids are increasing their risk for development of substance abuse and depression," says Franzen. He hopes that by showing neural circuitry shifts at work, eventually he can make a case for screening kids in the clinic and flagging the ones who may be headed for trouble. "Adolescence is perhaps a unique opportunity to prevent a problem from happening in the first place," he says.

SNORING: THE CINDERELLA OF SLEEP

Though still underdiagnosed, sleep apnea has gained attention as a serious public-health risk. The evidence continues to pour in. For example, Patrick Strollo—professor of medicine and of clinical and translational science, medical director of the UPMC Sleep Medicine Center, and codirector of the Sleep Medicine Institute—found a whole new reason these patients have such poor outcomes: They have higher levels of a particularly bad form of artery-hardening cholesterol called LDL subclass B.

But snoring? It's the other sister, just sort of *there*, like background noise. We've always taken for granted that, yes, people who report snoring tend to have health problems, but that's just because they have sleep apnea, right? In five decades of research on sleep disturbances and their devastating effect on cardiovascular health, we've never really monitored snoring.

But a few years ago, when Tom Rice (Fel '11) began working with Kim Sutton-Tyrrell, a cardiovascular epidemiologist in Pitt's Graduate School of Public Health, he read an Australian study with a small sample of snorers verses nonsnorers. It suggested that sawing logs—or rather, the resulting vibrations in the neck that rattle the carotid artery—might actually do damage, independent of sleep apnea.

Piggy-backing on a cardiovascular-risk study of Sutton-Tyrrell's, Rice studied young adults who were overweight but who had not developed cardiovascular disease, measuring the vibrations in the air flow in their noses as well as their carotid artery wear and tear over time. The results were more impressive than he'd expected: Nonsnorers in the study had healthy, thin carotid walls. People with sleep apnea, as it's long been known, have thick carotid artery walls. But the snorers in Rice's study were somewhere in the middle.

Snoring, it seems, could be part of a gradual progression to heart attacks and strokes.

"We don't know all the reasons sleep apnea leads to cardiovascular disease," says Rice, who's now assistant professor of medicine. He adds that fragmented sleep and lack of oxygen explain some, but not all, of it. "[Perhaps] snoring damages the arteries in the neck and then makes them more susceptible to the damage from the low oxygen level."

Rice presented the findings from his ongoing, now-NIH-funded study at the International Symposium on Sleep and Breathing in Barcelona last spring.

Assistant Professor of Psychiatry Wendy Troxel (PhD '05), another one of the many Pitt people who trained here in sleep medicine and stayed to join the faculty, has also made surprising discoveries regarding this Cinderella of sleep disturbances. In the journal *Sleep* in 2010, Troxel published the first prospective study showing that people who report snoring and insomnia complaints had greater risk of developing metabolic syndrome, a cluster of factors that increase the odds of getting heart disease. These findings are the first to show that commonly reported sleep problems, including snoring and difficulty falling asleep, can predict the onset of metabolic syndrome over a three-year follow-up period.

Some 40 to 50 percent of the U.S. adult population snores, and those are just the ones we know about. If you sleep alone, or if your better half is sleeping soundly, you could be a snorer and be none the wiser.



Sawing logs—all in a night's work? Evidence suggests that snoring may be part of a progression to cardiovascular disease.



MOTHER'S SLUMBER, SPOILED, SPELLS TROUBLE

Michele Okun (Fel '07) knows her preggos. She can even guess the exact gestational stage of a *Pitt Med* writer just by looking at her (33 weeks at the time I waddled into her office). "Glad I haven't lost my touch," she says. "I haven't worked with third-trimester women in a long time."

For 10 years, Okun, a PhD assistant professor of psychiatry and psychology and a psychoneuroimmunologist, has studied the impact of disturbed sleep on women's health. The past few years her focus has been on weeks 10 to 20 of pregnancy. This is when cells within the uterus begin to expand and remodel to conjure up that most crucial cauldron of baby-making magic: the placenta.

Okun explains that throughout pregnancy, the immune system churns in a delicate balance, its demands constantly changing. Too little inflammation at the onset, and the blastocyst can't implant properly. Too much immune response at various points thereafter, and the woman's body rejects the fetus.

When the placenta is developing is the most precarious time. The most dangerous outcomes of pregnancy—low birth weight, preterm birth, preeclampsia, you name it—are associated with heightened levels of cytokines, messenger cells that signal immune responses, during this critical interval.

And what's one common cause of climbing cytokine levels? Sleep loss, of course.

Okun says that in common lore as well as in ob/gyn literature, everyone assumes women are supposed to be cursed with crummy sleep pretty much the whole way through pregnancy. But in Okun's ongoing, four-year study, which was funded by a K99/R00 grant from the NIH, she has found that this is, first of all, not true. (In fact, in the first trimester, about 30 percent sleep very well, and another 30 percent sleep poorly.) And secondly, it is a potentially pretty dangerous assumption. As she follows the outcomes of the women in her study, she's finding that those who sleep poorly between weeks 10 and 20 are indeed having more complications. Eventually, Okun hopes her work will inform a new set of primer questions that ob/gyns can use to screen for problems from the get-go—an idea that's pregnant with potential.

HAUNTING

Sleep affects health, which affects sleep. It's a complicated mess to sort out, which is why most academic medical centers' sleep programs have single-disease foci. But Pitt's sleep think tank is different, says Martica Hall, associate professor of psychiatry and psychology and of clinical and translational science. "I think it's fair to say in Pittsburgh we've created the most diverse set of studies investigating the bidirectional relationship between sleep and health."

Hall, who came to Pitt for her PhD in biopsychology in 1995, was the first of Pitt's sleep peeps to study physical health, and she's proud to have fostered what's now a very big interest in this giant, sprawling family of researchers. "It's a big sandbox, and we're having a lot of fun."

Hall's particular interest is how stress affects sleep, which, in turn, affects stress, and how that whole ugly cycle has a way of throwing our health for a loop. She's studied how acute and chronic stress stymie sleep and health in a number of populations: adolescents, young adults, parents of sick children, people with insomnia or depression, caregivers, elders in bereavement. In measuring heart-rate variability—a sign of a healthy ticker capable of adapting to a changing environment—Hall has shown that everyone, even healthy young college kids, do worse by this measure when they're introduced to acute stress before they hit the hay. "I call it haunting," she says.

As principal investigator on the ancillary sleep study to the NIH's Study of Women's Health Across the Nation, Hall conducted the first multisite study to understand who develops sleep disturbances during menopause and why. So far, she and her collaborators have published numerous papers to this end, on everything from the intricate dance between hormones, hot flashes, and brain activity during sleep to how factors like marriage affect sleep.

One factor that's clearly accounting for significant differences is race. African American women have the highest risk for persistent sleep disturbances, she's found—even when you control for stress level, hot flashes, health complaints, medication, environment, depression, worries about money, and more.

However, there's something "very intriguing" going on that doesn't yet add up, she says.

"If you look at brain waves in African American women, they do not sleep as deeply as white women, but their periphery tells a different story. Their heart rate variability during sleep is more ideal than that seen in whites. So now we are taking a step back to try and better understand more about race differences in nocturnal physiology. Because we actually know very little."

A team of researchers is trying to understand who develops sleep problems during menopause and why.



TURNING THE PAGE

Imagine a truck lumbering down a dusty desert road. Out of nowhere, there's an explosion, an ambush, a threat that's audible with terrifying clarity, but you can't see it. The person in the seat beside you is hurt, but you can't tell how badly. You are scared, out of breath, and utterly helpless. And then you wake up.

This scenario is all too typical among the nearly 2 million who have served in the wars in Iraq and Afghanistan. For 90 percent of people with post-traumatic stress disorder (PTSD), the brain has a terrible habit of replaying nightmares night after night. The lack of sleep only compounds what they're going through: feeling anxious, irritable, depressed, and frustrated as they struggle to reenter school, family, friendships, and work environments. Concentration suffers. Tempers rise. Isolation, despair, and alcohol and substance abuse often follow.

Poor sleep is a risk factor for PTSD, depression, and substance abuse. But this newest generation of foreign-war veterans has given researchers the chance to, for the first time, study—and, more importantly, screen and intervene for—those returning from combat zones before a long descent into illness. "If we can fix this one aspect, sleep, we may have a broad impact on mental health," says Pitt's Anne Germain, PhD associate professor of psychiatry.

"And it's one that people want. They want to sleep well." In

addition, for many veterans, help with a sleep disorder—one mental health complaint that doesn't carry a stigma—is a gateway treatment to addressing other difficulties they may have.

Germain teaches veterans how to stop replaying their nightmares, which have become involuntary habits, default modes for their sleeping minds. Through writing and visualizing exercises that she's developed, Germain trains veterans to finally turn the page and dream about something else by focusing on a whole new set of images of their choosing.

She's also fine-tuning and packaging the treatment so that it's easy for primary care providers, nurses, social workers—any number of people with even minimal training in mental health—to provide the treatment, as well.

Germain is pressing on and digging deeper, trying to understand what happens in the sleeping brain of a person who's been exposed to traumatic events, in hopes of finding better treatments. In the past six years, she has studied some 400 veterans; one additional year's work will complete the data-analysis portion of this U.S. Department of Defense–funded project.

In imaging studies, Germain is showing that, in both waking and REM/dream-sleeping, the brains of veterans who have PTSD light up in regions of emotional reaction and alertness: the amygdala, the hippocampus, the medial cortex, and the arousal regions of the brain stem.

"Your brain is saying, 'Something's going on—better be ready.' You get stuck in this state of hypervigilance of threat, and you never get a chance to get out."

Germain is studying veterans before and after a successful course of treatment. She's also looking at veterans with PTSD who do not have sleep problems in hopes of figuring out what makes their sleep so resilient. These insights, she says, could be useful in helping veterans and civilians alike.

"These are people who are already more resistant to stress—I don't know about you, but I don't think I could get through boot camp—and they still aren't immune to the impact [trauma] has on sleep or mental health. If we can understand how to treat combat-exposed military veterans, we can generalize to anyone who's exposed to not just traumatic events, but milder stressors, too, and still have a big impact on sleep."

PRECUNEUS AND CURIOUSER

Trying—and failing—to fall asleep all night is exhausting. Typically, people with insomnia will sleep late whenever they get a chance. Their circadian rhythms get so out of whack that their bodies have no idea when it's time to settle down for the night.

But usually, people with insomnia find that their sleep improves once they learn a few basic principles: restrict the time you spend in bed; establish a regular waking-up time; put off going to bed until you're actually sleepy; and, if you find yourself stuck, wide awake, get out of bed and go do something else until you're tired.

"It sounds pretty obvious," says Daniel Buysse (Fel '89, Res '87), "but I can tell you, when you present these to people with insomnia, their jaws often drop in amazement. They've often been doing exactly the opposite."

Buysse, professor of psychiatry and of clinical and translational science, director of the Neuroscience Clinical and Translational Research Center, and codirector of the Sleep Medicine Institute, is one of the world's leading experts on insomnia. (In the late '90s, he spearheaded the now widely used Pittsburgh Sleep Quality Index.) He explains that sleep scientists have shown again and again that behavioral treatments are more effective than going down the rabbit hole with sleeping pills, the side effects of which often prove to be too much for people. Here's the problem: Behavioral treatments typically take eight weeks of one-hour sessions with highly trained clinical psychologists. "The prevalence of insomnia far outstrips supply of this treatment," Buysse says. "I ran into this in my clinic. I just don't have the time."

So starting in 2003, Buysse adapted and distilled the treatment to a one-month course of two in-office counseling sessions and two follow-ups over the phone that teach patients to realign their body clocks. They restrict their sleep at the onset, among other changes in their routines. They build sleep pressure so that when they finally hit the pillow, sleep comes quickly, and at the appropriate time.

Buysse and his sleep-medicine cronies on the 11th floor of Western Psychiatric Institute and Clinic of UPMC have used this treatment, dubbed BBTI (Brief Behavioral Treatment for Insomnia), with great success for years. And clearly, it's working—they just don't know why. That is, they don't know what makes the brain of a person with insomnia different from the rest of the waking-when-we're-supposed-to world, or what happens biologically to help people with insomnia snap out of it.

Buysse may be closing in on the reason, though—and it has to do with a particularly curious puzzle when it comes to people with insomnia. They complain not just of sleeping too



little, but also that the sleep they do get is lousy, like they were never really asleep at all. And yet when you bring them into the sleep lab and measure their brain waves, they seem to snooze no differently than the rest of us.

Using a brain-imaging technique called ^{18}F-FDG PET imaging, in conjunction with EEG sleep studies—a technique that was developed in the '90s by Pitt's own Eric Nofzinger (Res '91, Fel '93), professor of psychiatry—Buysse measured metabolism in the brains of people with insomnia. Buysse found that, both in sleep and wakefulness, these patients had unusually high levels of activity in regions called the precuneus and the posterior cingulate. These sites take over, essentially, when you put your brain in neutral—when you daydream, tease out your what-ifs, and let your mind wander to the other side of the looking glass.

But after sleep restriction (similar to what's used during BBTI), it's a totally different story. In Buysse's preliminary studies, he's found that the precuneus actually pipes down, allowing the person to sleep more deeply.

Buysse laughs, a Cheshire Cat grinning over the possibilities. "Behavioral treatments often cause the person to have less sleep, yet people say that they're feeling better. It just does not make sense! But maybe the thing we need to do with our treatments is not to increase sleep, but to decrease the activity in this self-monitoring center of the brain during sleep. It could be that all this sleep monitoring we've been doing with EEG may be a huge red herring. EEG tells us what the brain is doing globally, but insomnia may be something that happens locally in specific brain regions.

"This is potentially really cool. If it really holds up, it could be a pretty fundamental change in what we think of as insomnia."

PEOPLE WHO GO BUMP IN THE NIGHT

Say your grandpa falls asleep in his La-Z-Boy while watching a preprime-time episode of *Wheel of Fortune*. By the witching hour, he's already gotten most of the sleep he needs for the night, so naturally, by 2 a.m., he's wide awake. This becomes his habit, so he goes to the doctor and says he has insomnia. The doc then may prescribe a bottle of sedatives—potentially dangerous stuff to have onboard when Grandpa inevitably gets up in the middle of the night to empty his bladder.

Up to 10 percent of seniors have serious insomnia, and for this population, it's more than a nuisance. The wee-hour puttering of an elderly family member going bump in the night can be very disruptive to the other family members, who have work and school and a 6 a.m. alarm to worry about. And knowing that is distressing for Grandpa, too.

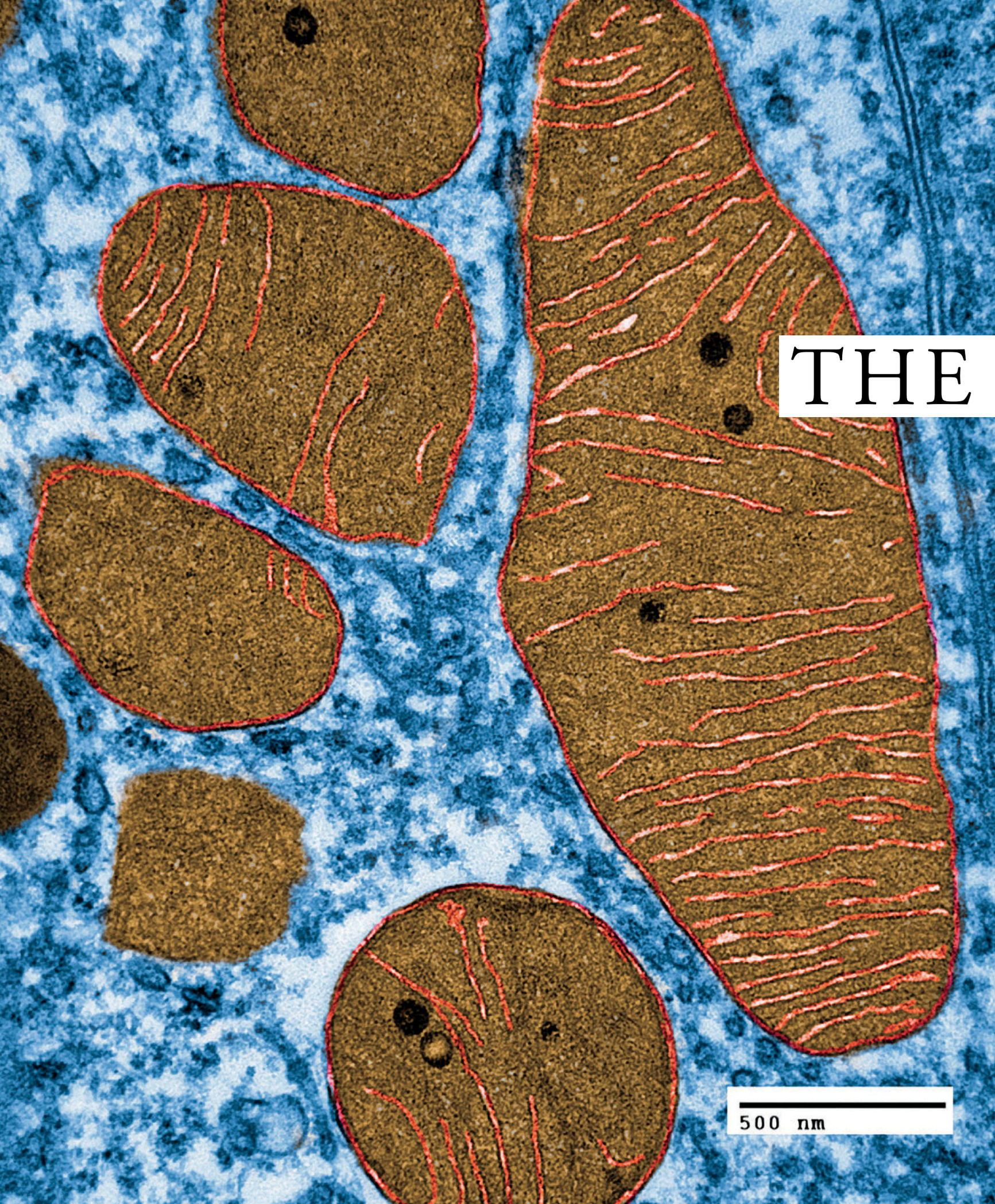
It all comes back to circadian rhythms, says Pitt's Timothy Monk, who directs the Human Chronobiology Research Program at WPIC. "The circadian signal isn't as strong as people get older," he says, though some people fare better than others. To discover exactly why—and how the strengths of the superior snoozers might inform better treatments for seniors with insomnia—he's leading Pitt's sleep dream team in AgeWise, a large, five-year study funded by the National Institute on Aging. It's an all-encompassing look at the role of seniors' circadian rhythms, sleep strength, stress reactivity, functional brain neuroanatomy, and genetics in these folks' responses to a standard behavioral treatment of insomnia. (So far, a good portion of the seniors in the study are responding well.)

If more and better therapies became available for seniors, the potential public-health impacts could be huge. Between the stress of disturbing the family's sleep and the very real threat of a hip-snapping trip over the cat, sleep problems are among the biggest reasons people transition to nursing homes.

Sleep makes or breaks us all, from cradle to La-Z-Boy. And it's worth the investment of our time, says Monk.

"You've got to think of sleep as something you do. It's not something that just fills the time when you're not doing things. It's something you do." ■

Pitt's sleep researchers are always looking for participants to volunteer for their studies. Call 412-246-6413.


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MIGHTY MITOCHONDRIA ENERGIZE THE CELL, AND MUCH MORE | BY JOE MIKSCH

MEANING OF LIFE,

TOLD WITH 13 POLYPEPTIDES

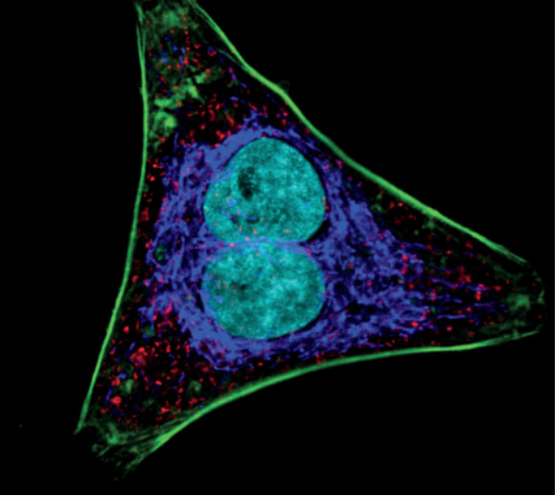
East Liberty's Sharp Edge Beer Emporium, as one might guess, has an awful lot of kinds of beer. Belgian brews are a specialty. As are craft beers. As are imports. The beer list is a novella-length testament to the art of zymurgy. It's a fine, homey place. Cheers with better beer and high-quality bar fare. A place with regulars.

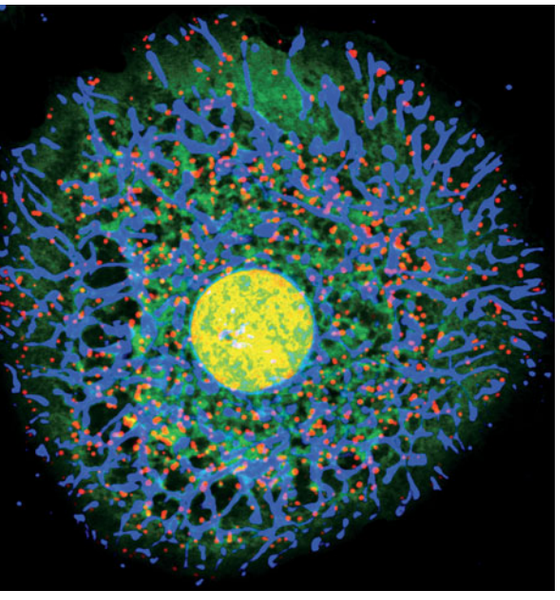
And on a fairly regular basis you'll find University of Pittsburgh scientists at the Edge—many from the nearby University of Pittsburgh Cancer Institute—sipping a tasty beverage and talking shop, or rather, lab.

A particularly spectacular spring evening finds Pitt's Bennett Van Houten atop a stool. He might have been there anyway, maybe with his wife and sometimes-collaborator, wildlife biologist Victoria Woshner, or Pitt colleagues and genial companions Michael Lotze and/or Simon Watkins. But at this particular moment he's there with an interested party to discuss mitochondria-related research at the School of Medicine.

Mitochondria have been instrumental to the development of life as we know it. Scientists are just beginning to understand their importance to our health.

ALL IMAGES | COURTESY UNIVERSITY OF PITTSBURGH CENTER FOR BIOLOGIC IMAGING





Mitos, in dark blue, dance around the nucleus of a HeLa cell. Below, blue mitochondria comingle in the green cytoplasm of a rat liver cell.

Mitochondria. It's not going too far to say that these energy-producing organelles—scattered about inside our cells and numbering up to thousands in each—are the reason we're here. Not just Van Houten and this reporter, but all of us and pretty much every other living thing that's more advanced than a bacterium. One could write a book about their evolution and purpose—British biochemist Nick Lane did with 2005's *Power, Sex, Suicide: Mitochondria and the Meaning of Life*. (The title is not at all hyperbolic. Really.)

The Dementedly Short Version in Which Dates and Occurrences Are Generally but Not Universally Agreed Upon: About 4.6 billion years ago came the Earth. Then, about 800,000 years later, life appeared on Earth in the form of bacteria. Bacteria ruled for a long, long time. About 2.4 billion years ago, Earth's atmosphere became oxygenated. A billion or so years after that, an archaebacterium (which could live under extreme conditions such as those found in geysers) without membrane-encased structures developed a symbiotic relationship with a eubacterium (bacteria we are more likely to come across today, which live under more conventional conditions). They eventually fused together and, more or less, became one. This "hopeful monster," as Lane calls it, became the first true eukaryote. Lots of true eukaryotes ganged up, diversified, specialized, and became the components of complex beings, ranging from plants to humans. And that eubacterium that fused? Seems that it helped create the mitochondrion and cell nucleus. Its own small genome stayed with the mitochondrion, but it also shed many of its original genes into the larger cell nucleus. It makes energy in the form of adenosine-5 triphosphate (ATP). It persuades a cell to die in a quiet and peaceful way when the cell has become damaged. The tiny little organelle has become a big part of us.

For us to thrive, mitochondria need to behave themselves and work well, generating the energy our cells need to live. We're in trouble when mitos go bad. That can mean cancer, neurodegenerative diseases, devastating endogenous mitochondrial DNA disorders, muscle wasting with age. Pitt investigators are part of a recent resurgence of interest in mitochondria, and they have a finger in every mitochondrial pie.

Van Houten has long been a student of DNA damage and repair in the cell's nucleus, a field of study considered important to understanding aging and cancer. But throughout the past decade or so, he has developed and acted on a hunch that the ability of the mitochondrion to repair its own DNA may be equally fundamental to our health. Van Houten believes that unrepaired insult or injury to the mitochondria's DNA (mtDNA) is the beginning of a nasty and self-perpetuating chain of events that may be responsible for the majority of adult-onset diseases, including cancer.

And work that began with a postdoc in his lab appears to reveal why many tumor cells can be so tenacious (it has to do with their feeding habits) and could pay dividends in the form of a novel mitochondria-targeted cancer treatment.

"The chemistry works," he says of this experimental work. "We don't know how, but that's okay. Nobody has ever shown this."

The buffalo bites come, and another beer is ordered. Time to get down to business. Van Houten, a PhD, the Richard M. Cyert Professor of Molecular Oncology in Pitt's Department of Pharmacology and Chemical Biology, was asked to think of a few promising mitoresearchers to be featured in this story. He opens a folder, pulls out two sheets of paper labeled "Pittsburgh Mitochondriacs"—those who are maniacal for mitochondria, of course. The list is 24 names long.

Asking Van Houten to narrow down the list is fruitless. "He does great work!" "She does great work!" "Oh, he does great work, too!" "Her work is excellent!" He scribbles a few diagrams on the pages. An alphabet soup of proteins follows. Another "(insert name here) does great work!" A shortened short list of Pitt research and researchers we really should know about, according to Van Houten: A postdoc with a potential biomarker for Parkinson's. A biochemist's long-standing work in mitochemistry. Mitos and the injury that results when blood supply is returned to oxygen-deprived tissue. An oncogene that actually controls mitochondrial biogenesis. A new compound that protects mitochondria from radiation. Aging mice with signs of mitochondrial dysfunction. Mitos and exercise. Mitos and fruit flies. … Van Houten is infectiously enthusiastic about most things, but nothing more than science and the people, particularly those here at Pitt, who do it.

Mitorelated research has become so fruitful in recent times that last year Van Houten and Lotze organized and executed the first Regional Translational Research in Mitochondria, Aging, and Disease Symposia. The second set of symposia is planned for Saturday, Oct. 20, at the UPMC Cancer Pavilion. (For those who want to start stressing their mitochondria first thing, there's an optional 10K "fun run" at 6:30 a.m.)

The buffalo bites are long gone, a plate of nachos has disappeared, and several pages of notes later, the whirlwind introduction to mitochondria is over, for tonight anyway. This writer's head is swimming, not from the beer but from mito info. So, with limited time and space, we begin our journey to the center of the mitochondria with Van Houten himself. (The stories of some of the others Van Houten effused over will be told in a future edition of the Pitt Mitochronicles.)

After earning his doctorate at the Oak Ridge Graduate School of Biomedical Sciences in Tennessee and completing a fellowship at the University of North Carolina, Chapel Hill, Van Houten, in 1988, found himself in New England, a young professor at the University of Vermont. He had been hired to

do research and teach graduate students about damage to, and repair of, nuclear DNA. As he left his course coordinator's office, he was told he also needed to prepare and deliver a series of lectures on mitochondria.

Back then, everyone knew that mitochondria were the cell's mighty ATP factories; but once the elements of energy production had been elucidated, the organelle just wasn't a hot topic.

"I said, 'I don't know anything about mitochondria,'" Van Houten recalls.

"I guess you'll learn," the course director replied.

Here's what he learned. "As I was reading, I was like, *Holy crap, nobody knows anything about mitochondria DNA damage and repair. I mean, zero! Zilch!*"

Nothing could be cooler to the curious mind.

By 1999, Van Houten had invented and patented a method that allowed him and many of his fellow mito-seekers across the scientific landscape to study mtDNA damage. Quantitative polymerase chain reaction (qPCR) allows for the amplification of small amounts of DNA. It had been around for some time, but Van Houten and colleagues determined that if DNA is damaged it will not amplify. Lots of DNA damage, proportionally little amplification—and vice versa. Though mitochondrial DNA makes up only about 1 percent of total cellular DNA, the Van Houten technique allows for both the amplification of mtDNA and a way to quantify the damage it has suffered.

(We pause here, as we enter Van Houten's office at the University of Pittsburgh Cancer Institute in Shadyside, to ask why mitochondria have hung on to their own genome, particularly after giving up almost all of their DNA to the nucleus. The answer is, No one knows for sure. There's really not even much agreement on why this *may* be the case. This much is true, though: mtDNA encodes 13 polypeptides, all of which are involved in creating proteins vital to the electron transfer chain, which generates energy for cells. Van Houten suggests that mtDNA is "kind of like the canary in the coal mine. The idea is if there's bad, toxic stuff in there, the canary will die before the miner." When mitochondria freak out because their DNA is being damaged, and they can't produce enough proteins to make enough energy, the cell at large can dedicate resources to the rescue or find ways to adapt. Sometimes, though, things can really get screwed up.)

So, Van Houten has used this qPCR trick to study mtDNA damage and repair in more than three dozen scientific papers. He posits that unrepaired mtDNA damage can cause mitochondrial dysfunction, which can increase the quantity of dangerous free radicals floating about, which may cause irreversible and deadly damage to the cell. This death spiral, the thinking goes, could be responsible for various diseases associated with getting older, such as cancer and Parkinson's.

Van Houten takes a few short steps across his office to a bookshelf and grabs a white binder. He sits down—affably grumbling about a lack-of-caffeine-induced headache—and flips to an illustration. "Okay, this is the electron transport chain …" The lesson begins. In brief, the electron transport chain moves, well, it moves electrons down a chain in the mitochondria. These electrons eventually meet with oxygen. As the electrons are passed along to oxygen, enzymes use the energy that's released to pump protons. The protons build up in what's called a proton gradient, which is used by a special nanomachine that makes ATP, which fuels our cells.

The whole affair is called oxidative phosphorylation (OXPHOS), and when it works correctly, the waste products are water and carbon dioxide. When OXPHOS is off, watch out, because here come the free radicals. They naturally occur during OXPHOS and, in

A TERRIBLE DEATH

"It has a horrible name," says Michael Lotze. "HMGB1, High-Mobility Group Box 1."

Perhaps so, but this protein a) is vital for mitochondrial quality control, b) can promote cancer cell survival and DNA repair, and c) is responsible for winning Bennett Van Houten, who is Pitt's Richard M. Cyert Professor of Molecular Oncology, a large bottle of Belgian-style beer.

Lotze, an MD, is a professor of surgery and of bioengineering as well as vice chair of research for the Department of Surgery at the University of Pittsburgh. He spends a lot of time thinking about the role inflammation plays in cancer and how to target a process called autophagy—literally "self-eating." He imagines that finding a way to rein in the process could result in a novel therapy for cancer.

One of the primary perpetrators of inflammation, in his view, is the mitochondrion. Mitochondria promote inflammation when they are released as a result of tissue damage or trauma. The right way for mitochondria to extinguish an ailing cell is apoptosis, or "programmed cell death"—the clean way to kill ailing cells without releasing signals that prompt an inflammatory response. Cancer, though, features cells that are truly messed up monsters that should die through apoptosis but don't. "Cancer cells just want to die, but they can't because they've compromised their ability to do apoptosis," Lotze says. They can eventually die if they run out of fuel or are subjected to chemotherapy. They can still perform autophagy, which is not so clean and nice. "They die a terrible, awful, horrible, screaming-out-loud, blood-in-the-streets death," Lotze says. This process puts all sorts of cell-junk into the bloodstream, causing further inflammation and perpetuating the disease through increased autophagy. And it's promoted, in part, by HMGB1. (Lotze, with the University of Pittsburgh Cancer Institute's Van Houten and Daolin Tang, addressed the clinical implications of the process in the *New England Journal of Medicine*'s March 22 edition.)

"I call this 'programmed cell survival,'" Lotze says. "All of our anticancer treatments are designed to kill cancer, kill cancer, kill cancer. But if you don't die the right way and release factors that promote the remaining cells' survival, it's like adding fuel to the fire."

"As for the beer bet," says Lotze, "that was kind of an aside related to how mitochondria make their energy. I suggested that HMGB1 was taking the mitochondria offline, and they weren't going to be able to do OXPHOS [the metabolic process mitochondria use to produce energy]. Ben said it was the other way around, and he was right. … Oh well!" *—JM*

small amounts, are helpful with cell signaling. But when the system goes haywire, and there are too many radicals, reactive oxygen species—such as superoxide, hydrogen peroxide, and hydroxyl radical—wreak havoc. This is oxidative stress. And it, in large amounts over time, is very, very bad.

Reactive oxygen species damage the mitochondria's DNA. Damaged mtDNA hurts the electron transport chain. When that's screwy, the cell produces less ATP and more reactive oxygen species, which, in turn, further damages mtDNA. It's a cycle, and it's vicious.

Otto Warburg won the Nobel Prize in 1931, having proven that cells consume oxygen. His investigations into cellular respiration—he thought that even in the presence of oxygen, tumor cells chose to make almost all their ATP through glycolysis rather than OXPHOS—led him to propose that cancer is caused by screwed up mitochondria.

As he put it: *Cancer, above all other diseases, has countless secondary causes. But, even for cancer, there is only one prime cause. Summarized in a few words, the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar.*

Warburg said the above during a lecture in 1924. Eighty-eight years later, Van Houten begs to differ. Or at least to add to the conversation.

"Warburg showed that despite the fact that tumor cells have access to a lot of oxygen, they make a lot of lactate (an indicator of glycolysis)," Van Houten says. "He didn't understand why, but he thought that the mitochondria must be broken because there was so much glycolysis going on."

Warburg was right about glycolysis. But he may have been wrong about the cell's mitochondria being on the fritz. Not exactly right, anyhow. Perhaps the mitochondria aren't broken in cancer, Van Houten says. Perhaps they get repurposed.

Van Houten and collaborators ran an assay on cells bearing a known cancer-causing genetic mutation, wanting to see how the cells made the energy they needed. "I expected glycolysis to go up, and it did, but OXPHOS did too," Van Houten says. "What that tells us is that tumor cells are metabolically flexible." So, the mitochondria are working. Yet the cells are also producing ATP through glycolysis, a much less efficient method than OXPHOS.

Van Houten and company then took a step back to look at the mitochondrion's own little metabolic lab, which does the chemistry that drives OXPHOS and other cellular affairs metabolic, including the manufacture of fatty acids and lipids. "So the idea is that rather than making ATP, the mitochondria are short-circuited. … Maybe they aren't broken but are being used to make precursors to fatty acids and lipids," Van Houten says.

The upshot, Van Houten thinks, is that cancer cells have turned to glycolysis to make their minute-to-minute energy because they've pulled their mitochondria away from their regular role on the ATP production line. Rather than making energy for the here and now, maybe mitochondria are being used to generate fatty acids that can be stored and later synthesized—by them!—to make energy down the line.

"This is all fresh data," Van Houten says. "My idea is that fatty acids are like a battery. Glucose is taken up in excess by tumor cells and converted to fatty acids and lipids and then used later for the generation of ATP by OXPHOS. The prediction is that tumor cells have very active mitochondria. This is cool; but it also says that if we're really going to attack this problem, we have to be pretty smart, because tumor cells can switch [how they feed themselves]. One anticancer agent is not going to be enough." How about two?

Van Houten is far from a lone wolf in the lab. One day in the not-too-distant past, postdoc Wei Qian came calling. Qian had a set of data showing that the breast cancer cells he was working with—he had altered them so they couldn't make a protein vital for mitochondrial dynamics—weren't fissuring and fusing like they usually do. The processes of fission and fusion allow the mitochondria to cut out damaged parts and again become functional organelles.

As Qian and Van Houten delved more deeply, they found that it wasn't just the mtDNA that was screwed up. Inhibiting mitochondrial division, it turned out, caused nuclear DNA to become abnormal as well. The cells were going nuts and starting to die. How about that? Mitochondria, as Van Houten thought, not only function in cancer, but their health is also vital to the survival of cancer cells.

"So we thought we would use the knowledge that [cancer] cells are using their mitochondria against them," Van Houten says. Qian's cells had been treated with something called mitochondrial division inhibitor 1 (mdivi-1), which inhibits small molecules. It was killing the cancer cells by stopping their mitochondrial ability to undergo coordinated division, causing cell cycle problems and chromosome instability. That, of course, was good. But the inhibitor could also affect the mitos of healthy cells in vivo.

"I don't think we can ever kill a cancer cell by totally knocking down its energy production, because the side effects on other tissue will be too hard," Van Houten says. "But we do want to cripple them. Keep them from going as fast. Maybe if we combine [mdivi-1] with normal anticancer drugs we'll have a fighting chance."

So that's what Qian and Van Houten did. They took cancer cells, then treated them with the inhibitor and cisplatin (one of the more effective cancer drugs out there, cisplatin cured famed cyclist Lance Armstrong's metastasized testicular cancer). And they watched.

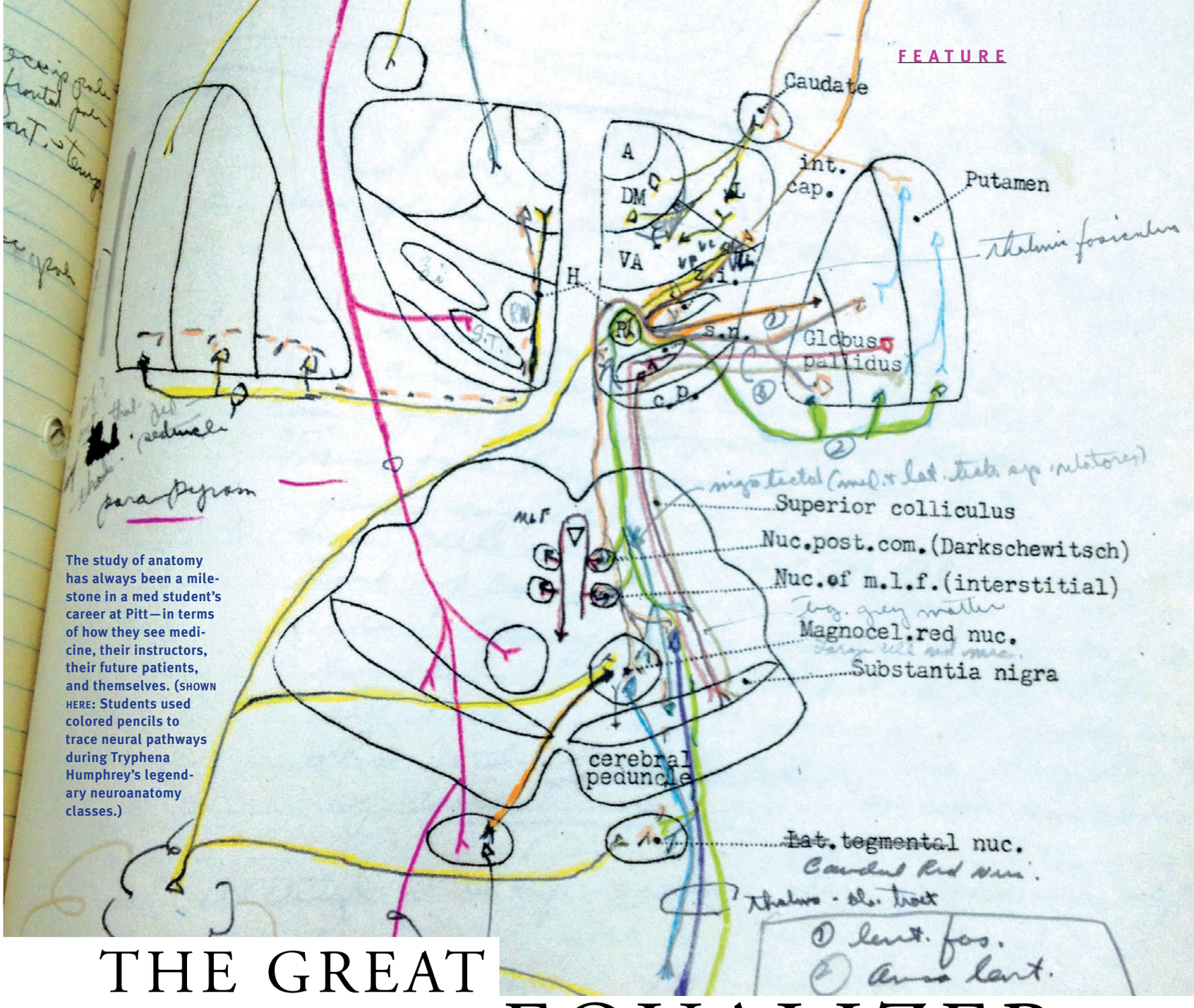
"Look at this synergy!" Van Houten exclaims at a figure in a draft paper. "Each of the drugs by itself isn't doing much, but the combination! Holy cow! We're really excited about this. We've patented the combination. This is really bad for cells, and it looks like tumor cells are especially inhibited. It looks awesome. This is synergy. What we're trying to do now is understand how it's actually working."

While that investigation is ongoing, Qian, Van Houten, and others plan to see whether the combination works as well in a mouse as it does in vitro. The preclinical trial will involve "nude mice" (those without immunity) injected with human cancer cells. Once the resultant tumors grow to a certain size, some mice will be given just the inhibitor, some will be treated with just cisplatin, and others will get the patented combo.

"If it works, we should see the tumors melt away!" Van Houten says, grinning and satisfied. "Of course, we need money," he adds, a little less excitedly.

Then, after a pause, the smile returns. "Wow! That's a long journey from when I got asked to teach some lectures on mitochondria!" ■

Up next in the Pitt Mitochronicles: What a pesticide and mitochondria tell us about neurodegenerative disease, especially Parkinson's. The model fly for mitochondrial disease. And the travails of restoring blood to oxygen-deprived tissue.



The study of anatomy has always been a milestone in a med student's career at Pitt—in terms of how they see medicine, their instructors, their future patients, and themselves. (SHOWN HERE: Students used colored pencils to trace neural pathways during Tryphena Humphrey's legendary neuroanatomy classes.)

THE GREAT EQUALIZER

HOW TO TEACH ANATOMY

BY JENELLE PIFER

ANATOMY NOTES COURTESY JAMES BONESSI (MD '56)

It was with resolve and optimism that, in the spring of 1923, Davenport Hooker set out to change the way medical students learned anatomy. He was a domineering man, a PhD gross anatomist with vast knowledge, unyielding expectations, and a speaking voice that fell on first-years' ears like cannon fire.

(His excessive volume, students said, was the result of his training as an artillery officer during World War I.)

Hooker was 36 and just four years prior had become the youngest chair of any anatomy department in the country. His idea for remaking the subject at the University of Pittsburgh was bold, but not entirely new. In fact, the notion had been circulating through the minds of the anatomy staff for years: Was it possible to teach the anatomical subjects—gross anatomy, microscopic anatomy, gross neuroanatomy, embryology, and organs of the senses—not as five courses that inevitably overlapped, but as one course, seamless and comprehensive?

In those days, Hooker was a giant in the University of Pittsburgh School of Medicine. He'd arrived at Pitt in 1914 as assistant professor of histology and neurology after a brief stint teaching anatomy at Yale, his alma mater. By 1919, he was appointed professor and chair in the Department of Anatomy, posts he held firmly for the next 37 years.

A small man, Hooker had blue eyes, sandy hair, and a dramatic manner. He would sit on the balcony in the anatomy lab and watch his students (he knew them all by name) dissect cadavers below. They worked four to a table, and a good number of them, mostly men, chewed tobacco to mask the room's odor.

Should Hooker spot a mistake, he'd bellow the offender's last name and send the student racing up the stairs to face him.

Hooker's insistence on time and punctuality earned him the nickname "Hurry-up Hooker" among students. "The medical student who arrived late for an eight o'clock lecture arose earlier thereafter," wrote Tryphena Humphrey, an MD/PhD colleague of Hooker's and eventually a professor of neuroanatomy in his department. "There was no tolerance of the lazy or dishonest student, but every effort to aid those in scholastic, financial, or other trouble. No one knows how many students Dr. Hooker helped at critical times in their lives, with encouragement, sound advice, a justly administered scolding or financial aid," Humphrey wrote in a profile of the doctor.

At age 17, Hooker developed an interest in biological research. He spent summers in college recording the behavior of newly hatched loggerhead turtles in Florida. As a graduate student, he studied the development of embryonic frog hearts. (He noted, to his great interest, that the animal's heart not only begins to beat before being reached by the nerve fibers, but also continues to develop normally, though still unconnected to the nervous system.) This early interest in nerve-muscle relationships would later inform his life's greatest pursuit, a series of groundbreaking reflex studies at the University of Pittsburgh.

But in the spring of 1923, seated in his top-floor office in the medical school, Hooker percolated about a new and better way to teach his students anatomy—one that would also challenge his staff and train its most junior members.

"The best way to learn a subject," he wrote, "is to bear the responsibility for teaching it to others."

The correlated course in anatomy was to be offered for the first time in the fall of 1924. "The purpose of the course is to give the student a more comprehensive and closely knit knowledge of the structure and development of the human body than was possible with the older method," Hooker wrote in notes on the course. It was to occupy 704 class hours during the first year. As students dissected a cadaver—from the head and neck to the thorax, abdomen, pelvis, and extremities—they would encounter new organs and systems, studying at once gross anatomy, cell anatomy, and embryology. ("It was difficult teaching for the anatomy staff since each instructor found it essential to be prepared on all three phases of anatomy rather than only one," Humphrey wrote.) Students hopped back and forth between the anatomy lab and microscopy lab, towing pieces of tissue or organs recently harvested for study. During the second year, they would spend another 66 hours learning the anatomy of the nervous system.



NATIONAL LIBRARY OF MEDICINE

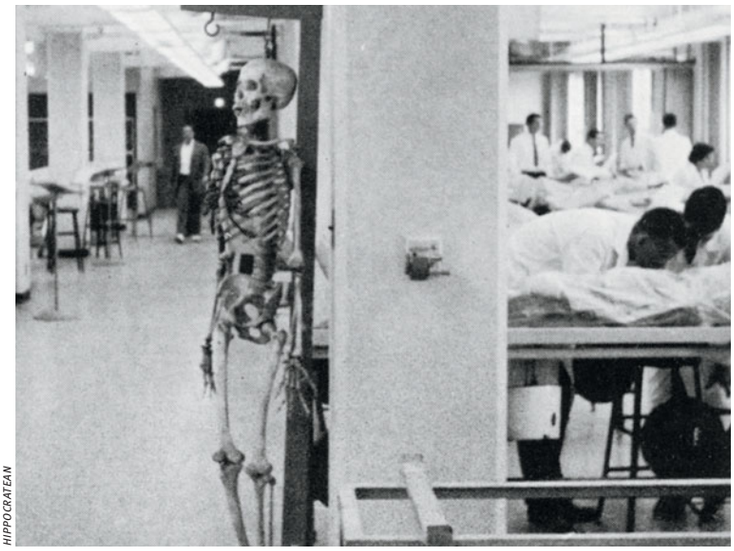
Davenport Hooker led the department for 37 years and fundamentally altered the way Pitt students learned anatomy.

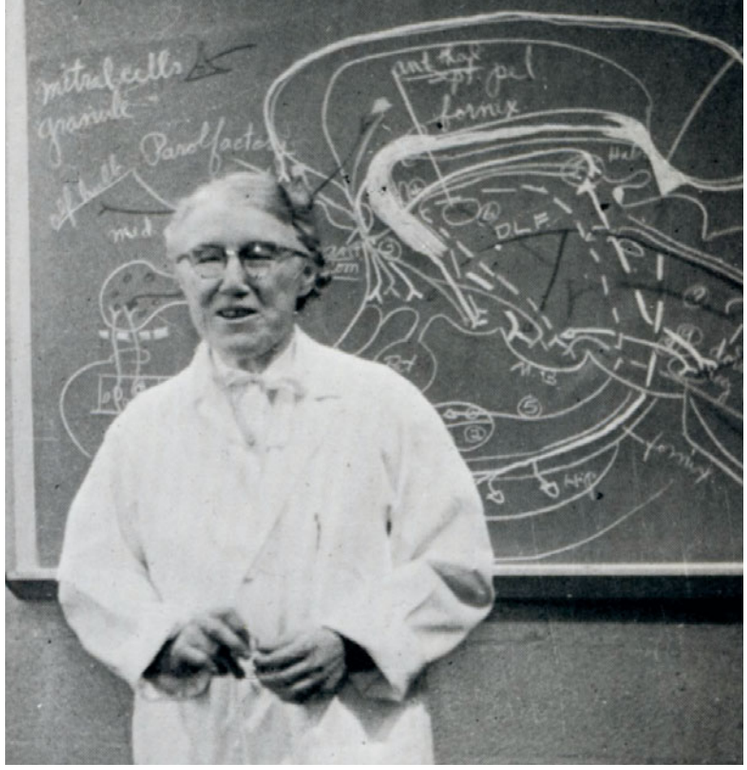
Hooker did not gloat over the boldness, newness, or inherent advantages he saw in such a course. Instead, he wrote, "This type of course is merely a means to an end. As a method it is valuable, but it is nothing more."

Still, the methodical doctor could not mask his growing anticipation that, in this way, he might be able to teach his students more, in less time.

Should Hooker spot a mistake, he'd bellow the offender's last name and send the student racing up the stairs to face him.

At the beginning of the school year, Hooker would issue his students a warning, says Perry Engstrom (MD '47), a former student later hired to teach in the department. "He would say, 'There are medical schools where they accept 200 students into a class with the idea that 100 of them are going to graduate. The University of Pittsburgh is different. In our class there are 86 students. We expect every one of you is going to graduate, and we're going to see to it that you do." Engstrom says it was a threat, in a way, but the kind that a well-respected





HIPPOCRATEAN

ABOVE: During Hooker's correlated course, first-year students spent several hundreds of hours in the anatomy lab. RIGHT: Using a piece of colored chalk in each hand, Humphrey made intricate drawings of the brain and spinal cord.

father might give a son.

Hooker's department was described by the American Association of Anatomists as "a harmonious one in which to work." Prior to the construction of Scaife Hall, the medical school occupied Pennsylvania Hall, a modest building on top of Cardiac Hill where a residence hall of the same name now stands. Students and professors would trudge upwards using a stairway carved into the steep hillside. At lunchtime, it was a nuisance to head down the hill into Oakland and back up again, says Engstrom. So Hooker hosted brown-bag lunches for his staff in the anatomy library. "We'd sit around a table upstairs and have lunch, talking about events of the day, what was going on in the medical school, and what students were having problems," Engstrom says. "Hooker was so sharp. He'd say so-and-so needed some special attention and ask if one of us would look after him and bring him up to date." To these lunches Hooker invited professors, junior instructors, and administrative staff alike. "Everybody came with a brown bag. Your rank had nothing to do with it," says Macy Levine (MD '43B), who worked in Hooker's lab as a student.

It was these interactions that lent an undercurrent of approachability to the giant. Colleagues trusted him and went to him with problems. Hooker and his senior staff would consider each issue with "cautious, careful scrutiny" and then incisively implement a solution, Humphrey wrote. It was clear "the final decision was his," she says, "but the evidence received careful thought, not lip service."

In the summer of 1925, after the first correlated class concluded, Hooker was quick to admit that the program was not without its flaws. "The results of our experience with this type of course have been interesting and in some respects unforeseen," he wrote in "The Teaching of Anatomy as a Correlated Course," an article published in *Methods and Problems of Medical Education* in 1930. Several early blunders in planning led to discouraging results and slow progress among students. These errors were later rectified, however, and students demonstrated a more lasting and thorough comprehension of anatomy than ever before. What they lacked, though, was the same intimate knowledge of the details of structure. "The reader is left to judge which is the more important: a genuine working knowledge of the body, or a rather facile (and, we believe, temporary) grasp of relatively unrelated details," Hooker wrote. "We prefer the former."

To his surprise, Hooker was also forced to note no time had been saved. In considering this truth, the staff agreed it requires as much mental effort for a student to grasp correlation as to study each component separately.

On the whole, however, Hooker and his team determined the experiment was a success. In the coming years, several other anatomy departments attempted a similar teaching method, but "none so satisfactorily or for so long," wrote Humphrey. The correlated course would continue to be taught at Pitt for the next 28 years.

For the success of the course Hooker felt indebted to two colleagues: J.S. Nicholas, a PhD who worked with him for five years at Pitt and later returned to Yale to become director and chair of the Osborn Zoological Laboratory, and John C. Donaldson, an MD whom he had met in high school. Early and long-lasting friendships formed between Hooker and both men.

Donaldson and Hooker had become reacquainted at Yale when Donaldson was a senior and Hooker, then serving as an instructor of anatomy, was helping teach a course in which he found his former high school classmate. Upon becoming chair at Pitt in 1921, Hooker promptly invited Donaldson to join his staff. One of Hooker's original hires, Donaldson was among the first at Pitt who taught students anatomy by making them see it.

A tall, quirky man, Donaldson was well liked by students. His office contained a large bookshelf of classic literature—specimens he readily lent out to those who dropped by, says Levine, who often took him up on the offer.

During his evenings at home, the doctor would gather cloth, wire, tubing, and clay and assemble anatomical models of the human body. One display demonstrated how the small intestine rotates during embryological development. "The intestine starts out as a straight tube but then develops rapidly and becomes 25 feet long. He showed how it coiled without tangling and knotting itself.

"It was amazing," says Engstrom. "You'd read about it in a book, and then you'd see his model the next day in class. He'd show you how it happens. My gosh, the book made sense after you saw the model." After class the doctor would make these tools available for





LEFT: HIPPOCRATEAN, RIGHT: NATIONAL LIBRARY OF MEDICINE

LEFT: Jacob Priman, a native of Latvia, joined the faculty in 1948 after serving as a physician for the displaced in post-WW2 Germany. RIGHT: John Donaldson was Hooker's right-hand man and a favorite among students for his colorful, interactive models, which he made by hand from clay and wire.

students to use. "He'd put his hand on yours so you could do the twisting and moving of the model to get the pieces into place. He'd be right there helping you," Engstrom says.

Later in life, Donaldson developed a moderate stoop but could still be seen jogging a few steps in the lecture hall (in his youth he was a track man), demonstrating how a reflex signal travels the pathway of a nerve.

Another beloved professor, Jacob Priman, would join the University in 1948. A native of Latvia, Priman arrived in Pittsburgh after treating refugees and displaced people in Germany. His English was poor at first, but it was no matter for anatomical terms were universal. Priman received emeritus status at the University and continued teaching into his 70s.

A correlated course in anatomy required a certain muddling of the department's hierarchy, which is why, Hooker wrote, "The instructional staff must be willing to cooperate wholeheartedly in the project." It was vital, he said, that each member act as chief in some parts and assistant in others, according to their specialties. This made even the chair merely a helper at times, Humphrey wrote, "a procedure only possible in a truly democratic department."

The course plan also offered, for a certain span of the year, a staff member respite from teaching. It was Hooker's firm belief that an academic department has three functions: the teaching of students, the training of staff, and research. For the lattermost, the course offered continuous time for thoughtful study, and soon, to the chairman's great fortune, a colleague worthy of his partnership in the lab would join the University.

Donaldson developed a moderate stoop but could still be seen jogging a few steps in the lecture hall (in his youth he was a track man), demonstrating how a reflex signal travels the pathway of a nerve.

Tryphena Humphrey, neuroanatomist and the Hooker chronicler quoted above, arrived at the University of Pittsburgh in 1939. Among friends and colleagues she was known as "Trap." Among students, "Ma." A short-statured woman, Humphrey came to class armed with a box of colored chalk. Though students scrambled to keep up with Humphrey, her lectures were among their favorites. (She received two Golden Apple awards for her teaching.)

Using both hands, Humphrey would create intricate drawings of neural pathways on the blackboard and lecture at the same time. "We all carried a box of pencils—just like a first- or second-grader," says Engstrom. "You had to. Otherwise, you put 150 lines on a piece of paper, and you can't sort them out. They cross and run parallel."

"There were very few [projectors] at this time," says Robert E. Lee (MD '56), "and her lectures were unique. She was ambidextrous. God help [you] if you dropped the pencil you were drawing with. By the time you found it on the floor, she had switched to another color," he says.

While Humphrey was still completing her doctorate at the University of Michigan (she studied under Elizabeth Crosby, a PhD neuroanatomist who later became her life partner and won the National Medal of Science), Hooker purchased a 35-mm motion picture camera. Having gained the trust and permission of the obstetricians at Magee-Womens Hospital, Hooker was able to observe therapeutically aborted fetuses removed by Caesarian section. Upon stimulating the skin, he recorded the degree of reflex development, and in January of 1933, created the first films ever made of human fetal movement. Humphrey saw great importance in the study and later joined Hooker for what she called "the momentous task" of documenting how reflexes form.

The records created, involving more than 135 fetuses and 20 premature infants, amounted to the most extensive investigation of human fetal behavior ever made, according to Humphrey.

Humphrey continued her research until late in life, by which time her glasses had grown thick after she'd spent decades peering into microscopes. She published numerous studies on the patterns of spinal nerve formation in embryos while at Pitt and traveled the world giving lectures. Colleagues noted her affection for the phrase: "Happy to meet, sorry to part, happy to meet again" during these whirlwind years. She left Pitt to become professor of anatomy at the University of Alabama at Birmingham in 1963. She died eight years later.

By the mid-1950s, Hooker was preparing to retire, and pressure was mounting within the department. An explosion in medical knowledge had begun (the double-helical structure of DNA had been discovered just years prior), and the devotion, by then, of more than 800 hours to the study of anatomy seemed to some on staff overblown, Barbara I. Paull wrote in her book, *A Century of Medical Excellence*.

In 1956, a new chair of the department was selected—Albert Lansing, a renowned scientist and PhD who used chemistry and electron microscopes to study cellular aging. The school soon changed the department's name





HIPPOCRATEAN

LEFT: Students gather in the anatomy lab (1957-58). Dissection has long been considered one of the best ways to learn gross anatomy. RIGHT: Humphrey was known by students as "Ma" and earned two Golden Apple awards for her teaching.

to Anatomy and Cell Biology to reflect an increased emphasis on teaching at the molecular level. This name would shift a number of times before the word "anatomy" would be dropped entirely. The anatomical subjects were again compartmentalized, and the course in gross anatomy landed within the jurisdiction of the present-day Department of Neurobiology.

Throughout the country, first-year medical education evolved to cover ever more subjects in less depth. As knowledge expanded in areas like genetics, pharmacology, and molecular biology, new curricula were added that pinched the time allotted for each course.

With the recent explosion of knowledge in the basic sciences, Pitt's faculty have rethought how to best incorporate the "pure" sciences into the curriculum. In their fourth year, Pitt students now revisit the basic sciences, selecting from a panel of integrated life sciences courses. First-year gross anatomy, now taught in approximately 150 hours, emphasizes radiological imaging and a clinical approach.

"We want students early on to be able to apply basic principles to clinical scenarios," says Cynthia Lance-Jones, associate professor of neurobiology and lecturer for medical embryology. "That means overtly showing them how to do it from day one." Students now interact with patients in class and meet in groups to discuss assigned cases.

"There is something magical about taking gross anatomy when students first start medical school," says Lance-Jones, who also coordinates the first-year basic science core. "It *means* being a doctor to them. And there's an element of that that extends to how they view the people who are teaching it."

The course continues to be "the great equalizer," notes Jack Schumann, a PhD and Pitt's current director of anatomy. "We have people who come with PhDs in biochemistry or PhDs in literature. None of the students have had any gross anatomy. It puts them on a level playing field."

When Lance-Jones arrived at Pitt in 1983, Nick Cauna, an MD/ScD anatomist and embryologist, headed the anatomy program. He, too, created models and drawings on the blackboard. (Like Humphrey, he was ambidextrous.)

"To watch him lecture was unbelievable," she says. "When I first started, I tried to draw things on the board, and I would literally go to class ahead of time. With dotted lines, I would label it left to right to make sure I didn't mess it up.

"This was a tradition. I bet [the anatomy instructors] all did it, and none of us can do anything like that now."

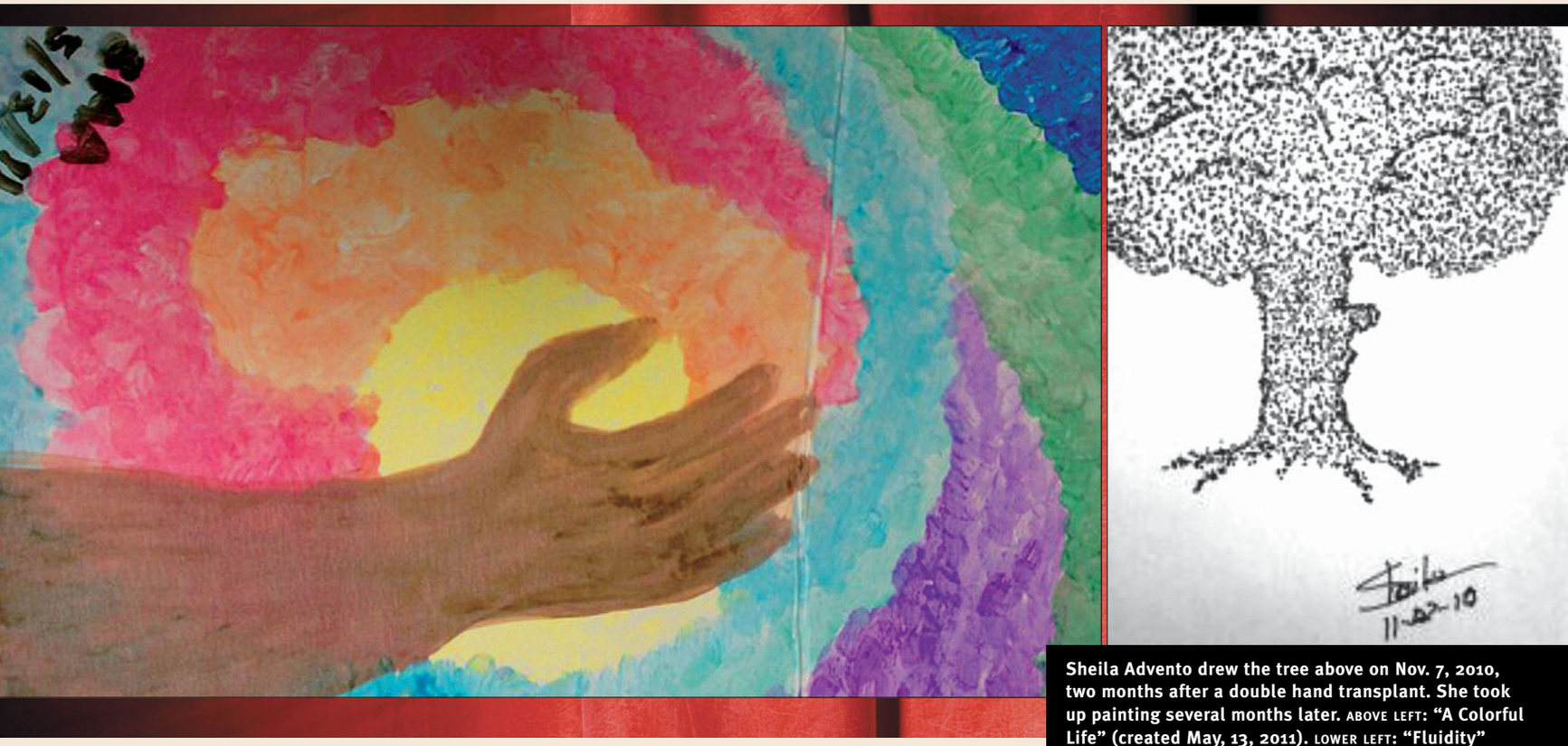
On Schumann's first day at Pitt, he walked into Cauna's office to find the man partially concealed behind a giant model of the human head. "So, you are the new anatomist?" Cauna said, "I am the very old anatomist." He promptly broke into a wide smile and shook Schumann's hand.

With Cauna's 1983 departure, traditions of handmade models and black-board drawings came to a close, but a fondness for such customs was not lost. Before Cauna left Pitt he provided materials for a museum in the back room of Pitt's anatomy lab. There, dissections are enclosed in cases, and his colorful-plaster models of the trigeminal nerve and embryonic development remain on display. Every year professors still lug certain structures out for lectures, because as Schumann has noted, in bold, near the top of his syllabus, ANATOMY IS A VISUAL SCIENCE.

Following his retirement from Pitt in 1956, Hooker lived and worked in New Haven, Conn., where a space was made available for him in the Osborn Zoological Laboratory. There, he hung a colored print of Rembrandt's "The Anatomy Lesson of Dr. Nicolaes Tulp" and continued ruminating over the fetal films he'd made at Pitt. Although he made extensive progress during these years, Hooker was not able to complete a comprehensive account of the study before his death in 1965. Nevertheless, the research yielded more than 40 scholarly publications. Hooker's work was written about in *TIME* and occupied three full pages in the 1947 *Encyclopedia Britannica.* His findings were printed widely in textbooks, and his films were made available to scientists interested in expanding the work.

"Those who were privileged to work closely with him are more conscientious research workers and better teachers because of this association," Humphrey wrote of her colleague after his death. "Likewise the medical students who passed through his hands … have become more valuable physicians and more honorable and tolerant men and women because of his influence."

During Hooker's last year at the University, the alumni association had his portrait painted. One former student, George Fetterman, MD '30 (who later joined the faculty), recalled it hanging outside an elevator near the anatomy lab and the chairman's former office. Every time Fetterman got off that department elevator, he was met by the master's careful gaze. ■

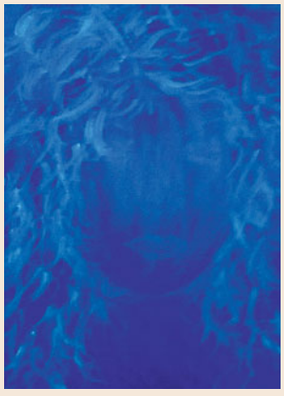


Sheila Advento drew the tree above on Nov. 7, 2010, two months after a double hand transplant. She took up painting several months later. ABOVE LEFT: "A Colorful Life" (created May, 13, 2011). LOWER LEFT: "Fluidity" (Nov. 23, 2011). LOWER RIGHT: When Advento drew "Precious" (undated), she still had prosthetic arms.

HARD BEAR WOMAN

THE ART OF LIVING

BY ERICA LLOYD





Sheila Advento's hands are not the hands she was born with.

In 2003, at the age of 26, Advento was living with her mom in Hackensack, N.J., and working in patient billing at Quest Diagnostics while attending community college. On July 4th, she came down with a devastating bout of meningococcemia and days later fell into a coma. While Advento lay unconscious at Hackensack University Medical Center, her family held vigil at the hospital. Tita Sally, her aunt back in the Philippines, recited novenas. Brother-in-law Hadrien, who had studied Native American healing practices, set up an altar in the ICU; he also called his mentor, Chief Phillip Crazy Bull, a Sicangu Lakota Holy Man, who proceeded to lead hundreds in a Sun Dance ceremony in South Dakota. In recognition of the healing powers of the bear, Advento would be offered the spiritual name *Mato Suksuta Win*, Hard Bear Woman.

On the seventh day of her coma, the doctors called a family meeting: They couldn't reverse the young woman's condition. It was time to consider ending life support. Advento's family refused to give up hope. Her mother, a nurse at NYU's rehabilitation center, directed the intensivist to continue support but lessen intravenous sedation. Also: If her daughter's vital signs deteriorated, the doctors should not attempt extreme measures to save her.

On the ninth day, Advento opened her eyes. Her family was jubilant. Advento was grateful to be alive; while comatose, she had a vision that she was lost in Calcutta.

But as the days passed, it became clear that Advento's hands and feet were infected and could not be saved. They would have to be amputated. During those weeks in the hospital as the amputations proceeded, there was despair but also love. At any given moment, a family member was by Advento's side. In the months afterward, she learned to walk on prosthetic legs. She learned to use prosthetic hands. She moved into her own apartment, with an assistant helping her in the mornings and evenings.

Seven years later, an opportunity arose. Advento would become the first woman in the United States to undergo a double hand transplant. On Sept. 18, 2010, four teams of surgeons at the University of Pittsburgh went to work. Two teams removed hands from the donor; two teams attached those hands to Advento. The surgeons fixated bone from the donor hands onto her forearms. They connected and repaired tendons, arteries, nerves, and veins. After 12 hours and 17 minutes, they were done. Advento was put on the Pittsburgh Protocol of immunosuppression.

She recovered from the procedures with no significant medical issues, but she would have to win back her independence. This meant six hours of occupational therapy a day. Advento would attempt to influence and feel her surroundings through an intricate network of 96 nerves and 56 muscles that once belonged to someone else. The simplest tasks, like turning a door knob, were formidable.

One month after the transplant, Advento drew the cartoon character Garfield. (She'd always liked drawing.) Four months after transplant, she wove a bracelet. That same month, she played darts for the first time, even pulling off a few bull's-eyes. She experimented with something else, too. At Hadrien's suggestion, she started painting.

"I wanted to keep trying things," she says. "Even if I was unsuccessful, at least I would know I was successful in trying."

She's back working at Quest and expects to continue with hand therapy (two or three hours a day) for the rest of her life. She has her own place again; about once a week an assistant comes by to help out.

What's been most rewarding about the journey: touching others—holding a hand or reaching out some other way. Advento has been featured in national media and given talks to amputees and other groups. It seems to help people when she shares her story. ■

ARTWORK COURTESY ADVENTO

People and programs that keep the school healthy and vibrant

BEYOND EXPECTATIONS

NEW SCHOLARLY PROJECT FUND HONORS LOREN ROTH

BY NICK KEPPLER

"I don't think there's anyone more willing to go not just the extra mile but the extra 10 miles," says Pitt's Ellen Frank, Distinguished Professor of Psychiatry and professor of psychology, of her colleague Loren Roth. Now some School of Medicine students will reap benefits from Roth's tireless, beyond-the-expected approach to patient care.



Roth

Anonymous donors have made a $100,000 gift to honor Roth, a psychiatrist who has held a variety of leadership positions in his 38-year history at Pitt and UPMC (including chief medical officer) and is now Pitt's associate senior vice chancellor for clinical policy and planning, health sciences. The donation will fund the Loren H. Roth, MD, Summer Research Program, which will help med students pay for travel, books, lab materials, and other expenses related to work on the research experience known as the scholarly project.

The donors, a husband and wife who have long supported the University, say Roth helped organize care for a loved one. His "breadth of experience allowed him to locate national resources, beyond what was available locally," says one of the donors.

This does not surprise Frank, who has worked with Roth for more than 15 years at Western Psychiatric Institute and Clinic, where he began his career at Pitt 38 years ago as director of the Law and Psychiatry program. She says Roth took notice of another WPIC patient who needed help and stepped into a variety of roles for her, even helping to fix her plumbing and arrange her finances.

Pitt's Margaret McDonald, a PhD and associate vice chancellor for academic affairs, health sciences, has known Roth since the 1970s, when she was a science reporter and he was one of her sources. McDonald calls him a man of "extraordinary intellectual curiosity who has taken the course of his career into several interesting directions." Before he was a psychiatrist, Roth was a general practitioner at the United States Penitentiary in Lewisburg, Pa., where he organized the prison debate team and treated James Hoffa. Later, he was the psychiatric leader for several State Department delegations to the Soviet Union, examining the Communist party's practice of locking up healthy dissidents in mental hospitals. On a previous visit to the U.S.S.R. in 1985, Roth was a member of a lay group that set up medical clinics with the underground and smuggled in medications.

At Pitt, Roth and colleagues created "The Basic Science of Care" course that was required for several years for second-year medical students. The course taught about hospital safety and how medical care is administered in the United States.

The med school course was "quite prophetic and ahead of its time," says McDonald. (By the way, the scholarly project fund is not the first program to recognize Roth; a UPMC annual seminar on quality and patient safety also carries his name.)

Roth has a special appreciation for the scholarly project experience that the $100,000 donation supports. The project was added to the School of Medicine's curriculum in 2004 and led to 18 fellowships, 22 awards, and 106 coauthorships in research papers among the Class of 2011 alone. Students work with mentors to research a topic of their choosing. The program was designed to spark curiosity and help students develop investigative skills. (Projects examining three broad subjects close to Roth's heart—medical ethics, psychiatry, and quality of patient care—will be given preference for funding.)

"Pitt has pioneered nationally by establishing these medical student research projects," Roth says, "lighting the fuse of discovery, thereby adding so much to student experiences analytically and attitudinally." *—Joe Miksch and Shermi Sivaji contributed to this story.* ■

MATCH RESULTS
CLASS OF 2012

ANESTHESIOLOGY
Bentley, Douglas
UPMC/University of Pittsburgh, Pa.
Garringer, Julie
Johns Hopkins Hospital, Md.
John, Erica
Beth Israel Deaconess Medical Center/
Harvard University, Mass.
Kolan, Michael
McGaw Medical Center of Northwestern Univ., Ill.
Le, Giang
NewYork Presbyterian–Columbia Univ. Medical Center
McGovern, David
McGaw Medical Center of Northwestern Univ., Ill.
Okafor, Dionne
Brigham & Women's Hospital/Harvard Univ., Mass.
Tuomala, Lumei
NewYork Presbyterian–Columbia Univ. Medical Center
Wilde, James
Loma Linda University Medical Center, Calif.
Wise, Eric
UPMC/University of Pittsburgh, Pa.

DERMATOLOGY
Andrulonis, Ryan
Geisinger Health System, Pa.
McGuire, Sean
Penn State Milton S. Hershey Medical Center, Pa.
Mirvish, Ezra
UPMC/University of Pittsburgh, Pa.
Secrest, Aaron
University of Utah Affiliated Hospitals

EMERGENCY MEDICINE
Behringer, Tiffany
Vanderbilt University Medical Center, Tenn.
Chowa, Phindile
Brigham & Women's Hospital/Harvard Univ., Mass.
Considine Courtelou, Honora
University of California, Davis Medical Center,
Sacramento
Downie, Steven
Vanderbilt University Medical Center, Tenn.
Fung, Christopher
University of Michigan Hospitals
Gandhi, Ruchita
Mt. Sinai Hospital, N.Y.
Gebhardt, Kory
McGaw Medical Center of Northwestern Univ., Ill.
Hemerka, Joseph
Denver Health/University of Colorado
Hughes, Katie
University of North Carolina Hospitals
Kralik, Kevin
Maine Medical Center
Mo, Larry
University of Chicago Medical Center, Ill.
Pfeiffer, Anthony
UPMC/University of Pittsburgh, Pa.
Roche, Bailey
University of California Davis Medical Center,
Sacramento
Saunders, Jason
York Hospital, Pa.
Shulman, Joshua
UPMC/University of Pittsburgh, Pa.
Smiley, Mark
Vidant Medical Center/
East Carolina University Brody, N.C.
Tawa, Lindsay
Advocate Christ Medical Center, Ill.
Yang, Fan
Brigham & Women's Hospital/Harvard Univ., Mass.

FAMILY MEDICINE
Archinal, Elizabeth
Summa Health/Northeastern Ohio Universities
Cooper, Mary
University of Massachusetts
Ruff, Joy
In His Image (St. John Medical Center,
other Tulsa and Claremore clinics), Okla.
Shah, Karishma
St. Joseph's Hospital/SUNY Upstate Medical Center
Taylor, Laura
UPMC St. Margaret/University of Pittsburgh, Pa.

INTERNAL MEDICINE
Bednash, Joseph
UPMC/University of Pittsburgh, Pa.
Berger, Christopher
UCSF Medical Center/Moffit-Long Hospital and
Affiliates/University of California, San Francisco
Bernard, Mark
UPMC/University of Pittsburgh, Pa.
Bonifacino, Eliana
UPMC/University of Pittsburgh, Pa.
Boyd, Cary
UPMC/University of Pittsburgh, Pa.
Chua, Abigail
Montefiore Medical Center/Albert Einstein College
of Medicine, N.Y.
D'Auria, Stephen
UPMC/University of Pittsburgh, Pa.
Ellis, Shane
SAMHS Lackland AFB, Texas
England, James
Vanderbilt University Medical Center, Tenn.
Evankovich, John
UPMC/University of Pittsburgh, Pa.
Giridhar, Karthik
UCSF Medical Center/Moffit-Long Hospital and
Affiliates/University of California, San Francisco
Halevy, Jonathan
Fletcher Allen/University of Vermont
Hintz, Lindsay
Beth Israel Deaconess Medical Center/
Harvard University, Mass.
Jarido, Veronica
Duke University Medical Center, N.C.
Khatana, Sameed Ahmed
Brigham & Women's Hospital/Harvard Univ., Mass.
Laux, Timothy
Barnes-Jewish Hospital/Washington University, Mo.
Lembeck, Meghan
Penn State Milton S. Hershey Medical Center, Pa.
Liu, Timothy
Kaiser Permanente Santa Clara Medical Center, Calif.
Livesey, Kristen
UPMC/University of Pittsburgh, Pa.
Lozano, Jose
Duke University Medical Center, N.C.
Mahmood, Deeba
Vidant Medical Center/
East Carolina University Brody, N.C.
Maurice, Nicholas
University of Michigan Hospitals, Mich.
Pishko, Allyson
Duke University Medical Center, N.C.
Sedighi Manesh, Reza
UCSF Medical Center/Moffit-Long Hospital and
Affiliates/University of California, San Francisco
Shah, Mirat
Vanderbilt University Medical Center, Tenn.
Shoukry, Alfred
UPMC/University of Pittsburgh, Pa.
Suresh, Tejas
Montefiore Medical Center/
Albert Einstein College of Medicine, N.Y.
Tavares, Robert
Beth Israel Deaconess Medical Center/
Harvard University, Mass.
Wan, Xiao
University of Chicago Medical Center, Ill.
Zikos, Thomas
Stanford University Programs, Calif.

INTERNAL MEDICINE/MPH
Wu, You
Kaiser Permanente Medical Center at Oakland, Calif.

INTERNAL MEDICINE—PEDIATRICS
Ramer, Sarah
University Hospital & Hackensack University Medical
Center/UMDNJ, N.J.
Zipkin, Jonathan
Penn State Milton S. Hershey Medical Center, Pa.

INTERNAL MEDICINE—PRELIMINARY
Wheeler, David
Albert Einstein Medical Center, Pa.

INTERNAL MEDICINE—PRIMARY
Murphy, Jessica
Hospital of the University of Pennsylvania
Silverman, Gabriel
Montefiore Medical Center/
Albert Einstein College of Medicine, N.Y.

INTERNAL MEDICINE—WOMEN'S HEALTH
Hamilton, Amy
UPMC/University of Pittsburgh, Pa.

MAXILLOFACIAL SURGERY
Li, Tony
UPMC/University of Pittsburgh, Pa.

NEUROLOGICAL SURGERY
Bales, James
University of Washington Affiliated Hospitals

NEUROLOGY
Hepner, Seth
Barnes-Jewish Hospital/Washington University, Mo.
Kang, Peter
Barnes-Jewish Hospital/Washington University, Mo.
Kim, Joseph
University of Southern California Affiliates

OBSTETRICS/GYNECOLOGY
Condon, Karen
Abington Memorial Hospital/Temple University, Pa.
Lee, Jessica Karen
UPMC/University of Pittsburgh, Pa.
Napoe, Gnankang
Brigham & Women's Hospital/Harvard Univ., Mass.
Pettigrew, Gaetan
University Hospitals Case Medical Center/Case Western
Reserve University, Ohio
Ryan, Audra
Albany Medical Center/Albany Medical College, N.Y.
Thomas, Semara
University of Virginia Health System

OPHTHALMOLOGY
Zhang, Matthew
Vanderbilt University Medical Center, Tenn.

ORTHOPAEDIC SURGERY
Singh, Keerat
Vanderbilt University Medical Center, Tenn.
Working, Zachary
University of Utah Affiliated Hospitals

JIM BURKE / CIDDE





Students and their cheering sections at this year's Match Day in March. Someone's name must be called last, eh? This year it was Beth Papas. But she was rewarded with the pot of gold (as her classmates learned of their matches, they each put a dollar in the kitty), as well as a residency at Children's.

OTOLARYNGOLOGY
Beswick, Daniel
Stanford University Programs, Calif.
Vella, Joseph
Strong Memorial Hospital/Univ. of Rochester, N.Y.
Wilson, Caleb
University of Tennessee Health Science Center

PATHOLOGY
Bartholow, Tanner
UPMC/University of Pittsburgh, Pa.
Chou, David
Massachusetts General Hospital, Harvard Univ.
Shyu, Susan
University Hospitals Case Medical Center/
Case Western Reserve University, Ohio

PEDIATRICS
Barreiro, Alessandra
DuPont Hospital for Children/
Thomas Jefferson University, Pa.
Carey, Regan
Harbor-UCLA Medical Center, Calif.
Christopher, Adam
Yale-New Haven Children's Hospital, Conn.
Conway, Susan
Cincinnati Children's Hospital Medical Center, Ohio
Ellsworth, Kevin
Children's Hospital of Pittsburgh of UPMC/University of Pittsburgh, Pa.
Kippelen, Fanny
Children's Hospital of Philadelphia/University of Pennsylvania
Leibowitz, Michael
Children's Hospital Colorado,
Denver Health/University of Colorado
Linakis, Seth
UPMC/University of Pittsburgh, Pa.
McBride, Joshua
Upstate Golisano Children's Hospital/
SUNY Upstate Medical University, N.Y.
Mistovich, Keili
UPMC/University of Pittsburgh, Pa.
Otto, Alana
Children's Memorial Hospital/McGaw Medical Center of Northwestern University, Ill.
Papas (Baker), Beth
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.
Pichler, Stephen
Children's Memorial Hospital/McGaw Medical Center of Northwestern University, Ill.
Predis, Erin
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.
Salimi, Umar
Floating Hospital for Children/Tufts University, Mass.
Thompson, Michael
Nationwide Children's Hospital/Ohio State University

PEDIATRICS/PSYCHIATRY/CHILD PSYCHIATRY
Graham, Kahleb
Rhode Island Hospital/Brown University, R.I.

PHYSICAL MEDICINE & REHABILITATION
Cassell, Andre
Johns Hopkins Hospital, Md.
Darrah, Shaun
UPMC/University of Pittsburgh, Pa.
Guirand, Alcinto
Spaulding Rehabilitation Hospital/Harvard Univ., Mass.
McClure, Matthew
Hospital of the University of Pennsylvania
Nora, Gerald
UPMC/University of Pittsburgh, Pa.
Pinto, Shanti
UPMC/University of Pittsburgh, Pa.

PLASTIC SURGERY
Bykowski, Michael
UPMC/University of Pittsburgh, Pa.
Lee, Jessica Ann
UPMC/University of Pittsburgh, Pa.

PSYCHIATRY
Cohen, Daniel
Western Psychiatric Institute & Clinic,
UPMC/University of Pittsburgh, Pa.
Deo, Anthony
NewYork Presbyterian–
Columbia Univ. Medical Center
Lundblad, Wynne
Western Psychiatric Institute & Clinic,
UPMC/University of Pittsburgh, Pa.
Israel, Benjamin
University of Maryland Medical Center,
Sheppard and Enoch Pratt Hospital
Zanoun, Rami
Western Psychiatric Institute & Clinic,
UPMC/University of Pittsburgh, Pa.

PSYCHIATRY/ADULT & CHILD
Pitskel, Naomi
Yale-New Haven Hospital, Conn.

PSYCHIATRY/FAMILY MEDICINE
Huijon, Roger
UPMC St. Margaret/University of Pittsburgh, Pa.

RADIATION ONCOLOGY
Boyer, Matthew
Duke University Medical Center, N.C.
Kim, Hyun
Thomas Jefferson University Hospital, Pa.
Olson, Adam
Duke University Medical Center, N.C.

RADIOLOGY—DIAGNOSTIC
Chen, Yin
Hospital of the University of Pennsylvania
Hattoum, Alexander
Robert C. Byrd Health Sciences Center/
West Virginia University
Mawn, John
UPMC/University of Pittsburgh, Pa.
Mayercik, Vera
Tufts Medical Center, Mass.
McGarry, William
McGaw Medical Center of Northwestern Univ., Ill.
Mehta, Ajeet
Emory University, Atlanta, Ga.
Mehta, Amar
University of Chicago Medical Center, Ill.
Ng, Timothy
Emory Healthcare, Grady Memorial
Pinnamaneni, Niveditha
NYU Langone Medical Center, N.Y.

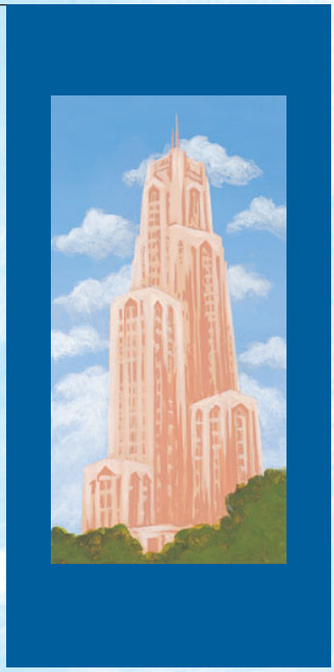
RESEARCH
Longhini, Anthony
UPMC/University of Pittsburgh, Pa.
(Vascular Medicine Institute)

SURGERY—GENERAL
Dyer, Mitchell
UPMC/University of Pittsburgh, Pa.
Gabrielian, Anna
Danbury Hospital, Conn./University of Vermont
Goodman, Laura
University of California Davis Medical Center, Sacramento
Huynh, Cindy
University Hospital/
SUNY Upstate Medical University, N.Y.
Johnson, Carl
University of Toledo Medical Center, Ohio
Ku, Natalie
University of California San Diego Medical Center
Murken, Douglas
Hospital of the University of Pennsylvania

SURGERY—PRELIMINARY
Go, Kristina
Shands Hospital/University of Florida
Singleton, Alex
UPMC Mercy/University of Pittsburgh, Pa.
Wynkoop, Aaron
Vanderbilt University Medical Center, Tenn.
Zaccheus, Oluleke
Beth Israel Deaconess Medical Center/
Harvard University, Mass.

UROLOGY
Packiam, Vignesh
University of Chicago Medical Center, Ill.

VASCULAR SURGERY
Domenick, Natalie
UPMC/University of Pittsburgh, Pa.



CLASS NOTES

'90s

During his residency, **David Rosenberg** (General Psychiatry Resident '92, Child Psychiatry Fellow '92) wanted to learn as much as he could about treating psychiatric disorders in youth: "I asked one of my attendings what textbook he would recommend I use to learn more about pediatric psychopharmacology. He told me there was no textbook." Rosenberg's response? Write his own. In 1994, Rosenberg, with **John Holttum** (Child Psychiatry Resident '94) and faculty mentor Samuel Gershon, now Pitt emeritus professor of psychiatry, published *Pharmacotherapy for Child and Adolescent Psychiatric Disorders*, which is still used by pediatric health professionals today (the third edition was published in March). Rosenberg, now chief of psychiatry and psychology at the Children's Hospital of Michigan and professor of psychiatry and behavioral neurosciences at Wayne State University, studies the genetics of children with depression and obsessive compulsive disorder.

A specialist in both minimally invasive spine surgery and advanced scoliosis, **Hooman Melamed** (MD '99) treats some of the best- and worst-case spinal scenarios. With the Scoliosis Research Society's Global Outreach Program, he has traveled to Colombia, where he says scoliosis in kids is often overlooked. Melamed, now spine consultant at Shriners Hospitals for Children in Los Angeles, describes seeing "horrible conditions" in teenage patients who should have been treated as toddlers. Both at home and abroad, the surgeon performs complex osteotomies, where the spine is broken and reset. Conversely, much of his California-based practice at DISC Sports and Spine Center treats less-severe disorders using minimally invasive techniques. "People are shocked when they find out you can have spine surgery as an outpatient and go home a few hours later."

'00s

When **Benjamin Davies** (Surgery Resident '02, Urology Resident '05) learned he could remove a kidney using one incision instead of three, he thought it was "crazy." The technique, called a laparoendoscopic single-site (LESS) surgery, requires Davies to manipulate traditional tools with his hands crossed. "It's not something that comes intuitively. … It just takes a little getting used to," says Davies, assistant professor of urology at Pitt. The surgery, which is often used to remove healthy kidneys for donation, is now being used by Davies to remove kidney tumors. Davies, a urologic cancer specialist, knew it wouldn't be an option for most of his kidney patients—because only small tumors would fit through a single site—but he wanted to offer it to those who qualified. This March he performed the first single-site kidney tumor removal in Southwestern Pennsylvaia. He calls LESS surgery a "boutique" part of his practice but predicts it'll become more common once robotic tools, currently in experimental stages, are approved.

Compared to traditional means of radiation therapy, the robotic CyberKnife system is extremely precise: It delivers multiple, pinpoint, high-dose beams of radiation with submillimeter accuracy. "This allows us to focus radiation doses more precisely so that critical structures surrounding the problem remain unaffected," says **Sarahgene Gillianne DeFoe** (MD '06, Intern '07, Radiation Oncology Resident '11). DeFoe trained extensively on the technique during her residency at Pitt, and in November she joined the Cape Fear Valley Health System in North Carolina to jumpstart a CyberKnife program there. DeFoe recently conducted a study demonstrating CyberKnife's efficacy in treating rectal cancer. She also specializes in treating patients with cancers of the breast, brain, and lung.

In 2010, cleanup crews and animal welfare experts scrambled to prevent massive ecological damage after the BP Deepwater Horizon oil spill. And in the midst of



DeFoe starts a CyberKnife program in Fayetteville, N.C.

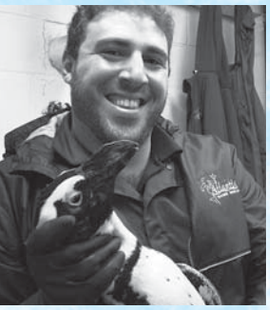
LIVE WITH NANCY SNYDERMAN

Doctors' offices are full of devices and instruments particular to each specialty, but they don't typically include a microphone and professional camera crew. As chief medical editor for NBC News, Nancy Snyderman (Pediatrics Resident '79, Otolaryngology Resident '83) regularly discusses health-related issues on *Today* and produces medical reports for programs like *Dateline NBC*, *NBC Nightly News,* and *Rock Center with Brian Williams*. Though her roles as physician and journalist may seem worlds apart, Snyderman says that she's a "perpetual student" in both positions. And she notes that her approach to communicating difficult scientific and medical concepts to patients and viewers is always the same: "My job is to take [complex medical] information and present it in a way that isn't condescending to people."

Snyderman's television appearances broadcast her medical expertise to millions; yet she doesn't believe that her views have more weight. "I don't think my opinion matters any more than [that of] someone's personal physician," she says. "As a journalist, I'm not necessarily supposed to have an opinion anyway."

In 2011, Snyderman received the School of Medicine's William S. McEllroy Award, which honors a resident alumnus each year. She was also awarded the Albert C. Muse Prize for Excellence in Otolaryngology from the Eye and Ear

COURTESY SNYDERMAN



Lustgarten with a penguin

chaos, they relied on an outdated, paper-based recording system to track the species affected and tag animals. That got **Jonathan Lustgarten** (Biomedical Informatics MS '06, PhD '09) thinking: Why would veterinarians rely on a system that's unreliable, easily damaged, and almost impossible to share long distance? Last year, he thought about developing a software solution, and he won the $100,000 Student Inspiration Award from the University of Pennsylvania, where he is a veterinary medicine student, to do so. Lustgarten says, "The software will help veterinarians and researchers manage information and provide the best care to animals in a variety of disasters and beyond."

'10s

It's not surprising that, as a family medicine doctor and Pitt associate professor of medicine and pediatrics, **Brian Primack** (Clinical and Translational Science PhD '11) is concerned about tobacco propaganda. But what he found in a recent study is surprising: In the *American Journal of Preventive Medicine*, Primack reported that of the hookah tobacco Web sites his team surveyed, more than half didn't include the word "tobacco." "We expected that hookah Web sites might de-emphasize tobacco, but we did not expect that many would leave out the word altogether," says Primack, who notes that none of the sites required age verification and less than 1 percent included a tobacco-related warning. Hookah tobacco, which comes in a variety of fruity flavors, is often wrongly perceived as less harmful; but Primack says studies show it exposes users to large amounts of tar, nicotine, and carbon monoxide.

—Jenelle Pifer and Shermi Sivaji

THE WAY WE ARE

CLASS OF '02

In the winter before their graduating year, pianist **Mark Lazarev** (MD '02, Gastroenterology, Hepatology, and Nutrition Fellow '08) and violinist **Amanda Pong** (MD '02) took the stage to perform a sonata movement by Sergei Prokofiev in the School of Medicine's annual talent show. He'd decided to study medicine after years of studying classical piano in the Oberlin College Conservatory of Music. The talent show was, for him, a night of personal transition. "[Music] was definitely something I was doing seriously," he recalls from his office at Johns Hopkins University, where he is now assistant professor of medicine. But his overriding interest in science (he also studied neuroscience as an undergrad at Oberlin) led him to pursue a path where he could "really really help people." Now, he focuses his research on inflammatory bowel disease, specifically Crohn's disease and ulcerative colitis. Because inflammatory bowel disease usually develops early, in the teens or 20s, there's a real opportunity to improve quality of life over the long term, he says.

Suzanne Atkinson (MD '02) remembers hearing Lazarev play. "He was excellent. … He really had a depth to his personality that went beyond the typical stereotype of a med student," she says. But atypical students were the norm at Pitt, it seemed to Atkinson. She herself turned to medicine after years spent teaching and practicing wilderness sports. During a mountaineering expedition in Mexico, she met **Jim Withers** (MD '84), a UPMC internist who inspired her to study medicine. Withers, who founded Operation Safety Net to bring medical care to people living on Pittsburgh's streets, taught Atkinson that physicians could practice medicine in uncommon ways. "I saw … the way that medicine can allow someone to communicate with another human in a way that otherwise wasn't possible," she says. Now a clinical instructor of emergency medicine at Pitt, Atkinson serves as a medical command physician with STAT MedEvac and also trains triathletes (she is a triathlete herself). "In both activities, you really need to have a connection with the human being," she says, "In the emergency room, it has to happen in a very compressed amount of time."

Bill Hobbs (Molecular Virology and Microbiology PhD '00, MD '02) performed at the talent show the same year as Lazarev. His band—which cycled through a number of names, including Fatt Man and Billy Hobbs Band—played "loud and obnoxious rock and roll," Hobbs says from his lab at the Puget Sound Blood Center in Seattle. There, he studies adult sickle cell disease, an interest he developed at Pitt while shadowing Timothy Carlos, then director of the school's Adult Sickle Cell Program. These days, Hobbs' research investigates a particular plasma protein (von Willebrand factor). "People who don't have enough [of the protein] have bleeding disorders, but we think people with sickle cell disease have too much," says Hobbs, who is also acting assistant professor of medicine in the Hematology Division at the University of Washington.

"It was a stressful time," Hobbs says of the MD/PhD program. The students still crammed in trips to Oakland bars and restaurants, but they'd study "before, during, and after." **Ilan Kerman** (Neuroscience PhD '99, MD '02) says that about sums it up. During his time at Pitt, Kerman explored how the brain maintains a stable internal environment, research he's now building on as assistant professor of psychiatry and behavioral neurobiology at the University of Alabama at Birmingham. Specifically, he's looking into the causes of the physical symptoms associated with depression. "There is a significant medical comorbidity with depression, including heart disease and diabetes. But in terms of causes, we don't really know," he says. *—JP*



Snyderman in Haiti

Institute and Foundation for her significant contributions to the medical field. "I was blown away by receiving those awards," she says. "I owe Pittsburgh so much. I started my journalism career there, and I've stayed very close to Pittsburgh and my mentors there." (Snyderman is also a clinical associate professor of otorhinolaryngology at the University of Pennsylvania.)

Snyderman spoke at the School of Medicine's graduation ceremony this May, stressing that it's important for new physicians to focus on the compassionate fundamentals of patient care. "A lot of it is getting back to basics," she says. "There is a basic need for humanity in medicine and science. And there is nothing more important than the human touch." *—Dennis Funk*

ACHIEL L. BLEYAERT

JUNE 23, 1931–OCT. 30, 2011



Bleyaert

In the 1970s, Achiel Bleyaert investigated brain function and ischemia after resuscitation at the International Resuscitation Research Institute, now the Safar Center for Resuscitation Research in the University of Pittsburgh School of Medicine. His animal studies showed that barbiturates after cardiac arrest protected the brain, says Ake Grenvik, an early colleague of Bleyaert's and physician at UPMC from 1968 to 2009. Though the findings could not be confirmed in repeated studies and the treatment was not as successful in humans, says Grenvik, "It was a big step—an important step—in research toward brain improvement after cardiac arrest and resuscitation." Bleyaert's initial inquiries sparked decades of research in this area, Grenvik adds, which eventually led to the current practice of using hypothermia to protect the brain from damage after cardiac arrest.

Bleyaert, a Pitt professor of anesthesiology and critical care medicine from 1980 to 1985, died in October at Clearfield Hospital, in Clearfield, Pa., where he had been a staff anesthesiologist since 1992. He was 80.

Grenvik remembers Bleyaert as an intelligent man who was easy to get along with. Though quiet, he was a diligent worker and a positive mentor. "He was a good teacher in the operating room for anesthesia residents and medical students." *—Dennis Funk*

JAMES SHAVER

JAN. 21, 1935–APRIL 13, 2012



Shaver

James Shaver, director of the Division of Cardiology in Pitt's School of Medicine for more than two decades and mentor to many, died in April.

In the 1960s, Shaver opened and directed the first cardiac catheterization laboratory at what was then Presbyterian University Hospital. His clinical and research interests included valvular heart disease, adult congenital heart disease, hypertrophic cardiomyopathy, and the physiologic basis of heart sounds and murmurs. But he may be remembered best for his teaching.

As a Pitt faculty member for more than 40 years, Shaver trained hundreds of cardiologists. William Follansbee, who teaches in the Division of Cardiology, says he will remember Shaver for his remarkable ability to teach medical students and cardiology fellows. "It was probably his greatest strength," Follansbee says. "I think the fellows in general who have gone through the program over the last couple decades all saw him as an important mentor."

For many years, Shaver designed and ran the fundamental cardiovascular course for second-year students. "An extensive amount of work goes into the course," says Follansbee. "The syllabus just for that course is two volumes thick."

A spirit of eternal optimism was part of what helped Shaver shape the curriculum and guide students in their careers, Follansbee says. He notes that in later life Shaver wouldn't let his own medical issues get him down, and that he still went skiing and traveled to conferences. "He was dedicated and motivated until the very end," he says. *—DF*

GERHARD WERNER

SEPT. 28, 1921–MARCH 26, 2012



Werner

Gerhard Werner, an MD and former dean of Pitt's School of Medicine, was an avid reader: He devoured books of philosophy and literature and encouraged his students to do the same. Werner's inquisitiveness was an essential part of him, says William de Groat, a former colleague.

"Werner was excited about research and was always thinking of something new to do," says de Groat, Distinguished Professor in the Department of Pharmacology and Chemical Biology. In the 1960s, de Groat joined Pitt under Werner, then the department's chair.

An innovative neuroscientist, Werner published more than 100 scientific papers and developed a muscle relaxant (succinylcholine), his first major invention; it's still used by anesthesiologists today. With a keen interest in computer science, Werner, while at Pitt, helped devise an early artificial intelligence-driven medical expert system.

"He was visionary, but also urbane and cultured," says de Groat, noting that Werner's worldliness was particularly evident in the classroom. Hoping to enliven lectures, he often shared witty stories about his extensive travels. (He graduated from the University of Vienna's medical school and worked in India and Brazil before emigrating to the United States in 1957.)

In 1974, he was appointed dean of the medical school. Although he was a basic scientist, one of his most lasting administrative contributions was a practice plan system that would prove key to turning the school's financial situation around during difficult times, Barbara I. Paull notes in *A Century of Medical Excellence* (1986).

Werner was honored with the U.S. Senior Scientist award from the Alexander von Humboldt Foundation in 1985.

After retiring from Pitt in 1989, he became an adjunct professor of biomedical engineering at the University of Texas at Austin. There, he stayed active in such research areas as artificial intelligence and neurodynamics. *—Dana Yates*

IN MEMORIAM

'40s

HARRY S. HARTMAN
MD '43A
DEC. 8, 2011

'50s

PETER P. STAJDUHAR
MD '52
DEC. 3, 2011

EDGAR S. HENRY JR.
MD '53
APRIL 4, 2012

MARTIN ARISTARK MURCEK
MD '58
MARCH 16, 2012

'60s

EDWIN DELROY STUTZMAN JR.
MD '61
APRIL 12, 2012

ROBERT EMERSON CAVEN
MD '64
JAN. 15, 2012

LOUIS D. META
MD '67
MARCH 15, 2012

'70s

ALAN JOHN KUNSCHNER
RES '72
MAY 2, 2012

'80s

JEFFREY S. GIBSON
MD '89
APRIL 9, 2012

'90s

AMY C. MASZKIEWICZ SOBIESKI
MD '97
MARCH 4, 2012

FACULTY

ANTHONY H. VAGNUCCI
APRIL 19, 2012

PATRICK G. LAING
MARCH 28, 2012

DAVID MADOFF
REGENERATE, WITH PRECISION

BY SHARON TREGASKIS



COURTESY MADOFF

Madoff helps make diseased livers strong enough for resection.

When it comes to cancer, the last thing a patient wants to hear is, "I'm sorry, it's inoperable." Interventional radiologist David Madoff (MD '95) hates for anyone to deliver such news. So he has dedicated the past decade to refining a pre-operative procedure known as PVE (portal vein embolization) that makes more patients with liver cancer eligible for surgery.

Unlike such organs as the kidney, lungs, or heart, the liver responds to severe injury with a growth spurt. It's like a starfish sprouting a new arm after a predator's attack: Remove a portion of the organ, and the remaining piece will regenerate to full capacity within months. But there's a catch: Take too much, and what's left shuts down, flooding the body with toxins and bacteria.

"People can die after surgery if they have a very small liver," says Madoff, now chief of the Division of Interventional Radiology at NewYork–Presbyterian Hospital and Weill Cornell Medical College. Without intervention, he says, just 25 percent of patients who need extensive resection would qualify.

Enter PVE, pioneered by Japanese surgeon Masatoshi Makuuchi in 1990 and since refined by Madoff, who's traveled throughout the world teaching the procedure. Like most techniques developed by interventional radiologists, it's minimally invasive. Using imaging technology to reveal the portal vein, the radiologist threads a catheter into the blood vessel to be embolized and then injects either a chemical solution or beads that block blood flow to the part of the organ slated for removal. Much as an arborist prunes diseased limbs to ensure enough sunlight and nutrients make it to healthy branches, PVE reduces blood supply to the portion of the liver slated for removal and concentrates resources in the rest of the organ, spurring liver regeneration before surgery. Four weeks later, after a CT scan confirms that the rest of the liver has gained volume, the patient, previously inoperable, is eligible for resection.

In 1991, the then-future radiologist Madoff discovered his love of imaging as a first-year medical student at Pitt, where he did independent research with faculty at the nascent PET Center. "I saw all of this new technology as the future of diagnosis and treatment," says the 44-year-old, who won a research award from the medical school's summer research program. "Pitt ... created a milieu where I could get excited about doing research and an academic career."

It wasn't until Madoff was a fellow in vascular and interventional radiology at the University of Texas M.D. Anderson Cancer Center that he came across PVE, then relatively unknown in the United States. His mentor had assigned him to present a case involving a patient whose PVE had led to complications. Madoff was hooked. "I wanted to make the procedure easier," he says, "with fewer complications. I realized there was a whole avenue of research just at its infancy."

Last year, Springer published a textbook, *Venous Embolization of the Liver: Radiological and Surgical Practice*, which Madoff edited with three others, including Makuuchi, now president of the Japanese Red Cross Medical Center in Tokyo.

Madoff has focused his PVE-related investigations on analyzing which patients are the best candidates and refining the devices and techniques involved to improve regeneration and reduce the risk of complication. He has also demonstrated that the procedure can be used with other tactics to starve out liver tumors while promoting function in healthy tissue, allowing some patients to avoid conventional surgery entirely.

"We've developed a safe technique over the course of years, where we've had very few complications," he says. "But some patients don't regenerate; we're still working on the predictors of who regenerates and who doesn't." ■

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THE GIFT NO PHYSICIAN EVER FORGETS

On the first day of anatomy lab in the School of Medicine, the entire first-year class gathers in groups of six, each with a cadaver they will carefully study for the next seven weeks. Here, they will learn the fundamentals of biology shared by all people, as well as the inherent quirks of individual anatomy. They will witness the scars, injuries, and evidence of how this person spent her days on earth. For budding physicians, the experience inspires awe and humbles. Medical anatomy becomes personal and profoundly human.

Every day in the anatomy lab is a reminder that men and women—perhaps when ailing, perhaps in the prime of life—decided to donate their remains to further medical education. To honor these people and to express gratitude, first-year med students gather in Pitt's Heinz Memorial Chapel annually.

On a brilliant spring day, families of donors fill the front chapel pews; white-coated students take the pews in the back. During one of many musical tributes, the congregation sits in stunned silence as eight students mesmerize with an a cappella performance of Palestrina's *Sicut cervus*, one of the greatest examples of religious choral art to emerge from the Renaissance. Seventy-one donor names are read aloud; a candle is lit for each. Class of 2015 president Lauren Zammerilla makes a pledge: With every patient they see, she and her classmates will repay these profound offerings with humility, respect, and compassion. As Loren Roth, associate senior vice chancellor for clinical policy and planning, health sciences, and a physician himself, notes, "These honored dead have made a gift that no young man or woman who becomes a physician ever forgets." *—Chuck Staresinic*

PHOTOS BY JOSH FRANZOS

CALENDAR

OF SPECIAL INTEREST TO ALUMNI AND FRIENDS

WHITE COAT CEREMONY
AUGUST 5
3 p.m.
Scaife Hall, Auditorium 6

MUSGRAVE LECTURESHIP
OCTOBER 12–13
J. William Futrell, MD, Speaker

2013 WINTER ACADEMY
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Naples, Fla.
For information:
Pat Carver
412-647-5307
cpat@pitt.edu
www.winteracademy.pitt.edu

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MAY 17–20, 2013
Reunion Classes:
2003 1998
1993 1988
1983 1978
1973 1968
1963 1958

UPCOMING HEALTH SCIENCES ALUMNI RECEPTION
DATE TBA
San Francisco, Calif.
St. Augustine, Fla.
For information:
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THE OWL, 1959

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If you would like to learn more about the ways in which you can arrange for your legacy to the School of Medicine, contact:

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60	4.4	$440	$2,231
65	4.7	$470	$2,956
70	5.1	$510	$3,691
75	5.8	$580	$4,268
80	6.8	$680	$4,791
85	7.8	$780	$5,502
90	9.0	$900	$6,190