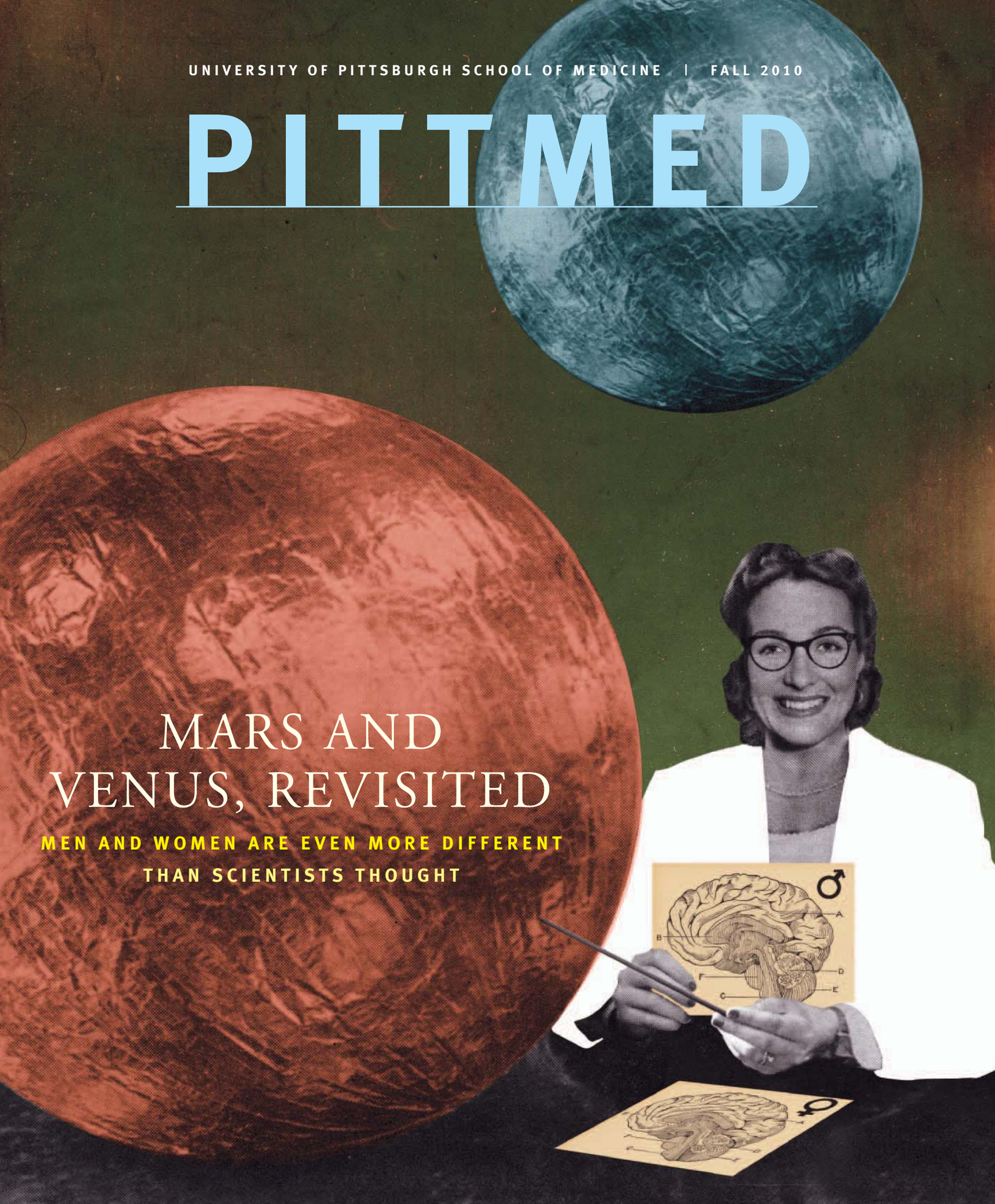
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | FALL 2010

PITTMED

MARS AND VENUS, REVISITED

MEN AND WOMEN ARE EVEN MORE DIFFERENT THAN SCIENTISTS THOUGHT





JIM BURKE / CIDDE

FRIEND US

OMG, the SOM is on FB! Check out the School of Medicine's new Facebook page for the scoop—news headlines, reunion updates, videos, and photos, including this pic from Match Day 2010. The about-to-be MD jumps for joy moments before presenting with acute ☺.

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VOL. 12, ISSUE 3



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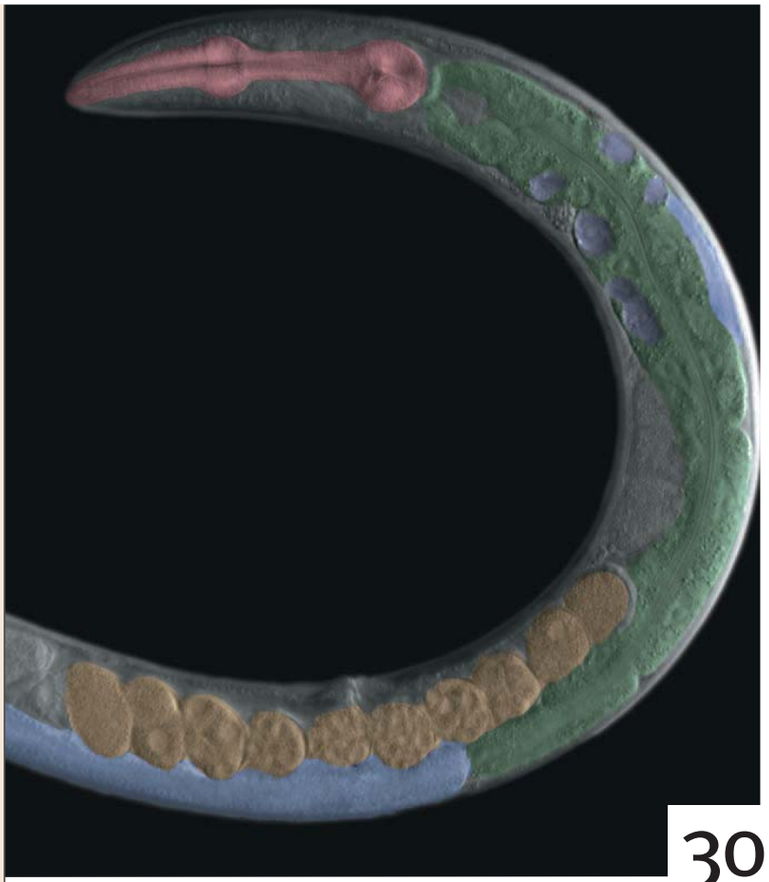
Illustrator JESSE LENZ [Cover, "Mars and Venus, Revisited"] was almost graphic designer Jesse Lenz, until he realized—shortly before graduating from West Liberty University in the spring—that the only thing he liked about that work was making pictures. To hone his illustration chops, Lenz created an image for Dictionary.com's word of the day each and every day. (Lenz also sought advice and critique from another *Pitt Med* cover artist, John Ritter, whose work often appears in *The New Yorker* and *The Atlantic*.) With a growing portfolio and growing confidence, Lenz submitted work to the annual *American Illustration* competition (the art world's who's-who for illustrators), getting two pieces accepted from a field of 8,000 total submissions.

Lenz calls his style "retro-futuristic collage"—"I love the juxtaposition of seeing what people in the past thought the future was going to be and what it actually has become," he says.

CHUCK JOY (MD '78) was inspired to write "Across the Mon" [Last Call] after attending a psychiatry conference at Pittsburgh's Station Square. Since his Pitt days, Joy has developed a community child psychiatry practice in Erie, Pa., where he also is known for his poetry. Joy says he likes the way poets can share their work more directly and more quickly than other writers can—as musicians do. He runs a local open mic, chairs the Erie County Poetry Committee (whose jury selects a county poet laureate), and has seen his work published in anthologies and chapbooks. His poems can also be heard on his CD, *Live at the Jive*, which combines poetry with improvisational music.

COVER

New research shows that men and women, and boys and girls, are even more different than doctors thought. (Cover: Jesse Lenz, © 2010.)



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David Gitlin was one of the world's first and best immunochemists. His Pitt legacy includes the discovery of widely used prenatal biomarkers, the guidance of young scientists, and the inability to suffer fools gladly.

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Pitt scientists are sorting out sex-based disparities in the nervous, cardiovascular, musculoskeletal, and immune systems and elsewhere that have important implications for health. Men and women seem to be more different than we'd imagined—even at the cellular level.

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What's a millimeter long, transparent, and a vital tool for scientific discovery? Look inside and *C. (elegans)*.

BY MELINDA WENNER MOYER

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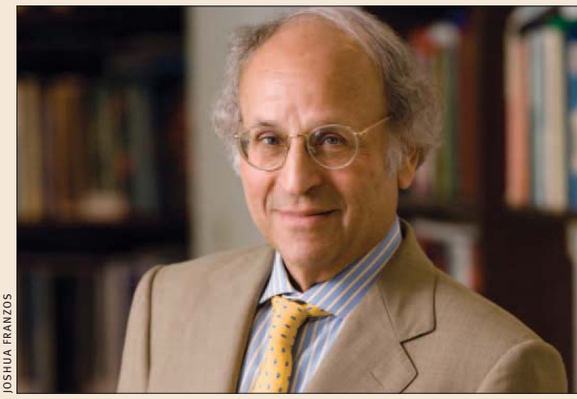
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JOSHUA FRANZOS

Action speaks louder than words but not nearly as often.
—Mark Twain

As we bid farewell to one class and place white coats on another pride of aspiring physicians, I want here to share some comments I made during a recent commencement at my own medical school alma mater. These were my thoughts: Taking a cue from Mark Twain, I encourage all of us, especially newly minted doctors and scientists, to be mindful of how we use words and to realize the potency they can have. I acknowledge my bias. I see myself a wordsmith, long engaged in creative writing and literature and, as you might expect, in the reporting of research.

First, please remember that modern health care is not just about patient-physician interactions. Nurses, physician assistants, radiology technicians, psychologists, respiratory therapists, and other staff are, of course, critical to excellent care. As a team, you can't recapitulate the Tower of Babel in your dealings with one another. Rather, you will need to adopt a shared and respectful language if you hope to establish common patient-care goals, resolve conflicts, and build consensus.

In terms of caring for our patients, our utterances can be as powerful as many drugs and as penetrating as our extraordinarily sophisticated modern imaging tools.

Carefully chosen words may enable you to get Mr. Smith to reveal, reluctantly, that he's taking his blood pressure medicine only every other day because the price is too high for his fixed income. Carefully chosen words may enable you to not only motivate a particularly stubborn patient with emphysema to finally give up smoking but also challenge all of your patients to assume a measure of personal responsibility for their health—to think about prevention before treatment becomes necessary. The right words will also help you convey heartfelt sympathy when medicine and technology have run their course, and there is nothing left for you to do but offer your humanism to a dying patient and that patient's family.

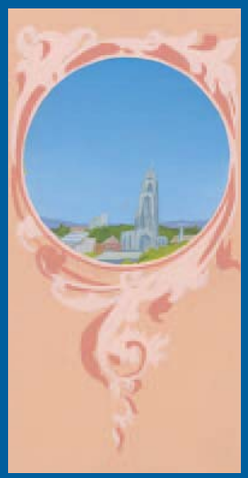
Easier said than done, you may be thinking. Whether you intend to spend your days in medicine as a physician, a scientist, or both, you will need to navigate yourself and others through substantial challenges—probably not infrequently. Some advice to the newbies from a veteran:

Be a poet! Choose innovative and imaginative words as you wrestle with a particularly perplexing diagnosis or the latest setback in your study. Such words will help you articulate, to yourself, innovative and imaginative alternatives and strengthen your conviction that you have chosen those alternatives well.

Choose fearless words, especially in the face of seemingly insurmountable hurdles and risks. Your own gentle and firm response confirming a frightening diagnosis, for example, can serve as a steady hand to a patient's family, helping them summon the fortitude and courage to face the adversity ahead.

Choose words like "how" and "why" that can lead to probing or challenging questions. The difference between good medical science and great medical science is often in the quality of the questions asked. Expect answers beyond the routine, beyond the current paradigms. As Annie Dillard observed, "If we were to judge nature by common sense or likelihood, we wouldn't believe the world existed."

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



Devoted to noteworthy happenings

at the medical school

FACE TRANSPLANTS APPROVED

UPMC, in partnership with the School of Medicine, has become the third American medical center certified to perform face transplants.

The University of Pittsburgh's Institutional Review Board and UPMC approved the procedure in June. Joseph Losee, MD professor of surgery and of pediatrics in the School of Medicine, heads the initiative.

With UPMC and Pitt's experience in allotransplantation, which involves tissue that isn't genetically identical, Losee says that his team is in an optimal position to join the Cleveland Clinic and Brigham and Women's Hospital in Boston as providers of this procedure. A transplant can offer some normalcy to people with devastating facial deformities.

"It is the next horizon in reconstructive surgery," Losee says. "And we at Pitt have both the technology and the innovative approach to minimizing lifelong immunosuppression."

There is no timetable for the first face transplant in Pittsburgh, Losee says, though the screening of prospective patients is expected to begin soon. *—Joe Miksch*

FOOTNOTE

Survey says: Pitt researchers are delivering the goods and enjoying their work at the same time. Pitt has climbed to 12th on *The Scientist*'s 2009 "Best Places to Work in Academia" list, up from 46th in 2008. Pitt receives the most federal funding of the top 15 institutions. Respondents cited research resources and a collegial work environment as among the University's greatest strengths.



Ginkgo biloba's reputation as a cognition enhancer doesn't stand up to rigorous study.

GETTY IMAGES

Supplement(al) Information

Ginkgo has been used in traditional Chinese medicine for ages and remains one of the most popular herbal treatments for improving cognitive function. A recent study suggests that, for such uses, ginkgo might better be forgotten. The research was led by Beth Snitz, a PhD research associate in the Department of Neurology, and Steven DeKosky, an MD and former chair of Pitt's Department of Neurology, who now serves as vice president and dean of the University of Virginia School of Medicine.

The Ginkgo Evaluation of Memory study, a six-year project that followed 3,069 older adults and spanned six U.S. medical centers, is the largest double-blind, placebo-controlled study of dementia prevention to reach completion. Each of the subjects began the trial with little to no cognitive impairment. Six years later, those who took ginkgo and those who didn't showed little disparity in tests of memory, language, attention span, visuospatial judgment, and executive function. The team's findings were published this winter in the *Journal of the American Medical Association*.

According to Snitz, the results suggest it makes more sense to "do things we already know are good for cognitive health rather than take medications or supplements that lack evidence of efficacy." *—Ben Korman*



CAMI MESA

A&Q

Rachel Berger and Janet Squires: Fighting Child Abuse

In 2006, the American Board of Pediatrics recognized a heart-wrenching new subspecialty. Two hundred U.S. physicians are now board-certified in child abuse pediatrics, including Pitt's assistant professor of pediatrics Rachel Berger (Res '99, Fel '01), shown left, and professor of pediatrics Janet Squires, shown right. Berger talked with us about the subspecialty.

Why the subspecialty helps

The number one advantage is that it draws attention to a group of kids who really need the voice. The constituency for children with autism is the parents of children with autism. The constituency for children with cancer is the parents of children with cancer. But there is no natural constituency for children who are abused. And there are three million children in the United States who are reportedly abused every year—that's more than almost any other disease that you can possibly think of.

On what it takes to be a child abuse expert

It's a unique amalgam of medical skills borrowed from a variety of subspecialties, like general pediatrics, orthopaedics, emergency medicine, neurosurgery, and radiology. And there are many different aspects to child abuse. The person who's a child abuse specialist really has to have a good knowledge of all of them—physical abuse, sexual abuse, emotional abuse, neglect. They're all things that the general pediatrician or any other subspecialist may not be very comfortable with.

On the hardest parts of the job

Telling somebody their child is being abused is probably one of the most difficult things that you do as a doctor. You have to be a very, very good communicator. You're dealing with families in crisis who are angry almost all the time. The other thing is being able to explain extremely complicated medical things to non-medical people. The decisions about child protection are made by child protective services and police. Their assessments need input from a medical expert.

A question for us from Janet Squires

We all know that it is very hard to see what we are not looking for. So how can we elevate the awareness of abuse and neglect in children among medical professionals and in the general population as a whole? ***—Interview by Melinda Wenner Moyer***



Next Generation

Six years ago, Pitt's School of Medicine implemented the scholarly project requirement to give students a taste of research early in their medical careers. The Bert and Sally O'Malley Award for Outstanding Medical Research recognizes those who excelled with their projects. Four members of the Class of 2010 were so honored:

Given the prevalence of coronary artery disease, Malolan Rajagopalan wants to make sure patients get an accurate diagnosis. **To image myocardial perfusion, doctors often use single photon emission computed tomography (SPECT). Yet during SPECT imaging, tissue and body fat can disrupt signaling and falsely create the appearance of blood-flow blockage to the heart. Rajagopalan found that taking a separate CAT scan with a timed respiratory protocol can clarify the SPECT image. Rajagopalan's project mentor was Pitt's Prem Soman, MD/PhD assistant professor of medicine and associate director of nuclear cardiology research.**

Alexandra Lewis, who worked with Pitt's George Michalopoulos, MD/PhD chair of pathology, studied hepatocellular carcinoma—the most common form of primary liver cancer. **For the study, samples of solid tumor tissue were analyzed to further understand what triggers the development of the disease. The study also provides insight into why some chemotherapy drugs don't perform as well in the body as in culture.**

Patients undergoing gastric bypass can lose hundreds of pounds, but they're left with excess skin that can become infected if not surgically removed. **Devin O'Brien Coon worked with Pitt's J. Peter Rubin, MD and associate professor of plastic and reconstructive surgery, to develop safer post-bariatric reconstruction techniques.**

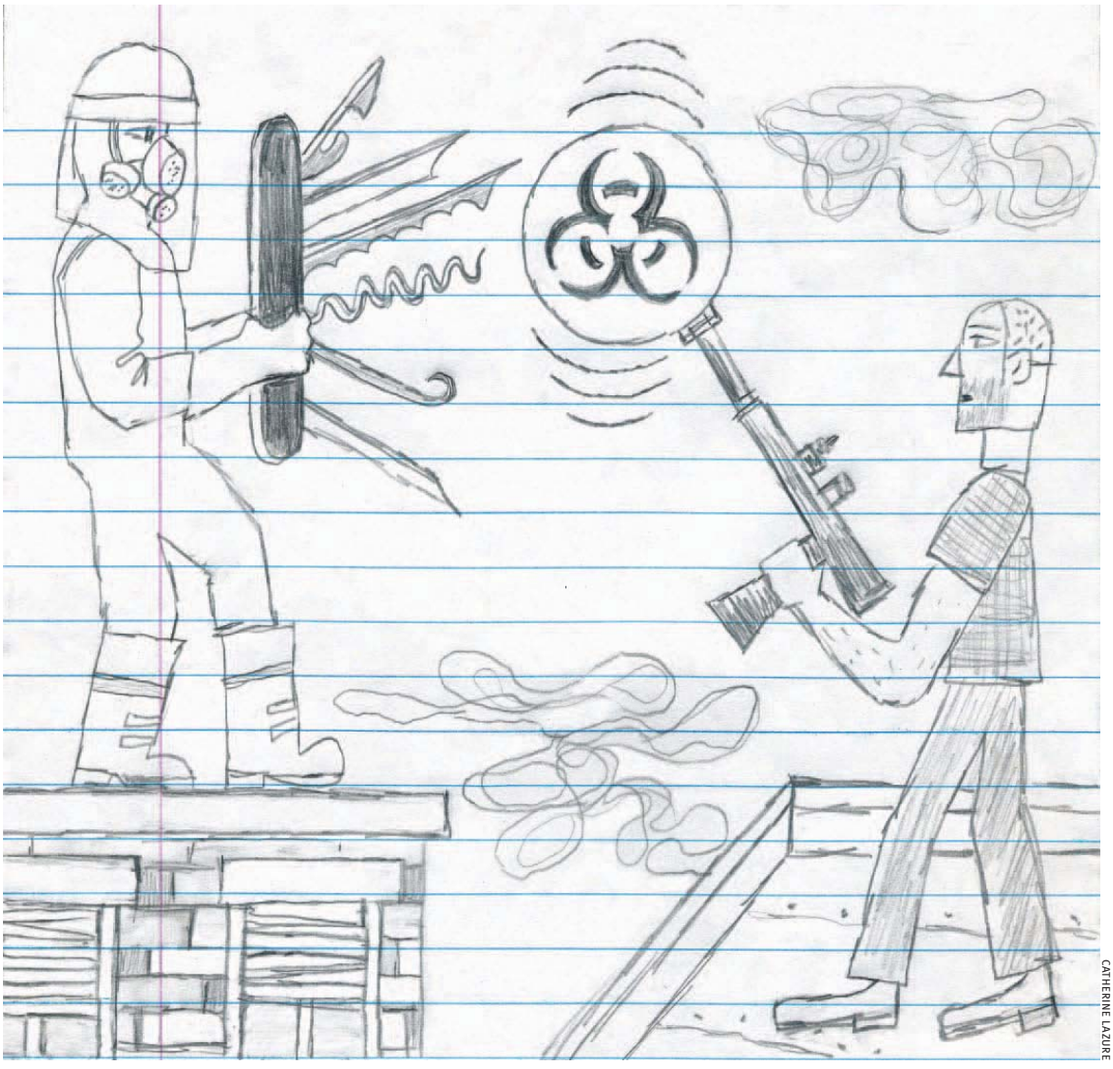
Survival rates of head and neck cancer patients haven't changed much for three decades. **Sun Ahn has contributed to the understanding of how these tumors relay messages. Head and neck cancer tumors secrete a protein that allows them to form additional blood vessels necessary for tumor growth. Ahn, working with Pitt's Seungwon Kim, MD assistant professor of otolaryngology, found that the protein also sends a message to the tumor itself to help it become more migratory and invasive.** ***—Keith Gillogly***

A Mesh of All Trades

Researchers in Alan Russell's laboratory at the University of Pittsburgh-UPMC McGowan Institute for Regenerative Medicine have developed a biological Swiss army knife—a polymer capable of fighting a range of biological and chemical toxins. Russell, a PhD, director of the institute, and Distinguished University Professor of Surgery at Pitt, hopes this versatile material will be an effective countermeasure against bioterrorism.

The material is a polyurethane fiber mesh that resembles a slice of a latex glove. It can be used to build detoxifying sponges, pellets, or wound dressings to safeguard victims of biological terrorism. In tests, the material was able to kill off one million bacteria per milliliter in an hour and detoxify 75 percent of a simulated nerve agent compound in seven hours.

"Terrorists are not going to announce what kind of agent they will unleash in their attack, and a single defensive material is easier to deploy and decreases the response time," says Gabi Amitai, a PhD visiting professor of pharmacology and the project's lead investigator. *—BK*



CATHERINE LAZURE

Teaming up

Delivering quality medical care is not a solitary pursuit. To get a handle on the teamwork necessary to properly treat a patient, a group of Pitt students—including Sean Tackett (MD '10), Garrett Eggers from the School of Pharmacy, and Maria Falcone and Debra Thompson from the School of Nursing—traveled to the University of Minnesota in April. There, they participated in the 2010 CLARION (Clinician/Administrator Relationship Improvement Organization) National Interprofessional Case Competition.

After spending hours studying a fictional scenario in which a 47-year-old woman with a spinal cord injury died while undergoing an MRI, the team presented its analysis of what went wrong to a panel of judges. They came back to Pittsburgh winners, sharing a $7,500 prize.

Loren Roth, MD/MPH associate senior vice chancellor for the health sciences at Pitt and co-advisor for the team, says that good cross-disciplinary communication is vital to good care, and building an awareness of that is an important part of Pitt's curriculum. To see how well the team competed suggests that this idea has taken root, he says. *—JM*

A BIG LITTLE DISCOVERY

Small discoveries can lead to big things. The University of Pittsburgh's Robert Squires—in collaboration with researchers at Indiana University, Riley Hospital for Children, and the Clinic for Special Children in Strasburg, Pa.—helped identify a gene responsible for a newly recognized disease in Amish children.

Squires, an MD and the clinical director of Children's Hospital of Pittsburgh of UPMC's Division of Pediatric Gastroenterology and professor of pediatrics at Pitt, is coauthor of a paper published in the March 12 edition of the *American Journal of Human Genetics*. The paper presents evidence that a mutation in a gene called ITCH causes an autoimmune disease that results in the enlargement of the spleen and liver, developmental delays, and chronic diarrhea.

Although the disease is rare and specific to the Amish, Squires thinks this sort of discovery can deepen our knowledge of how "the intestine handles immunological challenges," perhaps leading to advances in immunosuppression and the treatment of intestinal allergies. *—JM*







CAMI MESA

NICU @ ZOO

Erin Perry went into labor 12 weeks early after carrying six babies. "It was scary from the moment I became pregnant," she says. "I was lucky enough to have fantastic doctors." Today her sextuplets—the smallest was 1 pound 11 ounces at birth—are 7 years old and healthy.

This summer, Perry, now a member of the Magee-Womens Hospital of UPMC's parental advisory committee, and other volunteers organized a gathering at the Pittsburgh Zoo and PPG Aquarium of former patients of Magee's Neonatal Intensive Care Unit.

Organizers draped a large banner with marker tracings of children's hands over a table. Some of the kids insisted on tracing a hand themselves, resulting in a colorful, if slightly messy, display. Inside each print was the child's name, birthday, and birth weight. The banner was taken back to the NICU so everyone there could see how the children had grown. *—KG*

Faculty Snapshots

Nancy Davidson, director of the University of Pittsburgh Cancer Institute, has been honored with the 2009 Gianni Bonadonna Breast Cancer Award. The award, administered by the American Society for Clinical Oncology, carries with it a $10,000 honorarium (which Davidson has donated to the Frieda G. and Saul F. Shapira BRCA–Associated Cancer Research Program at UPCI) and $50,000 for her to hire a research fellow. The MD researcher investigates the role of hormones in gene expression and cell growth in breast cancer. She was elected to the Association of American Physicians this year.



Davidson

Physician-scientist Mark Gladwin has been elected to the Council of the American Society for Clinical Investigation. He is the first Pitt med faculty member to serve in this capacity at ASCI, one of the nation's oldest and most respected medical honor societies. Chief of Pitt's Division of Pulmonary, Allergy, and Critical Care Medicine and director of its Vascular Medicine Institute, Gladwin made a name for himself by discovering that the nitrite anion is a regulator of blood pressure and blood flow.



Gladwin

Pitt's Ian McGowan recently became the lead investigator of two multicenter federally funded projects intended to prevent HIV infection. McGowan, an MD/PhD professor of medicine and of obstetrics, gynecology, and reproductive sciences, will coordinate an $11 million effort to formulate existing retroviral drugs into a topical gel that can be applied to the rectum.

His other project, funded at $6.5 million over four years, will survey gay men about the acceptability of using such a gel while counseling them on safer sex practices.



McGowan

Susan Amara is president of the Society for Neuroscience. Amara, a PhD, is the Thomas Detre Professor and Chair of the Department of Neurobiology in the School of Medicine. Amara's research aims to sort out the molecular and cellular biology of membrane transporters.



Amara

Jennifer Rubin Grandis (MD '87, Fel '92, Res '93) was elected to the Association of American Physicians. The Pitt med alumna is vice chair for research and the UPMC Head and Neck Cancer Research Professor in the School of Medicine's Department of Otolaryngology. Grandis, an expert in head and neck cancer oncogenesis, also recently joined the American Association for Cancer Research's board of directors. *—JM*



Grandis



WE ARE FAMILY

Rebecca Leeman-Neill (shown center) is from the Boston area. She finished the University of Pittsburgh's MD/PhD program this year and has begun her pathology residency at UPMC. She recalls making her choice to come to the city and University: "I really liked it here, and I thought the MD/PhD program was fantastic—better than any MD/PhD program I had visited. And I went all over the place—Chicago, Wisconsin, Boston, New York."

She was the first, but not the only, Leeman charmed by the School of Medicine. She has since been joined by two of her brothers: Jonathan Leeman (shown right) is in the Class of 2013 and part of the physician-scientist training program (a five-year program, with one year of research between the second and third years of medical school). Joshua Leeman (left) is beginning the second year of a radiology residency.

"One reason I'm here is that Rebecca was here," says Jonathan, "and I knew that Josh would be here when I was accepted."

"We try to get together pretty regularly," says Rebecca. "I lived in Pittsburgh without my family for a long time, and it has made a big difference to have you guys here."

"It's good being in the same city for a number of reasons," says Joshua in agreement. "I get to mentor you guys and give you advice."

"Hey, I'm older than you!" his sister reminds him.

"But I've been through it, so I'm kind of in a mentoring role. When we do hang out, we tend to go overboard with the medical topics, I think. If anyone else is there, they kind of want to tear their hair out."

Jonathan chimes in: "Even when we go home, just talking to Dad, we end up talking about medical things." (Their father is a cardiologist—"He gets to do big procedures on a daily basis; gets to save lives," adds Jonathan. Heart disease will be Jonathan's own research focus.)

"I don't know how it happened that we all ended up going to medical school," his older brother muses.

"We do have a younger brother who's studying mathematics at Princeton," Rebecca says.

"Is he going into medicine?" Jonathan wonders aloud.

"Probably," says Joshua. ***—Chuck Staresinic***

—Photo by Annie O'Neill

Explorations and revelations taking place in the medical school



Recently, Pitt researchers uncovered how omega-3 fatty acids—which are found in fish and other foods—help to ebb the tides of inflammation that contribute to cardiovascular disease.

BIG CATCH

REELING IN THE SECRETS OF OMEGA-3 FATTY ACIDS

BY JOE MIKSCH

On the rivers, there are fishermen. In the Bible, there are fishers of men. In Bruce Freeman's lab, there are fishers of molecules. And he and his crew of investigators have nabbed a compelling catch.

Freeman, a PhD and the UPMC/Irwin Fridovich Professor and Chair of the Department of Pharmacology and Chemical Biology at the University of Pittsburgh, has recently developed an interest in the anti-inflammatory properties of omega-3 fatty acids, which are found in fish, some plant oils, and nuts. Research shows that those whose diets are rich in omega-3s have, as Freeman puts it, "a significant decrease in stroke, heart attack, and heart failure and other inflammatory disorders."

We know that much. What we didn't know—until Freeman, Chiara Cipollina, Alison Goeger, and Francisco Schopfer, among others, published a study in *Nature Chemical Biology* in May—was how omega-3s do their work.

To find out, Cipollina went fishing.

Cipollina, a PhD, spent the last two years at Pitt working in Freeman's lab as a Ri.MED fellow. The Ri.MED Foundation, founded in 2006, is a collaboration between the University of Pittsburgh, the Italian government, UPMC, and Sicily intended to improve public health in Sicily and worldwide.

Before going fishing, you might make sure the waterways are stocked. For this, Freeman's team employed activated macrophages—immune cells present in inflamed tissue. Macrophages use omega-3 fatty acids as signaling mediators.

Next, using the chemical compound beta-mercaptoethanol (BME) as bait, Cipollina "hooked" the omega-3 derivatives produced by the macrophages. "We always knew when 'fishing' was going on in the lab," says Freeman. "[BME] has a lot of chemical similarities to the odorant of skunks."

The researchers learned that the omega-3 derivatives are chemically modified by the active macrophages. They become electrophilic fatty acid oxidation products (EFOX)—metabolic byproducts that are attracted to electrons and react with important molecular targets in myriad cell types. The Freeman lab found that as EFOX binds to protein residues—such as those found in the BME bait—it stimulates antioxidant and anti-inflammatory responses, the actions that contribute to the beneficial outcomes of an omega-3-rich diet.

The Freeman lab's *Nature Chemical Biology* paper also elucidates how an enzyme called cyclooxygenase-2 (COX-2), the molecular bull's-eye for aspirin and similar drugs, manages the transformation of omega-3s to EFOX. Aspirin, it turns out, enhances the production of EFOX. Hence less inflammation.

"One of the beautiful symmetries of [Cipollina and Schopfer's] discovery is that the source of these activated omega-3 fatty acids is a pro-inflammatory enzyme [the aforementioned COX-2]," Freeman says. "What she and the others discovered is that when aspirin inhibits COX's inflammatory properties, it also stimulates COX's ability to add oxygen to omega-3 fatty acids."

Freeman, Cipollina, et al., think that understanding these mechanisms presents enormous potential for drug discovery, notably for new approaches to mediating inflammation. The omega-3 anti-inflammatory process works well enough in nature, Freeman says, given that its cardioprotective effects have been proven. But understanding how these benefits are arrived at opens up grand possibilities for designing molecules that can do the job even faster and more efficiently.

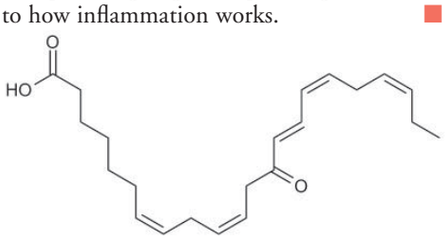
"Natural isn't always best," says Freeman.

This new EFOX insight could lead to new organic-synthetic therapies that improve on Mother Nature, Freeman says, "so that you can have the same clinical benefit from much lower concentrations given less frequently." Cipollina says that this work might, in fact, lead to completely different ways of treating inflammation.

"What we do now is kind of a negative approach in that we're trying to shut down or stop the inflammatory process with drug therapies," she says. Curtailing inflammation entirely, however, can have unpleasant consequences—inflammation is the body's vanguard against injury and infection.

But, she says, knowing the molecular ins and outs of inflammation might permit the crafting of drugs that can target individual parts of the process, taming inflammation when necessary and letting it do its thing in other cases.

Although Cipollina has completed her fellowship and is back in Italy, Freeman and Schopfer are going to keep fishing for clues as to how inflammation works. ■



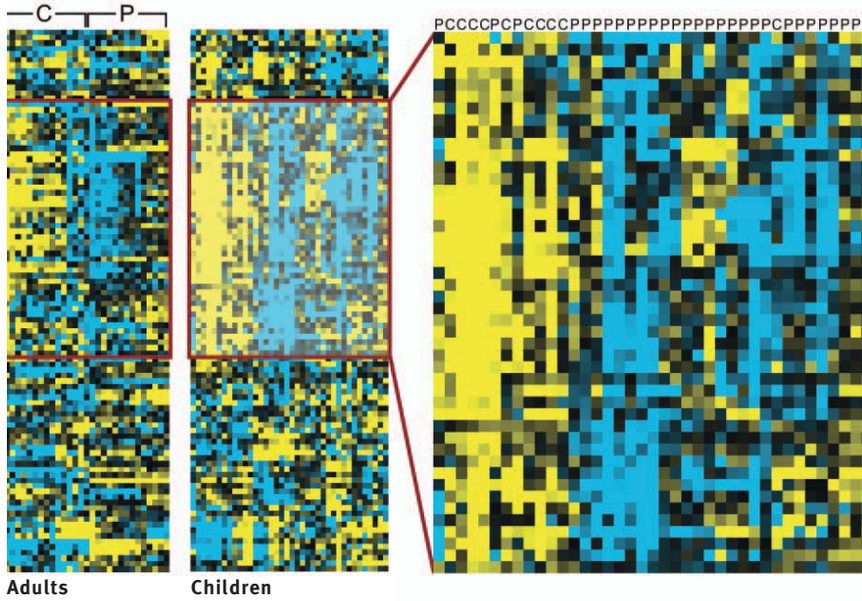
EFOX, shown here, is the key to tapping the anti-inflammatory potential of omega-3 fatty acids.

GETTY IMAGES

DNA DAMAGE PEGGED

NEW BLOOD ASSAYS FOR A DEVASTATING DISEASE

BY CHUCK STARESINIC



LEFT COLUMNS: Heat maps of adults and children reveal gene expression in FRDA patients (P) and controls (C). RIGHT COLUMN: A computer algorithm has sorted the patients based solely on gene expression. A detail of 46 genes known to be associated with one another suggests that the genes are relevant to the disease, as well, with patients and controls mostly clustering together on opposite sides of the column. Yellow represents higher gene expression and blue lower expression.

COURTESY *PLOS GENETICS*, JANUARY 2010, VOL. 6, ISSUE 1

"Bench to bedside" is one of the catch phrases in medicine these days. Another way to think of it is "yeast to human." That's the leap that was made by Ben Van Houten and Astrid Haugen at the National Institute of Environmental Health Sciences in 2005.

Van Houten, a PhD molecular biologist who is now the Richard M. Cyert Professor of Molecular Oncology and a professor of pharmacology and chemical biology in the University of Pittsburgh School of Medicine, had long had an interest in Friedreich's ataxia (FRDA), a neurodegenerative disease marked by low levels of an essential cellular protein. He had knocked out the gene for the protein in yeast to study the resultant DNA damage. A technician in his lab, Haugen, had the expertise to study gene expression in cells—whether human, mouse, or yeast. When the National Institutes of Health introduced a bench-to-bedside award, Haugen and Van Houten got the idea to expand this research to humans.

Friedreich's ataxia is a devastating disease both for those who suffer from it and for their families. It typically appears out of nowhere in young people between the ages of 5 and 15. Parents might notice that their child has trouble running in a straight line or is just not running as well as he or she used to. This is ataxia—an inability to coordinate voluntary muscular movements. Most FRDA patients use a wheelchair eventually. They develop speech problems. Their vision deteriorates. Heart problems begin in the teens. They develop cardiomyopathy and enlarged hearts. FRDA is uniformly fatal, with cardiac arrest often causing death in middle age. There is no effective treatment.

The disease results from a mutation to a gene called frataxin. In this type of mutation—triplet repeat expansion—a trio of nucleotides abnormally repeats several times within the gene. People who inherit this rare mutation from both parents are unable to produce the proper amount of the frataxin protein. Produced in the nucleus, frataxin is transported to the mitochondria, where it plays a key role in the creation of iron-sulfur centers—important components of a host of proteins and processes that begin in the mitochondria. Without frataxin or sufficient iron-sulfur centers, the cell sends out signals to take up more iron, too much of which can be destructive to a cell by damaging macromolecules like DNA.

"If you cut through the heart, you can see that there are large iron deposits," says Van Houten as he pulls up a pathology slide from a deceased patient with FRDA. "So there is this iron overload in the heart and other tissue because the protein frataxin is actually an iron shuttle. It takes iron and puts it into the iron-sulfur centers."

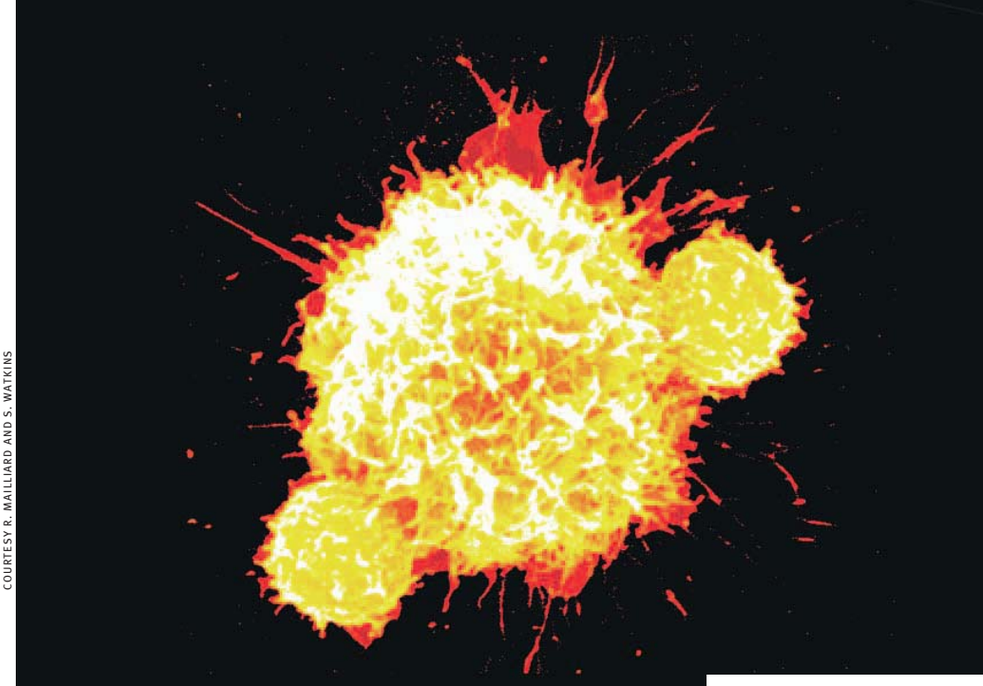
Haugen planned the experiments with Van Houten. "Astrid is a thinker and a doer," he says. "She drove this project." (Van Houten calls her a "supertech.") The researchers took blood samples from children with FRDA and compared the gene expression patterns with samples from young, healthy blood donors. They identified sets of genes that were very differently expressed in FRDA patients, including several sets associated with DNA damage. It was a very clear signal—and a novel finding—that FRDA patients were accumulating DNA damage.

In another first, the group used an assay developed in Van Houten's lab, called QPCR (quantitative polymerase chain reaction) to identify specific regions of DNA that were damaged. Using just a fingerprick of blood ("All we need is 5 nanograms," says Van Houten), the group compared FRDA patients and controls and found clear evidence associating FRDA with DNA damage—especially in the mitochondria. Their findings were published in *PLoS Genetics* in January.

These discoveries suggest the intriguing possibility that scientists could, in the future, routinely identify specific types of DNA damage in an FRDA patient with a single drop of blood. Further research along these lines could usher in the day when doctors evaluate a detailed list of biomarkers found in that tiny sample, then sit down at the bedside for a discussion of the disease mechanisms at work, prognosis, and therapeutic options tailored to the patient. ■

THERAPEUTIC HIV VACCINE TO GET THE IMMUNE SYSTEM FIGHTING AGAIN

BY SARA GOUDARZI



COURTESY R. MAILLIARD AND S. WATKINS

A dendritic cell (center) activates two T cells to tackle a foreign invader.

BACK IN THE RING

HIV is more persistent and evasive than most invaders of the human body. Without medications to suppress the virus, in about eight years, a person with chronic HIV infection will develop AIDS, and her immune system will fail. But what if there were a way to arm the immune system to take up the fight again and eventually eliminate the virus? That's the goal of MD Bernard Macatangay, assistant director of the University of Pittsburgh Immunology Specialty Laboratory.

Researchers are currently working to develop two types of vaccines for HIV, Macatangay explains: prophylactic and therapeutic. HIV prophylactic vaccines are designed to prevent uninfected persons from acquiring the virus; HIV therapeutic vaccines are used as part of a treatment regimen. Macatangay's group concentrates on the latter.

"When someone has cancer, they use chemotherapeutic agents," he says, "but at the same time, there are immunotherapeutic agents allowing the body's immune system to fight the cancer. That's what we're doing now in HIV."

Macatangay came to Pitt in 2006 on an infectious disease fellowship. In 2008, he began a second fellowship to study HIV/AIDS, joining the lab of Charles Rinaldo, a PhD and chair of the Graduate School of Public Health's Department of Infectious Diseases and Microbiology, who also has an appointment in the Department of Pathology in the medical school. When Macatangay arrived, Rinaldo and others—including Sharon Riddler (MD associate professor of medicine) and Theresa Whiteside (PhD professor of pathology)—had finished clinical trials of a therapeutic dendritic cell–based HIV vaccine in 2006 and had just published their results.

Dendritic cells are immune cells that capture foreign antigens and present them to killer T cells. In so doing, the T cells become activated and target the foreign antigen.

The treatment met with moderate and fleeting results. The 18 patients enrolled in Rinaldo's clinical trial responded, but only modestly. The reason, he and Macatangay discovered, involved regulatory T cells (Treg)—cells that keep the immune system balanced so it doesn't go haywire and attack the body. Once an infection is controlled, Treg shut off the killer T cell response.

For the patients involved in the trial, Treg were shutting things off too early and actually suppressing the immune system.

"We need to investigate what particular mechanisms these Treg are employing to suppress the immune response," Macatangay says. "By blocking their actions, we may be able to boost the immune response and control HIV."

Shutting off Treg is not without complications, however. Treg have the ability to control the immune response to infection. For instance, while wiping out harmful microbes, the immune system can also trigger chronic inflammation. Treg can rein in this inflammation, preventing the tissue damage that inflammation can cause when left unchecked.

If a drug completely blocked Treg action, patients could develop severe autoimmune symptoms.

The researchers are now conducting a second clinical trial of a vaccine. This time, each dendritic cell is loaded with the subject's own inactivated virus—instead of with HIV peptides (proteins thought to increase immune response), as in the previous trial.

Unlike prophylactic vaccines, which can be commercially manufactured and given to an entire population, the therapeutic vaccine is tailored to each patient.

So far, four patients have completed clinical trials for the vaccine and four are currently enrolled in the study. This new study is one of the most intensive and time consuming of the clinical studies conducted at Pitt; however, all subjects have tolerated the vaccine and its mild side effects.

"Most of these patients say that even if [this study] doesn't help them," says Macatangay, "if somehow what we're doing helps the next group of people, they would gladly go through it."

Macatangay and Rinaldo expect to have results to report by early 2012. ■



ABOVE: Andrew Maung smiles as he views a Lego replica of the new Children's Hospital of Pittsburgh of UPMC. His mom, Vivian Tsuei, did med school rotations at Children's when it was in Oakland. OPPOSITE PAGE: The view from the 40th Street Bridge, with Lawrenceville in foreground, includes the 10-story John G. Rangos Sr. Research Center. The center (behind parking garage) can house 70 principal investigators working in genomics, cellular imaging, developmental biology, neuroscience, and other fields related to pediatric medicine. (More photos of Children's on p. 14.)

"I CAN'T BELIEVE THIS IS A HOSPITAL"

TOURING THE NEW CHILDREN'S

STORY AND PHOTOGRAPHY BY JOHN ALTDORFER

A late-spring drizzle paints the city streets gunmetal gray as Karen Roche rests on a sofa in a quiet corner of the lobby of the new Children's Hospital of Pittsburgh of UPMC. In just a few minutes, University of Pittsburgh School of Medicine alumni from as far back as the Class of 1950 will join this 1975 graduate for their first look at the showcase hospital's sprawling 10-acre campus in Pittsburgh's Lawrenceville neighborhood.

"I can't wait to see everything," she says in anticipation. "It's going to be such a change from the Children's I remember."

Now a plastic surgeon in Pittsburgh, Roche cherishes the memories of physicians who mentored her nearly four decades ago and the young patients she cared for at the old Children's, just a few yards down Cardiac Hill from where Pitt Stadium once perched above Oakland. Yet, her most intense recollection of the place is a night she spent there as a mother, before her days as a medical student.

"My son had hernia surgery at the other Children's," she says. "He was 3 years old, and there were maybe two rooms where a parent could stay with a child overnight. I was an undergrad at Pitt then, but I knew enough to ask for one of those rooms.

"Now there are places for parents to sleep in all the rooms. This place seems more like home than a hospital."

After the tour group enters a soaring four-story atrium where giant, multicolor, neon-light dragonflies and butterflies flutter on the walls, Albert Rolle (MD '65) pauses to reflect. The Miami native is a veteran of the Korean War, where he gained experience as a surgical technician before enrolling in the medical school. He's now retired after 30 years of general surgery practice near Washington, D.C.

"The Children's Hospital in Oakland was wonderful for its time," he says. "There was no better place in the area for kids who needed the best medical care." Still, he points out, the Children's of his day was, architecturally, an institutional workplace, designed to accommodate the needs of doctors and nurses.

"What you notice about this place is that it was created for kids and their families."

The shift of focus is obvious to even the youngest tour participants. Born just a few weeks after the new Children's opened in May 2009, Sophie Maung immediately locks her big, dark eyes on the blue, green, yellow, and purple discs of a mobile that hovers over the hospital's lobby. They look like a fleet of playful spaceships. Tucked in her mother's arms, Sophie peeks at stuffed Dr. Seuss and S*esame Street* characters sitting on pint-size chairs in the library and at fish swimming through glass tubes that join a series of aquariums in a waiting room. Throughout the nearly 90-minute walkabout, she remains quietly interested in the surroundings.

"We're taught in medical school that distractions help take away some of the anxiety for parents if their kids are calm during a hospital stay," says Sophie's mom, Vivian Tsuei (MD '00), who is a general pediatrician in New Haven, Conn. "My little girl got that right away."

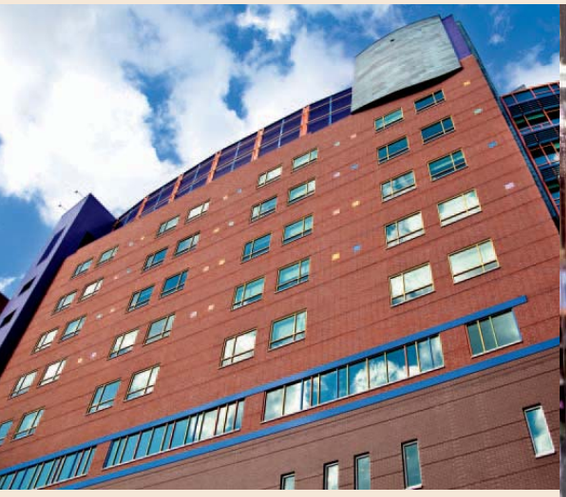
For Bill Werner (MD '75), a retired radiologist in St. Mary's, Pa., the tour is a journey to a place that no longer exists as he remembers it. After completing a diagnostic radiology residency at St. Francis Hospital, he accepted a pediatric radiology fellowship at the now-shuttered DeSoto Street site. In 2002, when it became clear that St. Francis was closing, UPMC entered into a contract to purchase the Lawrenceville property rather than construct a new pediatric hospital in Oakland as it had planned. Part of St. Francis was razed to make way for the new Children's. At one point, Werner crosses a line that connects his past to Children's present—a metal strip in the floor that demarcates the remaining section of St. Francis that was integrated with the current structure.

Whatever their links to days gone by at the old Children's Hospital, the alumni share the opinion that this tour is more than a trip down memory lane.

"There's no nostalgia here," says internist Marvin Levick (MD '55) in front of a mural that traces in words and photos the 120-year history of Children's Hospital in its many incarnations and locations.

"I can't believe this is a hospital. It almost feels like a camp. And that takes away a lot of a parent's pain of having a sick kid." ■







ABOVE: Exterior view of patient rooms from 45th Street. The private rooms include beds for parents and amenities like Internet access. RIGHT: Youngsters captivated by the bubble fountain in the Emergency Department. The hospital's ED and trauma center have 41 beds; Children's is the only Level 1 pediatric trauma facility in the region.



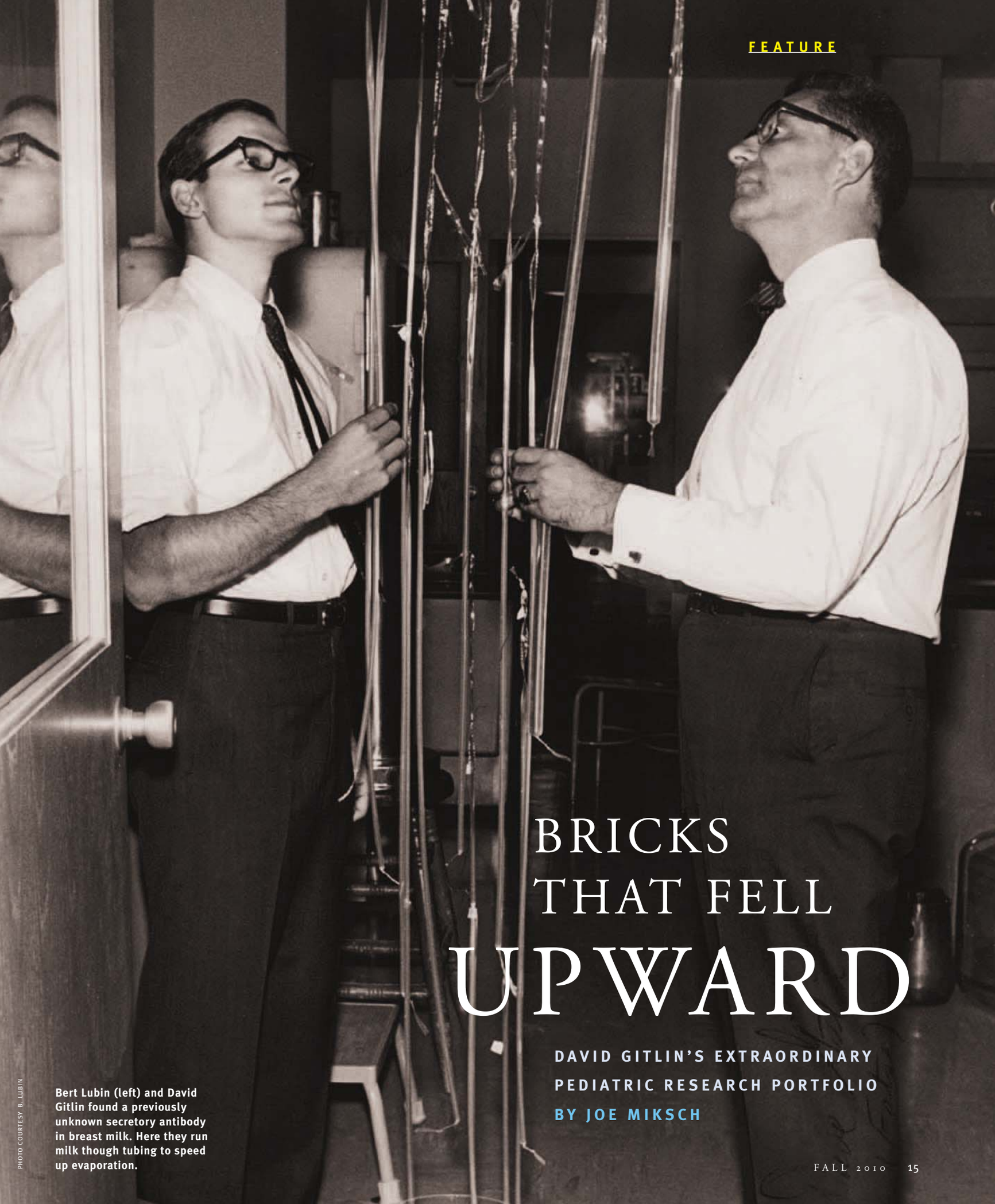


FAR LEFT: Fish tanks, red wagons, and popcorn help ease stress in the third-floor ambulatory waiting area. LEFT: Butterfly wall.



LEFT: A four-story atrium on the sixth floor, where giant neon butterflies and dragonflies flutter along the walls, serves as a town square for families. RIGHT: Staff and patients' families stream through the hospital entrance.





BRICKS THAT FELL UPWARD

DAVID GITLIN'S EXTRAORDINARY PEDIATRIC RESEARCH PORTFOLIO

BY JOE MIKSCH

PHOTO COURTESY B. LUBIN

Bert Lubin (left) and David Gitlin found a previously unknown secretory antibody in breast milk. Here they run milk though tubing to speed up evaporation.

In simple terms, David Gitlin wanted to know why some kids were more susceptible to infection than others.

He followed this line of inquiry from his 1947 graduation from the New York University College of Medicine through his years at Pitt, which began in 1963 and never really ended, as he remained an emeritus professor of pediatrics in the School of Medicine until his death, at 88, in January.

Gitlin melded biology, chemistry, and medicine to become a leading immunochemist—one of the first. He helped define and develop treatments for a host of immune disorders including agammaglobulinemia, an inherited disorder marked by very low levels of protective immune proteins called immunoglobulins.

Gamma globulin replacement therapy, which is still in use today, rescues thousands of children with agammaglobulinemia from their susceptibility to serious and repeated infection. Our understanding of how the immune systems of infants develop can be traced to his work involving the transfer of immunoglobulins from mother to fetus.

It's hard to overstate how prolific the scientist was: Gitlin unraveled the secrets of plasma protein metabolism in children with kidney disease, discovered how the intestine absorbs iron, found a biochemical marker for Wilson's disease, advanced the understanding of plasma protein production and distribution, and established that alpha-fetoprotein could be used to detect life-threatening birth defects in fetuses.

He was particularly proud of his alpha-fetoprotein work, says his son, Jonathan Gitlin. The work in plasma protein research initiated the start of a field that has led to the discovery of biomarkers for diagnosing diseases in infants.

"He always had the sense that there were many things you could monitor in maternal plasma that could give you a unique imprint of the fetus," Jonathan Gitlin says.

"He was a basic scientist, but he had a sense that true discoveries make a difference in the lives of children."

David Gitlin also liked to talk about bricks.

"He had this great expression, which I've never forgotten," Jonathan says of his father. "He said, 'Science is like sitting by a window, throwing a brick out the window, and you write down in your notebook, *Brick went down, brick went down, brick went down.*'" What if one day, you throw a brick out, and it goes up?

"'The difference between discovery and pedantic research,' he said, 'is that one person will write in the notebook, *Experiment didn't work; brick went up*. And the other person will stick his head out the window and say, *Where did the brick go?*'" He told me to always stick my head out the window and see where the brick went."

The younger Gitlin earned his BS from Pitt in 1974 and his MD from the School of Medicine in 1978 and is now chair of the Department of Pediatrics at Vanderbilt University and physician-in-chief at Monroe Carell Jr. Children's Hospital of Vanderbilt.

His father's pursuit of the upward-flying brick began in earnest in the early 1950s at Harvard University. There, he found himself in the lab of preeminent pediatrician Charles Janeway. Janeway, who was physician-in-chief at Children's Hospital Boston, had recruited Gitlin, a noted up-and-comer, to join the immunology lab he was starting in the basement of the Farley Building, which housed the hospital's inpatients.

Shortly after joining the lab, which included other pediatrics luminaries such as Fred Rosen, Gitlin played a key role in discovering the cause of and a treatment for agammaglobulinemia.

David Nathan, president emeritus of Boston's Dana-Farber Cancer Institute, was in hematology at Harvard, but regularly visited the lab.

"When I first went to [Gitlin], he was known as a guy who was a tremendous experimentalist, someone who could help you with any problem in the laboratory," Nathan says. "I was trying to measure hemoglobin synthesis, and I was trying to do it with radioactive amino acids. My problem was that I was worried that the glycine was being converted to serine. So I went to see him about that.

"He told me exactly what to do," Nathan says, admiration still in his voice.

In addition to being a savant of the bench, Nathan says, Gitlin possessed a formidable imagination. "He seemed to know exactly where the science would be going. He was such a curious man, like the Elephant's Child in [Rudyard Kipling's] *Just So Stories*."

Nathan says Gitlin—the man who used bricks as metaphors for good science—could also hurl verbal bricks at those he thought weren't making the most of their brain cells.

He remembers that first Gitlin encounter, when he needed help measuring hemoglobin synthesis:

"In this crowded laboratory," Nathan recalls with a laugh, "standing there was Gitlin's trainee, Fred Rosen [who went on to spend 50 years at Harvard, pioneered Boston's pediatric bone marrow transplant program, and made vital contributions to the understanding of immunodeficiency], washing Petri dishes. I'm asking this question, and Gitlin is listening. He looks up at me and says, 'You [idiot]!' And I said, 'What's that you said?' and he said, 'You've got a hearing disorder, too? You're an [idiot]!'"

Rosen, Nathan notes, continued to quietly wash his Petri dishes, "staying out of the line of fire."

But this unusual beginning wasn't an obstacle to admiring the man.

"He was amazing," Nathan says. "He was into everything from copper metabolism, to iron metabolism, to the turnover of immunoglobulins. His work on the absorption of iron

is such a famous paper. He clearly showed that there were two separate receptors for iron in the gut, and this precedes our knowledge of the receptor biology of iron by 40 years. It was an amazing paper. It just predicts everything we now know about iron absorption."

Nathan's stories—of David Gitlin's brilliance and prickliness—don't much surprise Jonathan Gitlin. He says his father had the kind of intellect that simply couldn't process how someone would make a mistake, in or outside the lab. "He could take some getting used to," Gitlin says with a chuckle. "The typical story is when we went on summer vacation, and he ordered ice cream with sprinkles. It came with chocolate covering instead of sprinkles. It was incomprehensible to him that it happened. His world was black and white in every possible way."

Gitlin's dedication to science was a direct function of this bichromatic way of living. Science was important, everything else, less so. When he needed a piece of equipment, David Nathan says, Gitlin wouldn't order it and wait for delivery, despite having the funding to do so. He'd rather make whatever he needed himself at home in his workshop. This was quicker, Gitlin thought, and the faster he could get back to his investigations the better.

Gitlin brought his black-and-white worldview to the University of Pittsburgh in 1963. While he was in great intellectual company at Harvard, the move to Pitt presented Gitlin with three great benefits: a promotion to full professor, the prospect of better funding, and a more collegial environment.

Richard Day was the chair of pediatrics at Pitt at the time. He, like Janeway at Harvard, wanted to invest money and intellectual capital into building pediatric immunology at Pitt. What better way to do so than poaching one of the earliest recruits to Janeway's lab?

Jonathan Gitlin says his father was in love with Pitt from the very beginning.

"He found the University of Pittsburgh to be a very collaborative environment for a university researcher."

Even when he didn't work directly with them, the younger Gitlin says, his father was thrilled to be able to bounce ideas off of investigators like Klaus Hofmann, the famed protein chemist. These were the sorts of things that didn't happen at Harvard, Jonathan Gitlin recalls his father saying.

"Pitt was ahead of its time in that way," Jonathan Gitlin says. "It was contiguous and integrated and was what everyone is talking about having these days: one university where the medical school wasn't divorced from the rest of the institution."

Because of this and the facts that Pitt had a freestanding children's hospital and put as much stock in teaching as in other aspects of medicine, the school was a comfortable home for Gitlin.

"More than anything he loved being a professor at this university," Jonathan Gitlin says. "If he met someone on a plane, he'd tell them he was a professor, not a doctor, not a scientist."

But a scientist he was. At Pitt, operating on the hunch that there were unique proteins made by the fetus transferred to maternal plasma—that might have a story to tell about fetal development and could be useful for diagnosing disorders in the unborn child—Gitlin delved into the world of protein synthesis.

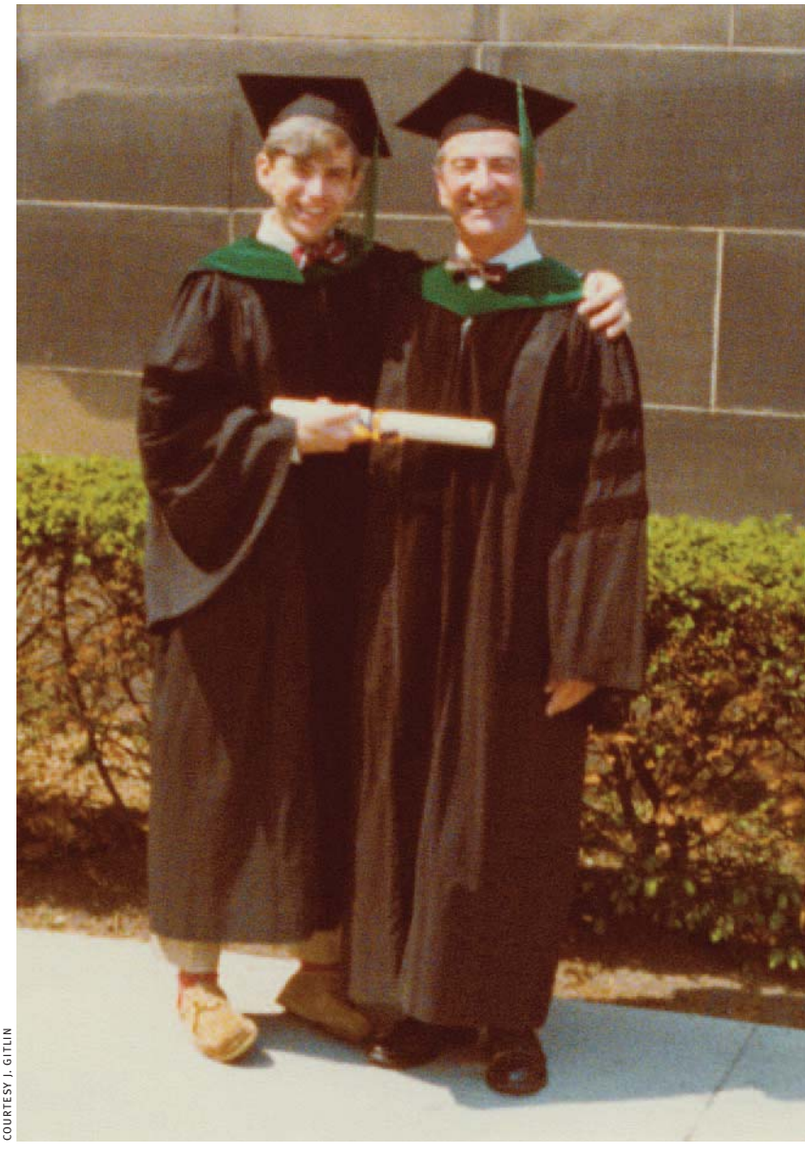
His hunch was spot on. That's when he began making critical advances in the understanding of alpha-fetoprotein. Studies resulting in papers in *The Journal of Clinical Investigation* (*JCI*) in 1966 and 1967 earned Gitlin the Medal of the University of Helsinki and the first Federico Gómez award from the Hospital Infantil de México in 1968. What Gitlin learned in terms of where, when, and how alpha-fetoprotein is synthesized led to its use as a tool to identify potential issues with fetal development.

(Gitlin also played a key role in developing the research arm of the Hospital Infantil de México. The relationship began during his time at Harvard and his main collaborator in Mexico City was the aforementioned Federico Gómez.)

Jonathan Gitlin considers the '67 paper a sign of things to come in medicine. "My father always looked at that one as the tip of the iceberg," he says. "I think what he did was very prescient. At that time, people were just beginning to think about [biomarkers]."

The level of alpha-fetoprotein is commonly used as a marker of risk for many birth defects during pregnancy, including spina bifida, and can indicate multiple births. Greater-than-normal levels can point doctors toward liver disease or certain cancers in adults.

David Gitlin was particularly proud of another *JCI* paper he authored while at Pitt. His co-author was a first-year medical student



COURTESY J. GITLIN

The Gitlins collaborated on research projects before celebrating Jonathan Gitlin's 1978 graduation from the University of Pittsburgh School of Medicine.

named Jonathan Gitlin.

"Protein Binding by Specific Receptors on Human Placenta, Murine Placenta, and Suckling Murine Intestine in Relation to Protein Transport Across These Tissues," by Gitlin and Gitlin dealt with how proteins crossed the placenta, addressing the issue of passive immunity.

The paper was important, the younger Gitlin says, but not as important as what he learned while working on it. "The terrific thing for me was that I got to learn to do science from someone who was extraordinary at it," Jonathan Gitlin says. "I had the chance to sit with him and see how he thought through things and how he imagined the next set of experiments."

The education paid off—the younger Gitlin received the prestigious E. Mead Johnson Award for Pediatric Research in 1998, the same award his father won in 1956.

Bertram Lubin (MD '64) also trained with David Gitlin. Now president and CEO of Children's Hospital and Research Center Oakland, in California, Lubin had decided as a third-year medical student that he wanted to gain some research experience in a pediatrics lab.

"I was having a discussion with [Pitt immunologist] Richard Farr," Lubin recalls. "In our discussion, he said, 'We have this really brilliant pediatric immunologist coming from Harvard to Pittsburgh named David Gitlin. Don't be afraid of him!'"

Lubin wasn't, though he came to understand what prompted the warning, "[Gitlin] had a reputation for being rough and critical and not afraid to say anything he believed in regardless of the audience."

While in Gitlin's lab, Lubin was assigned a project that involved seeking answers to why breast-fed babies suffered fewer gastrointestinal problems than their bottle-fed counterparts. "So [Gitlin] said to me, 'I'd like you to go to Magee [Womens Hospital], collect breast milk, and pool it. We'll see if there are the same antibodies in breast milk that you see in plasma.'

"So I was walking around Magee with a breast pump asking for milk," Lubin says laughing. "He realized I knew nothing about what was going on, so he coddled me. But lo and behold, we found a new secretory antibody that could kill bacteria, *E. coli* in particular."

Working with Gitlin was a transformative experience, Lubin says. "The man was just brilliant, and I loved him. He treated me like one of his kids. I called him before I took this job [in 2008], and he said, 'I'm very proud of you.'

"I'm thankful to him for all the things he taught me—creativity and innovation and to not give up on something you believe can be done."

Dorothy Becker, an MD, absorbed the same lessons when she landed her first faculty position at Pitt in 1976. Now professor of pediatrics in the School of Medicine and chief of endocrinology and diabetes and director of the diabetes program at Children's Hospital of Pittsburgh of UPMC, Becker was given lab space near Gitlin as she launched her career.

Though their scientific foci differed, Becker says, Gitlin taught her a great deal about lab techniques and gave her equipment and materials she couldn't afford on her own as a young investigator.

She, like seemingly everyone who met him, thought Gitlin a brilliant scientist and was well aware of his prickly side. She benefited from the former but, unlike many, avoided the latter.

"I think quite a few people were nervous about him, but he was very supportive of me when I was young," she says. "He really helped me establish my lab and, actually, when he retired (in 1978), he donated everything he had to me."

Doing science was everything to him, Becker says, and sharing that passion was a key part of his personality. "He not only talked to me, but he listened to me," she says. "He would bounce ideas off of me and listen to mine, which for a very junior person was wonderful. I would say that his best attribute, though, was bringing me into his excitement."

What didn't excite Gitlin was anything at all related to institutional politics. This aversion, Jonathan Gitlin says, is why his father never sought a department chairmanship or any other formal leadership role.

Becker agrees that such a role wouldn't have suited her early mentor. "He didn't have patience for fools," she says. "But if you could argue with him intelligently, he was great. He was a mentor and a champion of science."

"My father was either upset about parking or about [lab] space or—" the younger Gitlin says of how his father vexed his higher-ups. "I told him once, 'You're the 5 percent of faculty that's a nightmare to any chair.' But scientifically, he was an extraordinary mentor. When he passed away, people called me to tell me that. He was a scientist's scientist."

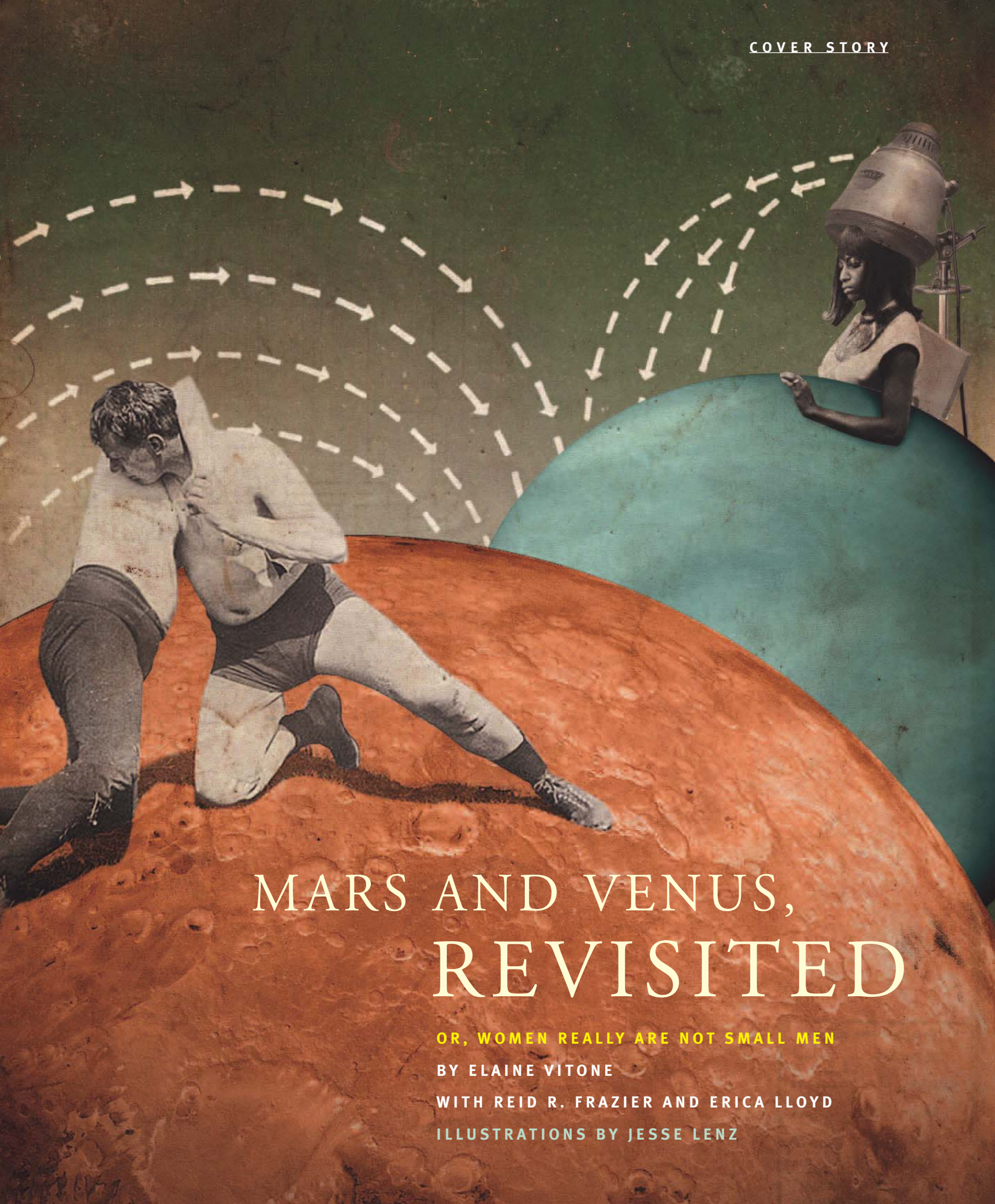
"More than anything he loved being a professor at this university," Jonathan Gitlin says. "If he met someone on a plane, he'd tell them he was a professor, not a doctor, not a scientist."

After David Gitlin's retirement, Jonathan lent a hand cleaning out his father's office. Although it's not unusual to find a filing cabinet full of manila folders lurking about at the end of a career, the contents in one cabinet were something of a surprise to Jonathan.

"There were about 40 folders in there," he says. "I looked through them and said, 'Pop, I never saw these published.' Forty papers over 15 years! And he goes, 'Yeah, I never felt completely comfortable with these.'

"These were papers which I imagined most people would have published."

Putting aside those not-quite-good-enough papers, Jonathan Gitlin says, was emblematic of his dad's expectations of himself, his science, and everyone around him: Care enough to ask why a brick went up and never be satisfied until you understand.



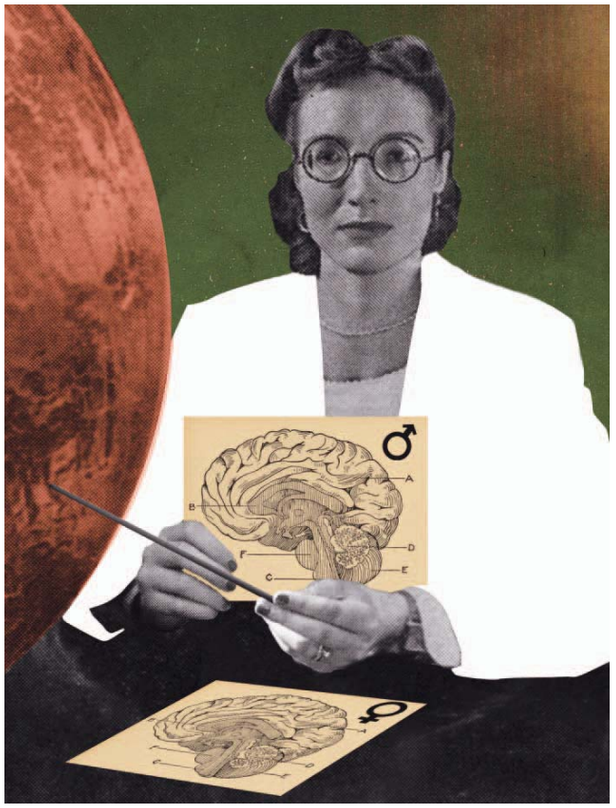
MARS AND VENUS, REVISITED

OR, WOMEN REALLY ARE NOT SMALL MEN

BY ELAINE VITONE

WITH REID R. FRAZIER AND ERICA LLOYD

ILLUSTRATIONS BY JESSE LENZ



At first, the idea of essential biological differences between men and women—beyond obvious things like sex organs and Adam's apples—might sound suspect, and perhaps for good reason. Misogyny has masqueraded as medicine all too often in our history. In 1873, the prominent physician Edward Clarke warned that education robs females of their vigor. *Girls lose health, strength, blood, and nerve*, he wrote, *by a regimen that ignores the periodical tides and reproductive apparatus of their organization.*

But once we separate societal influences from scientific fact, the evidence is compelling. Epidemiological studies have told us for decades that men and women and boys and girls are worlds apart in many diseases and disorders, from incidence to age of onset to severity. But historically, medical research has, for the most part, failed to analyze data by sex or to even consider it as a variable. For various reasons (expense, simplicity, potential risks in pregnancy, among others), the overwhelming majority of studies has focused on males only.

We've seen an increasing urgency to change that in recent history. In 2001, the Institute of Medicine published guidelines to promote research on sex differences—particularly at the cellular and molecular levels, but also at every stage of life.

At Pitt, scientists are beginning to sort out sex-based disparities in the nervous, musculoskeletal, respiratory, cardiovascular, and immune systems. They're finding strengths and vulnerabilities in each sex that further our understanding of certain illnesses overall. Such insights should eventually help to restore the "health, strength, blood, and nerve" of men and women alike.

—Elaine Vitone

OF DIFFERENT MINDS

To say that men and women are of different minds is a tired punch line, a fact of life we accept so fully that it's practically old hat. But if you try to talk about differences in terms of the structure and function of the brain—the organ itself—scientists stumble over the idea, hindered by certain hang-ups.

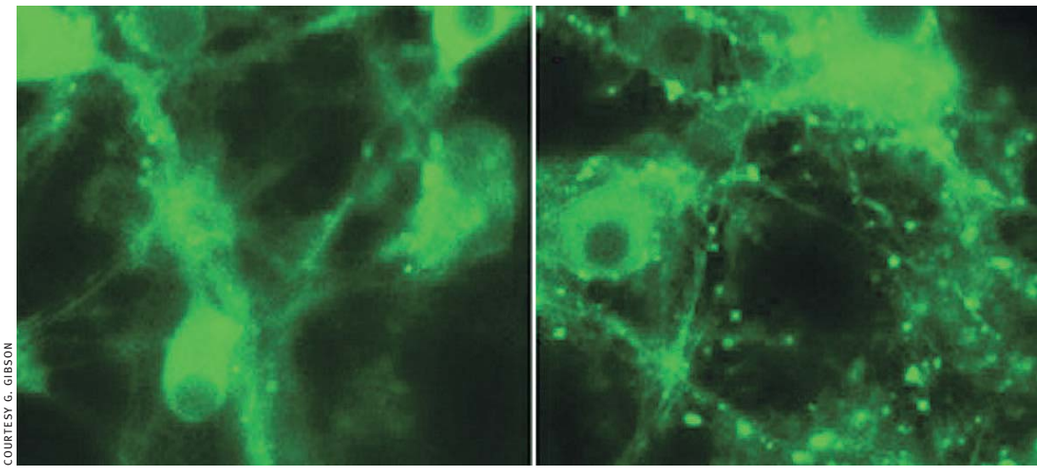
For one, throughout the history of our evolving understanding of human health, we've tended to chalk up every inconsistency between the sexes as a function of the circulating hormones that are so powerful through our reproductive years. For another, if you point out a difference—even something as statistically strong as the slant toward women when it comes to major depression—people shrug it off. "Women are more likely to seek treatment than are men," they say. "How can you be sure we're so different?" People tend to get caught up in the social construct of gender if you try to talk about the sexes in terms of biology.

But in recent years, scientific circles have begun to accept the notion that socialization isn't all to blame. If it were, why would women in Sweden—a place where education and labor laws have gone a long way to foster equality among men and women—be just as prone to depression as American women? Nor can we explain it all away with circulating hormones. For example, Alzheimer's disease—which emerges years after sex hormone levels wane—is more fatal in men than in women.

Investigators at Pitt and elsewhere are finding that we are built differently and wired differently, quite literally. The neurocircuitry that connects the parts of the brain has a very distinct way of evolving in males versus females.

It turns out, we are fundamentally different, even at the cellular level.

SNAKES AND SNAILS AND OXIDATIVE STRESS



COURTESY G. GIBSON

Neurons from female (left) and male (right) mice respond differently to starvation. In females, the cells live for days longer, sustaining themselves on lipids. In males, the cells eat their own organelles within their lysosomes, seen here as bright green dots.

An investigator/critical care doc who works with children, Bob Clark has a quiet manner and a collection of pictures of his young, dance-recital-costumed daughters around his office in the new Children's Hospital of Pittsburgh of UPMC, where he's chief of the Division of Pediatric Critical Care Medicine. He's also a Pitt associate professor of critical care medicine and pediatrics and associate director for molecular biology in the Safar Center for Resuscitation Research. On a recent day, a single speck of gold glitter shines on his forehead, the mark of a parent of tiny dancers.

Clark explains that in the 1970s, researchers ran rodents through intense exercise tests and found that males burn protein to push them through, while females draw their energy from stores of fat—which women tend to carry more of, pound-for-pound.

A few years ago, Clark's team modeled starvation in brain cells. They grew neurons from male and female rodents in separate cultures, then denied them nutritional sustenance. The males' died more quickly, they found. The famished neurons from females used their outer membranes to form a snack of lipid droplets, and also gathered fatty acids from outside the cell walls—a veritable cellular smorgasbord of fat stores.

The guys' cells, however, did none of this. Instead, they were all about protein. Their neurons resorted to killing and eating their own organelles.

In human history, we've seen women also do better in times of hunger. When Nazis starved concentration-camp prisoners during World War II, the women who were subjected to this torture survived longer than the men did.

"If you look at it, it makes sense that during times of famine you would favor women," says Clark.

"Just because we store more fat in general?" asks this (female) writer.

"Because you're more important, from a teleological perspective," he says with a smile. "You need more women, and you need them at a certain period of time—during childbearing years. And the way we [pediatricians] look at it is: Well, you can't get to be of child-bearing age unless you make it through childhood. So you have some mechanism that also protects you before puberty."

Like any scientist worth her or his salt, Clark doesn't like to speculate. But he'll humor a joke about the predominance of men as hunters, the fatherly fascination with barbecue grills. And if you look at dietary intake, Clark points out, "Clearly men eat more protein than women. Men have higher levels of carnitine, which you get from red meat." Maybe men are meat eaters by design, straight back to their earliest origins, straight down to their organelles.

The starving-neuron study generated some Internet buzz, with mentions in *Scientific American Mind* and elsewhere. It's the latest in a series of probing questions Clark has asked about the basic biology of various insults to the brain, each triggering many cascades of molecular ruination in varying degrees. He's found that how we weather the onslaught depends, in part, on our sex—regardless of whether we're in our hormone-laden reproductive years or not.

Seven years ago, Margaret Satchell—an assistant professor of pediatrics at New York City's Mount Sinai School of Medicine who was then a fellow working in Clark's lab at Pitt's Safar Center for Resuscitation Research—led a study of cytochrome C, a biomarker for apoptosis (or programmed cell death) in the spinal fluid of children with traumatic brain injury. Apoptosis is a normal cellular process; however, after injury, it can spiral out of control, killing cells before their time. Satchell checked for sex differences in this process merely as a matter of course; the average age of the patients was just 6 years old—prepubescent by a long shot—so she had no expectation of finding a sex difference.

But there was. Girls suffered far more apoptosis than boys.

Intrigued, the team launched an animal study and eventually found that the brain cells of female rats were more susceptible to apoptosis than those of the males. Further, male rats were more vulnerable to another cell killer, oxidative stress. Satchell, Clark, and Lina Du, research associate at the Safar Center and Pitt's Brain Trauma Research Center, detailed in several papers differences between how young males and young females respond to traumatic brain injury, and this work later made ink in *Nature*.

The findings make sense, Clark says. Young girls with certain cancers respond better to chemotherapy, and the way these agents kill cancer cells is—apoptosis. Men are more likely to fall victim to Parkinson's disease, which is thought to be influenced by oxidative stress.

Still, it took a couple of years to get the results of the team's brain-injury study published. Initially, reviewers weren't too keen on the idea of cellular-level differences between male and female brains. But other labs began supporting this claim with mounting evidence in cell-culture, animal, and patient-observa-

tional studies. It takes careful, thorough work to challenge the dogma, Clark says. "The last thing people wanted to hear was that they might have to use both males and females in their studies. It doubles people's workload."

For the most part, labs use males—and only males—in rodent experiments because they are easier to work with. (More on that later.) But Clark says also studying females would be well worth it if it leads to more tailored therapies and better outcomes. For example, Clark and Mioara Manole, a Safar Center investigator and Pitt assistant professor of pediatrics, are working on an animal study on the effect of antioxidant medication in cardiac arrest.

"It seems to be effective only in males," he says.

And perhaps something as simple as diet could be tweaked to the advantage of a recovering brain on the skids.

"If you're in the ICU right now, we just pull a bag of IV nutrition off the shelf, and we don't take into consideration whether you're a boy or a girl. But maybe they need different fat content versus protein content. To echo what *Scientific American Mind* said, there are dietary preferences in men and women, and it's probably for good reason."

THE BIRDS AND THE BEES

Bea Luna, Pitt associate professor of psychiatry and psychology and director of the Laboratory of Neurocognitive Development at the Western Psychiatric Institute and Clinic, studies brain development during adolescence. (This magazine did a cover story on her work in Fall 2007.) The number one question she's asked when she speaks at conferences is: *Have you looked at sex?* "There's this intuition that there are differences," she says.

Although sex differences haven't been a major focus in her studies, they are beginning to come to the fore. Early this year, Luna published in *Cerebral Cortex* a study examining sex disparities related to white matter—the connective fibers that enable the parts of the brain to talk to one another. At the start of puberty, males and females both have a growth spurt in their white matter tracts, sprouting more than anyone would ever need. As the brain matures, white matter tracts become increasingly insulated with a protective, conductive layer of fatty material called myelin. The result is a quicker, more streamlined, and capable brain. In other words, an adult's brain.

Luna looked at connections throughout the brain that change during human neurocircuitry development. She found that in the prefrontal-striatal connections—part of the neurocircuitry network that helps us control our impulses and act more like grown-ups—most females reached maturity in the window of ages 13 to 17. The males were still hemming things up, in terms of white matter, much later—in the 18-to-22 range.

What that means, really, we haven't figured out yet, Luna says. There could be pluses and minuses for each sex. Point for the boys: Perhaps a longer period of myelination means a brain that's more finely tuned and better adapted to his environment. Point for the girls: Perhaps if you're early to complete one stage, then you're sooner on to the next one—a stage of specialization, of learning to use the tracts you've developed with more practiced precision.

Luna is mapping out templates of normal brain development and of the abnormalities that cause psychopathologies. Her studies include ADHD and autism—overwhelmingly male disorders that hit in early childhood.

"But the interesting thing is we haven't thought of looking at sex differences in autism," Luna says. "It's very difficult to do that because it's hard to find the females that have it. To find a female with autism is so odd that you think maybe it's something completely different. It's not representative of the disorder."

As she charts out the developmental progress of healthy young people in her long-term imaging studies, she's struck by the way disorders like depression seem to creep in out of nowhere. "We have a lot who are in our normal population, and then all of a sudden, [sigh], depression," she says. Though Luna's team is not studying this disorder specifically, they are "keeping an eye on" these youths who stray from the healthy course, watching for any signs of what might distinguish them. Luna recalls a conversation she had with David Kupfer, Thomas Detre Professor of Psychiatry and professor of neuroscience and clinical and translational science, when she first came to Pittsburgh several years ago. Kupfer was head of psychiatry at the time, and the number of young depressed women he'd been seeing in the clinic concerned him. He wanted to know why this was happening. What was going on?

Indeed, after puberty, females are two to three times more prone to depression than males, even after accounting for all possible alternate behavioral explanations.

EVEN MOUSE GIRLS GET THE BLUES

Etienne Sibille, Pitt associate professor of psychiatry and principal investigator at Pitt's Center for Neuroscience and the Pitt/Carnegie Mellon University Center for the Neural Basis of Cognition, says it's no wonder no one has made any significant breakthroughs in the treatment of depression in the half century since monoamine oxide inhibitors were discovered. Depression is a complex, multifactorial disorder, with possible roles for genetics, organ mechanics, and environment. Most research has focused on existing drugs—rather than the source of the disorder.

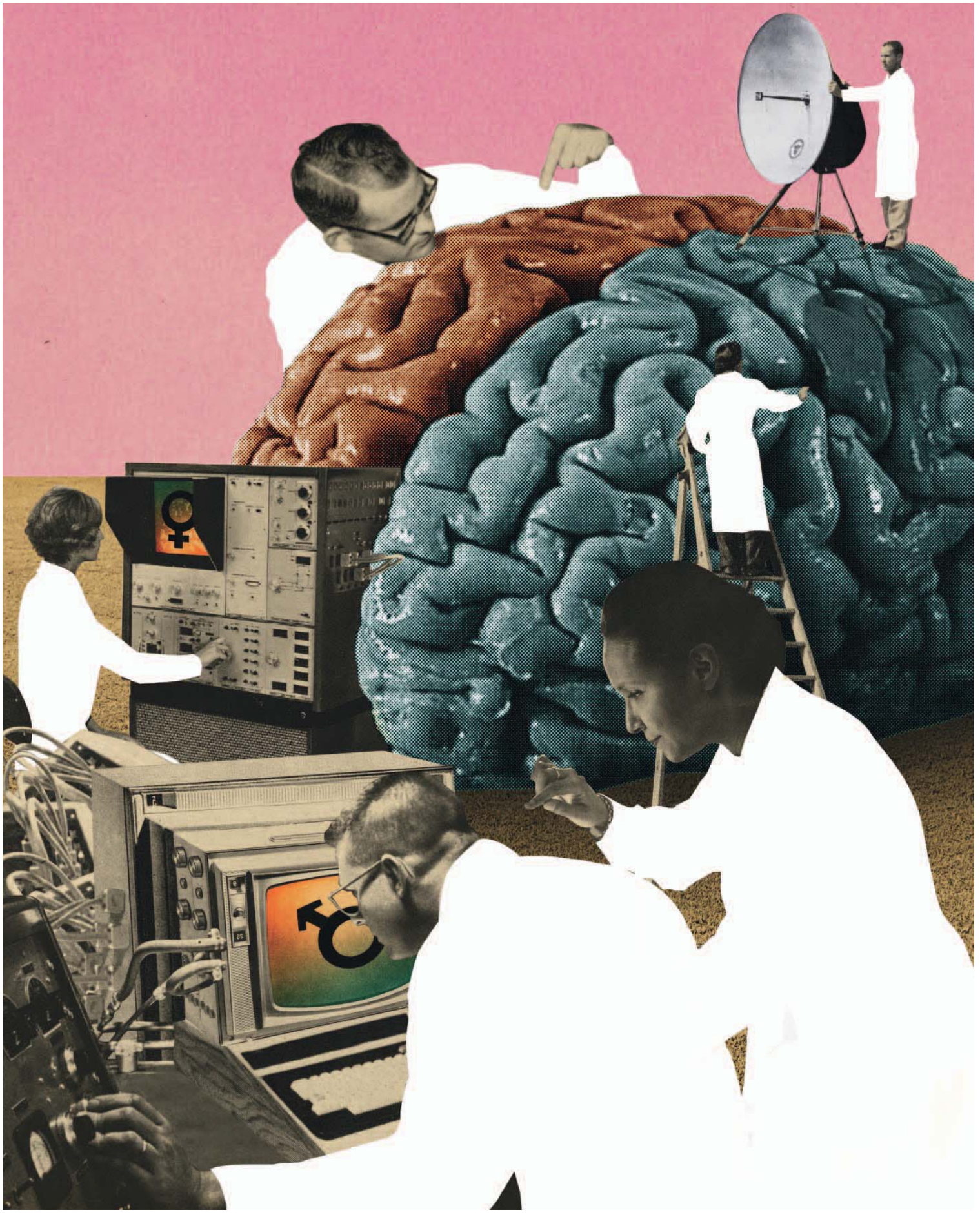
"There are a lot of variables, so it's very difficult to study," he says.

It certainly hasn't helped that the overwhelming majority of animal studies focusing on this predominantly female disease have used male mice only. Female mice are more expensive and more difficult to work with because of their estrogen cycles, an added experimental variable that must be measured through regular vaginal smears. "We can do it; but if people aren't well trained, then it's very stressful to the mice," Sibille says. And so there you are, performing a stressful procedure on the females that you don't do on the males—and doing it in an animal model of psychological distress. "It gets complicated," he says.

But nobody said this work would be easy.

Sibille suspects that, for each sex, there are several subgroups—distinct combinations of factors—that conspire to cause what appears on the surface to be the same disease: major depression. To disentangle all of that, an accurate animal model—with both sexes represented—is key.

For weeks on end—in an unpredictable, random fashion—Sibille's lab exposes the male



The brains of men and women are built and wired differently.

and female mice to several mild stressors: the scent of a predator, changes in light that undermine their biorhythms, wet bedding, or no bedding at all. In time, certain mice lose weight, their coats thin out, and their stress-hormone levels climb.

"It mimics real-life stress in humans, without being the kind of acute stress that induces post-traumatic stress disorder," he says.

And, just as in humans, female mice are far more likely to lapse into this depressive-like state than their male counterparts. Sibille's results are beginning to characterize the biology of male and female "depressed" mice.

Our emotional lives depend, to a large extent, on the white-matter networks that connect our emotion-processing brain areas to our emotion-regulating brain areas. To better understand these networks, Sibille is conducting large-scale studies of humans postmortem and looking at the function of genes within an important emotion-regulatory tract, the corticolimbic network. In people with depression, the genes in this network are altered.

"We don't know if the gene is creating this [altered] function, or if the function of the brain somehow modifies the genes," Sibille says. He's examining levels of RNA, a product of genes, as a measure of their function. So far in this ongoing study, it appears that for each sex, partially overlapping sets of at least 40 genes will be implicated in depression.

Sibille's lab is also looking into the effects of hormones—both in the circulating-during-reproductive-years sense people usually think of, and in terms of what's called the organizational effect—where hormones present during certain stages of development can influence the way our neurocircuitry sets up shop.

The organizational effect of hormones is well documented. It was first noted back in 1959, when a group of researchers at the University of Kansas found that a single dose of testosterone was enough to masculinize the brains of fetal female mice. But the study of how distinctly male and distinctly female wiring patterns lead to mood disorders—and exactly what mechanisms form those patterns in the first place—is a new frontier.

Incidentally, last year, Pitt's Mary Phillips—professor of psychiatry and director of the Functional Neuroimaging Program—and Jorge Almeida, a postdoc in her lab, stumbled upon evidence of gender-specific wiring in the living human brain, a finding that they expect will lead to a promising collaboration with Sibille. It happened as Phillips was using diffusion tensor imaging (DTI)—a kind of MRI technique that measures the diffusion of water to map out the structure of living tissues—to investigate the differences between major depression and bipolar depression.

As they analyzed the data, the researchers found that, consistently, in the brains of women with major depression—and only women—there were two abnormal tracts in the connections to the amygdala, a brain region involved in emotion processing. One was to the orbital frontal cortex and the other to the subgenual cingulate gyrus. Both of these brain regions are important for our ability to appraise emotional input, put it into context, and carry on. With these wiring abnormalities, however, this process is stymied. Instead of working with the amygdala, these two brain regions were dampening its effect.

Further, Phillips and Almeida found, these abnormal connections in the female patients with depression were on the left side of the brain only—the hemisphere associated with positive feelings.

So, what does all that mean? Most likely: These women had brains that were hardwired to overlook—effectively eliminate—the positive.

"This could be really important," Phillips says, "because it's what cognitive therapists have been saying for years: that certain types of people who are depressed will ignore positive things—no matter what. The negative is all they see."

This happy accident of a finding was included in the bipolar/unipolar study her team published in *Biological Psychiatry* this year, though not as a main focus. Phillips and Almeida have been awarded several new federal grants that will allow them to examine sex differences in the brains of depressed adolescents and adults in more detail.

"And we've replicated our findings on a completely new group of people, in a slighty different cognitive test, and in a different scanner. The only thing that's the same is that it's Pittsburgh, and it's us," Phillips says, laughing, "and yet we

Hysteria!

Before there was conversion disorder—the current *DSM IV* term for a kind of psychological stress with physical symptoms—there was hysteria.

But unlike conversion disorder, hysteria, for much of history, was unique to women. It first emerged in America during the industrial revolution. As housework suddenly became much simpler, scholars were plagued by the question of what women should do with themselves, and to this, the then-nascent field of modern medicine answered: as little as possible. In 19th century urban America, women were thought to be innately frail, and the best way to protect what doctors saw as their sole function—reproduction—was through a life of seclusion and rest. Popular culture idolized a pale, tightly corseted image of woman; her practically invalid condition became a kind of status symbol. Among moneyed women, an epidemic began to spread—episodic fits of excitability, crying, screaming, or laughter. In time, any woman's act of defiance or dissatisfaction with her station would be dubbed "hysterical."

In the Freudian era, the condition came to be classified as a mental illness. (Freud's teacher, French neurologist Jean-Martin Charcot, penned the first accurate definition of hysteria in both men and women in the 1860s.) But prior to that, dating back to the early centuries, hysteria was considered a disease of the uterus. The Greeks thought that when a woman abstained from sex or engaged in excessive "male activities," the uterus would "wander" and wreak havoc on other organs, including the brain. The root of the word hysteria, of course, means womb. —*EV*

still show the same thing. So this suggests that it might be generalizable to female depression."

For male patients with depression, a distinct signature in the circuitry will take time to sort out, she says. "There's not a clear picture, but our findings suggest there may be something about processing negative emotions—anger, fear, threat, and things like that—rather than avoiding the positive."

DOUBLE TIME

In March, the Institute of Medicine hosted a workshop in San Francisco called Sex Differences and Implications for Translational Neuroscience Research, and Sibille gave a panel presentation on depression. (Pitt's Katherine Wisner, professor of psychiatry as well as of obstetrics, gynecology, and reproductive sciences, was also on the panel.) The effort was organized in response to growing concern over the differences between men and women and boys and girls when it comes to physiological responses to drugs and the particular challenge of understanding these differences in complex mental, neurological, and substance abuse disorders.

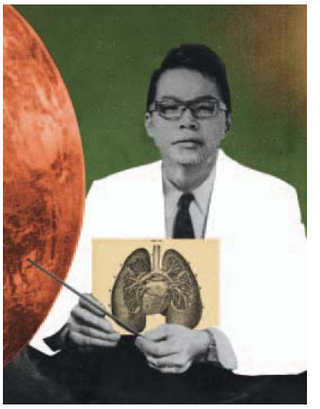
Teasing out the logistics—and, indeed, even convincing everyone that sex differences are potentially significant—is still an "uphill climb," Sibille says.

Jill Becker, president of the multidisciplinary Organization for the Study of Sex Differences, says the issue is at least beginning to show up on the radar for the scientific community at large, not just in neuroscience and psychiatry. The biggest challenge now is convincing everyone that it's important enough to fund research on the topic, she says. "I think part of the problem is that people worry they'll fail to advance science if they have to study both males and females. They think you have to use more animals, [yet] money isn't spent advancing what we already know about males.

"But if you're not learning about whether it's also applicable to females, you're really not advancing science in general. You're really just advancing science for one half of the population," she notes.

"What's important," says Sibille, "is that you assess whether sex has an influence on what you're studying. It may, but it may not. And if it does, then you have to take it into consideration." —*EV*

IMMUNE DIVIDE



Women live longer than men, on average, by about five years. The reason for this difference—as the old epidemiological saw goes, often uttered with a chuckle—is that women are smarter. Or, more precisely, men are more reckless. Men drink and smoke more. They drive faster. They eat more cheeseburgers at 3 in the morning. They get into fights more often with guns, knives, fists, rocks, and nunchaku. Call it the death-by-testosterone theory of life expectancy.

"The general notion is men … are out there trying to kill themselves as much as possible throughout their lifetimes whereas women are far more cautious," says Sachin Yende, assistant professor of critical care medicine at the University of Pittsburgh.

For a few years, however, scientists like Yende have known there may be more to it than the recklessness of boys and men. Men get more infections than women do, and when they get infections, they are more likely to die.

Theories abound about this discrepancy. It could be the effect of estrogen and testosterone in immune response, or the withering effect of all the chronic diseases men tend to accrue as a result of their risky behavior. Or it could be something else entirely.

Yende and his collaborators have performed one of the bigger tests to date exploring this question. The group took blood samples of more than 2,000 patients who'd come down with community-acquired pneumonia, one of the leading causes of infection-related hospitalizations in the United States.

Men had higher levels of inflammatory molecules and blood coagulators than women did in the study. And they were 35 percent more likely to be dead one year after diagnosis than women. Even when the researchers controlled for the higher rate of chronic disease among men, the men with pneumonia simply did worse than the women.

Because the mean age of patients in his study was about 65, and testosterone and estrogen production generally decreases with age, Yende tends to downplay the role hormones had in his results. One theory is that the X chromosome could play a role in the differences in the expression of interleukin-1 (IL-1), another immune trigger. Women, of course, have two Xs, while men have an X and a Y. The X is home to IRAK-1, which regulates transcription and production of the IL-1 gene. The thinking goes that having two Xs, and thus two copies of IRAK-1, could result in different gene expression for IL-1 for women than for men.

Do men have a heightened immune response because they are sicker than women? Or does the heightened response make it harder for them to recover? Consider the case of severe sepsis, in which the body's own immune and inflammatory response becomes so strong that it can cause multiorgan failure and death. In sepsis, heightened immune response can actually be more harmful.

A study of 1995 data by Pitt's Derek Angus, the Mitchell P. Fink Professor and Chair of Critical Care Medicine, found that women with severe sepsis had lower mortality rates than their male counterparts—their bodies behaved about five years younger than men's.

Scott Watson—also a member of the critical care medicine faculty, as well as pediatrics—had similar findings when he examined a large cohort of young people with severe sepsis. His most significant finding was that boys ages 1 to 10 had about a 10 percent higher rate for the condition than girls. And Jason Sperry, assistant professor of surgery, found that male trauma patients had "excessive" levels of interleukin-6, an immune-triggering protein.

If the female immune response is less intense, shouldn't girls get sick more often? They don't. Girls' immune systems seem to be able to fight infection off well with a lighter touch. Watson wonders whether something basic is at play: "[These differences] could be related to the fact that women are built to have this partially foreign creature growing inside them, and the immune system has to be tuned to not interfere with that," he says.

The immune systems of women may be smarter after all. —*Reid R. Frazier*

A MATTER OF HEART

You don't have to look at the personal ads to know the hearts of men and women act differently. Just look at an EKG.

The QT interval—a measurement of the length of the electrical pulse that controls the contraction of the heart's ventricles before returning it to a "resting" state—is longer on a woman's EKG than on a man's. This is normal, but it exposes women to different kinds of risks. The longer a person's QT interval gets, the greater her risk for arrhythmia, a fluttering of the heart muscle that can lead to heart failure and sudden death. This is the case in a congenital disorder, long QT syndrome, which can produce a Torsade de Pointes, a highly lethal type of arrhythmia. The disorder occurs in about 0.1 percent of the population.

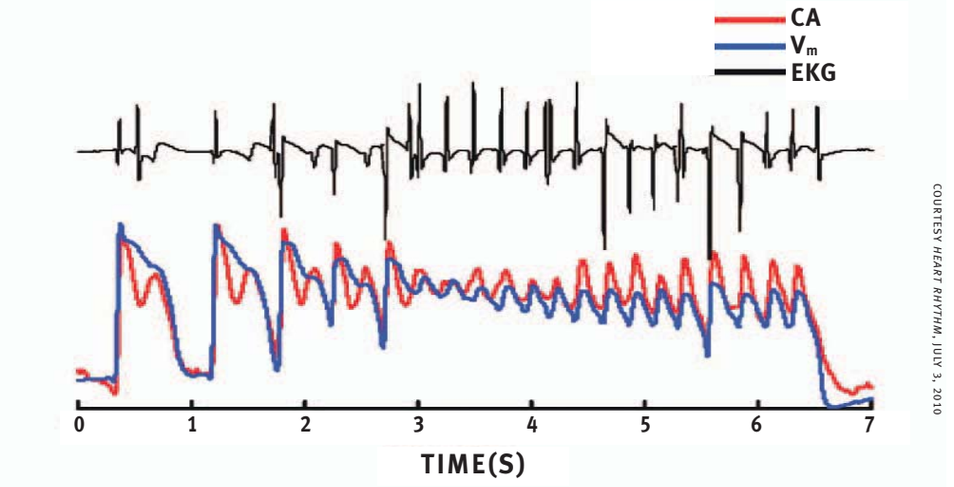
Why do male and female hearts behave so differently? Guy Salama, PhD professor of cell biology and physiology at the University of Pittsburgh, thinks it has something to do with the effect sex hormones have on the heart's electrophysiology. Ion channels are the heart's version of the World Wide Web: Ions pass through these cell membrane pores to send electrical impulses from cell to cell with instructions on how to pump blood throughout the body. Testosterone and estrogen can increase or decrease the number of available ion channels, amplifying or limiting different messages. In men, the potassium ion channel is busiest; the calcium ion channel activity is more robust in women.

What happens when drugs change "normal" ion channel activity? Things get dicey. The level of electrical activity surges at different times, and the QT interval can lengthen, especially in women, producing an arrhythmia. Salama and his collaborators found that when a drug that restricts the calcium ion channel was administered to rabbits, the adult females were much more susceptible to arrhythmia than were their male counterparts. In juveniles, with much lower levels of sex hormones, the effects were reversed.

"With the female rabbit, you add half a micromole per liter of a drug, and *Bang!*, you get arrhythmia. In the male, you get nothing; they're fine. When you don't pay attention to how old they are, you get confused because the young females have no arrhythmia at all."

This fine-grain understanding of the heart's circuitry could affect which drugs are considered safe. Currently, any new drug found to block the potassium current is almost always shelved. Yet if the relevant ion channels can be fine-tuned and perhaps targeted specifically according to the sex of the patient, then a drop in the potassium current might be tolerated.

"There could be good drugs that were thrown away that we don't know about because we didn't give them a second chance," Salama says. —*RRF*



COURTESY *HEART RHYTHM*, JULY 3, 2010

Hormones affect the heart's electrophysiology, making females more susceptible to a rare but lethal type of arrhythmia known as Torsade de Pointes. Here, measurements of intracellular calcium and voltage across the membrane are shown with an EKG just before an episode of arrhythmia in a rabbit.

"YOU'VE COME A LONG WAY, LUNG CANCER RESEARCH"

One in five women diagnosed with lung cancer has never smoked; in men, it's one in 12. Jill Siegfried—a PhD and coleader of the University of Pittsburgh Cancer Institute's Lung and Thoracic Malignancies Program—suspected estrogen might be a factor in the heightened risk for women, and she was right. Five years ago, she became one of the first to demonstrate that the estrogen receptor beta is expressed in the lungs and overexpressed in up to 85 percent of lung tumors. Surprisingly, Siegfried found, this is the case in both men and women. "We think the difference is how much estrogen you're exposed to in your lifetime," she says.

Siegfried's team found that estrogen-dependent lung cancer cells thrive not only on the estrogen that naturally circulates through men and women (to different degrees), but also on a supply they make in-house. (Lung tumors express aromatase, an enzyme that synthesizes estrogen.)

When estrogen binds with its receptor on lung tumor cells, it not only kick-starts growth by interacting with the usual suspects—genes that are known players in cancer—but also through an infamous cancer-causing protein, EGF (epidermal growth factor). Siegfried found that estrogen actually makes the EGF receptor pathway more active.

EGF-targeting drugs help about 10 or 12 percent of lung cancer patients. Siegfried hopes that adding estrogen-targeting therapies will boost the efficacy of these drugs. A 100-patient clinical trial that started this summer will test that hypothesis.

Recently, her group has been studying progesterone, and as it turns out, progesterone receptors can also be overexpressed in the lung tumors of both sexes. But unlike estrogen, progesterone hinders tumor growth rather than helping it. Now, Siegfried is looking at what different levels of all three receptors mean for patients in the long run. She's been able to outline outcomes for several distinct patient profiles. For example, patients whose estrogen and EGF receptors (cancer helpers) are high and progesterone receptors (cancer hinderers) are low are five times more likely to die.

These insights hold promise for a more personalized approach to the second-most common cancer in both men and women. In a few short years, the field has, truly, come a long way. —*EV*

SEXUAL (RESEARCH) REVOLUTION

The University of Pittsburgh's Johnny Huard and Bridget Deasy are quietly fomenting another sexual revolution. This one starts at the cellular level.

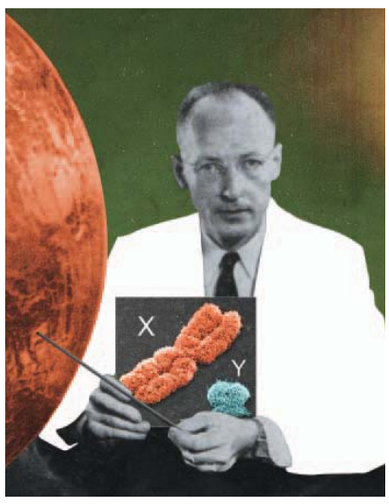
A decade or so ago, Huard made a big splash. His and other labs showed that adult stem cells—that is, cells that rebuild and repair tissue throughout our lives, not just the precious cells that build bodies from embryos—could regenerate tissue outside of their supposed preordained realms. For instance, if you put them in the right place under the right conditions, muscle-derived stem cells not only regenerate muscle, they regenerate blood, bone, even nerve. *Wow*, scientists realized. *All along we've been carrying around the potential to heal ourselves from all sorts of injury and disease. Now we just need to figure out how to manipulate these cells in the right way for therapeutic uses.*

But amid all the buzz, there was a sticking point for Huard, who holds appointments in a number of Pitt departments and is the Henry J. Mankin Professor of Orthopaedic Surgery Research and director of Pitt's Stem Cell Research Center. "There was a huge variability," he says.

Sometimes the stem cells his lab took from musculoskeletal tissue regenerated heart and other damaged muscle well, and other times they didn't. Naturally, he wanted to find out why.

So he designed a system that would track what happened to the cells after they were put into a mouse. His plan: Tag the Y chromosome in male stem cells and inject the cells into female animals. This way his lab colleagues would be able to track the stained Y chromosome to find out what the stem cells were up to. Sounded good. One problem: All the stem cells they had been using in their muscle studies turned out to be from female mice. They hadn't thought much about it, but the stem cells that had been working nicely had come from the critters without a Y chromosome.

"Is it possible we are working with female stem cells because they repair muscle better?" Huard recalls wondering. A study, run by Deasy, an assistant professor of orthopaedic surgery and bioengineering, showed that was exactly what was happening. When Deasy injected muscle stem cells from females into mouse models of muscular dystrophy, the mice were more successful regenerating tissue than when she administered male stem cells. Huard's team is seeing the same pattern in humans. (And Deasy hopes to soon publish new research showing that stem cells from baby girls' umbilical cords repair muscle better than cells from boys' cords.)



"Maybe estrogen is good for stem cells and testosterone is not that good," Huard conjectured. But trying to stimulate muscle stem cells with estrogen didn't seem to make a difference.

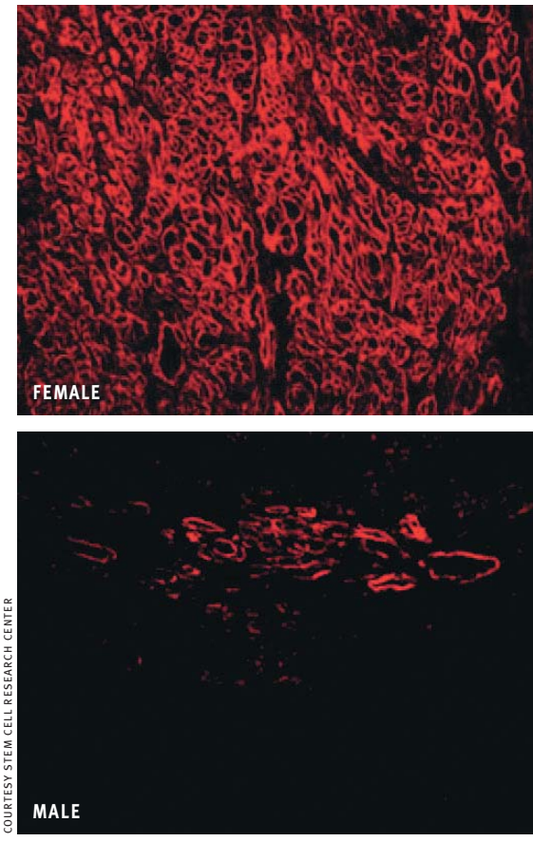
So what's going on? No one knows, but Huard offers some other possible explanations.

"Maybe our genetic constitution is different," he says. Perhaps that extra chromosomal limb (XX v. XY) contains genetic information that gives females a muscle-building advantage.

Alternatively, because a man's muscle mass is typically larger than a woman's, "maybe the woman has more [stem cell] reserves or 'less-tired' stem cells," offers Huard.

It does appear women end up with more reserves. At first, the male stem cells actually do a good job. Then they peter out. "At 48 hours, male cells are doing better," explains Huard. "But at 10 days, the female cells are doing better." As it turns out, the female stem cells take time to proliferate before regenerating muscle fiber. The male stem cells build muscle quickly but not much of it; they max out after a couple of days.

The sex of the host matters, as well. When Deasy put female stem cells into female mice, they regenerated muscle beautifully. What about female stem cells in male mice? Those results were pretty good. Male stem cells in female mice? So so. Male stem cells in male mice? Not promising.



COURTESY STEM CELL RESEARCH CENTER

Arnold Schwarzenegger, watch out. Turns out, muscle-derived stem cells from females are much better at rebuilding muscle than stem cells from males. Here the cells regenerate tissue in mouse models of muscular dystrophy.

But female stem cells are not always the best choice. Not if you want to regenerate bone or cartilage.

"I thought females would be able to regenerate everything better, but that's not the case," Huard says.

He knew that muscle-derived stem cells could build bone and cartilage, as well as muscle. When his colleagues tried coaxing muscle-derived stem cells to regenerate bone or cartilage, the stem cells from male mice performed the best.

"We can look for 20 years to find the reason for this," says Huard.

In the meantime, the stem cell community's reaction to these sorts of findings may be tepid, notes Deasy. She points out that if she and Huard are on the right track, it means scientists like them should be doing their experiments on stem cells from both male and female donors—*and* studying how those cells perform in both male and female hosts. That takes money and time.

But few revolutions come easily. —*Erica Lloyd*

WORLDS APART?

Throughout their lives, men are more vulnerable than women in many ways. As children, boys are more susceptible to neurobehavioral disorders, neurodevelopmental disorders, and genetic disorders. At puberty, boys start to become more vulnerable to schizophrenia (for adolescent girls, it's depression and bipolar disorder). As adults, men typically suffer heart attacks five years earlier than women. In old age, men are more likely than women to die from Parkinson's and Alzheimer's diseases. And telomeres—the ends of chromosomes that relate to the life spans of cells—are shorter on older men than on older women. Add to that these recent findings from Pitt researchers:

When neurons from males and females are exposed to stroke-related compounds in culture, both die, but they do it via different mechanisms and to different degrees. Overall, more cells from males die than from females.

Neurons from men and women also differ in how they die of oxygen deprivation. In a cell-culture model of this process, levels of glutathione crashed in cells from men, which has possible relevance to suffocation, heart attack, and severe bleeding. Glutathione levels did not crash in females.

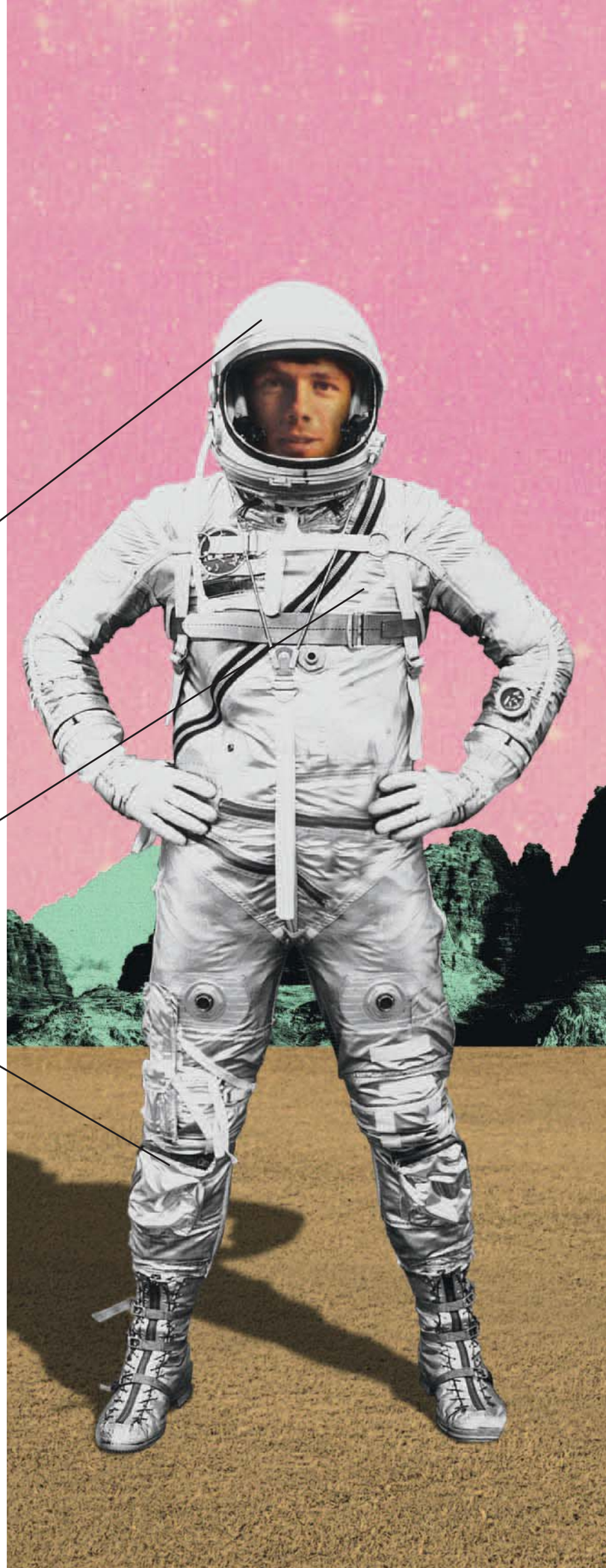
Omega-3 fatty acids help stave off cardiovascular disease in men with type 1 diabetes, but not in women with the disease.

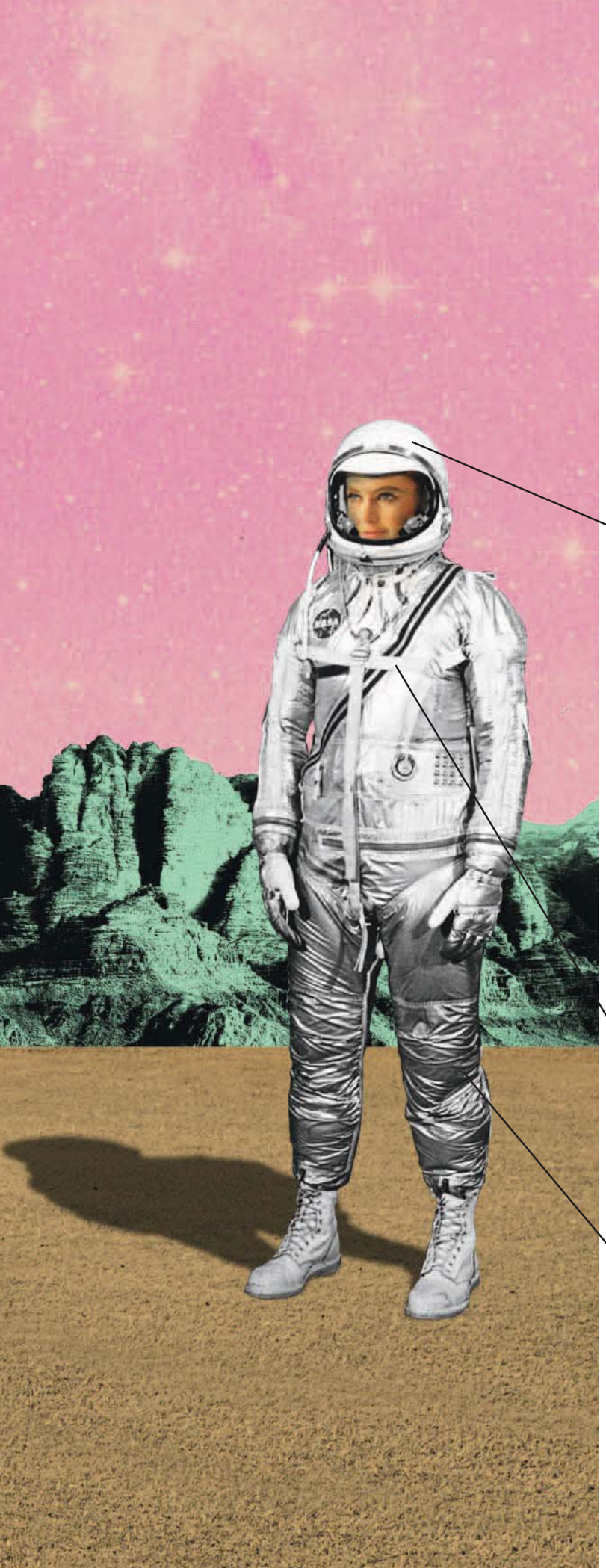
"Good" cholesterol (HDL) is cardioprotective in men but not women with type 1 diabetes. In women, HDL actually increases risk.

Men are better at rebuilding bone and cartilage with muscle-derived stem cells in therapeutic studies. They are also better at building cartilage with bone marrow stem cells; this ability declines with age in males, but not in females.

Males and females have very different immune responses to foreign invaders. Newborn boys are more likely to develop sepsis, to require mechanical ventilation, and to land in the neonatal intensive care unit.

Older men hospitalized with community-acquired pneumonia are more likely to succumb to the disease. They seem to generate a stronger inflammatory and coagulation response and, perhaps, break up blood clots more quickly than women do in response to infection.





There are plenty of reasons to enjoy being a girl. Women are healthier during their reproductive years, when estrogen levels are highest. The hormone is known to protect them from strokes, heart attacks, and head trauma, and to ward off oxidative stress. Of course, being female is a mixed bag. We've long known women are more prone to rheumatoid arthritis, lupus, multiple sclerosis, eating disorders, chronic fatigue syndrome, mood disorders, asthma, and breast cancer (men get that too, don't forget). After menopause, women are just as susceptible to heart attacks as men, though they do experience them differently (pain in the shoulder and jaw, a queasy stomach, and heartburn). So Professor Higgins, there are many reasons a woman can't be more like a man. And Pitt researchers keep unearthing more and surprising findings:

The neurons of female mice in culture survive starvation for days longer than those of male mice. Ladies' brain cells subsist on fat stores; the gents', however, nosh on their own organelles.

The neurocircuitry networks that help us control our impulses and act more like grown-ups reach maturity years earlier in females than they do in males.

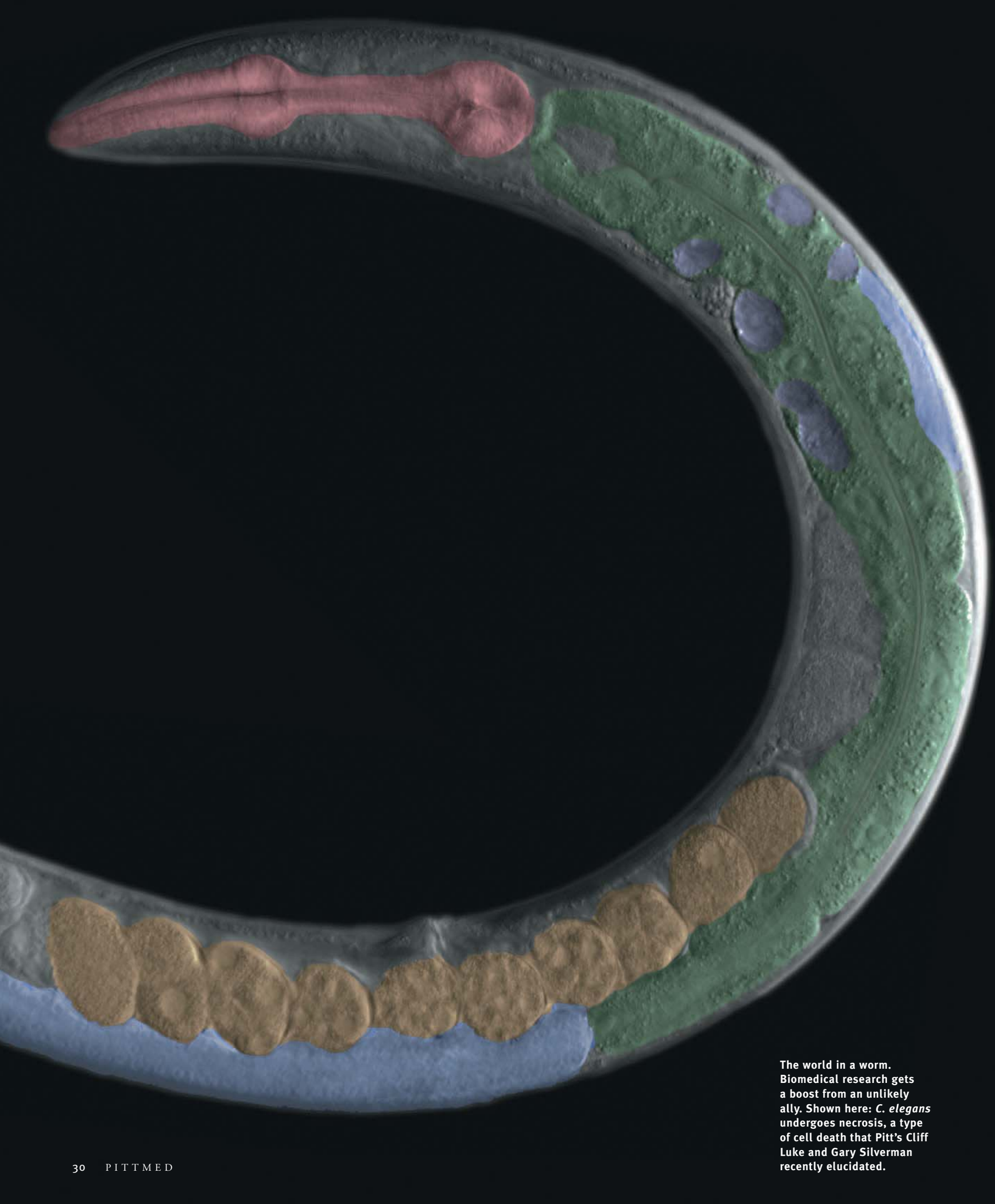
In brain scans, depression looks very different between the sexes. For women with the disorder, the neurocircuitry appears to be hardwired to block positive emotions at certain points. In contrast, males with depression may have trouble processing negative emotions like anger and fear.

Though protective in some situations, estrogen may also contribute to electrical disturbances leading to certain types of arrhythmia, including a rare but lethal condition known as Torsade de Pointes.

Most lung tumors—in both men and women—have estrogen receptors, meaning they grow in the presence of this hormone. The fact that women have more estrogen on board throughout their lives may explain why they're at higher risk for lung cancer, regardless of smoke exposure. (One in five women diagnosed with lung cancer has never smoked; in men, it's one in 12.)

Adult stem cells from women are better at rebuilding muscle in therapeutic experiments. Somehow, women's bodies also give muscle-building stem cells a needed boost that men's bodies don't, no matter the sex of the cell donor.

—Compiled by Elaine Vitone



The world in a worm. Biomedical research gets a boost from an unlikely ally. Shown here: *C. elegans* undergoes necrosis, a type of cell death that Pitt's Cliff Luke and Gary Silverman recently elucidated.

OUR PRIMAL ROOTS

BY MELINDA WENNER MOYER

MISSION CREEP

Physicists may need 17-mile-long particle colliders, and chemists expensive chromatographs, but biologists answer some of their most difficult questions using tiny tools. A number of this century's celebrated biomedical discoveries—three of which were honored with Nobel prizes this decade—have relied on the help of one particularly basic and infinitesimal laboratory tool: a one-millimeter-long worm called *Caenorhabditis elegans.*

Thankfully abbreviated as *C. elegans*, the worm—or nematode, as it is called by those in the know—has a number of things going for it. It matures from embryo to adult in three days (just feed it bacteria), reproduces by itself, and is completely transparent, so researchers can observe its biological processes in real time, much like the internal workings of a Swiss watch. It's also the first multicellular animal to ever be used to test drugs in robotic drug discovery systems.

COURTESY C. LUKE

Best of all: "If you look at a human and you look at a worm, they look very dissimilar," says Lewis Jacobson, a PhD professor of biological sciences at the University of Pittsburgh. "But the more you go down toward the molecular level, the more similar they look."

It's astonishing. These worms have 19,000 genes to our 25,000, but up to three-quarters of the ones we have in common are identical. "In fact, they are often interchangeable," Jacobson posits. It would theoretically be possible, then, to engineer a human so that three-quarters of his genes came from this worm—and perhaps no one would be able to tell the difference.

In the 1960s, biologist and 2002 Nobel Laureate Sydney Brenner chose the worm as his second-in-command to chip away at one of the biggest biological mysteries of all: how, exactly, our genes all come together to make us functional organisms. By eliminating genes one by one, or tinkering with them so they didn't work properly, Brenner defined the roles that many individual genes play in making us, well, *us*. Today hundreds of labs and thousands of investigators around the world use *C. elegans* to answer burning biological questions.

The University of Pittsburgh is certainly no exception. In recent years, Pitt scientists have employed the worm to probe the causes of human disease, aging, and infertility. One lab has even sent the worms into space to observe how their muscle cells respond.

The more time Pitt researchers spend peering inside these tiny transparent tools, the more of life's mysteries they crack.

When asked which diseases his lab's research could eventually help treat, Cliff Luke, a PhD assistant professor of pediatrics in Pitt's School of Medicine, laughs. "Pretty much everything," he says. He's hardly exaggerating. In 2007, Luke and his colleagues, who include his lab's lead investigator, Gary Silverman, MD/PhD chief of newborn medicine in Pitt's Department of Pediatrics, made the cover of *Cell* after discovering that a common form of cell death called necrosis—a direct cause of much of the damage triggered by heart attacks, strokes, and lung disease—is not, as had been previously assumed, disorganized and uncontrolled. Using *C. elegans*, they found that necrosis actually proceeds in an organized, stepwise fashion. This begs the question: Might it be possible to undo it in a stepwise fashion, too?

Their 2007 discovery centers around a protein called SRP-6, whose job is to protect cellular organelles called lysosomes. Lysosomes are like the stomach of the cell—they digest proteins that the cell uses for food. Sometimes, they suffer from their own form of acid reflux disease, leaking dangerous enzymes called peptidases into the cell body. SRP-6, one of a class of proteins called serpins, is like the lysosome's antacid. It "sequesters the peptidases from damaging the normal parts of the cell," Luke explains.

Luke and his colleagues bred *C. elegans* so that they lacked the gene for SRP-6 (see "An Elegans Solution" in our Spring 2008 issue). The worms quickly died from the damage caused by necrosis, a finding that suggested that this particular form of necrosis is "actually a very structured routine that is controlled by peptidases" rather than some uncontrolled violent reaction, Luke says. Recently, the lab has shown that a mammalian version of the SRP-6 protein works in a similar manner. In an experiment they conducted in 2009, they inserted the mouse version of the gene into the genome of a SRP-6-deficient worm. The worm survived.

It would be tough to insert these genes into people, but it's not ridiculous to wonder whether simple compounds might be able to halt necrosis, too. To find out, Silverman's lab has teamed up with Stephen Pak, a research assistant professor of pediatrics at Pitt, to develop one of the world's first, and the highest-throughput, drug discovery platforms using *C. elegans*. Typically, when labs and companies screen compounds as possible drugs, they use molecules or single cells as targets. Problem is, these screens say nothing about whether the compound actually has the intended effect on a whole animal. But by using *C. elegans*, their platforms is much more powerful, because if a compound "has an effect on one animal, there's a good chance it'll have an effect on another," Silverman says.

Here's how it works: The lab has engineered thousands upon thousands of *C. elegans* to contain markers that light up when a compound interferes with the biochemical pathway involved in necrosis. Robots plop one worm into each well of a 384-well microtiter plate and add possible antinecrosis compounds to the mix. Then, a fluorescent-monitoring microscope scans the wells to see which cells light up.

These "hits" are then cherry-picked as possible drugs that may one day find their way to the clinic to safely and effectively prevent the cellular damage that is the hallmark of so many conditions.

Luke points out that it might sometimes be useful to induce necrosis, too: Some cancers may be resistant to chemotherapy because serpin levels in the tumor are too high, preventing the necrotic damage necessary to eliminate the tumor. By manipulating serpin activity in various ways, it would be possible to prevent damage when you don't want it, and boost it when you do.

In collaboration with David Perlmutter, Vira I. Heinz Professor and chair of pediatrics at Pitt, Silverman and Pak are also using *C. elegans* to model a disorder called alpha-1 antitrypsin deficiency. Caused by a mutation in the gene for alpha-1 antitrypsin—another serpin—the disorder results in an accumulation of the mutant protein in the human liver and is the primary cause of liver transplantation in children. *C. elegans* doesn't have a liver, but it's been enormously useful in investigating the disease. Using their *C. elegans* screening platform, the team has already identified one molecule that breaks down and removes the toxic protein from the worm.

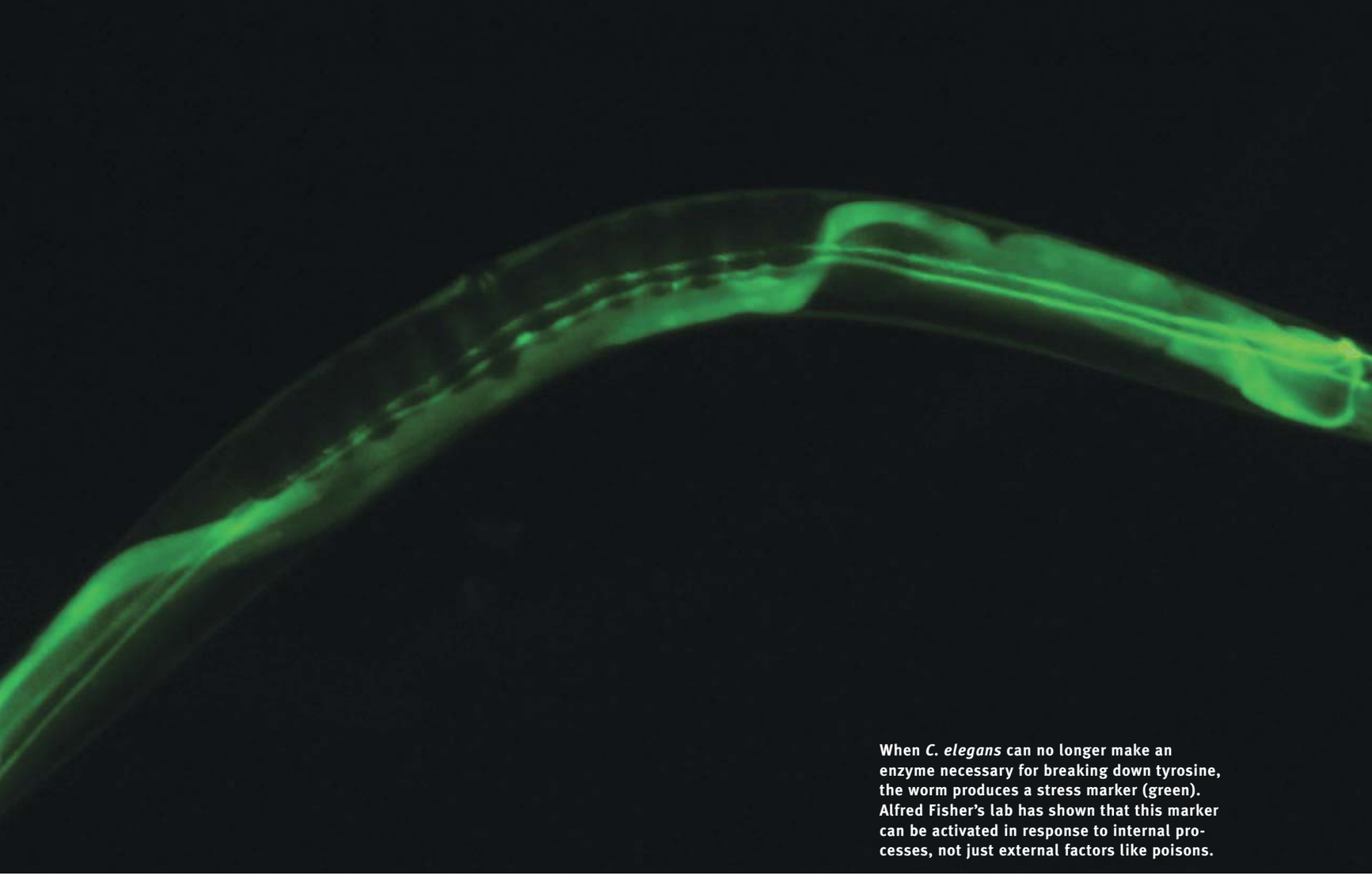
Their findings could have far-reaching implications, because drugs that clear this particular mutant serpin may also help clear the protein aggregates that characterize other neurodegenerative diseases.

"What's so exciting is that this class of drugs, called autophagy enhancers, has the potential to work on multiple substrates," Perlmutter says.

Serpins are, of course, only one of many classes of proteins that are protective. Others include the Aip-1/AIRAP proteins, short for arsenic-inducible RNA-associated proteins, which are within the purview of Alfred Fisher, an MD/PhD assistant professor in the Division of Geriatric Medicine in the School of Medicine. These proteins were first discovered for the role they play in the body's response to arsenic exposure: Their job is to clear other proteins from the cell that have been damaged by the poison. Since then, researchers have learned that the Aip-1/AIRAP proteins are also produced after other external stresses like heat shock, and that they do their dirty work by binding to a protein-degrading cellular body called a proteasome, ramping up its activity.

In research published in the June *Molecular and Cellular Biology*, Fisher showed, using *C. elegans*, that these proteins are also produced when the body has trouble breaking down the amino acid tyrosine, which it frequently does to create energy. Fisher bred *C. elegans* so that they

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When *C. elegans* can no longer make an enzyme necessary for breaking down tyrosine, the worm produces a stress marker (green). Alfred Fisher's lab has shown that this marker can be activated in response to internal processes, not just external factors like poisons.

could not produce an enzyme necessary for tyrosine degradation; they suffered from intestinal problems and early death. But before they died, the worms also produced Aip-1/AIRAP. This was the first example of a completely internal process—as opposed to exposure to heat or poison—triggering the production of the proteins.

Fisher is now working to uncover what other genes and internal processes might have the capacity to turn the proteins on. His hunch is that ramping up the activity of these proteins in a safe manner might alleviate damage caused by a number of environmental insults and stresses. It might even open up doors for treating the many conditions linked to proteasome dysfunction. These include neurodegenerative diseases like Alzheimer's and Parkinson's, as well as viral and bacterial infections, he says.

There's another question percolating in Fisher's mind. Previous research has shown that animals that cannot make Aip-1/AIRAP die early. So will animals live longer if they make lots of it? "My guess is, they might," he says. To find out, his lab is developing worm constructs that produce different amounts of the proteins. Then he will wait and see which, if any, end up with a particularly long life span.

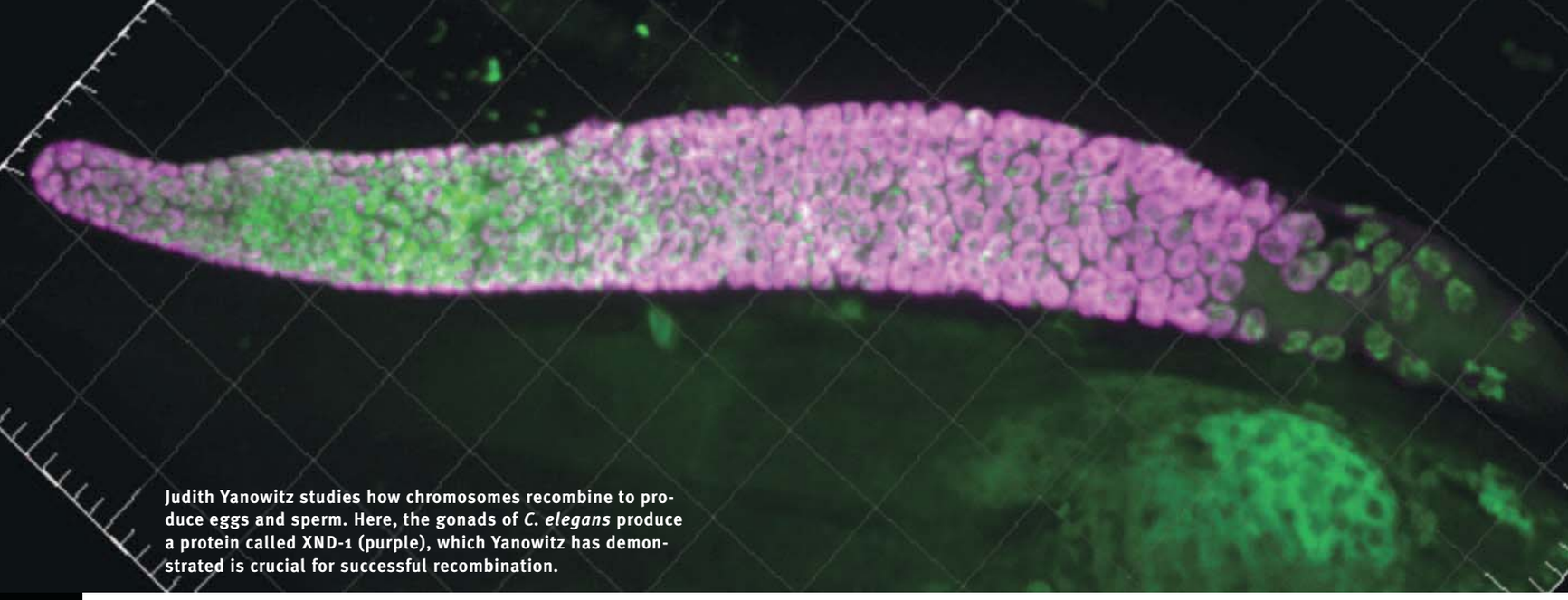
"For a lot of the things we do in the lab, we say, 'Let's see what happens if you do that,'" Fisher says. "You often find interesting and surprising things that way."

While Fisher tinkers away at extending life, Judith Yanowitz, a PhD assistant professor in the Department of Obstetrics, Gynecology, and Reproductive Sciences at Pitt and member of the Magee-Womens Research Institute, is conducting experiments with *C. elegans* in the hopes of ensuring that life can happen in the first place. A newcomer to Pitt—she joined the faculty last year—Yanowitz is striving to understand the many things that can go awry when gametes (eggs and sperm) form.

To do so, she focuses on meiosis, the form of cell division that produces gametes. One key aspect of meiosis is the crossing over, or recombination, that occurs between homologous parental chromosomes, as this ensures DNA exchange—and such exchange is necessary for the production of offspring that are genetically different from each parent. As it turns out, "that process of crossing-over is actually essential for the chromosomes to segregate properly," Yanowitz explains. "If you don't do it, you end up with a disease like Down syndrome—with too many or too few chromosomes per gamete," or what scientists call nondisjunction. Other forms of nondisjunction lead to miscarriage.

C. elegans is the perfect organism to use to study chromosomal recombination. Because the worm is transparent, "We can see the chromosomes going through what we call the meiotic dance," Yanowitz says. What's more, the events that take place during worm recombination are identical to those in humans. "Some of the proteins that are specifically involved are different, but the process itself is highly conserved," she says.

In 2005, Yanowitz performed a screen from which she identified 20 proteins that play a role in regulating recombination on *C. elegans* chromosomes. These proteins, she discovered, affect the higher-order structure of DNA known as chromatin. This makes sense. For crossing over to occur, each homologous parental chromosome first has to be "snipped"



Judith Yanowitz studies how chromosomes recombine to produce eggs and sperm. Here, the gonads of *C. elegans* produce a protein called XND-1 (purple), which Yanowitz has demonstrated is crucial for successful recombination.

COURTESY J. YANOWITZ

so that DNA can be exchanged; the proteins her screen uncovered seem to facilitate this strand-cutting by affecting DNA structure. "They're like the homing proteins," she explains. They say, "Come over here, there's nothing around, so you can make your break." Recently she has zeroed in on understanding the mechanism employed by one of these proteins, XND-1, which influences crossing-over on all *C. elegans* chromosomes.

Another mystery that Yanowitz's lab is trying to solve: What, exactly, happens to cause older women to be more likely than younger women to have miscarriages and babies with genetic defects (what's known as "reproductive aging")? Worms also experience these problems: During the late stages of their reproductive capacity, their gametes are 100 times more likely to form improperly. "Now we're testing to see if we can see changes in higher-order DNA structure during reproductive aging," she says. By uncovering the molecular problems at the root of this phenomenon, it might be possible, she says, to prevent them.

As any of us age, many things can go wrong, of course. And lots of them involve our skeletal muscles, which make up a whopping half of all of our tissues. "It is immensely expensive in a biochemical sense, and in terms of nutrition, to build and keep all of that protein," explains Jacobson. Muscle "is something that you can afford if and only if there's a good justification for it."

Our bodies are constantly evaluating whether to keep muscle or get rid of it—the latter being much more common during aging—and Jacobson is striving to understand, with the help of his favorite worm, exactly how they do this.

C. elegans' muscle cells do something surprising: They constantly produce a muscle-degrading protein called fibroblast growth factor (FGF). Although that might sound suicidal, Jacobson discovered why it isn't. In a 2007 paper he published in *EMBO Journal*, Jacobson reported that worms have a signal moderator molecule that notes the presence of both FGF and a muscle-saving hormone called insulin-like growth factor (IGF). When both signal to the muscle, he found, the cell is spared. But when Jacobson prevented IGF signaling in the worms, their muscles broke down. The finding could explain why people with diabetes, who have impaired insulin signaling, frequently suffer from muscle atrophy.

The question that Jacobson's lab is now trying to answer is what, exactly, naturally shifts this balance in favor of degradation. One cause is well known: lack of use. When muscles are not utilized, as anyone who has ever taken a six-month exercise hiatus and then attempted to run three miles knows, they break down.

This is partially because the muscle cells stop releasing calcium, a natural byproduct of muscle use. Jacobson has recently found that the same signal moderator that monitors FGF and IGF also pays attention to calcium levels. When they are low for long periods of time, the molecular moderator tips the balance in favor of breakdown.

Muscles break down naturally in the elderly in part because "it is a pro-survival trait in any organism, from worms to humans, to give up a muscle if giving up the muscle is important," Jacobson says. Better to lose your biceps and save your brain and heart. Historically, scientists have had difficulty teasing out the molecular mechanisms involved in the body's decision to sacrifice muscles during aging, but Jacobson is breeding *C. elegans* with different muscle signaling profiles in the hopes of finding out. To date he has produced more than 280 mutant strains, because many signals are likely involved. "It's clear that muscle is listening to a lot of things," he says.

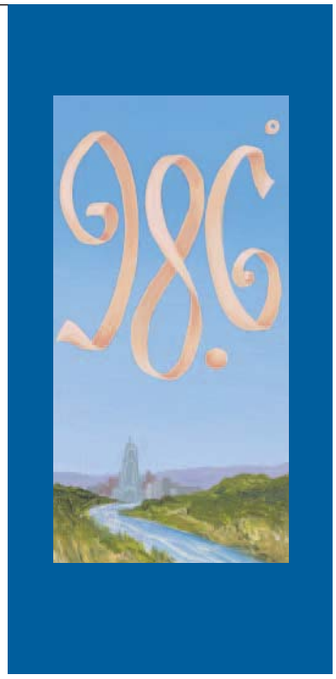
Jacobson's lab has a side project: sending worms into space. Astronauts have long lamented the fact that even if they exercise, their muscles atrophy more quickly in space than on Earth. In a recent experiment, Jacobson and his colleagues measured the levels of expression of two-thousand worm genes while the worms were aboard the International Space Station. Several genes involved in the attachment of muscle cells to each other and to skin changed their expression patterns. "It looked like the attachment complexes that were keeping the muscles tightly glued together were being down regulated in space," Jacobson explains.

So what does that mean? Space flight "causes protein breakdown in the muscles, and the issue is why and how," Jacobson says. "I don't think we have a lot of answers yet."

It may seem crazy to think that a one-millimeter-long worm could be at the root of so many discoveries. But nature knows when it has found something good. "Even though worms and humans separated probably a billion years ago or more in the course of evolution, nature is very parsimonious," Jacobson says.

So as researchers study the delicate *C. elegans*—as they watch the inner workings of its evolutionarily ancient organs—they are, in a sense, peering inside every animal that has evolved in the epochs since. Looking inside these worms, then, isn't all that different from looking inside ourselves. "The important stuff doesn't change," Jacobson says. ■

People and programs that keep the school healthy and vibrant



A PATHOLOGIST CHAMPIONS FAMILY MEDICINE

BY JOE MIKSCH

As Larry Nichols puts it, he's at the age where having to go to the doctor is, let's say, not particularly uncommon. Along the way he has noticed, firsthand, the need for more family physicians. "We have a situation in this country where there are not enough primary care physicians," he says.

This fact got the MD associate professor of pathology at the University of Pittsburgh wondering whether he could do anything about it. Nichols, who has not only an MD but also an MA in philosophy from the University of Wisconsin, is the chief of the autopsy service for UPMC and teaches basic pathology and cardiac pathology in the School of Medicine.

"As a pathologist—and an old pathologist—I really can't be going and doing family medicine," he says. "So how can I help?"

Nichols did a little math. Med students graduate with crushing debt. This debt can compel someone whose heart may be in family medicine to instead become a specialist who earns much more than a family practitioner. *What could help stem this tide to other fields?*, he wondered. *Money!*

Nichols began to seriously consider establishing a scholarship for family medicine practitioners.

"I figured out how much I can afford," he says, "and contacted the family physicians I know to ask them if this sort of donation might help students decide to go into family medicine. They said, 'Yes.' They loved it!"

And so was born the Larry Nichols Family Medicine Scholarship Award. Any Pitt med student who is matched to a family medicine residency is eligible for the annual $20,000 prize. The winner is selected by the attending physicians who supervise the candidates on their family medicine rotations. "They just try to determine who is most likely to make the greatest contribution to the field," Nichols says. The first recipient is Nadine Champsi (MD '10), who is doing her residency at UPMC St. Margaret.

Champsi first learned of the scholarship at this spring's senior class award ceremony. Nichols says she seemed happy enough when he summoned her to the podium to receive an award she'd never heard of. Her happiness turned to sheer joy when she was told the amount of the award. "You should have seen the expression on her face. Absolute glee," Nichols recalls with a laugh.

"The award from Dr. Nichols was a total shock to me," Champsi says. "I was in awe of his generosity and of his commitment to supporting a cause we both believe in—primary health care in this country."

Champsi, who had her first child in April, says the debt relief will give her greater flexibility in her career choices. Her husband, Kevin Carl (MD '09), is a psychiatry resident at Western Psychiatric Institute and Clinic.

Still, Nichols thinks, $20,000 isn't enough.

"The sad part is, that's only about 10 percent of the debt," he says. "My goal is to get more people to join in this with me. It would be so good if we could pay off the whole debt." Nichols adds that though the scholarship bears his name, it doesn't have to. "If others join the cause, we can pool the money and call it the Family Medicine Scholarship. I just want to help as much as possible." ■

J. BURKE/ CIDDE



Nadine Champsi was thrilled when she learned she would receive $20,000 as the winner of the Larry Nichols Family Medicine Scholarship Award. She's shown here with her benefactor, Professor Nichols.

BOOSTER SHOTS

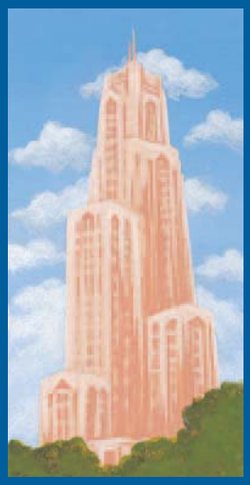
During their typically long stays, young patients in the transplant unit at Children's Hospital of Pittsburgh of UPMC have a new remedy for boredom—24 donated Xboxes. In April, **Make Room for Kids**, a fundraising project undertaken by **Virginia Montanez**, of the Pittsburgh blog *That's Church*, teamed up with the **Mario Lemieux Foundation** and local **Microsoft** workers to fund the venture. Together, they raised more than $15,000.

Microsoft donated many gaming units and videogames, yet patients benefited from more than Xboxes. Montanez's readers made donations used to bring in handheld gaming devices, iPads, and Toughbooks. Nancy Angus, executive director of the Mario Lemieux Foundation, says there are still more accessories coming in. "It was very gratifying to be able to assist in this project," she says.

When **Anette Duensing**, an assistant professor of pathology, presented her research on gastrointestinal stromal tumors at a conference in Boston in 2005, the **GIST Cancer Research Foundation** (GCRF) took notice and began donating to her lab at the University of Pittsburgh Cancer Institute. Recently, the Duensing Lab received another gift, this time $165,000 from GCRF.

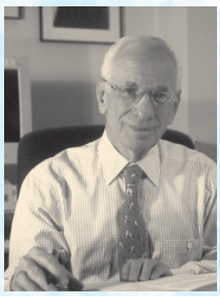
Duensing and her lab colleagues are attempting to develop new therapies and screening approaches to GIST, a fairly rare form of cancer. But, as medical researchers know, it's costly to buy new equipment and conduct experiments. The pathologist says she feels lucky to receive GCRF's donation. "The extra boost of money lets us do things we otherwise wouldn't be able to do," she says. —*Keith Gillogly*

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CLASS NOTES

'50s



Bluestone

In July 2009, **Charles Bluestone** (MD '58), a pediatric otolaryngologist in the University of Pittsburgh School of Medicine, was promoted to Distinguished Professor, considered the highest honor the University can bestow upon an active professor. The appointment is the apex of his prolific and ongoing career, during which he has become world renowned for his research that has influenced the diagnosis and treatment of otitis media (middle ear disease). With Sylvan Stool, he founded the pediatric otolaryngology fellowship at Children's Hospital of Pittsburgh of UPMC—the first otolaryngology subspecialty program to receive accreditation.

'60s

James A. Garrettson (MD '65) is so good at balancing the professional and extracurricular that he had an award named after him. The MD, recreational pilot, and tireless community volunteer is now retired from active staff at Indiana Regional Medical Center, where he worked for 37 years. In his honor, the hospital established the James A. Garrettson MD Physician Excellence Award in December 2006. Among the award's criteria: high quality patient care, vigorous community service, and commitment to professional development of self and others. Garrettson will devote his newfound "leisure" time to his community, making rounds as a driver for Meals On Wheels as well as the Citizens' Ambulance Service. He has been doing both since the '70s.

'90s

John Pacella (MD '98, Res '00) takes his work to heart. He researches coronary collateral blood vessels—for which he received the American Heart Association's Claude R. Joyner MD Research Award this year. And the assistant professor of medicine at Pitt and member of the UPMC Cardiovascular Institute squeezes in his own cardio whenever possible. Last September, Pacella completed the IKEA and UPMC Urgent Care Montour Trail Half Marathon in one hour and 45 minutes. He credits his wearing days as a cardiologist-in-training for his physical fortitude. "Between getting into med school, then training to become a doctor, you learn to do things you never thought you could," he says. Pacella left with more than an MD and a work ethic: He also met his wife, **Charissa Pacella** (MD '98), now chief of emergency services at UPMC Presbyterian and assistant professor of emergency medicine at Pitt.

'00s

Jaya Aysola (MD '00) is in the Department of Health Care Policy at Harvard after completing a Commonwealth Fund/Harvard University fellowship in minority health policy. Her move to Boston comes on the heels of an eye-opening stint as medical health director for the New Orleans Children's Health Project, where she provided pediatric and adult care



Aysola (far right) with Brad Pitt and Angelina Jolie at the Martin Luther King Jr. Charter School in New Orleans in December 2007.

ZANE GATES

COMPASSION IN ACTION

Too much income to qualify for medical assistance but not enough to afford insurance. It's an all-too-common story, says Zane Gates (MD '95). Day in and day out, Gates sees what the newspapers keep reminding us of: For the working poor, the current health care system just isn't working.

Since 1999, Gates has headed Partnering for Health Services, a free clinic in his hometown of Altoona, Pa. "We're taking care of 3,500 people on a million bucks a year," says Gates. "And we're giving them everything the insured have." As of this spring, the clinic's patients can buy a hospital-only insurance plan offering some inpatient care plus a wellness program for less than $100 a month.

Gates' compassionate approach to health care is rooted in his upbringing. His mother, Gloria, would routinely take in and counsel at-risk youth in the Altoona housing projects where they lived. He further honed his vision during his residency, when he took time out to volunteer with Operation Safety Net, a program that has provided on-the-street care for Pittsburgh's homeless since 1992.

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to areas devastated by Hurricane Katrina. Aysola describes what she saw there as more of a health policy issue than a medical crisis. "In the Gulf, the breach of the levees—that was an infrastructure issue," she says, adding that medical care is a similar story. "The resources are there, but the political will isn't. That's why I'm in policy now."



Huang

Despite high survival rates, prostate cancer treatments are known to leave patients with such symptoms as incontinence and erectile dysfunction. But how these symptoms evolve in the long run has been unclear—that is, until a recent study by **George Huang** (MD '00), assistant professor of urology at Pitt. The study followed 1,269 prostate cancer patients throughout four years and was published in *The Journal of Urology* in June. Prostate cancer is unique in that patients often choose treatments—most commonly surgery, radiation, or a combination of both—based on their associated side effects, Huang explains. His hope is that patients can now make more informed decisions. "[The study] gives them a timeline—if they're going to recover, when they're going to recover—instead of [a doctor] just saying, 'It'll get better; it'll get better.'"

The majority of medical schools don't teach students about orthopaedics until the third year, despite the prevalence of orthopaedic diagnoses in our aging population. That's why **Charles Day** (Res '01) recently implemented orthopaedics courses for first- and second-year students at Harvard Medical School, where he is associate professor in orthopaedic surgery and the director of the orthopaedic curriculum. He says his MBA from Pitt's Katz Graduate School of Business ('02) helped him take a business-savvy approach to launching new classes by asking questions like, *How do you bring something into a curriculum that's a new product? How do you bring a new product into the marketplace when the shelf is already full?*

A native New Yorker who earned a BA in philosophy and worked at several law firms before even taking his first premed course, **Jacob Larkin** (MD '04) has strayed a bit from his arts and letters roots. Now he's a maternal-fetal medicine fellow at Pitt and the recipient of a three-year, $300,000 award from the American Association of Obstetricians and Gynecologists Foundation and the Society for Maternal-Fetal Medicine. The award will fund his research into a protein, NDRG1, which he suspects could be involved in regulating the placenta's response to low oxygen, or hypoxia. His wife, **Allyson Larkin** (MD '04), is an allergy/immunology fellow at UPMC and a Pittsburgh native. Larkin says he's glad his family no longer has to seek out "Philosopher Wanted" ads, now that he seems to have found his niche.

Brian Suffoletto (Res '06, Fel '08) is big on personal preference. The assistant professor of emergency medicine recently led an HIV screening program that lets patients decide how they received their results (via mail, voice message, or e-mail), yielding a 98 percent follow-up rate for its first 400 subjects. (Usually, such studies report 70 to 80 percent at best, using other approaches.) His next project, funded by the Emergency Medicine Foundation, will offer college-age patients admitted to the emergency department the opportunity to be screened for risky drinking behavior. Those who screen positive can choose from three follow-up programs (one of which includes a weekly text message questionnaire, complete with personalized feedback and motivational support).

Suffoletto's father was an engineer. "He always imbued in my brother and me a sense of wonder and discovery, and I pursued medicine as a natural extension of that," says Suffoletto. His brother, **Matthew Suffoletto** (MD '01, Res '04, Fel '09), is now a cardiologist in the VA Pittsburgh Healthcare System. Matthew's wife, **Jo-Anne Suffoletto** (Res '07), is also at the VA; she's a women's health primary care specialist.

When the National Survey of Family Growth reported in 2002 that tubal sterilization accounted for 40 percent of contraceptive use among Black women—compared to 24 percent among White women—Pitt's **Sonya Borrero** (Res '04) was intrigued. The assistant professor of general internal medicine investigated the social factors driving this trend, hypothesizing that insurance-coverage issues and provider recommendations might be steering African American women toward the procedure. Borrero and her colleagues were relieved to find this was not the case. Rather, the contributing factors were a generally higher rate of unintended pregnancies in non-sterilized Black women; positive attitudes about sterilization; and less awareness of other highly effective—yet reversible—methods of contraception.

—Keith Gillogly and Ben Korman


Gates (right) and Deshea Townsend after a meeting about Gates' free clinic in Altoona, Pa.

Gates is now working with a bipartisan contingent of Pennsylvania House reps—and "goodwill ambassador" Deshea Townsend, 12-year veteran of the Pittsburgh Steelers—promoting a bill that would set aside $50 million to support other community-based clinics across the Commonwealth. Those efforts are paying off. Senate Bill 5 passed unanimously in March. (It now must pass in the House and is currently in the Health and Human Services Committee.)

Gates is also a novelist. Two of his medical thrillers are already on shelves, and a third is in the works. Proceeds go to the Gloria Gates Memorial Foundation, which he established in his mother's honor. The foundation funds an after-school program for children living in two Altoona low-income housing projects—including Evergreen Manors, which Gates and his mother once called home. *—Ben Korman*


Members of the Class of 2000 get carried away at the reunion gala in May 2010. LEFT TO RIGHT, FIRST ROW: Manuel Hernandez (being lifted by his former classmates), Renee Cassidy, Debi Gilboa, Michael DiCaprio, Abigail Schlesinger, and Greg Jesteadt. SECOND ROW: David Hackney, Chad Viscusi, Lawrence Mathers, John Whiteford, Hugh Pratt, Alda Gonzaga, Ankur Doshi, Shari Hicks-Graham, and Jaya Aysola.

THE WAY WE ARE
CLASS OF '61

Retiring from a long career in medicine can leave some feeling restless for a new "all-consuming monomania," as **Joseph Sapira** (MD '61, Fel '65, Res '66) puts it. For Sapira, the answer was homebrewing. "Never made a bad batch of beer," he says. When he became diabetic, he started making his own wine instead. The process requires meticulous reading and study, which Sapira says he's no stranger to thanks to his medical background. His papers on internal medicine, its subspecialties, psychiatry, and psychosomatic medicine have been published in all the major journals. He served as president of the American Psychosomatic Society in 1991. He has worked as a visiting professor at more than 60 medical schools in the United States, as well as some in Canada and Japan. He spent much of the 1990s teaching at large hospitals in cities throughout Japan, as well as smaller hospitals in Okinawa and other islands. Sapira's *Art and Science of Bedside Diagnosis* (1990) has been called a "masterpiece."


Richard


Askin


Amalong


Mihm

As chief of pediatric nephrology at the University of Florida, **George Richard** (MD '61) established the country's first statewide pediatric kidney program in 1973. It began with centers in Gainesville and Miami; there are now four centers and 15 clinics throughout the state. As head of the program, Richard helped train about 22 pediatric nephrologists.

Faculty member Edward Saitz drove Richard and **Stephen Askin** (MD '61) to class each day. While discussing upcoming exams in the car, Richard recalls, "Steve could cough up the information just by hearing it." After graduation, Askin practiced general surgery in San Francisco and served as chief of surgery at that city's St. Luke's Hospital.

Askin was quite involved in the 1961 Scope & Scalpel production, *A Stitch in Time*, and fondly remembers singing in it. He struggles for a moment to remember some of the lyrics. Then, a flash of recall: *With his hand inside his coat, Napoleon looks like a rube,* he sings. *Clearly he was emptying his ileostomy tube.* Askin retired at age 69. He sings in the Marin Men's Chorus, farms fruits and vegetables on three acres, and golfs in his free time.

Ronald Amalong (MD '61) recalls a favorite prank from his Pitt days: Paging "Dr. Roscope…. Dr. Mike Roscope" over the school's PA.

Amalong specialized in ophthalmology and began working abroad when he answered a medical-newspaper ad for a job in Ecuador. He went on to cofound and direct Vision Health International in 1984. The organization of volunteer medical experts still takes two trips a year, providing cataract-removal procedures and eyeglasses to patients in Costa Rica, Nicaragua, and Poland, among other countries.

Recently, **Martin Mihm** (MD '61) has also made contributions to global health. He established a free clinic for children with vascular anomalies in Ho Chi Minh City, Vietnam. By the clinic's first anniversary this past January, more than 2,500 children had been treated. He also helped found clinics in Greece and Spain.

In 1966, while teaching at Harvard Medical School, Mihm cofounded the world's first multidisciplinary melanoma clinic. He later became chief of dermatopathology at Harvard in 1976. This year, he assumed directorship of the melanoma program at Brigham and Women's Hospital and also helps direct the program at the Dana-Farber Cancer Institute.

At 76, Mihm continues to study at Harvard the prognosis of malignant melanoma.

And what of retirement? "If God gives me the ability," he says, "I will work until I die. I find medicine still very stimulating." *—Keith Gillogly*

WILLIAM B. MILLER

NOV. 9, 1922 –APRIL 2, 2010


Miller

After receiving his bachelor's degree from Pitt, William Miller (MD '48) applied to the University of Pittsburgh School of Medicine and was accepted, but with a one-year deferment. (Pitt only accepted one African American a year in those days.) He was then drafted. As the family story goes, while he was aboard a ship en route to Germany, Miller's captain reviewed his file, saw his admission status, and arranged an honorable discharge. "You're not going to war," he said. "You're going to medical school."

Miller, who was the School of Medicine's oldest living African American alumnus, died in April. He was 87.

Miller loved the city and his alma mater. (His three sons are Pitt medical and dental school alumni.) During his third year in medical school, William Miller was awarded the James D. Heard prize, which is awarded to the student with the highest performance in internal medicine. Following his internship in St. Louis, Mo., he returned to Pittsburgh, completed his residency at the VA, and served the Hill District as a general practitioner for 55 years.

From 1968 until he was well into his 80s, Miller was a physician and later medical director for Tadiso, a drug rehabilitation center on the North Side. He was known for his gentle, caring nature. Among his many honors was the 2006 Nyswander/Dole Award, presented by the American Association for the Treatment of Opioid Dependence.

—KG

IN MEMORIAM

'40s

WILLIAM MACLACHLAN
MD '48
APRIL 30, 2010

WILLIAM PARSONS
MD '48
JUNE 16, 2010

'50s

ARTHUR KELLEY
MD '50
JUNE 1, 2010

LOUIS "SKIP" CHERRY
MD '53
MAY 7, 2010

CHARLES WELLS
MD '59
APRIL 15, 2010

'60s

BILL SHAW
MD '62
JUNE 2, 2010

MORTON GOLDSTEIN
MD '63
MAY 16, 2010

'70s

DONALD KILPELA
MD '74, RES '77
JUNE 23, 2010

WE KNEW YOU WHEN

GERALD LEVEY

BY BEN KORMAN



SHELLY STRAZIS

Levey just stepped down as dean and vice chancellor of medical sciences at UCLA.

Gerald Levey remembers the days of house calls fondly. Years before he served as chair of medicine at the University of Pittsburgh, Levey was a patient of a doctor named Rosenstein, who made regular visits to Levey's family home in Jersey City, N.J. Rosenstein treated viruses and stitched up broken noses at the kitchen table.

"I never forgot the kind of doctor he was," recalls Levey, "and, going forward, I tried to conduct myself as he would."

When Levey left his post as Howard Hughes Medical Institute investigator at the University of Miami in 1979 for Pitt, he brought his longtime family doctor's congenial approach, even as he spearheaded an organizational and financial overhaul.

He also brought a sense of obligation, he says, to rebuild the department to what the famed former Pitt chair Jack Myers would have demanded. "Jack was one of the great figures in American medicine in the 20th century. We quickly became friends since his office was a short walk down the hall from mine on the ninth floor of Scaife Hall, and I had much to learn." Levey started by implementing a long-overdue physician practice plan. He then brought in a new cadre of distinguished faculty. Within the first three years, the department, which had been struggling financially, was back in the black. By 1991, when Levey left for a position as Merck & Co.'s senior vice president for medical and scientific affairs, he had reduced the department's reliance on University funds and built a research powerhouse.

As chair, he would visit every division in the department—academic house calls, if you will—to answer questions and update faculty. He cut back on work-related travel so he could focus on internal issues; that was much appreciated by his wife, Barbara Levey, an MD and former associate dean and director of admissions at Pitt med who is now assistant vice chancellor of biomedical affairs at UCLA.

Levey says a memento from his time at Pitt still hangs on his wall: "Jack [Myers] walked into my office one day and gave me this picture on which he had written, 'To Jerry in great respect, Jack Myers.' That is one of the most special gifts he could have ever given to me. I felt that I had achieved one of the major goals I had set out to accomplish."

Levey eventually became dean of the David Geffen School of Medicine and vice chancellor of medical sciences at UCLA, where he built on his Pitt legacy of leadership, overseeing the construction of the Ronald Reagan UCLA Medical Center and five research buildings, as well as a program that encouraged new physicians to become comfortable with laboratory research.

Earlier this year, Levey's career entered new and unfamiliar territory: freedom. Stepping down as dean and vice chancellor of medical sciences at UCLA in January (remaining on the full-time faculty), Levey moved on from the practice of leadership to its theory, planning a book and developing a new course on the topic. He's quick to cite Pitt's former senior vice chancellor for health sciences, Thomas Detre, as a case study.

"Figuring how much I've learned since I left Pitt—most of it was inspired by Detre," says Levey. "I learned from those around me."

On the subject of his semiretirement, he quotes an old UCLA colleague: "I deserve just to be able to do what I want, when I want to do it." ■

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of our personal Monongahela River
see a great city
and seek ourselves, in vain

the streets we walked
our Ruskin Avenue, the number
67 bus, the cafeterias
all empty of us

and our friends
in love with every one of them
the city our playground
our workspace, a stage

oh we were eager
crowding the gray hallways
our faces pressed to the glass
so eager, blind as bats

now we live in other cities
different cities, some very far away
but none too far to hear our singing
we are still singing

—Chuck Joy (MD '78)

PHOTOGRAPH, c. 1923-1937: COURTESY AERIAL PHOTOGRAPHS OF PITTSBURGH COLLECTION, ARCHIVES SERVICE CENTER, UNIVERSITY OF PITTSBURGH

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HIPPOCRATEAN

These aspiring physicians of the School of Medicine's Class of 1955 had no idea how much future Pitt med students would pay for a hamburger, not to mention textbooks and tuition. Now the class has banded together to raise money for a scholarship to offset the financial burden of today's med school graduates. Along with annual gifts to this fund, some classmates have made provisions in their wills. Others have arranged charitable gift annuities that will ultimately benefit this same fund, but, in the meantime, provide donors with income streams. (One of these now 80-year-old alumni qualifies to receive a rate of 7.2 percent on his annuity!)

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

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