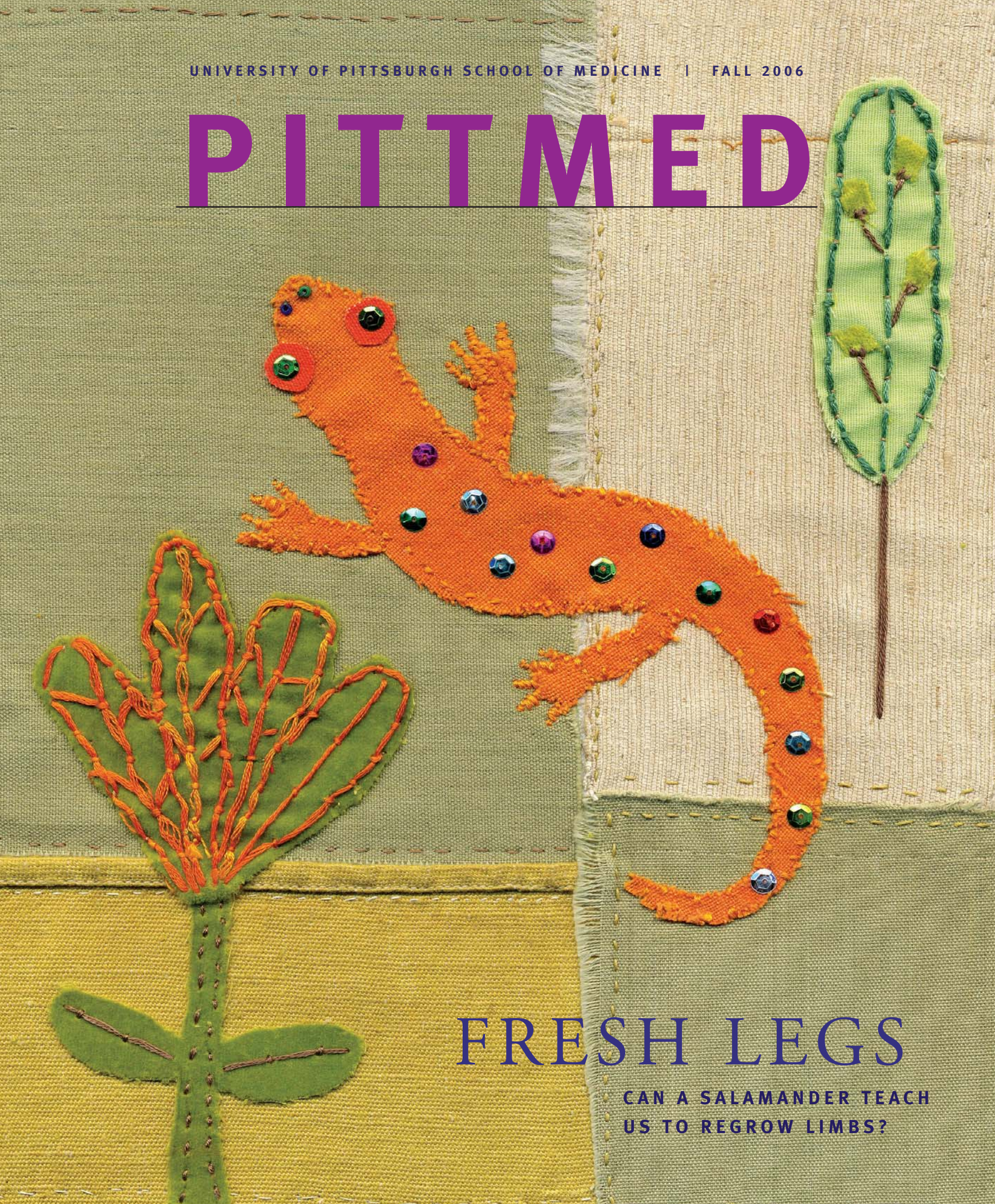
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | FALL 2006

PITTMED



FRESH LEGS

CAN A SALAMANDER TEACH US TO REGROW LIMBS?

ONLY STARZL DARED TO

Pitt Med began showing up at my house when my husband became a med student at the University of Pittsburgh two years ago. I picked it up once out of curiosity and didn't put it down again until I'd read the whole thing from cover to cover. The quality is excellent, and I can't imagine that another medical school in the country has a finer publication. However, this May's "Only Starzl Dared To" has set a new standard. Kudos to Chuck Staresinic for one of the best articles I've ever read about hope and perseverance. I'll be anxiously awaiting the August issue and part two of the article.



Christy Rippel
Pittsburgh

One error marred what was otherwise a terrific article on Thomas Starzl. Not all of the residents and interns in the Department of Medicine signed a resolution "denouncing liver transplantation as unrealistic and potentially unethical." I know this because I did not.

As senior medical resident in the old Presbyterian University Hospital ICU when those first postop liver transplant patients came through the door, I had the privilege of experiencing firsthand Dr. Starzl's intense focus on the welfare of his patients. At the time, I distinctly remember thinking that if every one of my peers could see this doctor's devotion and dedication to his craft, no such petition would have existed.

Richard Hahn (MD '78, Fel '81)
Washington, Pa.

A brief note to express my thanks for your article "Only Starzl Dared To" in the May 2006 issue.

As a liver recipient (July 28, 2002) at Tampa General Hospital, I have much to be thankful for. Now to read about Dr. Thomas Starzl and his history as written by Chuck Staresinic was very informative.

As a member of Florida Governor Jeb Bush's Task Force on organ donation, I am forwarding this material and the Pitt web page highlighting "Transplanting Mozart" to my colleagues for their reading and enjoyment.

I look forward to reading the continuing article in the August issue.

Richard E. Swett
Punta Gorda, Fla.

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

Pitt Med
400 Craig Hall
University of Pittsburgh
Pittsburgh, PA 15260
Phone: 412-624-4152
Fax: 412-624-1021
E-mail: medmag@pitt.edu
http://pittmed.health.pitt.edu

For address corrections:

***Pitt Med* Address Correction**
M-200k Scaife Hall
University of Pittsburgh
Pittsburgh, PA 15261
E-mail: medalum@medschool.pitt.edu

RECENT MAGAZINE HONORS

AAMC Robert G. Fenley Writing Awards of Distinction (2 awards)

IABC Best of Show

IABC Golden Triangle Award of Excellence
Magazine Design

CASE District II Accolades
Silver, Visual Design in Print, Covers

CASE District II Accolades
Bronze, Best Article

CASE Circle of Excellence
Bronze, Special Interest Magazines

CASE Circle of Excellence
Bronze, Periodical Staff Writing

SCIENCE2006
FEEL THE POWER
University of Pittsburgh

THE UNIVERSITY OF PITTSBURGH'S SIXTH ANNUAL CELEBRATION OF SCIENCE AND TECHNOLOGY

DICKSON PRIZE IN MEDICINE LECTURE
Roger D. Kornberg, Ph.D.
Stanford University

MELLON LECTURE
Carla J. Shatz, Ph.D.
Harvard University

KLAUS HOFMANN LECTURE
Baldomero M. Olivera, Ph.D.
University of Utah

PROVOST LECTURE
Nathan S. Lewis, Ph.D.
California Institute of Technology

Plus...
Symposium sessions, exhibits, networking opportunities, a career development workshop, poster sessions, and special events

THURSDAY, 5 OCTOBER
FRIDAY, 6 OCTOBER

Alumni Hall
(former Masonic Temple, Fifth Ave. and Lytton Ave., Oakland)

Free and open to the public

For information and registration:
WWW.SCIENCE2006.PITT.EDU

PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, FALL 2006 (AUG/SEPT/OCT)

VOL. 8, ISSUE 3



DEPARTMENTS

OF NOTE 3
Why are some generations more violent than others?
Can aspirin kill cancer?

CLOSER 7
Skulldiggery.

INVESTIGATIONS 8
Omega-3s and the other white meat.
A student probes how environmental and genetic factors relate in Parkinson's.
In the future, we may cure "senior moments."

ATTENDING 32
The graduating class president on losing and finding yourself in med school.
Katrina Firlik on memorable stains.



MATCH RESULTS 35
And they're off ...

ALUMNI NEWS 36
Toxic avenger.
Doctoring in rural America.

LAST CALL 40
The Starzl trainee migration.



CONTRIBUTORS

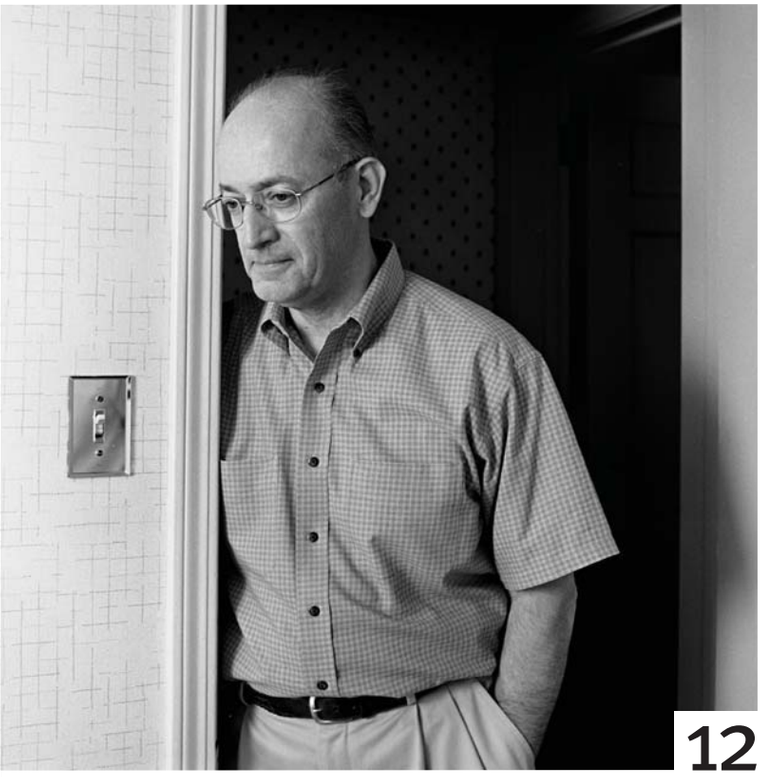
When CATHERINE LAZURE [Cover, "Make Like a Salamander"] finishes a piece, out comes the tape. Sticky side down, she dabs at cloth and stitching, hoping to rid the creation of feline detritus. Having three cats can complicate matters for an illustrator who works with fabric.

To find the right velour or paisley for her appliqué technique, Lazure frequents thrift stores and cannibalizes her wardrobe. Her artistic influences include Joan Miró and Paul Klee. *The New Yorker* and *The New York Times* are among Lazure's clients. Lazure also is the illustrator and coauthor of *Agathe, la Diva de Zambalou* (2000, Les 3 Orangers), a children's book about a singing giraffe. The Montreal native lives and works in West Harlem.

Simultaneously riveting and tranquil, the photographs of CHARLEE BRODSKY ["Next of Kin"] are inherently sympathetic. Brodsky, a professor of photography in the design department of Carnegie Mellon University, concentrates her work largely on social and community issues. Although she does not take assignments often, Brodsky made a second exception for *Pitt Med* (the first came in our August 2004 issue with "Ghost Body"). She considers herself a documentarist and says that she tries to enter her subjects' lives as gently as possible in an effort to understand their stories. Currently, Brodsky is pursuing a project that focuses on the distress involved with mental illness.

COVER

Salamanders and newts do it, so why not us? With funding from the Department of Defense, a multidisciplinary team will attempt to grow back mammalian digits. (Cover: Catherine Lazure © 2006)



12

FEATURES

Next of Kin 12
In the world of organ donation, tens of thousands of second chances begin with a tragic loss. Families of deceased organ donors let us into their lives.
PHOTO-ESSAY | PHOTOGRAPHY BY CHARLEE BRODSKY
TEXT BY ELAINE VITONE

Break on Through 18
Our Thomas Starzl story continues with talk of tolerance and snail fur. Starzl Institute leaders ponder these topics in their attempts to do away with the need for immunosuppressive drugs.
BY CHUCK STARESINIC

Make Like a Salamander 23
Can a salamander teach us how to grow back limbs?
COVER STORY BY JOE MIKSCH

Difficult Gifts 28
What a rare and harrowing disease can reveal.
BY ERICA LLOYD

PITTMED

PUBLISHER
Arthur S. Levine, MD

EDITOR IN CHIEF
Erica Lloyd

ART DIRECTOR
Elena Gialamas Cerri

SENIOR EDITOR
Chuck Staresinic

ASSOCIATE EDITOR
Joe Miksch

PRODUCTION COORDINATOR
Chuck Dinsmore

STAFF CONTRIBUTORS
Alicia Kopar, Jaclyn Madden

OBITUARIES CONTRIBUTOR
Macy Levine, MD '43

CIRCULATION MANAGER
Crystal Kubic

CHIEF EDITORIAL ADVISOR
Kenneth S. McCarty Jr., MD, PhD

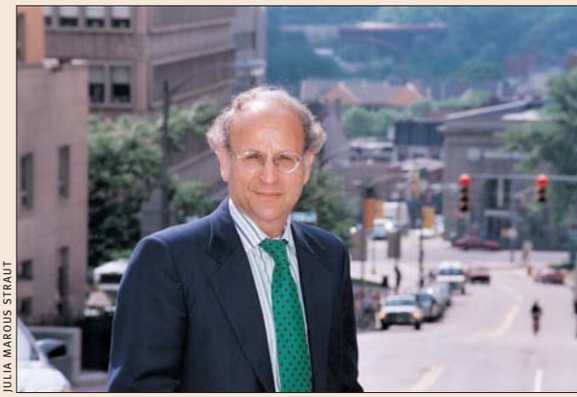
EDITORIAL ADVISORS
Edward Barksdale Jr., MD
Steve N. Caritis, MD, Res '73
Paula Davis, MA
Susan Dunmire, MD '85, Res '88
Jonathon Erlen, PhD
Joan Harvey, MD
John Horn, PhD
Steven Kanter, MD
Joan Lakoski, PhD
David Lewis, MD
Margaret C. McDonald, PhD
Ross Musgrave, MD '43
David Perlmutter, MD
Gabriel Silverman, Class of '09
Peter Strick, PhD
Gerard Vockley, MD, PhD
Simon Watkins, PhD
Marshall Webster, MD, Res '70
Julius Youngner, PhD

OFFICE OF PUBLIC AFFAIRS
Robert Hill
John D. Harvith, JD

University of Pittsburgh

Pitt Med is published by the Office of the Dean and Senior Vice Chancellor for the Health Sciences in cooperation with the alumni and public affairs offices. It is produced quarterly for alumni, students, staff, faculty, and friends of the School of Medicine. PR 5645

The University of Pittsburgh is an affirmative action, equal opportunity institution. © 2006, University of Pittsburgh



JULIA MAROUS STRAUT

Some people, says Bloom, can see the mote in others' eyes but they can't see the beam in their own.

—James Joyce, *Ulysses*

In the "Cyclops" chapter, modeled after Homer's tale, Joyce's Bloom narrowly escapes from "the citizen," a blowhard nationalist he meets in a tavern. Although Bloom's nemesis has both eyes, he can't see more than one viewpoint. Here's another cyclops story—in this one, the characters can recognize complexity and keep their eyes wide open.

I was pleased to host recently Dr. Philip Beachy as one of our Laureate Lecture series speakers. Dr. Beachy is a professor of molecular biology at Johns Hopkins University, a Howard Hughes investigator, and a member of the National Academy of Sciences. He is known for revealing how the secreted proteins of the Hedgehog gene family mediate the proliferation and differentiation of embryonic cells. The peculiar Hedgehog name comes from Christiane Nüsslein-Volhard and Eric Wieschaus, who won the Nobel Prize for their classic mutant screens. In 1977, they identified a mutation in the fruit fly affecting its outer body layer. These scientists observed that the mutant fly embryo, with small spiky projections instead of orderly segments, resembles a hedgehog. Beachy cloned the fly's Hedgehog gene; he and others then went on to show that the gene is highly conserved in evolution and that the best-studied one, Sonic hedgehog (named for the video game character), regulates the organization of the midline structures of the brain in vertebrates. Mice with a disrupted Sonic gene are cyclopic. Mutations in the human version of the gene cause holoprosencephaly, a defect in which the embryonic forebrain doesn't divide into hemispheres and which can result in cyclopia. Dr. Beachy found that too much Hedgehog activity is equally bad: It's responsible for some cases of basal cell carcinoma (the most common human cancer) and the childhood brain tumor, medulloblastoma—both driven by excessive proliferation of precursor stem cells.

The plot thickens: In the 1960s, it was noted that sheep who graze on corn lily give birth to cyclopic lambs; the plant contains cyclopamine, a teratogen. Dr. Beachy found that this molecule blocks the Hedgehog signal and inhibits the growth of medulloblastoma as well as human prostate cancer cells transplanted in mice. (In fact, the level of Hedgehog gene activity may be helpful for prostate cancer prognosis: Metastatic prostate cancer cells have increased expression of the Hedgehog gene, and nonmetastatic cells do not.)

Several companies are now developing cyclopamine-like drugs as potential cancer therapies, and others are developing drugs that might augment Hedgehog expression. Given that Down syndrome patients have too few brain cells, it could be that treating a Down fetus in utero with such a drug might reverse some of the defects found in this syndrome. Such a drug might even help with myocardial ischemia. In any case, the moral of this story: Starting with an observation 30 years ago by the keenest of basic science eyes, a fruit-fly mutation now promises to illuminate the most fundamental mechanisms critical both to normal human development and to cancer, leading to possible remedies as well. What more could one ask of basic science, and what better definition of "translational research"?

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



Devoted to noteworthy happenings at the medical school ... To stay abreast of school news day by day, see www.health.pitt.edu.

Biosensible

One's got the imaging equipment and know-how. The other has some of the most advanced fluorescent dyes available.

Together, the University of Pittsburgh and Carnegie Mellon University will be able to delve more deeply into how cells work and make the body function.

With a $13.3 million grant from the National Institutes of Health, Pitt and CMU are creating a National Technology Center for Networks and Pathways that's housed at CMU's Mellon Institute. In the words of Simon Watkins, director of Pitt's Center for Biologic Imaging, the technology center will "help develop and build new ways of studying the molecular pathways that exist inside a cell."

The grant will allow Alan Waggoner—director of CMU's Molecular Biosensor and Imaging Center, who is known in scientific circles as the king of fluorescent dyes—and Watkins—widely acknowledged as a guru of biologic imaging—to combine their complementary skills to probe and observe cells in novel ways.

Already, Watkins says, they have plans to obtain the first hand-held confocal probe, a device with an imaging tip the size of a pencil eraser. "It allows us to probe things you can't get an ordinary microscope into." —*Joe Miksch*



COURTESY S. WATKINS

Pitt and CMU partner to probe cells in new ways.

FOOTNOTE

As Pitt students explore the Wyoming "Dinosaur Graveyard," which rancher Allen Cook deeded to the University this year, they needn't look for a T-Rex old folks home.

Adolescents experience bouts of angst. *A zit!?!?! On prom night!?!* But usually they mature into well-adjusted adults. More than *Sturm und Drang* was in store for dinosaurs at puberty, though. In many cases, researchers say, sexual maturity led to the end of life. Child-rearing stresses for females and fights between males over mates meant few saw the far side of 16.

KILLING CANCER WITH ASPIRIN

Yong Lee believes he has found a novel and cheap way to curtail aggressive recurring cancer: aspirin.

Lee is a PhD professor of surgery and pharmacology at the University of Pittsburgh. He's found that cancer cells in culture resistant to a new treatment called TRAIL respond to the treatment after being dosed with aspirin for at least 12 hours. TRAIL is designed to induce programmed cell death. Aspirin, Lee says, blocks signaling pathways that cancer cells need to survive and allows TRAIL to do its job on cells that would otherwise have developed resistance to it from a first round of therapy.

Lee says his lab will soon experiment with animal models and is working on developing aspirin/TRAIL human protocols. He can't predict when the therapy might become available in the clinic but notes that TRAIL is in clinical trials and aspirin already has FDA approval, which could expedite the process. *—JM*



CAMI MESA

A&Q

with Anthony Fabio on Violent Generations

One line from Hannah Arendt's *On Revolution* sticks with Anthony Fabio (shown above), a University of Pittsburgh assistant professor of neurological surgery. His recollection of it is written on a dry-erase board in his office in Pitt's Center for Injury Research and Control: "The hope of man in his singularity is in the fact that not man but men inhabit the Earth and form the world between them." As an epidemiologist, Fabio wonders about society's influence on young people, particularly in relation to shifts in rates of violence. Following his curiosity, he teamed up with Distinguished Professor of Psychiatry Rolf Loeber, principal investigator for a longitudinal study of inner-city boys known as the Pittsburgh Youth Study, to look at the issue from a generational perspective.

What they asked and found:

We focused on two generations. ... The oldest generation, even at the same age, reports more violence than the younger generation. And so then our question was: Why? [Our] results suggest to us that the difference in reported violence isn't due to the generations being different, i.e., they are not worse kids, but that some macrolevel effects—period effects, such as the economy or changes in cultural norms—are the reason behind the differences in the generations. So if we could magically switch the generations between the time they grew up we would see the [younger] generation now report more violence because they are now the ones exposed to this period effect.

How this approach stands out:

In the early '90s we saw a decrease in violence. [*Freakonomics* authors Steven Levitt and Stephen Dubner] estimated that up to 50 percent of the decrease had to do with the legalization of abortion. [They reasoned that] there were fewer unwanted children. My results really don't support that at all.

Many [other studies about the causes of violence are looking at] things like the unemployment rate, and the census data, and the rate of violence in a specific area. It's important to move beyond that. ... If we can find out what this period effect is, we could [try to] find the right data ... to predict future epidemics of violence.

His questions for us:

Is there anything you can do as an individual to affect societal forces? Is there anything you can do as an individual in response to societal forces? *—Interview by Elaine Vitone*

Faculty Snapshots

Merrill Egorin has won the American Association for Cancer Research's (AACR) Joseph H. Burchenal Clinical Research Award. The award recognizes Egorin's contributions to making chemotherapy safe and effective.

Egorin, professor of medicine and pharmacology in the University of Pittsburgh School of Medicine, began his life as a cancer researcher in 1968; he has been at Pitt since 1998. The MD has developed rules for using chemotherapy drugs based on their pharmacologic features, toxicity profiles, and effects on body function.

His efforts, the AACR says, enabled doctors to administer drugs whose toxicity allows for little error in terms of dosing.



Egorin

Pitt's Bernard Fisher was honored at the same meeting this year with the AACR's Award for Lifetime Achievement in Cancer Research. Fisher, who earned his MD from Pitt in 1943, did early groundbreaking work in breast cancer metastasis, led clinical trials that found lumpectomy to be just as effective as total mastectomy, and established the effectiveness of the synthetic estrogen tamoxifen in treating breast cancer and as a preventative measure against the disease. The Distinguished Service Professor of Surgery received the Burchenal award in 1998.



Fisher

For 60 years, the American Cancer Society (ACS) has supported research at Pitt. Robert Sobol is the latest Pitt researcher to be awarded an ACS grant.



Sobol

Sobol, a PhD assistant professor of pharmacology, recently received $720,000 from the ACS to pursue research into temozolomide (TMZ), a novel chemotherapeutic agent being used to treat glioblastoma, considered an essentially incurable form of brain cancer. Sobol seeks to understand the molecular basis for resistance to TMZ in some brain cancers. The grant runs until July 2009.

Pitt has 10 other active ACS grants totaling about $6 million. Christopher Widnell, ACS scientific program director for extramural grants (and a professor emeritus in the medical school), says that figure puts Pitt at number six nationally in terms of ACS funding.

Sobol sees an ACS grant as an important step for a junior investigator: "I'm extremely pleased with the help of the ACS in getting my research lab on solid footing." Pitt and ACS will celebrate their long-standing relationship in a September award ceremony. *—JM*

Young Scientist, Get a Life



JULIETTE BORDA

It's a life that has been in sync with the academic calendar since kindergarten. Imagine you're a scientist who has finally worked your way into a junior faculty position. With the right combination of luck, work (lots of work), and ingenuity, you'll get tenure, your own lab, and make a significant contribution to your field.

But, silly you, you also got married, have two young children, like to go out to a movie once in a while, and have a hankering to, on occasion, read something that's not a scientific journal. Well ...

Well, reportedly, it can be done. Melissa McNeil, who has an MD and MPH, is chief of women's health and associate chief of general medicine at the University of Pittsburgh. She was among those giving advice during a panel discussion titled "Striving for Sanity" that was part of a three-day course in scientific management and leadership for young investigators. To the budding scientist looking to make a mark and have a life, McNeil offered these and other tips:

• Schedule fun time and stick to it. You schedule your workday and never shirk obligations. Do the same with your free time.

• Learn to say "no." If at all possible, find a mentor who will help you decide what's worth going the extra mile for and what you should pass up.

With support from the Burroughs Wellcome Fund and Howard Hughes Medical Institute Partners in Scientific Training Program, the Office of Academic Career Development offered the sessions designed to help attendees on the path through academia. The program touched on such topics as how to navigate the politics of the academy and apply for grants. *—JM*

PITT/UPMC TO RUN SICILIAN SCIENCE CENTER

Last year, an 11-year-old Sicilian boy affected by severe respiratory failure was the recipient of the first pediatric double-lung transplant in southern Italy. The Mediterranean Institute for Transplantation and Specialized Therapies (ISMETT), which UPMC cofounded seven years ago, has been home to other medical firsts in the region. In light of ISMETT's successes, the University of Pittsburgh and UPMC have been asked by the Italian president, the president of the region of Sicily, and Italy's National Research Council to run a major new research center in Sicily. The $400 million Biomedical Research and Biotechnology Center (BRBC) will house programs that build on Pittsburgh's strengths in computational and structural biology, vaccine development, drug discovery, molecular imaging, tissue engineering/regenerative medicine, and neuroscience. Italy will construct the 400,000-square-foot center in the province of Palermo. The facility will open its doors perhaps by 2010, though collaborations may begin as soon as this year.

Organizers say no other center in Italy has the critical mass of scientists and research projects proposed for BRBC. They envision the center strengthening Italy's scientific position in relation to other industrialized nations and spurring biotechnology research and commercial activity in Italy and Pittsburgh. *—Erica Lloyd*

For more information on potential BRBC collaborations:
Arthur S. Levine at levine@hs.pitt.edu

Medical Journalism 101

At 2:30 one afternoon, the Falk Library of the Health Sciences' computer lab has become a newsroom. Six University of Pittsburgh med students type urgently. Deadline is in half an hour, and they need 500 words on a British study of how breast asymmetry may be a risk factor for breast cancer.

Each of those 500 words has to be comprehensible to a layperson. The first rule of the School of Medicine's minicourse Medical Journalism 101: Know your audience. The professor, KDKA's medical correspondent Maria Simbra (MD '93), reminds her students to imagine they are writing to a "really smart 5th-grade science student." They're getting used to it.

Homework for the third meeting of this four-session, ungraded course asked them to explain an organ, medical device, or drug. Gaurav Shukla, a second year MD/PhD student, wrote about the chemical processes smokers undergo. Using analogies, Simbra says, helps readers comprehend scientific concepts. So Shukla compared the adrenaline rush smokers get to the feeling of "being late for a big meeting."

MD/PhD student Aaron Secrest, who studies epidemiology, says that he entered the course because of the inadequacies he sees in medical journalism. "A lot of it oversteps its bounds or is just wrong," he says. But the course is giving him a new view of the field: "Journalism, in general, is very difficult."

As students devise a KDKA broadcast plan for the breast cancer study, Simbra advises Secrest that they probably can't use a graphic displaying how to measure cup size.

"I don't know what you can and can't do with TV," he says. "If it was Fox, you could probably do more." *—Sydney Bergman*



JIM JUDKIS

FLU!

The morgue piled high with bodies. Pressure mounted as infected patients inundated the hospital. Disoriented and alarmed, med students shouted, "Where is the ICU?" They wore facemasks and protective jackets designating their roles on a team. When team members fell ill, remaining students, already hampered by limited resources, did double duty, filling vacant positions on other teams. The intensity was only somewhat mitigated by the fact that the bodies were cardboard cutouts and the scene at Scaife was just a drill for responding to an avian flu pandemic, part of a day-long pandemic training program in May.

—Alicia Kopar

Name-Dropping

The School of Medicine was in very good company this spring.

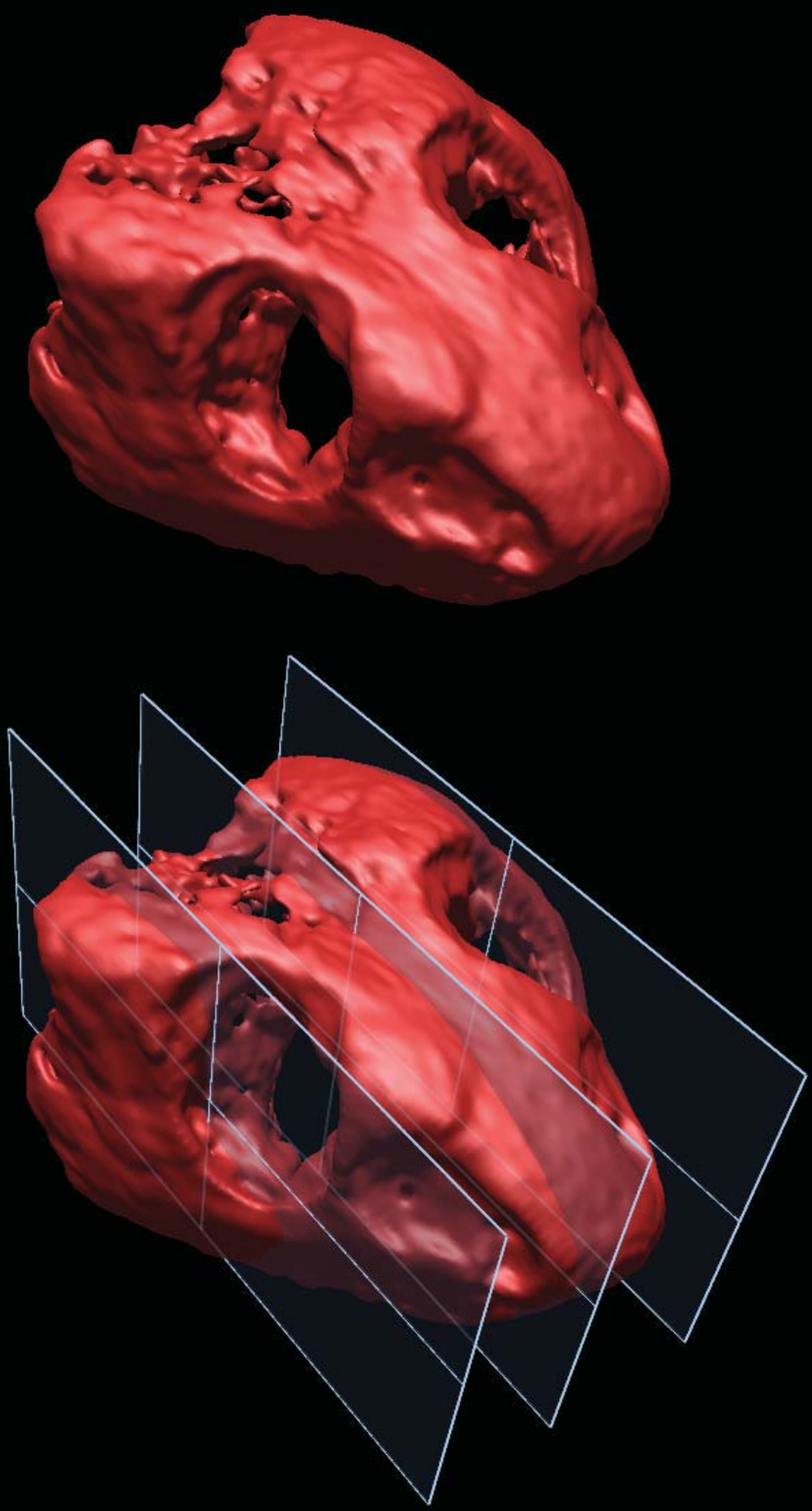
Ferid Murad, cowinner of the 1998 Nobel Prize in Physiology or Medicine for discovering that nitric oxide can signal blood vessels to relax and widen, thus lowering blood pressure, visited in April as a lecturer in the Senior Vice Chancellor's Laureate Lecture series. The Distinguished Chair of Physiology and Medicine and director of the Institute of Molecular Medicine at the University of Texas, Houston, spoke about a nitric oxide–related signaling pathway and drug development.

In May, Philip Beachy, professor of molecular biology and genetics and a Howard Hughes Medical Institute investigator at Johns Hopkins University, also visited as a Laureate Lecturer. Beachy is a member of the National Academy of Sciences and a fellow of the American Academy of Arts and Sciences. He discussed how cell differentiation and the growth and development of malignant cells are influenced by what's known as the Hedgehog signaling molecule, a protein secreted during embryonic development. (See the Dean's Message on p. 2 to learn how sheep and cyclopes fit into the Hedgehog story.)

After having a chance to learn more about the med school, Beachy notes, "The growth there is very impressive, as is the magnitude of resources that are available. It seems pretty clear that Pitt is headed for great things."

Risa Lavizzo-Mourey suggested to the Class of 2006 that truly great things can come their way. The class had invited her to help mark their graduation as the commencement speaker. Lavizzo-Mourey is president and CEO of the Robert Wood Johnson Foundation, a private foundation dedicated to improving Americans' health.

She told the graduates, "Each of you will have the chance to enrich the human condition and enhance the quality of life of people you will come to know and love—and people you perhaps will never meet at all." *—JM*



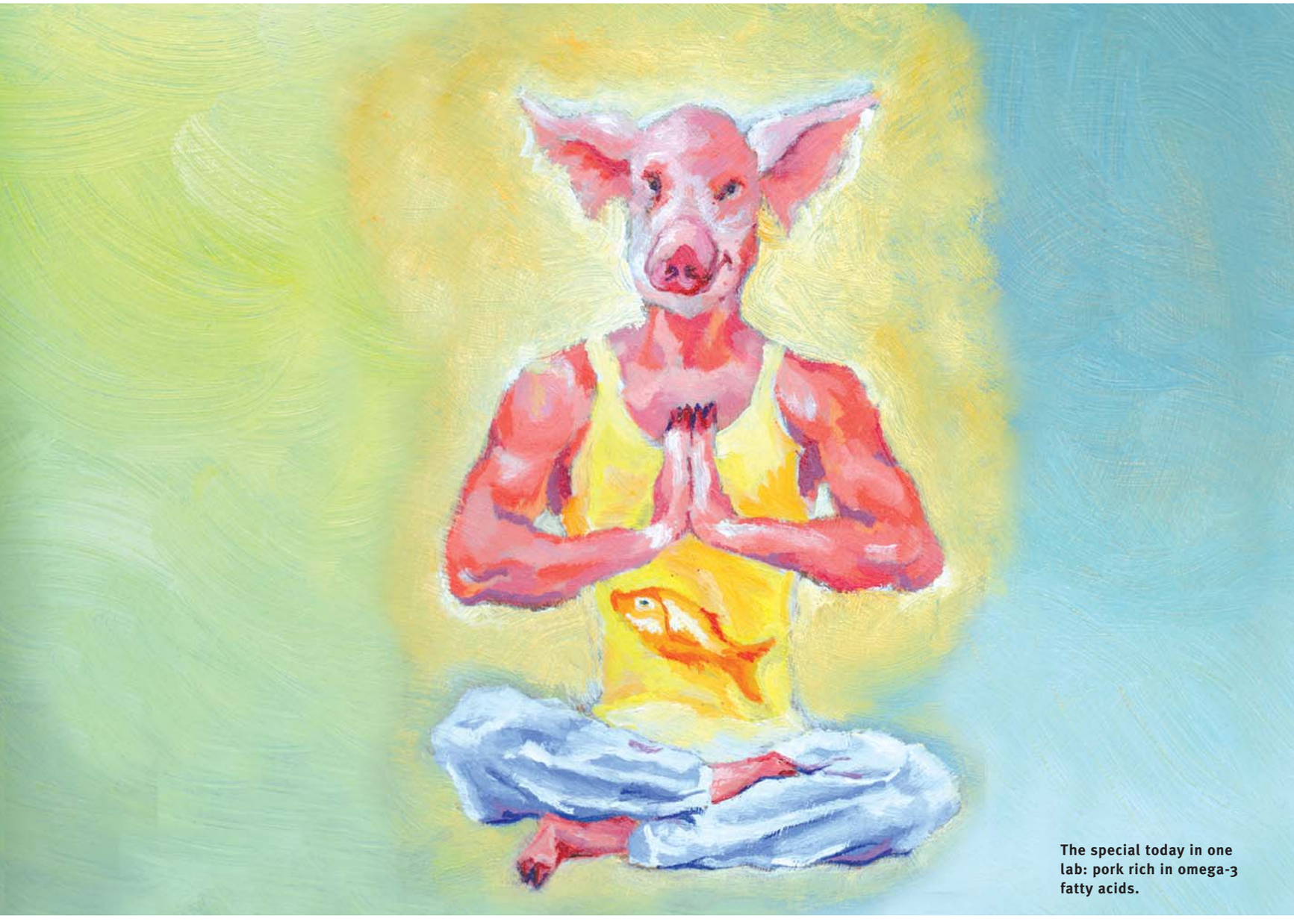
SKULLDIGGERY

In 2004, Adam Striegel, a University of Pittsburgh undergraduate on a geology class field trip near the Pittsburgh International Airport, picked up a softball-sized rock that appeared to be a fossilized skull. He thought it should be examined further.

Eventually, the fossil ended up in the hands of Carnegie Museum of Natural History paleontologist David Berman. He identified it as the skull of a 300-million-year-old trematopid amphibian, evolutionary kin of the frog and thought to represent a new genus and species. Researchers know of only two other such fossils. So, how to divine the details of this find without risking damage to the fossil by chipping away stone? Skull in hand, Berman recently approached Douglas Robertson, associate professor of radiology and director of the Musculoskeletal Imaging and Biomechanics Laboratory at Pitt. Robertson took 1-millimeter-thin readings of the rock-encased skull with a 64-slice CT scanner—"The latest and greatest in clinical scanners," Robertson says. It differentiated the density of the rock surrounding the fossil and the fossil itself. Robertson, an MD/PhD, took data from the scan and created a 3D image that can be flipped, spun, and turned any which way, so that paleontologists can closely study the prehistoric amphibian while keeping the actual fossil protected.

Priceless study subjects may be routine to Robertson by now. He has used CT scanners to create a model of a 5,300-year-old funerary mask. He has served up x rays of dinosaurs. More typically, he employs imaging technology to design longer lasting and better functioning replacement joints for patients. ***—Joe Miksch***

IMAGING
DOUGLAS ROBERTSON



The special today in one lab: pork rich in omega-3 fatty acids.

SOME PIG!

THE ALPHA AND OMEGA OF OMEGA-3 FATTY ACIDS

BY JOE MIKSCH

Dragging a makeshift anchor in its wake, the brakeless monorail hurtles through Springfield at speeds of up to 180 mph. The conductor, one Homer J. Simpson—cartoon icon, Duff Beer connoisseur—awaits death.

Suddenly, the anchor hits a snag—the Lard Lad donut shop sign. Latching onto an enormous representation of a donut, the monorail comes to a halt. Homer, his passengers, and the rest of the town are safe.

Reflecting, Homer utters these immortal words: "Ah, donuts. Is there anything they can't do?"

Replace "donuts" with "omega-3 fatty acids," and you may be onto something. Work at the University of Pittsburgh shows that in addition to omega-3s' recognized benefit to cardiovascular health, these vital fatty acids appear to improve mood and kill liver cancer cells. Another Pitt project could help get the critical fatty acids on the traditional American breakfast table.

Tong Wu's lab has found that omega-3s appear to have an inhibitory effect on the growth of liver cancer cells. Wu, an MD/PhD associate professor in the Division of Transplantation Pathology, says that for some time, omega-3s have been known to inhibit certain kinds of cancer cells.

Wu and Kyu Lim, a PhD research scholar in the Department of Pathology, decided to look at liver cancer cells, hoping to identify the mechanism by which omega-3s fight cancer. They found that these essential fatty acids, which are not produced by the body, induced programmed cell death in liver cancer cells. Additionally, they discovered that omega-3 treatment reduced the presence of beta-catenin, a protein found in overabundance in tumors.

Their findings, Wu says, show that omega-3s operate on at least two pathways as they control the growth of liver cancer cells.

As a control, the investigators treated another set of liver cancer cells with omega-6 fatty acids, which are found in vegetable oil and are known to contribute to cardiovascular ailments. The cells, like those treated with omega-3s, stewed in their fatty acid bath for 12 to 48 hours. The researchers observed no significant changes to the cells.

Wu and Lim plan to extend their research into animal studies.

"This could be a good treatment for patients who cannot tolerate other chemotherapeutic agents," Wu says, "and may be used in combination with other therapies."

Sarah Conklin notes that omega-3s not only help the body, they can help the mind. She is a postdoctoral scholar with the Cardiovascular Behavioral Medicine Program in the Department of Psychiatry.

Omega-3s are thought to alleviate symptoms of those with severe mental disorders. Yet little research has been done looking at what role they might play in sustaining the mental health of adults.

As a graduate student at Baylor University in Waco, Texas, Conklin worked on studies showing that anticonvulsant drugs reduced aggressive outbursts in men. But the side effects of such drugs, she says, were troubling. After she read a study equating a combination of multivitamins and omega-3s with reduced aggression in prisoners, Conklin became interested in learning more about how diet affects mood and behavior.

When she came to Pitt, Conklin and her coinvestigators (including mentor Matthew Muldoon, associate professor of medicine) studied 106 healthy volunteers. Those with lower blood levels of omega-3s were more impulsive and had a negative outlook.

Conklin believes that increased levels of omega-3s balance out omega-6 fatty acids, which are known to have inflammatory effects on cells. Inflammation generates an immune response, she says, and overactive immune responses have been implicated in various disorders, including major depression.

Although none of these investigators is ready to promise that omega-3s are a cure for anything, all say that they are potentially palliative for much more than cardiovascular ailments. One day, consumers may be able to gain such benefits from—of all things (and this would appeal to Homer Simpson's palate)—bacon.

How so? Well, Pitt researchers have helped genetically engineer pigs to produce omega-3s typically derived from fatty fish and some nuts.

Yifan Dai, associate professor of surgery and member of the Thomas E. Starzl Transplantation Institute, was intrigued by the work of Massachusetts General Hospital researcher Jing Kang. Kang had transferred a gene called fat-1 into mice, which resulted in their converting unhealthy omega-6 fatty acids into beneficial omega-3s.

The MD/PhD thought that if he could make this work in larger animals—namely livestock—perhaps we could get more omega-3 into our diet without having to rely on fish. In 2004, Dai began transferring the fat-1 gene into pig cells. But to get real, live swine he called upon Randal Prather, leader of the pig cloning center at the University of Missouri–Columbia.

Prather removed DNA from pig eggs and inserted Dai's cells.

He ended up with five pig litters. One piglet was found to be a fine producer of omega-3s. Five of its clones became a breeding line of omega-3 rich pigs. The results of this work were published in *Nature Biotechnology* this spring.

"For agriculture, I think this will be very useful," Dai says. "Not only for nutrition, but if these pigs are healthier than others [their omega-3–rich bodies could ward off heart disease], it may reduce costs for farmers." He adds that for scientists, the animals could be excellent research models.

Omega-3–rich pork rinds are a way off, Dai says. First, the genetically modified pigs must win FDA approval. And other questions may arise: Will palliative pork appeal to taste buds? Will people be hungry enough for omega-3s to eat engineered pigs? ■

HELEN GRIFFIN



ALFRED PASIEKA / SCIENCE PHOTO LIBRARY

PIECING TOGETHER PARKINSON'S

A STUDENT RESEARCHER LANDS IN THE RIGHT PLACE AT THE RIGHT TIME

BY ELAINE VITONE

A man moves slowly, stiffly, and yet when his limbs are at rest, they quiver. When he wants to move, he can't. When he doesn't want to, he can't stop. Cells in his brain are dying at an alarming rate, and no one knows why. A University of Pittsburgh med student has positioned himself well to help figure out why this cellular slaughter happens in patients with Parkinson's disease.

There are two basic forms of Parkinson's—young-onset, a rare form affecting people younger than 40 that tends to run in the family, and late-onset, a common sporadic condition the incidence of which is higher in later life. The result is the same for either: progressive, wholesale destruction of cells in many parts of the brain, including those that produce dopamine, a chemical critical to fluidity of motion.

Thus far, at least two things are certain. For one, the disease has a genetic component. Young-onset cases have been linked to the inactivity of genes known as DJ-1, pink1, and parkin and to abnormal metabolism of the neural protein alpha-synuclein. For another, certain toxins such as pesticides and industrial chemicals play a role in late-onset Parkinson's. Scientists believe that most Parkinson's cases result from a combination of environmental and genetic factors; however, little is known about exactly how they work together to cause cells to die.

This summer, third-year Pitt med student Vipul Shah began a two-month break from his rotations to conduct research under the guidance of Edward Burton, assistant professor of neurology and of molecular genetics and biochemistry. Shah hopes to help broaden our understanding of the causes of Parkinson's—and satisfy his scholarly-research-project requirement at the same time. For the project, he'll continue to meet with Burton and other mentors throughout his Pitt med schooling and eventually present his results to an executive committee of faculty members and deans.

Shah reflects on the disease: "There's a lot of work that needs to be done. … It's unclear whether every single [form of Parkinson's] has the exact same pathogenesis. We're trying to figure out how they interrelate."

Burton says that the Pittsburgh Institute for Neurodegenerative Diseases (PIND) is an ideal setting for Shah's explorations. "We're in the right place at the right time."

Historically, coming up with an animal model for Parkinson's has been tricky: How do you create Parkinson's in a rat if you don't know what causes it in humans? Previous attempts to simulate the disease involved poisoning the animals with potent neurotoxins that target the dopamine-producing part of the brain. Because this method killed off all the neurons at once rather than gradually, the progression of the animals' symptoms was a far cry from that of humans with Parkinson's.

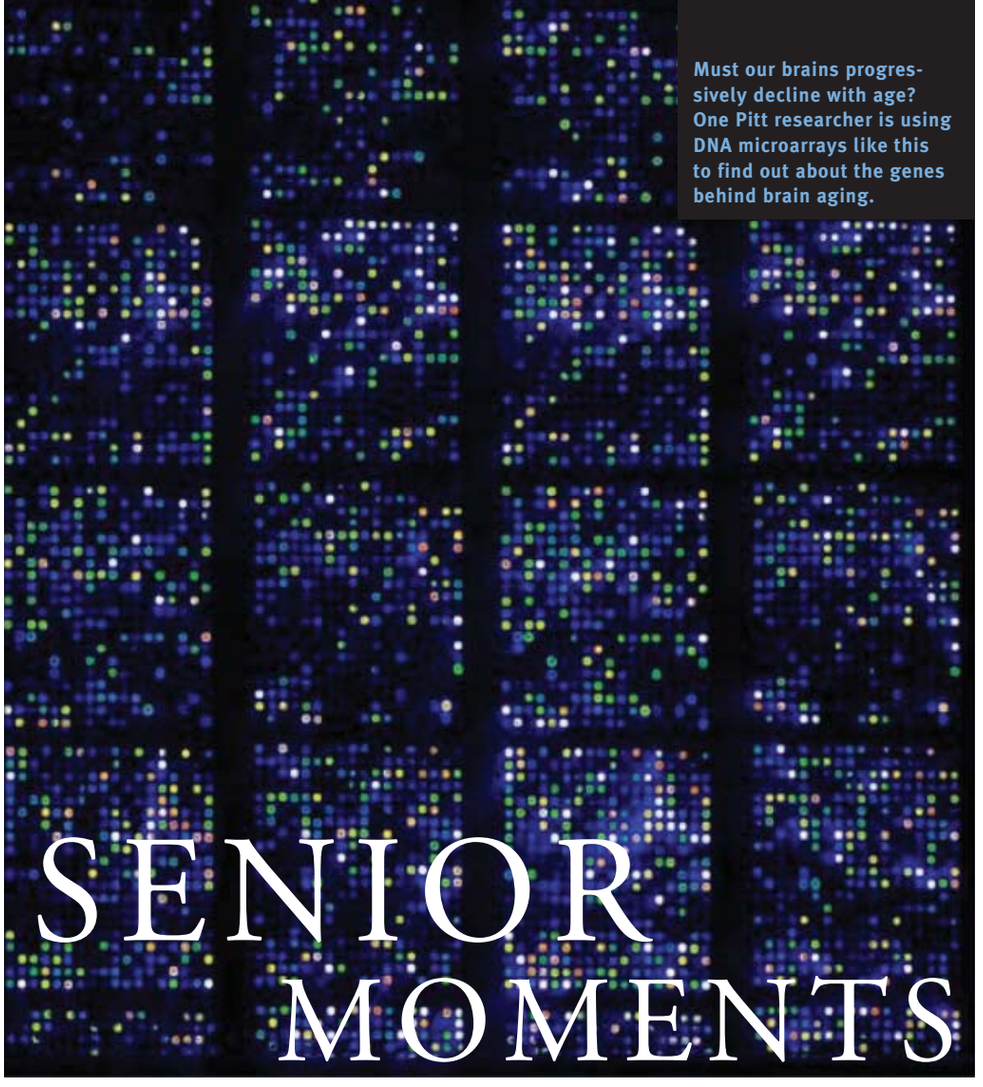
In the past two decades, several labs have shown that Parkinson's patients carry defects in their mitochondria, a key discovery that led PIND director Timothy Greenamyre to, in a sense, build a better rodent. As a faculty member at Emory University in 2000, Greenamyre found that when animals are chronically exposed to low levels of the pesticide rotenone (which is toxic to mitochondria), they develop abnormal brain pathology and progressively worsening symptoms that mirror those of human Parkinson's patients. His rotenone model—which six years ago was the first confirmation of the long and widely held suspicion that pesticides can induce the disease—is ideal for testing questions Burton's lab is exploring.

Shah will use genetically engineered viruses on Greenamyre's rats to explore these questions: How do genetic and environmental factors relate in Parkinson's? Can you prevent or treat environmentally induced Parkinson's by overexpressing parkin, DJ-1, or pink1 or by removing alpha-synuclein?

Shah likes the way Burton is open to input. The two meet regularly, but how Shah goes about obtaining usable data is largely up to him. For example, at first they debated whether Shah's project should concentrate on in-vitro or in-vivo experiments. "I am really interested in the behavioral experiments that may allow us to see actual Parkinsonian behavior in rats," says Shah, "so that is the path we are pursuing."

Perhaps giving Shah that freedom is easy enough. Shah worked in an Alzheimer's lab as an undergraduate at the University of Florida, which was where he first developed an interest in neuroscience.

"He's incredibly independent as students go," Burton says. ■



Must our brains progressively decline with age? One Pitt researcher is using DNA microarrays like this to find out about the genes behind brain aging.

COURTESY U.S. DEPARTMENT OF ENERGY

SENIOR MOMENTS

CAN SCIENCE END THEM?

BY JIM SWYERS

As we age, many of us begin to notice that our memories aren't what they used to be. We forget the names of people we've just met, regularly misplace our glasses or car keys, or lose the ability to store and retrieve numbers the way we used to.

We often dismiss these instances of forgetfulness as "senior moments" and move on with our lives. We accept that a progressive decline of memory, as well as other cognitive and motor abilities, is inevitable, like death and taxes. It seems there's nothing we can do about it.

However, according to research being conducted by Etienne Sibille, a PhD assistant professor of psychiatry at the University of Pittsburgh, such notions may not be accurate. His work is demonstrating that many long-held conceptions about aging, particularly the notion that irreversible and generalized biological decline accompanies normal aging, are dead wrong.

Using DNA microarrays—a technology that allows researchers to read the activity, or expression patterns, of all 22,000 genes in each cell simultaneously—Sibille was surprised to learn that only a small number of genes are involved in the biological decline that can be associated with an aging brain.

Sibille's team made this discovery by analyzing preserved brain tissue samples from autopsies of 39 people who ranged in age from 13 to 79. The analysis found changes in gene expression patterns in only a small subset—about 10 percent—of the total genes in the brain cells.

According to Sibille, these findings suggest that the aging process in the brain is limited in its scope: "We thought that the genetic signs of aging in the brain would be more complicated and involve many more genes. Because only a limited number of genes are involved, it means that aging in the brain is a selective event."

More importantly, Sibille believes the process may be malleable. Indeed, he and his colleagues found different patterns of age-related genetic changes in glial and neuronal cells—the two main types of brain cells. Genes in glial cells became more active with age, and genes in neuronal cells became less active.

"The fact that it is limited to a relatively few number of genes and possibly cells, and that the effect is different in the types of brain cells involved, may allow us to delay and, possibly, alter the aging process in the brain," Sibille says.

It's a bold thought. Yet Sibille believes he has evidence that such a scenario is possible. When his laboratory researchers began examining age-related genes they'd identified, they found that many of the genes were involved in the regulation of mood. By disabling, or "knocking out," the same genes in mice, they discovered one that, when absent, initiated the aging process. It turns out that the gene, called Htr1B, codes for a receptor that interacts with the neurotransmitter serotonin.

"It has long been known that there are changes in the serotonin system with aging, which are considered [to contribute] to the development of age-related mood disorders, such as depression," notes Sibille.

"When we knocked out the gene for this receptor in mice, it caused an early onset of age-related behavioral deficits."

Sibille says that by manipulating this receptor, his lab showed it was possible to "alter the trajectory of age-related events."

Much more work remains to be done before the full story of aging in the brain is known. Meanwhile, Sibille's lab is continuing to disable genes in mice that appear to be involved in brain aging and observing the subsequent behavioral changes. The investigators also are using microarrays to see what happens to the rest of the genes when some of these age-related genes are disabled.

"We need to keep deciphering what these genes are telling us to get the complete picture of what is happening at the cellular level," he says.

He believes that in the not-too-distant future it may be possible through lifestyle or drug interventions to delay the onset of the brain-aging process in humans. Even a delay of this process by as little as a few years would dramatically lower the percentage of elderly people living with cognitive or other brain-related deficits, he suggests. ■



Three of Pat Strobel's five grandchildren—11-year-old twins Nicholas and Samantha (left and right) and Tommaso, 8—sit on the porch swing where Pat used to "interview" the children with a video camera, asking them questions like "What's your name? What do you want to be when you grow up?"

IN THE WORLD OF TRANSPLANTATION, MOST SECOND CHANCES BEGIN WITH A LOSS

PHOTOGRAPHY | CHARLEE BRODSKY
TEXT | ELAINE VITONE

NEXT OF KIN

Right now, more than 92,000 people are on the national waiting list for a vital organ transplant. Their best chance for survival is probably a rare and tragic turn of events for another family. Last year, UPMC (including Children's Hospital of Pittsburgh) and VA Pittsburgh Healthcare System performed 686 transplants with organs from donors who appeared to be alive but were actually brain-dead. These people were still breathing with the help of a ventilator and yet already gone. Such cases amount to 2 percent of all deaths, and among them, only about half result in organ donation, despite the critical need.

Without a donor card or designation on a driver's license, it is up to the next of kin to make the sensitive decision about organ donation as they say goodbye to a loved one who appears to be merely sleeping. Three Pittsburgh-area families who gave the gift of organ donation in this way consented to share their stories with us here. They remind us of how some remarkable second chances began with a loss.

Like with the Strobel family. Back when Raymond, Bonnie, and Herb Jr. were growing up in West Homestead, Herb Sr. used to sell his blood to afford Christmas gifts. Mounds of gifts by the tree, their Uncle Casey filming the kids' faces—Christmas meant more to their mom, Pat Strobel, than anything.

Three years ago, Pat was hospitalized for congestive heart failure. "She wasn't on the phone crying," says Raymond. "She called just to say we had to postpone Christmas Eve because something came up." According to the family, Pat was treated with blood thinners, inadvertently opening a floodgate of bleeding in her brain. Cerebral hemorrhage runs in the family—it killed Pat's mother, grandmother, and uncle years ago. Then, seven months after Pat's death, her younger brother, Casey, followed. Both Pat and Casey became organ donors.

The Strobels are the kind of family who, with little notice, will assemble three generations around a table to tell you about Pat and Casey. They'll tell you about when Pat used to listen to the scanner to make sure her two police-officer sons were okay. "I don't like that dispatcher," she'd say. "She's not nice to you."

They'll tell you about the scores of Kaufmann's employees who showed up for Casey's funeral, remembering their coworker with story after story. "He would meet this one lady every morning at 5 a.m. just to open the door for her and carry her bags upstairs," Bonnie says. They'll tell you how upset Pat was when Herb Jr. got his first tattoo, and it didn't say "Mom." In January 2003, he inked three new letters into his arm.



Jim and Jan Eddy in the family's home in North Huntingdon. The couple light a candle for their son Mike every night.





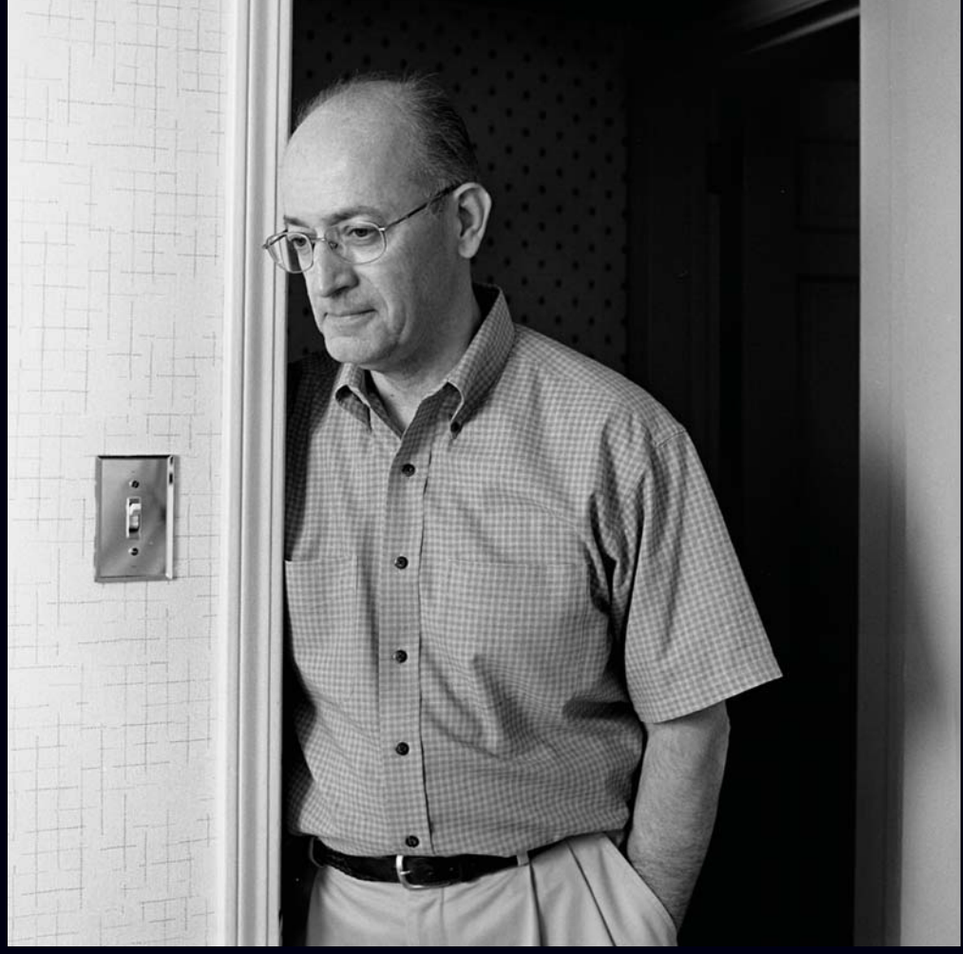
LEFT: After their son Mike died, the Eddys began collecting boy angels. This one was a Christmas gift from a woman who received one of Mike's kidneys. ABOVE: Jim Eddy holds the chain his son kept attached to his wallet.

Now as Jan and Jim Eddy reminisce in the living room of their North Huntingdon home, they laugh about the things that used to frustrate them. When Mike was little, he'd stash food around the house—eggs on the bed, fish sticks in the dryer. When he got older, it was his socks. Once, they found a pair in Jim's tackle box.

Mike's older brother, Adam, and younger sister, Angela, worked hard to keep their grades up. "Mike didn't care," says Jan. "He was there to socialize, play sports. He had 16 years of fun. He'd say, 'Mom, chicks dig me.'"

The accident happened 10 years ago this summer. Mike had been so good that week that Jim said he could stay out until 11:30. A friend was driving him home to make curfew when another car ran a stop sign, broadsiding them.

Months after the accident, Jan found a pair of socks in the living room couch. "I said, 'Now I get it.' This was not to drive me crazy while he was living. It was to make me laugh after he was gone. I sat down and just cried. I laughed and cried."





Frank Holby stands in the doorway, looking into his daughter Michelle's old bedroom, now empty, as he and his wife, Judy Holby, prepare to move. Judy holds a "Get Well Soon" balloon, still inflated 19 years after Michelle's friends left it at the family's door while Michelle was in the hospital.







LEFT: Michelle was about as tall as her doll when she received it as a gift at age 2. Judy created a painting of it a few years after Michelle died. **MIDDLE:** Frank holds an academic-achievement medal Michelle's teachers presented to the Holbys at the end of the school year and another medallion similar to those given to recipients of the Michelle Holby Memorial Scholarship, which friends and neighbors created in Michelle's honor. **RIGHT:** Judy still wears the necklace that Michelle gave her. Michelle had saved the money for it after starting her first job.

Frank and Judy Holby remember that September 10, 1987, was a muggy, overcast day because Michelle was up to her usual sighing and kidding around. "Dad, I really hope they don't make us run on the track. It's so humid. My hair's gonna fall."

To this day no one knows why Michelle collapsed that morning in gym. At first, they couldn't help wondering: *What if there had been a phone down by the track? The full-time nurse was at a training class—for, of all things, CPR—and what if she'd been there?*

But as time passed, they found that wondering wouldn't change what had happened: the loss of their oldest, a 17-year-old girl at the top of her class. A burial on the birthday of her idol, Bruce Springsteen. Letters arriving at their home in Pleasant Hills months after she'd died, congratulating her for her National Merit Scholarship.

They thought that donating her organs was what Michelle would have wanted—they hoped so, anyway. Then six weeks after Michelle died, they found a donor card in her purse. They'd signed it themselves more than a year beforehand, when Michelle came home from an assembly. They had forgotten all about it. ■


THOMAS

THOMAS STARZL SAYS TOLERANCE IS ON THE OTHER SIDE OF REJECTION

BY CHUCK STARESINIC

BREAK ON THROUGH

CONTINUED FROM OUR MAY ISSUE

In 1986, Thomas Starzl flew to Japan for a chance at a few drops of an experimental drug known by the unwieldy designation of FR 900506. The response to his inquiry was, essentially, "Maybe." After Starzl's formal request, a Japanese pharmaceutical executive immediately jetted off to London to talk things over with officials from a British company with which his firm collaborated. Starzl, then a Pitt professor of surgery, waited in Japan for a definitive answer.

He was 60 years old. He had a reputation for boundless intellectual and physical stamina, not to mention unparalleled skill and drive as a surgeon. He was the man who had made liver transplantation a reality when many had insisted it could not be done. But now he felt chronically fatigued. He was becoming careful instead of bold, he would later reflect in his 1992 memoir, *The Puzzle People*. And he privately wondered whether this drug was better left to someone else to champion or reject.

Researchers at the Thomas E. Starzl Transplantation Institute believe that decades of laboratory research and clinical experience will yield a systematic way to help transplant patients tolerate their new organs with little or no medication. One avenue of investigation reaches into the depths of the sea for answers. Oddly enough, jellyfish that live on the backs of hermit crabs have offered clues.

ILLUSTRATION | JACOB THOMAS AT DECO ZONE

In Pittsburgh, transplant patients carried on the all-consuming struggle to live. Drained of color and vigor, jaundiced, incoherent, and perhaps even comatose, they waited for organs without which they would die. Families wrestled with the knowledge that their prayers could only be fulfilled through someone else's tragedy. The lucky ones weathered the aftershocks of transplantation: Their tissues were inflamed as a result of incisions and the stitching together of foreign blood vessels and ducts. More ominously, their white blood cells—roving protectors of the status quo that are born in the bone marrow—diligently attempted to seek out, identify, and destroy any cell from the donor organ so carefully stitched into place.

It was on behalf of these patients, and all those to come after, that Starzl, now a Distinguished Service Professor of Surgery, waited in Japan for one-hundredth of an ounce of FR 900506. Starzl's patients in Pittsburgh were being treated with cyclosporine then, a drug that Starzl had begun experimenting with in 1979. When he first demonstrated to the medical community that a careful blend of cyclosporine and steroids could control the assault of the immune system upon a donor organ, the field of transplantation took an enormous leap forward. Survival rates surged upward. Unfortunately, cyclosporine was somewhat toxic. It could lead to serious kidney damage or outright failure. Some patients in early trials without steroids had developed white blood cell cancers. Starzl avoided such catastrophes through the addition of steroids and by administering the lowest dosage possible, but some patients rejected their new organs despite the help of cyclosporine.

Standing in the lobby of the Fukuoka Hotel one week after his arrival in Japan, Starzl got his answer. At the end of a slow, almost ceremonial discussion translated by a Japanese surgeon, Starzl was entrusted with a vial of liquid FR 900506. The contents would not have filled a thimble. He rushed back to Pittsburgh with it and with the promise of more.

Like cyclosporine, FR 900506 (which now goes by the names FK 506 and tacrolimus) suppressed a subset of white blood cells that helped the immune system target the new organ for destruction. Researchers at other institutions cautioned Starzl that it was prohibitively toxic—a probable dead end, they told him. But Starzl had patients who were running out of options, and he believed that, like cyclosporine, this drug could work if carefully combined with steroids.

Eventually, tacrolimus was approved for patients who had rejected multiple organs—they were facing either another risky transplant or death. Starzl's first was a woman rejecting her third liver in eight months. Then came a man rejecting his fifth liver in four years. Tacrolimus stopped rejection in both of them. After two years, seven of the first 10 people who'd switched from cyclosporine stopped and reversed a deadly immune response. Patients with failing transplants came to Pittsburgh from around the world.

Tacrolimus is used widely to this day, yet it's long been clear that suppressing the immune system with highly toxic drugs is an imperfect way of making transplants stick. Patients who are saved by new livers or kidneys are forced to endure side effects like debilitating pain, nausea, tremors, excessive hair growth, high blood pressure, diabetes, and tumors. You could survive a liver transplant at 35, but die at 50 from the side effects of your medication.

When Starzl came to Pittsburgh in 1981, his goal had been to prove that organ transplants were possible on a large scale, especially bloody and technically challenging liver transplants. He had accomplished that in Pittsburgh. Now, there was a new peak to bag: tolerance—a state in which an organ would be accepted without immunosuppression.

Tolerance was not complete fantasy.

As early as the 1960s, Starzl had taken patients off immunosuppression on a hunch. A few showed no ill effects and remained drug-free. Those who showed signs of rejection went back on their meds. Yet the science of immunology had no clear explanation for why one patient could achieve tolerance and another would fail to. To add to the mystery, it would later become clear that patients who'd had transplants in the 1960s were more likely to achieve tolerance than those transplanted later, say, in the 1990s. While surgeons had gotten better at doing transplants and had found better drugs to stop rejection, their patients seemed less likely to achieve tolerance.

Starzl walked out of the operating room one day in 1990 and decided he wasn't going back. He was done salvaging healthy organs from those unfortunate enough to no longer need them. Done standing all night sewing livers into those who would die without them. He found it a great relief.

With more time on his hands, Starzl decided to scratch a mental itch he'd had for years concerning his most successful patients. In 1992, he invited 30 of the world's longest-surviving transplant patients to Pittsburgh. Among them were a man who had lived 29 years with someone else's kidney and a woman who had lived 23 years with a transplanted liver. The 30 were on various levels of maintenance immunosuppression, and at least one was drug free.

According to the prevalent immunological theories of the day, their donor organs were islands amid hostile seas. To keep the immune system from swelling into a tidal wave, doctors calmed the seas with drugs. Cells from a donor organ that dared to set foot off the island invited destruction. Starzl suspected there was more to the story than that. He asked his patients to provide blood and tissue samples from several parts of their bodies, even biopsies of various organs. He then enlisted the help of Pitt experts in, among other techniques, the sort of DNA fingerprinting that allows criminal prosecutors to identify an individual from the DNA in a tiny trace of blood or a hair.

Whom did Starzl want to identify in these various bodily tissues? The donor—long dead but for a transplanted organ pulsing along in a foreign body. Starzl found what he was looking for. A woman who had undergone a successful liver transplant years ago, for example, had the cells of the donor throughout her body, not just in her secondhand liver. A population of the donor's white blood cells had "hitchhiked" on the transplanted organ and migrated to her hands, her heart, her lungs. These migratory hitchhikers had not met with destruction. They were quietly swimming in her bloodstream and nestling into her internal organs.

Not everyone in the fields of immunology and transplantation accepted what Starzl had found. It went against the accepted understanding of organ transplants: The body would never accept an organ that did not come from an identical twin, so the immune system must be suppressed indefinitely.

Starzl described what he saw as "chimerism." In ancient Greek mythology, the chimera was a fantastical creature with the body of a lion, the head of a goat, and the tail of a serpent. Starzl's patients exhibited microchimerism, harboring living cells that had originated with two individuals.

He pointed out that chimerism had been witnessed for decades in successful bone marrow transplants.

In cases of leukemia, for example, the patient's marrow and blood cells—including

the white blood cells that are the workhorses of the immune system—are wiped out with radiation and replaced by cells produced by the donor's transplanted bone marrow. When the new cells circulate throughout the body and take up the work of the recipient's immune system, the patient is a chimera. Starzl suggested that successful organ transplantation fit the same paradigm, though they had been thought of as different phenomena for decades.

Before he became scientific director of the Thomas E. Starzl Transplantation Institute and before he'd even met Starzl, Fadi Lakkis had heard about his theory.

"But my view of chimerism," says the Pitt professor of surgery and of immunology, "was like the view of most people out there—skepticism, because this Tom Starzl is famous for pushing the envelope to a limit that most mortals are not willing to go to. And like everybody else, and being naïve at the time, I thought, 'This is very interesting,'… but I never really thought about it seriously because the view out there was—I'll tell you honestly—*that's Tom Starzl again, trying to say something that's not possible.*"

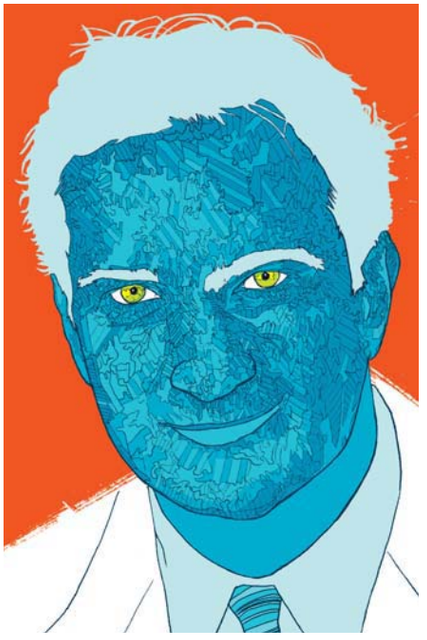
Lakkis points out that this is the same thing the medical community said decades ago when Starzl advocated for liver transplantation—once thought impossible and now an accepted cure for liver disease.

Lakkis, who recently moved to Pitt from Yale University, is still settling into his office at the Starzl Institute. He is tall and friendly, is easy to engage in conversation, and becomes downright animated when discussing how the immune system works or *might* work. (It's humbling to realize how much remains to be discovered about how the immune system works.) Lakkis, an MD, was a practicing clinical nephrologist and director of transplant medicine at Yale, but his affinity has long been for scientists who can happily spend years in the lab investigating the immune system and can pass hours pontificating about its evolution. In the course of his laboratory investigations when he was at Emory University, Lakkis had unwittingly found evidence to support Starzl's theory.

Lakkis first visited Pittsburgh in 1999 to give a talk on his immunology research.

"It was a meeting of the minds," says the once-skeptical Lakkis, explaining that he and Starzl discovered they were thinking about immunology in very similar ways. Lakkis presented research on a molecule produced by the immune system—interleukin-2 (IL-2). It was well known that IL-2 was involved in rejection. When the immune system identifies a foreign invader such as a transplanted organ, IL-2 activates T cells (a type of white blood cell) that recognize and attack the invader. Lakkis and his team experimented with a mouse that did not produce IL-2.

"To our surprise, the organs still rejected," he says.





Two for one: Starzl's successors, Fadi Lakkis (left) and Amadeo Marcos (right), now lead the institute's efforts in research and surgery, respectively.

"So we hypothesized that T-cell activation is required for achieving tolerance. And the reason it is required is it prepares the cell for death. IL-2 activates the cell but also plants the seed of death in it, which makes sense, because you don't want immune responses to keep going and going and going. You want T-cell activation, lymphocyte activation, but you want to ensure that this dies off. … You can get very bad infections as a child, and your lymph nodes can get bigger when you get a sore throat, but then they shrink back. So there are things that regulate the immune system. What we found is that what activates it also regulates it.

"It fit very nicely with what Starzl had been trying to tell the world," says Lakkis. "You've got to let the immune system get activated. Let this battle go on, and that's how you will eventually get tolerance. Instead, in the clinic, people were going around and giving heavy immunosuppression to patients from the get-go, which definitely protects the organs, but then you cannot get off immunosuppression, because once you take them off, those T-cells are still there. So the only chance to get the T-cells to die out is to let that battle happen."

Chimerism, Starzl says, is not just a discovery that cells had migrated from transplanted organs and taken up residence in far corners of the recipients' bodies. The very phenomenon demonstrated why there had to be a mechanism for tolerance.

"We're all exposed to viruses all the time," says Starzl, offering an example. "Eighty-five percent of the population carries antibodies to cytomegalovirus and other hepatitis viruses. I'm swimming in antibodies—you probably are, too—against the B-virus or C-virus." If the immune reaction had as its goal the determination to get rid of every last virus, Starzl says, "85 percent of the world would be dead. So the immune system has found a way to switch the immune reaction off, and that is tolerance."

At Pitt, Lakkis is setting up a lab that will allow him to explore another great mystery of immunology that may help scientists understand tolerance: the innate immune system. In his lab, the research subjects are tiny jellyfish of the genus *Hydractinia*. These are not free-floating jellyfish. In the wild, some species grow on the backs of hermit crabs and are called "snail fur." In Lakkis' lab, they ride glass slides submerged in saltwater.

Jellyfish do not have the highly evolved immune systems of humans and other large animals. They have no lymph nodes, no white blood cells—what immunologists call the adaptive immune system—but they recognize "self" and reject "nonself." When two jellyfish, sponges, or other primitive invertebrates attempt to live side by side on the same surface, they may even begin to fuse together into one larger organism. That's when the battle of the innate immune systems begins. If the individuals are of the same species, and especially if they are related and have genetic similarities, they may eventually tolerate one another and become, essentially, one fused organism with living cells from two—a chimera. The description is reminiscent of what happens when a

mother donates a kidney to her child.

In humans, Lakkis suggests, the innate immune system is like a giant doorbell that can wake the major players of the adaptive immune system.

All sorts of things can ring the bell: inflammation or infection, for example, or a common virus. In a transplant recipient, any event that triggers the innate immune system could initiate a cascade of events that ends with the adaptive immune system vigorously rejecting a transplanted organ. In his jellyfish, Lakkis hopes to answer some fundamental questions that could apply to humans—questions like, what are the mechanisms that turn the innate immune system on and off?

Investigations like these at the Starzl Institute can be applied directly to the hundreds of patients who come here each year for organ transplants.

It's early Tuesday morning on the sixth floor of UPMC Montefiore, and the clinical work of the Starzl Institute is in full swing. At the nurses' station sits a stack of coolers for transporting organs. Beginning as early as 6 a.m., surgeons, nurses, anesthesiologists, and coordinators trickle in, stash their gear, don their caps and masks, and check the white board for their assignments. On a recent day here, surgical teams performed eight transplants: two each of livers, intestines, pancreases, and kidneys. Few other centers have the staff or the space to perform so many in a day.

In a surgical suite down the hall, an organ donor is a few hours into one-half of a living donor liver transplant under the direction of Amadeo Marcos, professor of surgery and clinical director of the Starzl Institute. The recipient will be prepared for the transplant by another team in an adjoining room. In this long, complex procedure, surgeons will remove 60 percent of the donor's perfectly healthy liver as a replacement for the failing liver of the recipient. Marcos pioneered this procedure. He has done more than 300 of these, more than anyone else in the world. At Pitt, around 40 such procedures are performed each year—approximately 25 percent of all liver transplants done here.

The procedure would be almost unrecognizable to someone whose only knowledge of liver transplants was from witnessing Starzl's first attempts in Pittsburgh in 1981. Those operations were done in a crisis atmosphere and required dozens of units of blood. The transplant division created a citywide uproar by draining local blood banks. Today's procedures will be accomplished with no blood transfusions at all.

Starzl and Marcos believe that they are close to achieving tolerance systematically in these patients.

"Living donation creates the scenario for tolerance to occur," says Marcos. "We're in the process of a breakthrough protocol for tolerance. We are still too early in the process to talk to you about results, but it will change transplantation. The patients will not require immunosuppression."

Starzl qualifies, saying that a small percentage of patients will remain on medication, but at such a low frequency—once per week, for example—that it will be nearly the same as being drug free. The side effects at this dosage, he says, are minuscule or impossible to detect.

The living donor procedure, with very few exceptions, usually occurs between blood relatives. Genetic similarities between the donor and the recipient make it easier to achieve tolerance, and the two patients submit to a battery of tests to determine whether they match well in terms of size, blood type, and tissue type. An added benefit of the living donor procedure is that the recipient can be prepared to receive this foreign tissue beginning days or weeks before the actual surgery—something rarely possible with an organ from a donor who may have died suddenly and unexpectedly.

Marcos is cagey about providing details, but the gist of the protocol is this: The recipient is exposed to cells of the donor before the transplant. The immune reaction that is the inevitable—and perhaps necessary—result of transplant begins before and continues after transplantation. Marcos and his colleagues carefully dampen the immune response with steroids and immunosuppressive drugs like tacrolimus so that rejection does not get out of control.

Starzl, who turned 80 this year, continues to quietly move between the lab and the clinic as director emeritus of the institute. His long experience tells him that transplant recipients must go through a bout of rejection in order to reach tolerance. The immune system must be allowed to mount an attack against the foreign tissue and then to become exhausted. The end result, he says, is tolerance, with donor cells being accepted as self throughout the recipient's body.

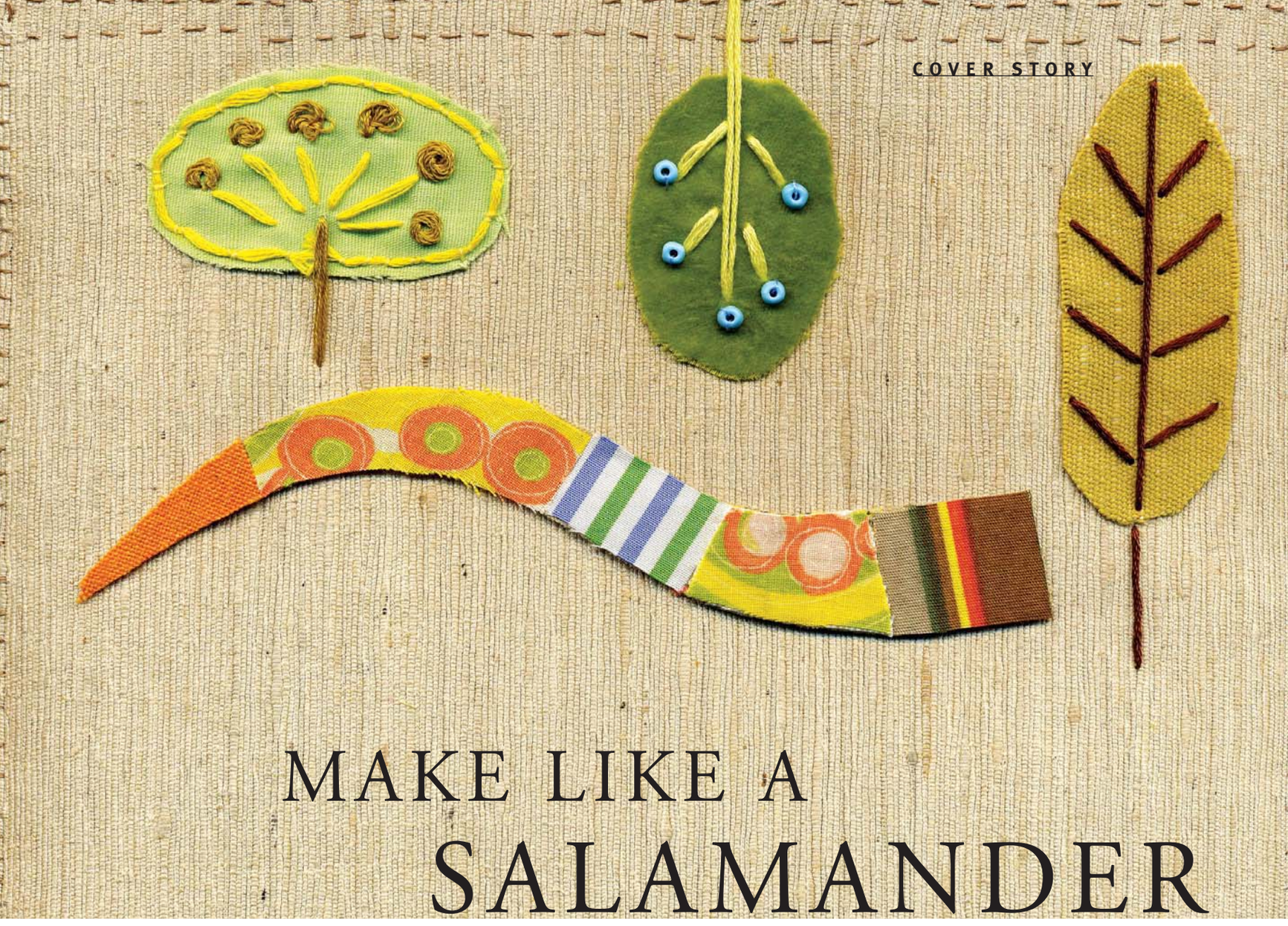
With his colleagues, Starzl has been praised for showing that transplant patients can have excellent short-term success on relatively modest amounts of tacrolimus—though organ rejection occurs, it is easily reversed. However, the success of a transplant must be measured in decades. Anthony Monaco of Harvard University and Peter Morris of the Royal College of Surgeons of England cautioned in a 2004 forum in the journal *Transplantation* that: "the high incidence of rejection reactions with this strategy may presage late organ injury or loss. Only time will tell. It is incumbent on the authors to provide long-term follow-up of these patients."

Starzl and his colleagues have found that the timing and the dosage of immunosuppression are important at the outset. This evidence may help to explain why Starzl's patients in the 1960s were more likely to achieve tolerance than later patients. The early patients suffered through worse bouts of rejection and then recovered. The later patients received their transplants in the age of advanced immunosuppression, when doctors had gotten very good at preventing rejection. Patients did better in the immediate postoperative period, but because their immune systems had not been allowed to mount a vigorous attack and become exhausted, there was always a possibility of a serious rejection episode, especially if they went off their meds.

Achieving tolerance systematically in a large group of patients would be a breakthrough in both clinical transplantation and in immunology. Starzl is eager to play down his role in these attempts, but Marcos and Lakkis consistently credit him for his regular input and his unusual insight into the mystery that is immunology. (According to the Institute for Scientific Information, Starzl once averaged one paper every 7.3 days, making him one of the most prolific scientists in the world. In 1999, ISI identified Starzl as the most-cited scientist in clinical medicine.)

"He has an unbelievable knowledge of the science of immunology," says Lakkis. "He doesn't want to be the person who can tell you about every single molecule involved in rejection, even though he knows them. He's more interested in the big picture."

"My predecessor, John Fung, and I have just been followers of his ideas," says Marcos."I cannot imagine what we would be without him. I hope that when the time comes that we are somehow ready, but there will never be another Dr. Starzl. Ever. I can tell you that." ■



MAKE LIKE A SALAMANDER

Salamanders and newts do it, so why not us? Pitt's Stephen Badylak coordinates a team that hopes to learn how to regrow a mammalian digit. They believe these amphibians can show them how.

LIMBS ON DEMAND?

BY JOE MIKSCH

You really don't need to think much about this one: A pig's bladder is a very good thing to have … if you're a pig.

But if you've amputated the tip of your pointer finger above the first joint while handling a model airplane as its propeller was still spinning, perhaps the organ isn't the first thing to look for in your medicine chest.

However, when a Cincinnati man in his 60s lost the pointy part of his pointer in the manner described above, he sought out the University of Pittsburgh's Stephen Badylak,

ILLUSTRATION | CATHERINE LAZURE

understanding that, in his particular case, one might come in handy. One of Badylak's colleagues had told the man that the doctor had done impressive feats with pig tissue.

Badylak is a research professor in the Department of Surgery with a secondary appointment in bioengineering at Pitt. He has a PhD, a DVM, and an MD and directs the Center for Pre-Clinical Tissue Engineering in the McGowan Institute for Regenerative Medicine.

Badylak placed a piece of biologic scaffolding—derived from a pig bladder by stripping the organ of cells—on the injured finger. A similar and commercially available material has been used in half a million patients to regenerate tissue, including those who would like to regrow rotator cuffs, Achilles tendons, and other soft tissues. Could Badylak's experimental scaffold cultivate an entire tip of a finger? He didn't know.

Six weeks later, the man who once faced deformity was made whole again. Molecules within the scaffolding drew stem cells to the amputation site. The cells differentiated and multiplied, and the fingertip—bone, blood vessels, nerves, skin, fingernail—grew back. It looked perfect and was perfectly functional.

Then Badylak did the same for a Boston man in his 70s who nipped a fingertip with a band saw.

This is the stuff of salamanders and newts, a pair of amphibians who have the ability to regenerate lost limbs. When it happens in a person with the aid of the structural material that helps support and organize cells in a pig's urinary bladder, it's the stuff of science fiction.

"The chances of this happening," Badylak says, pausing, "I mean, it's really rare. I'm not saying it's impossible, but nobody would have predicted it [working]. Now, it didn't go across a joint, so we didn't regrow a joint, and that's going to be a real challenge."

It's a challenge Badylak, with five other scientists from across the United States, has accepted. The group is equipped with a $3.7-million, 12-month grant from the Department of Defense's Defense Advanced Research Projects Agency (DARPA). The researchers hope their efforts will result in a mouse regenerating a functional digit—much in the same manner a salamander or newt regenerates a limb. The grant could be worth up to $15 million throughout four years.

Badylak's former boss, retired Purdue University President Steven Beering (MD '58), believes the group has an able coordinator. Beering is a member of the University of Pittsburgh Board of Trustees, and was recently appointed chair of the National Science Board, which serves as the science adviser to the president and Congress and oversees the National Science Foundation. He says that Badylak is "the most innovative researcher I've ever met. I'm a great admirer of his work and his research."

Badylak began meeting with team members—experts in places as far-flung as Lowell, Mass., and Salt Lake City, Utah—two years before they received any funding.

"We've got two developmental biologists, a great classical cell biologist, an excellent molecular biologist, and an immunologist who's spent her life understanding the role of the immune system in regeneration," he says.

"If we're smart enough, we'll combine the right talents and discover things we never would have discovered on our own."

Hans-Georg Simon is a developmental biologist, an assistant professor of pediatrics at Children's Memorial Research Center and Northwestern University in Chicago, and a member of the DARPA team. He expects the team's diversity will result in "great quantum synergy."

So where does the A team begin? With the salamander.

One day, a salamander—let's call him Jimbo—is minding his own business near a little stream. Nice and pastoral. Calm. But danger lurks in the weeds. A garter snake attacks, lunging at our little mudpuppy. Jimbo's leg gets trapped, then the bone snaps, the muscle and skin tear off, and he scurries to safety on three legs.

A couple of months later, a four-legged salamander is lolling about near the same stream. Looks a bit familiar, no? Well, he should. That's Jimbo with a full complement of legs. How the heck did that happen?

"Salamanders are champions of regenerative ability," says Simon.

When a salamander loses a limb, molecular signals compel the surrounding tissue to produce cells that divide and accumulate at the wound site. The resulting cell mass, called a blastema, specializes as it matures, forming all the necessary components of the missing limb. Here, an adult human would form a scar.

"Salamanders replace lost structures without forming a scar," Simon says, "but the process is slow. Our wounds heal fast, and the expense is a scar."

"That's the default healing mechanism in adults," says Badylak. "Fetuses don't form scar tissue; they regenerate."

Likewise, doctors can perform heart surgery on fetuses in utero without risking loss of function because of scarring. Badylak thinks adult humans lose their regenerative potential in maturity because the genes that govern the process in fetuses and infants have been turned off.

Adult humans do have some regenerative abilities, producing red blood cells, liver cells, and skin cells continually. Compared to a fetus or a salamander, though, this is bush league.

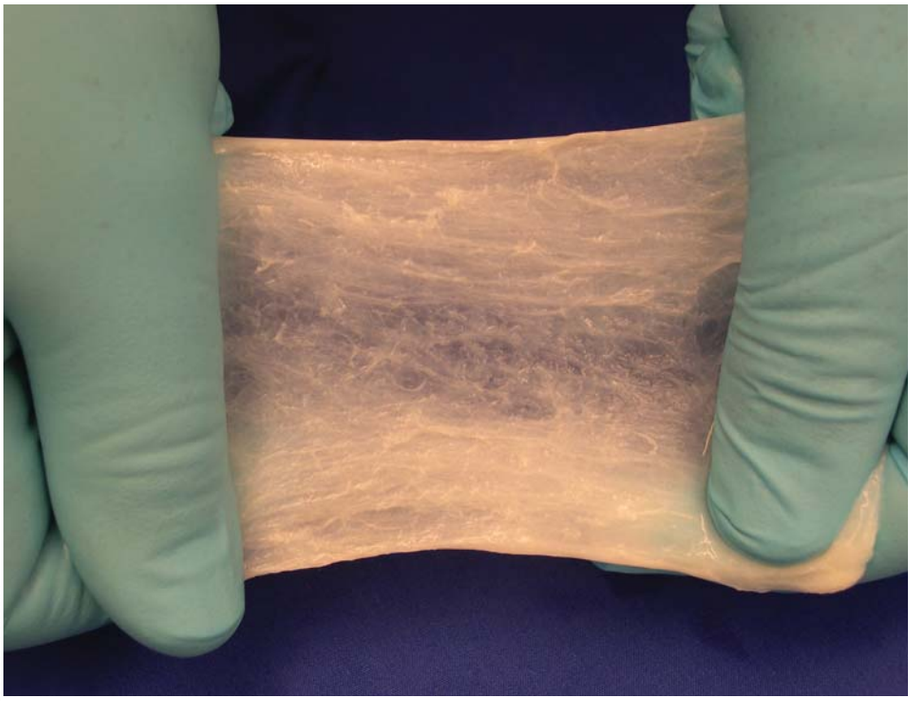
"We're asking ourselves what genes get turned on and off differently between a newborn and an adult," Badylak says. "Is it possible to reverse the gene expression pattern to that of a fetus, at least temporarily and at the site that you're interested in? If we can do that, maybe we can reprogram the local cells that we get [at an amputation site] to think that they need to form a new limb."

Simon says that understanding the regenerative ability of animals such as the salamander is key to tapping into human regenerative potential.

Cells that form a blastema, he says, seem to have control over what they become. They are aware of where they are in the sense that they can tell if the salamander lost his front leg or back. They can tell whether the amputation is near the shoulder or foot. They know the structure of what it is they are to replace.

The fingertip—bone, blood vessels, nerves, skin, fingernail—grew back. It looked perfect and was perfectly functional.







GLOVED HAND WITH SCAFFOLD: COURTESY J. MURPHY. JUNCTION DEVICE: COURTESY T. GILBERT.

ABOVE: Stretched between two gloved hands, this piece of biologic scaffolding, derived from a pig's bladder, is ready to be used as a kind of trellis upon which new tissue can grow. LEFT: The upside-down funnel is a similar piece of scaffolding built to help the body repair the junction between the esophagus and the stomach.

"They never make anything extra, and they never leave anything out," says Simon.

"We're trying to follow nature," he adds. "Nature has millions and millions of years of experience. And us human beings, what do we have comparatively? Nothing." People are just starting to understand the mechanisms behind regeneration, he notes.

A class of genes called TBX is linked to the blastema's special knowledge. In salamanders, these genes are, obviously, active. In mice and adult humans they are not. When a certain TBX gene malfunctions in a mouse, the mouse doesn't grow forelimbs. When it's mutated in the human genome, problems can range from missing thumbs to truncated, flipper-like arms.

But check that bit about mice being nonregenerative. One transgenic mouse surprised scientists by making itself whole again.

One of the ways scientists mark individual mice in the lab for identification is to pierce their ears. When small holes were punched in the ears of a breed known as MRL mice, DARPA team member Ellen Heber-Katz, a professor in the molecular and cellular oncogenesis program in the Wistar Institute in Philadelphia, noticed that the holes filled in.

"This isn't supposed to happen," Badylak says with a laugh.

But it did give the team an idea. "One of our approaches is to take a regenerating species [salamanders], a partially regenerating species [MRL mice], and a nonregenerating species [conventional mice] and look at common things among them and the different things."

Susan Braunhut's lab at the University of Massachusetts Lowell has taken a major role in sorting out the commonalities and differences. A professor of biological sciences, Braunhut is attempting to identify the biological factors, genes aside, that cause cells to participate in blastema formation.

Being able to harness such a molecule could translate to therapies that eliminate scarring as well as regenerate tissue.

Braunhut's work, Badylak says, is vital for the team to meet its first-year goal: DARPA has challenged the team to identify at least one molecule that shows bioactivity toward a progenitor cell, a cell that participates in blastema formation.

"We need to know the regulators of these processes," Badylak says. "We need to know what molecules recruit these cells as well as which ones regulate gene expression."

Braunhut has made inroads in this area on her own. Three years ago, she built a "smart" bandage. It's an extracellular matrix enriched with specific growth factors that speed healing in specific types of wounds. This accomplishment serendipitously led to her collaboration with Badylak.

"The work was funded by DARPA, and my program manager had been working with Steve," she says. "He knew about my basic research into matrix and growth factors and told me to call [Badylak]. He said we were meant to meet. We did, and by the time we left, we had agreed to collaborate."

The pair found out about a DARPA opportunity and began searching for other researchers to join them, including Braunhut's former postdoctoral advisor, Lorraine Gudas, Revlon Pharmaceutical Professor of Pharmacology and Toxicology and chair of pharmacology at Cornell University, and regenerative gene expert Shannon Odelberg, assistant professor of internal medicine and of neurobiology and anatomy at the University of Utah.

On their own dime, the six met in Washington, D.C., and began to pursue the DARPA money with tenacity. "When this project came, it resonated with this team," Braunhut says. The idea had been "cooking" for some time with each of them, she notes.

Wrapped up in Braunhut's work is another mystery to solve. Some members of the team have already identified possible factors that propel progenitor cells to wound sites. What they don't know is whether these cells are derived from the adjacent tissue at an amputation site or are drawn from bone marrow. Could be both, Badylak notes. And once all this is understood, there's still the question of how to stimulate a regenerative response rather than a scar tissue response.

In 12 months, the team is expected to isolate a molecule that causes cells to migrate to a wound site and cause those cells to multiply and differentiate. The mystery molecule also must be genetically related to a blastema cell. "That's a lot of work," Badylak says.

But Braunhut is ready to go with assays that will help distinguish molecules in Badylak's biologic scaffolding or in Simon's salamanders that beckon cells or tell them to commit to becoming nerve, bone, or muscle.

If the team meets with success here, the next goal is to form a blastema in a nonregenerative animal. From there, a functioning digit on a mouse. And, further down the line, this team or another group of scientists will attempt to regenerate a fully functional limb on an adult human being. Of course, doing all this requires understanding not just the individual pieces of the puzzle, but also how all the components fit together. Braunhut is humbled but unbowed:

"If five or 10 years ago you were to say we'd be able to get a very complex three-dimensional structure to regrow in an adult, I'd say we wouldn't be able to do it.

"Today I say we might be able to do it. We're at the edge of what's in the realm of possibility."

The other team members also talk with cautious optimism. The six senior investigators think that not only are they well prepared in their individual areas of expertise, they're getting the right kind of support from the right kind of funding agency.

Typically, Badylak says, once investigators receive grants—from, say, the National Institutes of Health—they've got funding for a finite number of years, do their work, publish what they can, and file periodic progress reports throughout.

DARPA, he says, is different: "They give you extremely challenging problems and say, 'If we take away all the barriers, if we eliminate money as a limiting factor, we expect productivity. That's why each of the principal investigators on this project [has] gotten more money for this grant than they've gotten for any single activity in their career.

"Basically, they're buying our attention."

The team holds an hour-long biweekly conference call during which every team member plays a part, even when traveling abroad. A DARPA officer—who's also a scientist—participates in each of these calls.

The calls help DARPA assess the team's progress. If the team doesn't meet its goals, it could lose funding.

"But it also means that they know what the roadblocks are, what problems we have, what accomplishments we make," Badylak says. "I've worked on DARPA projects before. If things don't progress, they say, 'What's the issue? How can we help?'"

A lot of good can come from the attempts, notes Simon: "Even if we fail to make a digit regrow in a mouse, we could revolutionize how we deal with wounds in the clinic. To achieve better wound healing, less scarring, would be a major advance in medicine."

When officials at the defense department found out about Badylak's success in using biologic scaffolding to regrow the fingertips of the men from Cincinnati and Boston, they wanted to see whether the technology could help wounded soldiers.

"We told them it's not ready for prime time," Badylak says.

But the DOD pressed, saying that any finger regrowth—even a couple of centimeters—could greatly improve a wounded soldier's quality of life.

"They're saying if you can get extension of what's left of a finger, the finger can appose [think a pinching motion] the thumb," Badylak says, allowing a wounded vet to perform simple tasks such as putting a car key in the ignition or picking up silverware.

From the Civil War through the first Gulf War, the ratio of injured to killed soldiers stood at about 2.5 to 1, according to Badylak. In Afghanistan and Iraq, the DOD reports, the ratio is more like 9 to 1.

Because of advances in body armor, Badylak says, "Soldiers can withstand impact that would have killed them before, and the army is saying, 'What are we going to do with all these injured? What can we do to improve their quality of life?'"

So now Badylak is the principal investigator in two DOD-funded clinical trials set to take place in San Antonio, Texas, before the year is out.

Between five and 10 soldiers at Brooke Army Medical Center will participate in a trial that will attempt to regrow portions of their fingers. Twenty others at the hospital will take part in a second trial examining the effectiveness of biologic scaffolding in regrowing skin.

Doctors will apply scaffolding to the donor sites of burn patients who have had skin grafts, with the hope of accelerating the healing process at that site.

Why not the burn site itself? The donor site is cleaner and easier to work with, notes Badylak.

"If this works, that will give us the confidence to go to the primary wound," he says.

Badylak's lab is a noisy place. More than two dozen people work there, which is part of the reason. Another is the perpetual hum coming from the convenience store–style cooler against the wall.

Inside it are two clear plastic containers. One sits on an orbital shaker, the other on a rocking platform. Pale blobs slosh about in each. The blobs going in circles are pig bladders, the ones rocking back and forth are dog pancreases.

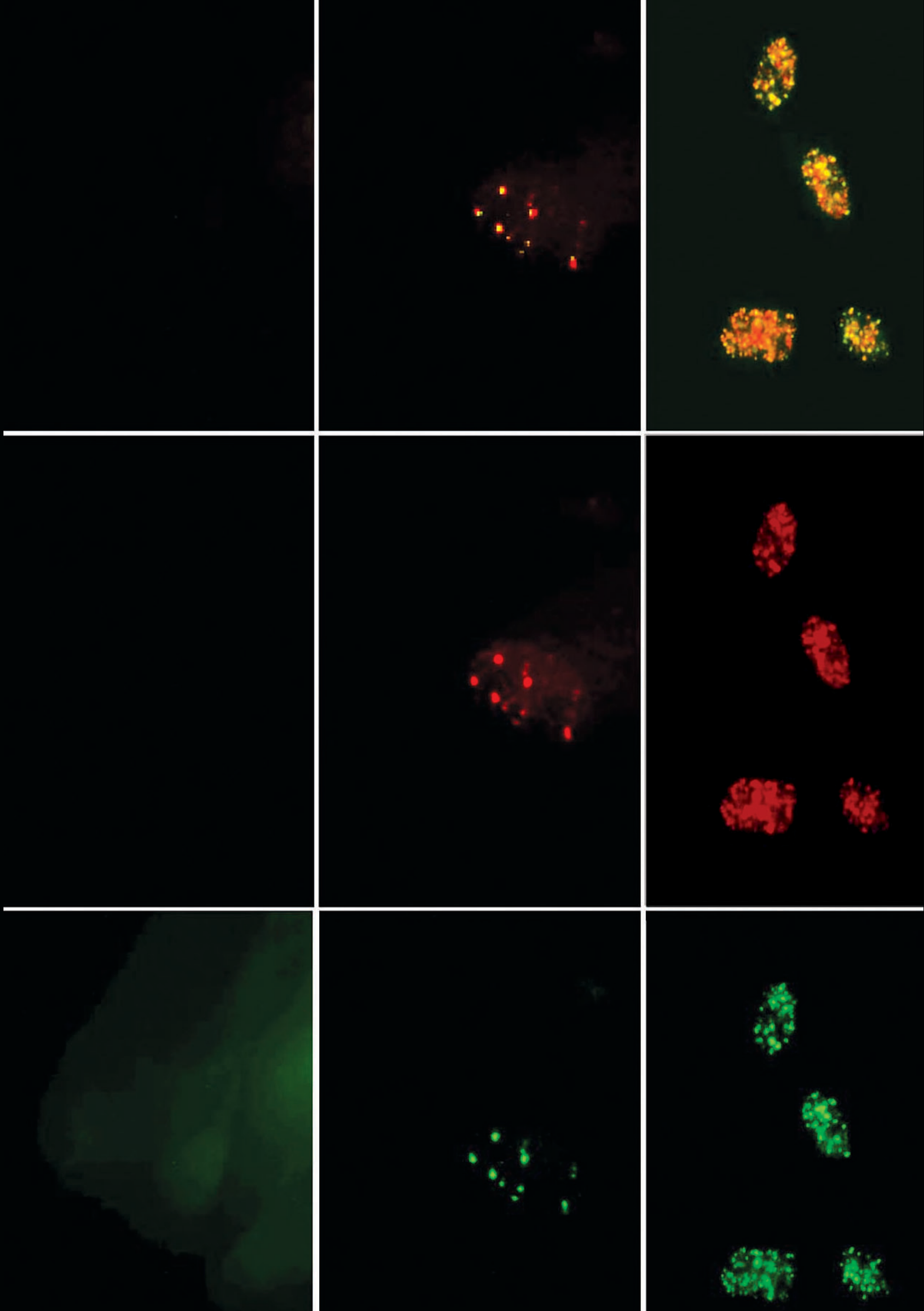
"It's a little gross," Badylak admits. "The reason they're so white is that the tissue no longer has cells in it." The organs are being washed in a solution that's stripping them of everything but the matrix, the material that cells hold onto as they form tissue. It's this material that Badylak used to help regenerate the fingertips of the men hurt by the band saw and model plane.

Two aisles over from the cooler, instruments are at work screening for the molecules within the matrix that prompt the kind of biologic response that allowed the men's fingers to become whole again and may contribute to the DARPA project's goal of regenerating an entire digit.

Badylak rattles off the list of questions this screening process could help answer: Why do stem cells accumulate? Why does biologic scaffolding have antimicrobial and antibacterial properties? Why do cells proliferate in the presence of the matrix? "We're developing assays to measure all of those things—proliferation, chemoattraction," he says.

Later, Badylak talks more reflectively: "If we can understand how to regrow a digit, why can't we use those same principles to regrow a kidney for patients on dialysis? Or a piece of the heart that was damaged by a heart attack? Or how about a lung for patients with emphysema?"

"That's what's gotten me really excited," he says, running his finger along a section of scaffolding formed like a trachea. "We're going to learn principles that will make many things possible." ■



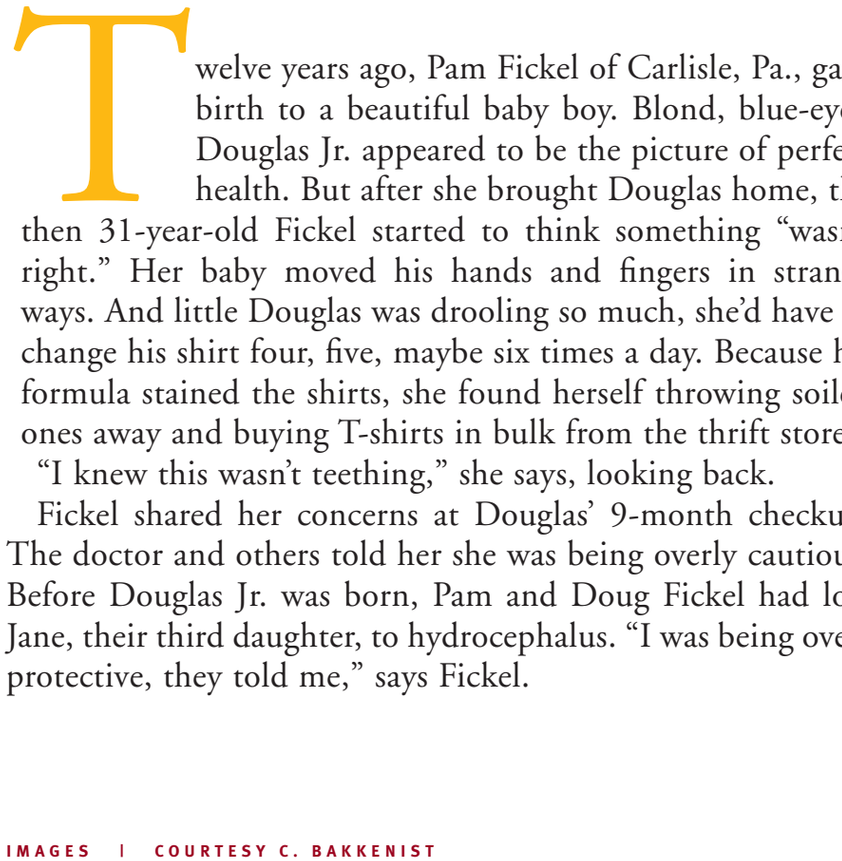
A PITT RESEARCHER AND A FAMILY IN CENTRAL PENNSYLVANIA ARE LEARNING FROM THE SAME RARE DISEASE | BY ERICA LLOYD

DIFFICULT GIFTS

Twelve years ago, Pam Fickel of Carlisle, Pa., gave birth to a beautiful baby boy. Blond, blue-eyed Douglas Jr. appeared to be the picture of perfect health. But after she brought Douglas home, the then 31-year-old Fickel started to think something "wasn't right." Her baby moved his hands and fingers in strange ways. And little Douglas was drooling so much, she'd have to change his shirt four, five, maybe six times a day. Because his formula stained the shirts, she found herself throwing soiled ones away and buying T-shirts in bulk from the thrift store.

"I knew this wasn't teething," she says, looking back.

Fickel shared her concerns at Douglas' 9-month checkup. The doctor and others told her she was being overly cautious. Before Douglas Jr. was born, Pam and Doug Fickel had lost Jane, their third daughter, to hydrocephalus. "I was being overprotective, they told me," says Fickel.



Imagine having cerebral palsy, cystic fibrosis, muscular dystrophy, and AIDS—and being highly susceptible to cancer. That's what it's like to have ataxia telangiectasia (A-T). This rare disease has pointed scientists toward a DNA damage control pathway central to good health. LEFT: Young human cells contain no detectable DNA damage (column 1). After more than 60 divisions (column 2), a protein called ATM (green) detects where both strands of DNA have been severed. ATM marks the breaks by labeling histone (red; it appears yellow when shown with ATM). Zapping the cells with ionizing radiation activates nearly all the ATM protein (column 3), which is responsible for kicking off the DNA repair process. Children with A-T don't have this vital protein.

IMAGES | COURTESY C. BAKKENIST



Douglas Fickel

COURTESY P. FICKEL

At a year, she tried again. *Please listen to me*. No one heard.

By the time Douglas' 15-month well-baby checkup came up, he was falling down 30 times a day. He'd knocked himself unconscious twice. The doctor watched Douglas take a few steps. He saw an eager boy toddling his way across the room and was about to pronounce him fit as a fiddle.

Fickel stopped him.

"I want to strip him down to his diaper," she announced.

Then Fickel suggested the little boy walk for the doctor again—this time all the way down the hall.

Without the cloak of cloth on the child, the doctor could see how Douglas' gait was different from that of other boys and girls. The toddler waddled forward, arms raised and contorted like duck wings, back arched, wrists limp, pointer and middle fingers spread out as though he was "signing a K badly," his mom recalls. This was how he always walked.

The doctor wanted to schedule a scan immediately. It could be a brain tumor, he said. It was Thursday, and the MRI people could fit Douglas in that day.

Fickel, who knew her boy had been living with whatever this was all his short life, said the appointment would have to wait until Tuesday. That's when Doug Sr. was returning from his hunting trip, and the couple had vowed they'd never again put the other in the position of hearing what they suspected would be a bad diagnosis alone.

"When I found out about Jane, I was by myself," says Fickel.

Fickel held her breath all weekend, hoping she'd made the right decision. Tuesday came and the doctors found nothing. More MRIs at the medical center in Hershey followed. Douglas was poked, prodded, and scanned for months, then years. The doctors always came up empty.

When Douglas turned 4, Fickel cancelled his appointments. Her son was walking pretty well. He wasn't falling down. Could he be getting better? At least he'd have some time away from all those tests.

At 5, red spider veins appeared in Douglas' eyes. When the Fickels went back to the doctor, he said, "The monster has reared its head."

He wasn't speaking of the Fickels' sweet son. The doctor was speaking of a rare disease known as ataxia telangiectasia, or A-T. When Douglas turned 4, his growth had outpaced the progression of his disease, so he seemed to get better for a while. But then the disease asserted itself again.

Ataxia refers to a patient's lack of motor control owing to progressive neurodegeneration. (The doctors in Hershey couldn't see anything on the brain scans because Douglas' brain probably appeared normal.) Telangiectasia (pronounced *teh-LAN-jick-TAY-sha*) refers to the fine spidery burst veins that often appear on the eyes and ears of children with the disease.

The burst veins are harmless. But most of the other symptoms of this childhood disease aren't.

A-T gradually cripples the development of the cerebellum so that as children with the disease grow older, they lose motor control. They have difficulty walking, and by their second decade, they are probably in wheelchairs. Eventually, their eyes won't stay on a page, so reading, as well as writing, becomes next to impossible. It's hard for them to talk. They are in constant motion—even as they sleep—so they are often very thin. It's not unusual for a bit of food to end up in a lung and cause pneumonia, which is particularly dangerous for them because A-T also compromises their immune systems. It is an exhausting disease.

The Fickels felt a strange sense of relief on hearing the diagnosis, as awful as it was. No more MRIs. And at least they knew what they were up against.

Imagine having cerebral palsy, cystic fibrosis, muscular dystrophy, and AIDS—that's analogous to what these kids and their families are dealing with. A-T–afflicted children are also highly susceptible to cancer. They are 1,000 times more likely to develop malignancies of the blood than the general population. Making matters worse, radiation therapy causes awful burns and is likely to kill them.

Why does it seem their own bodies have it in for them? It comes down to a gene called ATM, first cloned in the '90s by an Israeli researcher. The ATM cloning was "one of the last great" traditional cloning efforts before the Human Genome Project, says Christopher Bakkenist, assistant professor of radiation oncology at the University of Pittsburgh.

Only one in 40,000 children get A-T. But it turns out, the biology behind this rare disease is relevant to all of us.

Since the gene was cloned, scientists have learned that the ATM protein sits at the top of the DNA damage repair pathway. It's in charge of getting our bodies to respond appropriately when the most profound kind of DNA damage occurs—that is, when both strands in the double helix are completely severed.

We all experience double strand breaks throughout our lives. An x ray at the dentist's office induces them. Cosmic rays probably do. More importantly, the process our cells routinely go through to use oxygen results in double strand breaks. They are insidious. The good news? Unless you have A-T, your body knows how to cope with these lesions. It will either repair the problem or arrange for the cell to kill itself so it doesn't do something unwelcome as a mutation.

But Douglas and others with A-T don't have the ATM protein. So their bodies are subjected to the whims of rogue and mutant cells. Imagine trying to keep a Fiat running without a mechanic to fix and replace parts as they inevitably break. You'd probably need a push now and then.

When Douglas gets tired, he gets lots of help from his family, friends, and community. He was on a baseball team during elementary school. He didn't make many practices though—they were too taxing. Just sitting on the bench without losing his balance was a struggle. Sometimes at a game he'd sit in the outfield, and if a ball came his way, he'd yell to a teammate, "Could you get that for me?"

He learned to put his energy toward really important things. Like sliding into base. He'd say to his mom, "I've got to slide! I've got to slide!" That was the coolest thing to do, after

all. But the chance never seemed to present itself—until one time, when he was about 8. Douglas got all the way to third base and tagged it. Then he announced, "Okay, I'm safe. I'm safe, right?!" When the ump and other players agreed, he took several steps back toward second and slid into third.

"He was the happiest child in the world. He wouldn't let me wash his uniform," says Fickel.

She kept hoping that Douglas would be the exception, that he wouldn't end up in a wheelchair. He played kickball at the party for his 9th birthday. By 10 he couldn't; he depended on his wheelchair. Douglas, now 11, thinks it would be a good idea for him to meet the Steelers' Bill Cowher and give him some ideas for plays. He loves skateboarder Tony Hawk. His best friends are his older sisters, Sam and Emma. The world stops when country music star Toby Keith is singing.

Douglas still plays baseball, but now he rides an electric retrofit bike to get around the bases.

He hasn't been able to read since third grade, but he has a sharp memory. For a spelling test, he and his classmates were told to each pick 10 or so words from a list of 244. They would each be tested on the words they'd chosen.

Fickel got a call from the teacher.

"Douglas wants to do all 244," she said.

"Let him."

Guess who scored highest for accuracy.

Maybe you've heard this annoying adage from a wise grandmotherly type: Difficulty teaches us things we might not otherwise have known about ourselves. In the world of biomedical science, it's not unusual for researchers to study an anomaly to learn about what healthy bodies do. A-T offers a particularly revealing molecular dance. This harrowing and rare disease has pointed scientists toward vital clues to understanding the mechanisms involved in cancer and DNA repair.

Christopher Bakkenist has never met Douglas Fickel. But he, too, spends his days with A-T, though he doesn't have the illness.

Bakkenist, who was raised in the middle of England, studied and trained at the University of London, Oxford University, and St. Jude Children's Research Hospital in Memphis. Last year he joined the faculty at Pitt. He is 38, reserved, a still talker, and gravely serious about his research. His work is inspired by the idea that scientists can "actually make an impact and change the way people look at the world." If you ask how, he'll say the path is simple: "You put the diseased children first. As soon as we put ourselves first, we've lost it."

Before coming to Pitt last year, he worked as a postdoc with prominent ATM researcher Michael Kastan at St. Jude. By then, scientists had identified a number of important proteins that the ATM pathway activated, including a tumor suppressor called p53. This protein itself is profoundly powerful.

"It's mutated in 50 percent of all 100 kinds of cancer," notes Robert Abraham (PhD '81), vice president of oncology for Wyeth Research in Pearl River, N.Y., who studied pharmacology at Pitt.

"There's a very solid argument out there that if [cancer] patients don't have a p53 mutation, they have a mutation somewhere else in the p53 pathway. It's like a necessary milestone a cancer cell has to pass to become a fully malignant cell."

Several labs identified other important proteins that are set off downstream of ATM (which is a kinase, so it sets off chemical reactions). But no one could figure out exactly how ATM sounded the alarm that DNA damage was taking place, notes Abraham.

"One of the burning questions in the field was, *How does ATM actually respond to double strand breaks?"*

During his fellowship, Bakkenist created a sensitive reagent that allowed him to see in detail what was happening during the ATM response. Bakkenist and Kastan were then able to show that ATM is made up of at least two inactive molecules. When both DNA strands break after a blast of ionizing radiation, ATM releases two single, and no longer dormant, ATM molecules. The scientists also described the unexpected transfer of phosphates that takes place within the protein itself before the single ATM molecules send phosphates downstream to activate important proteins like p53. Those downstream actors stop the cell cycle to allow repair to occur or to set in motion the extinguishing of unrepairable cells.

A news article in *Nature* notes that Kastan and Bakkenist revealed that "the sensitivity, extent and speed of the ATM response are truly astonishing. Doses of irradiation that cause only a few [double strand breaks] in a human cell activate the majority of ATM within minutes."

It was a seminal finding, says Abraham: "The failure of this pathway explains the whole syndrome."

But how is ATM tipped off to a double strand break?

Chromosomes are made up of building blocks called chromatin that include DNA and proteins. Kastan and Bakkenist showed that changes to chromatin structure let ATM know there's a problem.

Bakkenist can see how such findings could open the door to better cancer therapies:

"If you can inhibit the [ATM] protein, you may be able to increase the efficacy of DNA damage therapy, including radiotherapy, in human cancer. The other approach is, if you can activate ATM artificially, you may be able to temporarily activate p53 as well. If you transiently activate p53, before the cancer is actually developed, you may be able to use the p53 to kill off precancerous cells.

"So you may be able to use it as a prophylactic cancer therapy, to prevent human cancer."

ATM has a sister protein that sits next to it at the top of the DNA damage pathway. It's called ATR (ATM related) and orchestrates the response to another brand of DNA damage—that caused by UV light. This response blocks the progression of DNA replication. (Mutations that pass through this pathway can show up as skin cancer.) Bakkenist is now interested in studying ATR, and Abraham is optimistic about what he'll find:

"This is really important work. I think that Chris is better positioned than just about anybody else to pursue this work. These are very large proteins that pose many challenges."

Because her son is at risk of developing cancer, Pam Fickel carefully monitors his lymph nodes to make sure they don't grow larger.

She had uterine cancer a few years ago. Fickel is a carrier of the mutated ATM gene (as is her husband; both parents must be carriers for a child to get the disease). There's a school of thought that says if she had been given radiation therapy or a drug that mimicked strong doses of ionizing radiation, the results could have been fatal.

Fickel knew about this risk only because of Douglas' strange disease. So Douglas, just by being himself, may have saved his mom's life. ■

FOR MORE INFORMATION, WE RECOMMEND THE A-T CHILDREN'S PROJECT: www.atcp.org

AN HONOR AND A PRIVILEGE

THE STORY OF A MEDICAL STUDENT | **BY THOMAS CONLON**



The following is an edited version of Thomas Conlon's graduation address. Conlon (MD '06) served as president of his class and delivered the speech at May's graduation ceremony.

You did it … with hard work and support from friends and family, the University of Pittsburgh, one of the finest medical schools in the nation, opened the door for you to attain your dream. And there you are, day number one. You are amazed by the diversity of your classmates—not necessarily in race or gender as we are so ingrained to take note of—but rather their dynamic personalities, how they carry themselves so differently but with such presence.

And you sit down in your sparkling new white coat and hear Dean Levine discuss the honor and privilege of medicine. You're hardly able to keep your jaw from hitting the floor. The painted portraits surrounding you, the cameras flashing from proud parents above, the oath taken. Your dream is realized. What an honor and privilege it would be.

And first year rolls on, and you're finding that, while you were a star in college, you are struggling to remain at average here. Or maybe you're at the top of the heap, and nobody can imagine the strain of living up to continued expectations. And you're finding that you aren't talking to your friends from home as much as before because, well, frankly, they just can't understand. And you're in a long-distance relationship, which is strained because you know that for every hour you aren't studying that likely means another point off your test, and you can't afford that. But of course your boyfriend or girlfriend doesn't understand that. Or you go home to your spouse and, though you thought it would be a welcome thing to have something outside of the medical world, you find you're becoming more detached. And your parents call, but they don't understand the world of medicine, or conversely one of them is a practicing physician and keeps telling you that she "understands." But she's not here, and she doesn't know.

The end of second year comes, and you have to sit for boards. Mr. Levitt has warned you of an eight-week schedule of insanity, which you scoff at and discard for your own schedule. That turns out to be 10 weeks of even greater insanity. This one test determines whether you can be an orthopod, a neurosurgeon, whether you can match where you want. The test comes and goes. Immediately afterward you drive out to a friend's cabin in the middle of nowhere, and you sit with a fishing rod between your legs and a glass of milk at your side, finally able to feel as though you've escaped. That's when it hits you: You don't really know if you like the person you're becoming.

In third year your clinical rotations begin, and you don't know the computers, and you're not answering the attending's questions right, and you've got to go into the patient's room right now to get a full history and physical to turn in by morning, and you sit down at the bedside, shuffle some papers, look at your watch then lift your head up—and your eyes meet. Looking back at you are the eyes of a male, a female, a white collar, a blue collar, a no collar, a broken hip, a stage-four cancer, a 10-year-old, a 100-year-old. And *wham.* You only knew vaguely this feeling when applying to medical school. You tried your best to put it into words when asked, "So why do you want to become a doctor?" Here it is, and words don't suffice. Those eyes read of fear, of realized mortality, of experience. They want your help. At that moment, you recognize your responsibility. And you're partially stunned because you want nothing more than to embrace it—the whole thing. At that same moment, you gain some understanding of the first two years, how they provided you with the intellectual and emotional framework you'd need.

It's 4:30 in the morning and you wake up and you're tired but ready to roll. And you hop on the bus and you look at the worn faces of the janitors, the security guards, the line cooks, and you realize the difference between people who go to work and what you get to do. And you get off the bus and the driver says, as always, "Have a nice day," 'cause that's what they do in Pittsburgh. And you get off and, even though it's Wednesday and summer and 4:45 in the morning, blurt out, "Go Stillers," because that's what they do in Pittsburgh.

And you walk into the building and, as a potted plant is to someone with pica, so is that morning cup of Joe to you that you're brewing in the conference room. And you're in Children's and you watch as 2-year-old Sally, who came in with a septic joint, waddles with her back to you, her little hand completely engulfed by her father's massive paw, she in only a diaper. And you can't help but smile. And you're at the VA, and there's old man Dawkins with his IV pole and his back to you in the hall, gown on, but he is in neither diaper nor any sign of undergarments, and again, you can't help but smile. And you're on ortho rounds, and you just benched 250. And you're in surgery and you—cut that fascia really well (or whatever gets you surgeons excited). And you find that attending who loves to teach and does it in such a way that you actually learn, and you really want to go home and read to continue the conversation at another level.

And it's 5:30 p.m. and you're getting out a little early because it's short call. All your patients are tucked in; you're thinking about dinner; then your pager goes off. You dial the number and on the other end of the line you hear, "This is UPMC quality control. We have a report of inappropriate touching of one of our elderly female patients and would like you to swing by our office immediately." Your stomach drops. You try to figure out whether you even have an elderly female patient in your care when you start hearing childish giggling over the other end of the phone. "Real funny … Thomas." It's the standard happy hour page, the bat sign that someone had a rough day and needs to unwind, and you wouldn't mind a quick glass of milk yourself.

As your friends roll into the bar, you remember you have to call one of your buddies, so you stand outside and get in touch with Joe—one of your closest pals from college. He asks about school, and you tell him that it's brutal, torture, all the words you've used in the past with him during your infrequent conversations. But he knows you love it. And for the first time in months, you stop yourself midsentence and ask—for real this time—"Joe, how the heck are you?"

When you get home, you check the alarm to make sure it's set for … oh, four hours from now and turn on the radio to make sure the volume is high enough. Then you are reminded by the sports commentator that yes, it's true, the White Sox really did win the series and are world champions. And you can't wait to wake up tomorrow.

Doctors, sharing this with you has been the absolute highest honor and privilege. ■

JIM BURKE

DISTURBING DEVIATIONS

JUST ANOTHER DAY IN THE FRONTAL LOBE

BY KATRINA FIRLIK

Katrina Firlik (Res '02) is a neurosurgeon practicing in Greenwich, Conn. In her recently released memoir, Firlik recalls stories from her days training at the University of Pittsburgh, including the scarce details she was able to learn of "Mr. Doe"—a patient who died within 24 hours after entering the hospital with multiple traumas. She admits he was someone she might have otherwise forgotten but for a drop of blood a bad cut on his scalp left on her white coat. The drop served as a reminder of the man the rest of her busy week. She writes, "If every patient left a stain, a resident's life could very well become an unbearable mess. A stain every once in a while, though, can probably help keep us human. That realization must have been one reason I kept a journal during my training. I knew I would otherwise forget along the way, partly because there was too much to remember and partly because I might want to forget." The following is another memorable "stain" Firlik shares in her book.

I had the privilege of working with stellar pediatric neurosurgeons whose reputations brought patients in from all over the neighboring states and beyond. We saw the most complex, most bizarre, and most tragic of cases. Because modern medicine has become so good at treating every symptom, I was continually amazed at the children who were able to survive so long with so little brain function, with mothers, fathers, and hired help attending to every need and hauling around what amounted to miniature ICUs in their minivans. I became comfortable with conflicting emotions, thinking both "How touching!" and "How strange!" at the same time.

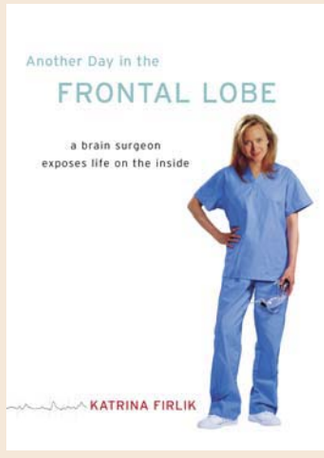
I had to perform a spinal tap on a child who had been neurologically devastated at birth. While I had the needle in his back, his mother mentioned that it was a good thing that she had forgotten to bring his Passe-Muir valve (an insert for a tracheostomy that allows a patient to talk). She explained that, this way, he would remain quiet through the spinal tap. I expressed some surprise that he actually had a Passe-Muir valve. I knew that his brain was not capable of speech or even thought. "No, you're right, he's completely nonverbal," she confirmed, very matter-of-fact and even smiling, "but he does make noises." This was not the first time I made a mental note to avoid making assumptions.

At one point, late into my senior resident year, I was rudely awakened to the fact that I had become perhaps too jaded in dealing with the tragedies of neurological devastation. I had become overly accustomed to our clinics, going from exam room to exam room, one featuring a mother waiting quietly while she casually suctioned her daughter's tracheostomy, another featuring a 12-year-old boy whose legs were so rigid and contorted that it was nearly impossible for his mother to change his diaper.

I walked into yet another examining room after checking the patient's chart. It was a brand-new consult: 18 years old, cerebral palsy, spasticity. Okay, okay, I've seen this before, I just need to get a good history before my attending walks in. Efficiency is key. I looked at the patient for a second: very skinny, special wheelchair, arms contracted, head support in place, mouth hung open. It was clear I wasn't going to get the story from him, so I turned to the parents, my back toward the patient, and started to take down the history. The mother's account went back 18 years, recounting her pregnancy in detail. She was helpful but a bit long-winded, so I jumped in after a few minutes with some pointed questions. As a rule I make an effort to let people finish their stories before I butt in, but sometimes I have to break my own rule. There were a number of other patients waiting, and I didn't really need to know all the specific dietary details.

As I sat, dutifully recording the list of medications, allergies, and operations, my mentor walked in. I cringed. I was hoping to have at least the history done so I could present him with a nice summary. He sat down on the examining table, the only seat left in the cramped room. After introducing himself, he surveyed the compact scene—the patient, the parents—and then focused his gaze back on the patient. After what seemed like several, almost uncomfortably quiet, seconds, he looked the patient in the eye and asked: "So, when did you graduate from high school?" The young man's face lit up like I had no idea it could.

My mentor had noticed something I'd missed. The patient was wearing a large high school ring, so large that it looked a little silly on his bony finger. His body, far more than his mind, had borne the brunt of his cerebral palsy. He was a proud, beaming high school graduate. His mother pointed out the specialized computer, attached to his wheelchair, that helps him communicate. For the remainder of the visit I sat in the corner, duncelike, humbled by the enormity of this ring. ■



Excerpted from Another Day in the Frontal Lobe *by Katrina Firlik. © 2006 Katrina S. Firlik, MD. Reprinted by arrangement with The Random House Publishing Group.*

MATCH RESULTS
CLASS OF 2006

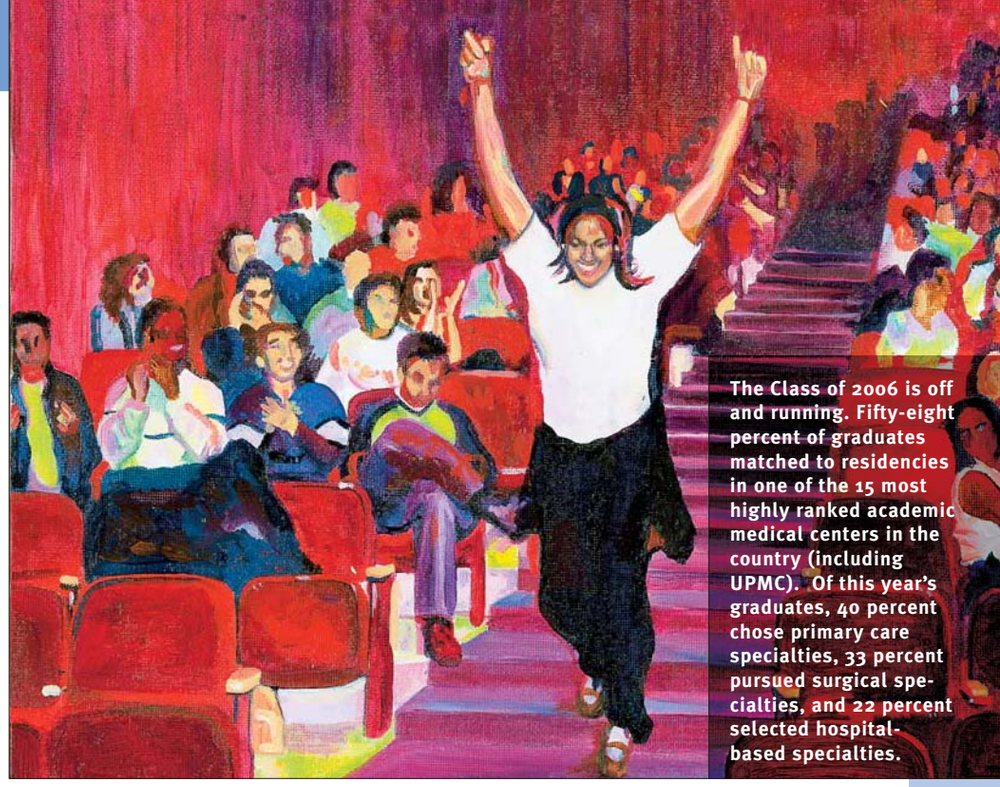


ILLUSTRATION ALISON ZAPATA / PHOTO CIDDE

The Class of 2006 is off and running. Fifty-eight percent of graduates matched to residencies in one of the 15 most highly ranked academic medical centers in the country (including UPMC). Of this year's graduates, 40 percent chose primary care specialties, 33 percent pursued surgical specialties, and 22 percent selected hospital-based specialties.

ANESTHESIOLOGY
Desciak, Matthew
Milton Hershey Medical Center/Penn State, Pa.
Hache, John
UPMC Medical Education Program
Hall-Burton, Denise
UPMC Medical Education Program
Hsieh, Vincent
Stanford University Programs, Calif.
Lee, Jerome
UPMC Medical Education Program
Malec, Chris
Case Western/University Hospitals, Ohio
Muhly, Wallis
UPMC Medical Education Program
Nguyen, Jessica
Brigham & Women's Hospital, Mass.
Steinoff, Stephanie
Hospital of the University of Pennsylvania
Yuditskaya, Susan
New York Presbyterian Hospital—Columbia

EMERGENCY MEDICINE
Beierle, Jessica
UPMC Medical Education Program
Betz, Amy
UPMC Medical Education Program
Ferguson, Erika
University of Chicago Hospitals, Ill.
Landry, Jonathan
Albert Einstein Medical Center, Pa.
Miller, David
Geisinger Health System, Pa.
Shum, Leo
UPMC Medical Education Program
Tobias, Adam
UPMC Medical Education Program
Weinberger, Lauren
Hospital of the University of Pennsylvania

FAMILY PRACTICE
Dacal, Kirsten
UPMC St. Margaret
Forrest, Paige
UPMC St. Margaret
Milne, Holly
UCLA Medical Center, Calif.
Torres, Carlos
UPMC St. Margaret

INTERNAL MEDICINE
Afshar, Kia
Johns Hopkins Hospital, Md.
Altman, Richard
Mt. Sinai Hospital, N.Y.
Balfour, Pelbreton
University of Virginia
Brown, Daniel
UPMC Medical Education Program
Charlton, George
University of Virginia
DePaul, Scott
Wilford Hall Medical Center, Lackland AFB, Texas
Diederich, Emily
Northwestern McGaw/NMH/VA, Ill.
Downing, Tricia
Einstein/Jacobi Medical Center, N.Y.
George, Ezmin
University of Chicago Hospitals, Ill.
Geynisman, Daniel
UPMC Medical Education Program
Hong, Eric
UCLA Medical Center, Calif.
James, David
New York Presbyterian Hospital—Cornell
Kim, Young-Sin
California Pacific Medical Center, San Francisco
Levinthal, David
University of Michigan Hospitals—Ann Arbor
Lin, Eleanor
Mayo Graduate School of Medicine, Minn.
Madathil, Ronson
Case Western/University Hospitals, Ohio
Muldrow, Lekisha
UPMC Medical Education Program
Patel, Kartik
Thomas Jefferson University, Pa.
Prentice, Nikkisha
Hospital of the University of Pennsylvania
Ranganathan, Anjana
Boston University Medical Center, Mass.
Rockacy, Matthew
UPMC Medical Education Program
Sallam, Karim
Stanford University Programs, Calif.
Scheers-Masters, Joshua
SUNY HSC Brooklyn, N.Y.
Vitale, Matthew
Brigham & Women's Hospital, Mass.

INTERNAL MEDICINE—PEDIATRICS
Conlon, Thomas
UPMC Medical Education Program
Krier, Joel
Rush University Medical Center, Ill.
Patel, Sapan
University Hospital, Cincinnati, Ohio

INTERNAL MEDICINE—PRELIMINARY
Brennen, Peter
UPMC Medical Education Program
Vilsaint, Kevin
Maimonides Medical Center, N.Y.

INTERNAL MEDICINE—PRIMARY
DallaPiazza, Michelle
Hospital of the University of Pennsylvania
Mavrich, Kate
Rhode Island Hospital/Brown University
Muo, Ijeoma
Einstein/Montefiore Medical Center, N.Y.
Sinton, Toby
University of Washington Affiliated Hospitals

MAXILLOFACIAL SURGERY
Yeung, Alison
UPMC Medical Education Program

NEUROLOGICAL SURGERY
Abla, Adib
Barrow Neurological Institute, Ariz.
Grosvenor, Ashley
Stanford University Programs, Calif.
Jian, Brian
University of California, San Francisco
Lehmann, Emily
University of Michigan Hospitals—Ann Arbor
Tormenti, Matthew
UPMC Medical Education Program

NEUROLOGY
Reichman, Jordan
New York Presbyterian Hospital—Cornell
Stephenson, Sharisse
Tufts University School of Medicine, Mass.

NEUROLOGY—PEDIATRICS
Sundararajan, Kripa
New York University

OBSTETRICS/GYNECOLOGY
Byno, Ashley
Christiana Care Health Services, Del.
Donnellan, Nicole
UPMC Medical Education Program
Dryden, Emily
Ohio State University Medical Center
Jacobs, Stephanie
Einstein/Montefiore Medical Center, N.Y.
Reinhart, Gretchen
Medical University of South Carolina
Warner, Sarah
University of Rochester/Strong Memorial Hospital, N.Y.

OPHTHALMOLOGY
Ali, Tofik
Albert Einstein College of Medicine, N.Y.
Joshi, Amar
UPMC Medical Education Program
Reese, Matthew
Medical University of South Carolina, Charleston
Wu, Eric
UPMC Medical Education Program

ORTHOPAEDIC SURGERY
Aboka, Alexander
University of New Mexico School of Medicine
Amorosa, Louis
New York Presbyterian Hospital—Columbia
Rabuck, Stephen
Northwestern McGaw/NMH/VA, Ill.
Schulz, Jacob
Albert Einstein Medical Center, Pa.
Westrick, Edward
UPMC Medical Education Program

OTOLARYNGOLOGY
Dunklebarger, Joshua
UPMC Medical Education Program
Sneshkoff, Nikolaus
Tripler Army Medical Center, Hawaii
Sun, Gordon
University Hospital, Cincinnati, Ohio
Tobey, Allison
UPMC Medical Education Program

PATHOLOGY
Biller, Elizabeth
Ohio State University Medical Center, Columbus
Uchin, Jeffrey
Cleveland Clinic Foundation, Ohio

PEDIATRICS
Abikoff, Cori
Children's Hospital of Pittsburgh of UPMC
Beck, Andrew
Cincinnati Children's Hospital Medical Center, Ohio
Brown, Crystal
University of Maryland Medical Center, Baltimore
Campfield, Brian
Children's Hospital of Pittsburgh of UPMC
Castiglioni, Cynthia
Northwestern McGaw/CMH, Ill.
Gokhale, Janaki
Thomas Jefferson University/Dupont Children's Hospital, Pa.
Haupt, Alicia
Children's Hospital of Philadelphia, Pa.
Jerardi, Karen
Cincinnati Children's Hospital Medical Center, Ohio
Kiger, James
Medical University of South Carolina
Kim, Nahmah
Children's National Medical Center, Washington, D.C.
Rice, Carryn
Palmetto Health Richland Hospital, Columbia, S.C.
Srinath, Arvind
Johns Hopkins Hospital, Md.
Stenger, Elizabeth
Children's Hospital of Pittsburgh of UPMC
Welter, Jacqueline
Northwestern McGaw/CMH, Ill.

PHYSICAL MEDICINE & REHABILITATION
Johnson, Jeffrey
Northwestern McGaw/RIC, Ill.

PLASTIC SURGERY
Keith, Jonathan
UPMC Medical Education Program

PSYCHIATRY
Asare, Akua
Jackson Memorial Hospital, Fla.
Walters, Julian
University of Arizona Affiliated Hospitals, Tucson

RADIATION ONCOLOGY
DeFoe, Sarahgene
UPMC Medical Education Program

RADIOLOGY DIAGNOSTIC
Chang, Wilson
Stanford University Programs, Calif.
Gold, Michelle
Thomas Jefferson University, Pa.
Lynn, Karen
William Beaumont Hospital, Mich.
Shah, Vinil
University of California, San Francisco

RESEARCH/ADVANCED STUDIES
Bataille, Feguens
Research
Harewood, Peter
Advanced studies/MPH
Ryan, Alexander
Advanced studies/PhD
Swihart, Andrew
Anesthesiology research

SURGERY—GENERAL
Brown, Nefertiti
SUNY HSC Brooklyn, N.Y.
Bucher, Brian
Barnes-Jewish Hospital, Mo.
Erickson, Andrew
Washington Hospital Center, Washington, D.C.
Falcone, John
UPMC Medical Education Program
Hsu, Albert
Beth Israel Deaconess Medical Center, Mass.
Johnston, W. Cory
University of Utah Affiliated Hospitals, Salt Lake City
Neal, Matthew
UPMC Medical Education Program
Nordman, Cory
UPMC Medical Education Program
Siriratsivawong, Kris
Naval Medical Center, San Diego, Calif.
Suydam, Erin
Medical College of Georgia
Torres, Arturo
Naval Medical Center, San Diego, Calif.
Trivedi, Premal
Case Western/University Hospitals, Ohio
Washington, Christopher
Allegheny General Hospital, Pa.

PRELIMINARY SURGERY
Campbell, Brian
Washington Hospital Center, Washington, D.C.
Forbes, Jonathan
Johns Hopkins Hospital, Md.
Gallup, Theresa
University of Texas—San Antonio

UROLOGY
Bassett, Jeffrey
UCLA Medical Center, Calif.



CLASS NOTES



Ruth Snyder Masters and Raymond Masters met on the first day of class.

'30s

One of only two women in the class of 1935, **Ruth Snyder Masters** (MD '35) says she picked her future husband of 64 years, the late **Raymond Masters** (MD '35), out as "one of the nice ones" on their first day of medical school. The two married in 1936, though the infamous flood of that year left the groom tending to flood victims and delayed their wedding by two weeks. Ruth Masters' career in family practice spanned seven decades. She estimates she delivered 3,200 babies, including more than 200 home deliveries. She saw patients at her East McKeesport office and McKeesport Hospital. In 1979, she became the first woman to be elected president of the hospital staff. Since retiring four years ago at the age of 88, Masters has remained an active member of the hospital's ethics committee.

'70s

As a medical student at Pitt, **Michael Wusylko** (MD '77) never imagined that he would stay so close to one of his favorite professors, infectious disease specialist and Pitt professor **George Pazin** (MD '64). Wusylko, an internist, currently shares his practice in Cranberry, Pa., with Pazin's son John Pazin. As a clinical preceptor, Wusylko welcomes Pitt medical students into his practice each year for three-week rotations. Last year, Pitt med students honored him with the Award for Excellence in Clinical Precepting.

'80s

Frightened, desperate, and ill, lupus patients travel from as far away as the Middle East and South America for a diagnosis. Pittsburgh is where many of them finally learn the cause of their debilitating and unpredictable symptoms. Lupus is notoriously difficult to diagnose. On average, a lupus sufferer waits four years before the disease is recognized. **Susan Manzi** (MD '85, Rheumatology Fellow '91), cofounder and codirector of the Lupus Center of Excellence at Magee Womens Hospital and Pitt associate professor of medicine, developed a blood test using complement C4 positive proteins that will help physicians detect lupus. Her research shows that the protein binds to red blood cells during lupus flare-ups. With this test, physicians will be able to better diagnose the disease and start appropriate treatment.

Donald Yealy (Emergency Medicine Resident '88, Airway Management and Out of Hospital Cardiac Arrest Fellow '89) is professor and vice chair of emergency medicine at Pitt. In the past 15 years, he has won five teaching awards, including the 2001 National Teaching Award from the American College of Emergency Physicians. Most recently, Yealy received the Hal Jayne Academic Excellence Award from the American Society for Academic Emergency Medicine for work that helps emergency room physicians determine the severity of community-acquired pneumonia and heart failure. He is currently working with Pitt professor of medicine **Michael Fine** (Chief Medical Resident '87) and Pitt professor of critical care medicine **Derek Angus** (Critical Care Medicine Fellow '91) on ways to identify and treat acute pneumonia and sepsis in the emergency department.

Steve Burton (Internal Medicine Resident '89, Hematology/Oncology Fellow '92, Radiation Oncology Resident '95) is at UPMC Shadyside. Burton uses "high-tech toys" like linear accelerators to treat cancer. The machines precisely target tumors and destroy them with radiation, saving patients from invasive surgery. Burton, who is a clinical assistant professor of radiation oncology, is conducting research to demonstrate the effectiveness of image-guided radiation treatment for tumors.

'90s

Dave Thomson (Emergency Medicine Resident '90) came to Pitt hoping to be on the front lines of

GARY WILLIAMS

TOXIC AVENGER

Ask Gary Williams (MD '67) what he considers to be the most dangerous substance that humans ingest, and you'll receive a surprising answer: food.

"Think," he says, "every plant is a little chemical factory with substances to fight off its natural pests." He explains that these toxins also can affect humans. Other natural toxins run rampant as well, including dangerous molds on peanuts and corn, which contribute to the high incidence of liver cancer in humid Asian climates.

Williams, professor of pathology at New York Medical College, discussed other food-borne dangers as a delegate in the World Health Organization's Expert Committee on Food Additives' June meeting in Rome. An expert in toxicological pathology and chemical carcinogenesis, Williams researches everything from off-the-shelf consumer products to pretrial pharmaceuticals. New York Medical College recently recognized him with the 2005 Dean's Distinguished Research Award for his innovative methods and discoveries.

Williams recalls a recent incident in the United Kingdom in which six volunteers nearly died during a drug trial. His work attempts to prevent such things from happening. It includes discoveries such as an antibiotic that caused sunlight to mutate

medicine. In Pittsburgh, he had the chance to work outside of the hospital with Pittsburgh EMS as part of his hospital rotations. "It was an incredible experience," he says. Thomson was recently named director of emergency medicine at St. Joseph's Hospital Health Center in Syracuse, N.Y., where he still enjoys working with the local EMS providers as medical director for ambulance and emergency services. He also collaborates with fellow Pitt trainee **Kevin Hutton** (Emergency Medicine Resident '90), CEO of Golden Hour Data Systems, developing software and communications tools for air transport providers.

Padmavati Garvey (MD '92), a classical Indian dancer, has trained in the ancient *Bharatanatyam* style since her childhood in Pittsburgh and now performs with a dance troupe in New York. She and her daughter are eagerly learning the *Kuchipudi* style. In her professional life, Garvey, whose father worked in Pitt's pathology department, is an ob/gyn at the Westchester Medical Center of New York Medical College. Her research examines how economic factors influence a woman's decision to use or not to use contraception. She also is studying the relationship between breast-feeding and premenopausal breast cancer.

As a child, **Teresa Smith** (MD '97) admired the Pitt degree hanging over the desk of **John Bono** (MD '48), who removed her tonsils. He was one of many Pitt doctors who impressed Smith with their intellect, compassion, and skill. Although she had always been interested in medicine, Smith spent 10 years teaching high school chemistry and physics, until, she says, "I realized it was time." She took the MCATs, thinking that a bad score would show her that she should give up all thoughts of medical school. After doing well on the exam, she then applied only to Pitt, sure that a rejection letter would offer proof that she didn't belong in medicine. She is now one of around 150 neurointensivists in the United States. She became director of neurosurgical intensive care for the University of Michigan Health System last year.

Eileen Everly (MD '99) is the new medical director of the Reach Out and Read program at the Children's Hospital of Philadelphia. The national nonprofit campaign provides children from birth to age 5 with a new, age-appropriate book at each well-baby visit. Everly, who fell in love with the program during her residency at the University of Maryland, encourages parents to spend time every day reading aloud to their children, even as newborns. For bilingual families, the program provides books in other languages, including Korean, Spanish, French, and Vietnamese. Although she arrived at Pitt intending to become a neurosurgeon, Everly is now a pediatrician. She says, "Kids are just the best people. They're full of joy and hope, and every day at least one of them makes me laugh."

—Alicia Kopar, Jaclyn Madden



Members of the Class of 1996 and family gathered at Doc's Place in Shadyside before this year's Scope and Scalpel. From left: Karen Kreiling, Leila Kahwati, Richard Oh (with daughter, Elena), Anna Peris, Marshal Peris, James Jarvis, Elizabeth Woo, Erica Jarvis, Nickie Kolovos, and Benedict Woo recall the glories of performances past.



Williams

DNA—until Williams determined what was responsible and guided the pharmaceutical company to engineer it out—and an anti-estrogen drug that induced liver tumors in rats, but not humans. "We have to have the greatest assurance of safety before administering drugs to any people," he says sternly.

Williams is especially proud of receiving the Enhancement of Animal Welfare Award from the Society of Toxicology for developing testing systems that don't use animals. The nutrient medium he developed for culturing liver cells in vitro led to a pioneering way to assess chemical DNA damage and was one of the many reasons the American Chemical Society named him a distinguished scientist.

In his consumer product studies, Williams has calmed fears about popular substances like tooth whitener and hair coloring. The bottom line for those products? "No harmful substances are released into the body," he says.

It's nice to hear some things in the grocery store are safe.

— Jennifer Dionisio

THE WAY WE ARE
CLASS OF '96

During med school, the Class of '96 used to get together at Doc's Place in Shadyside for camaraderie and cheesy pizza. What better place to gather before attending the Class of 2006's production of Scope and Scalpel and recall their own? Ten years before, they parodied *A Chorus Line* and themselves. They danced in lab coats and silver top hats, but instead of singing, "One singular sensation, every little step he takes," they sang "Done with confabulation and the new curriculum."

Nickie Kolovos (MD '96) is credited with the chorus line idea. She's currently assistant professor of pediatrics and medical director of the trauma unit in the pediatric ICU of Washington University in St. Louis. One Christmas Eve, a 6-year-old girl with influenza myocarditis, a rare inflammation of the heart due to influenza infection, was rushed to Kolovos' unit. Her team performed CPR for two hours. Kolovos doubted her patient would live. Now every few months, she gets a friendly visit from her healthy young patient and the child's father.

Kolovos says she enjoys working with children because their health issues are uncomplicated by a history of life choices: "Everything about their physiology makes sense."

Marshal Peris (MD '96, Res '01, Fel '02), the class president who admits to stumbling through Scope and Scalpel choreography 10 years ago, now lives in a place named Mount Kisco. But his New York plates read: BLKNGOLD, and he holds Steelers season tickets. For Super Bowl XL, he traveled to Detroit with **Louis Klieger** (MD '96, Res '00), **Walter Delgaudio** (MD '96), **James Jarvis** (MD '96, Res '99), and **Benny Woo** (MD '96, Res '00) to watch the Steelers win the Lombardi Trophy.

At Northern Westchester Hospital Center, Peris is the only full-time orthopaedic spine surgeon. He treats degenerative conditions of the spine as well as traumatic injuries. Peris says he is impressed that many of his classmates went on to pursue specialized training.

One such colleague is **Brian Pettiford** (MD '96, Res '01, Fel '03). His father and grandfather were mechanics well known in Tifton, Ga. Their hands could fix anything. After his maternal grandmother died from a heart attack, Pettiford was moved to devote the skilled hands he inherited to thoracic medicine. He is now a Pitt clinical assistant professor of surgery, working primarily with lung afflictions. He attempts to uphold his soft-spoken grandmother's gentleman ideal through his interactions with patients and colleagues. — *Alicia Kopar*

IN MEMORIAM

'40s

HERMAN BEARZY
MD '43B
MARCH 18, 2006

WILLIAM F. BAIRD
MD '45
APRIL 15, 2006

'50s

JAMES L. HOOBLER
MD '55
DEC. 5, 2005

THOMAS E. CADMAN
MD '56
MARCH 15, 2006

RICHARD DOBIES
MD '57
MARCH 16, 2006

'60s

MELVIN KADEN
MD '63
APRIL 1, 2006

'70s

RANDALL KRAMER
MD '72
MARCH 1, 2006

'80s

D. RICHARD STRAUSBAUGH
MD '80
MAY 13, 2006



Hogarty

GERARD HOGARTY

JULY 14, 1935–APRIL 7, 2006

Gerard Hogarty was a rare gem. With no MD or PhD degree, he was a self-taught psychiatric researcher who had an enormous impact on the way we treat schizophrenia. The professor of psychiatry came to the University of Pittsburgh in 1974 with a master's degree in social work and a decade of experience in schizophrenia research.

When Hogarty entered the field, schizophrenia treatment was limited mostly to medication, because it had been demonstrated that psychoanalysis did not work, says his colleague, Rohan Ganguli, Pitt professor of psychiatry. "Gerry showed that there was a powerful role for psychological treatments in improving the lives and the outcomes for those with schizophrenia." With colleagues at Pitt, Hogarty demonstrated that early intervention that involved and educated the patient's family could reduce the chance of relapse and improve outcome. "That has become absolutely standard treatment around the world," says Ganguli. —*Chuck Staresinic*



Leon

DONALD LEON

AUG. 19, 1932–JUNE 21, 2006

Donald Leon (Fel '64) began and ended his medical career at Georgetown University Hospital, but his years there were bookends to a quarter century of service at the University of Pittsburgh. The noted cardiologist was a master of the American College of Cardiology and former dean of Pitt's School of Medicine.

Leon arrived at Pitt in 1963 as a research fellow in cardiology. Five years later, as an assistant professor, he was selected as one of the first six American Heart Association Teaching Scholars in Cardiology.

"It was quite a feather in his cap," notes James Shaver, a Pitt professor of cardiology. "He excelled in bedside teaching and lecturing."

Leon was dean of the school of medicine from 1979 to 1984. He was instrumental in the recruitment of transplant surgeon Thomas Starzl in 1981, oversaw the restructuring of the school's basic science departments, and was one of the founders of Family House, a nonprofit that assists and houses families traveling to Pittsburgh for lifesaving care.

"It really made an impression, both on the city and on those coming," says Shaver regarding Family House. "It helped to build the image of Pitt that drastically changed in the 1990s as people came from all over the country and all over the world." —*CS*



Wallace

BILL WALLACE

FEB. 26, 1944–MAY 28, 2006

Those who knew him say Bill Wallace changed Pitt's School of Medicine forever and for the better in just two years. Arriving as assistant dean of student affairs in 1979, Wallace became the school's first dean of minority affairs before he left in 1981.

"He rallied the medical students, became actively engaged in the admissions process, met with faculty to emphasize the benefits of diversity, and began surveying all applicants," said Jeannette South-Paul (MD '79), Pitt's Andrew W. Mathieson Professor and chair of the Department of Family Medicine. "His persistence, dedication, and focus created a foundation for reaching out to minorities."

Wallace was a graduate of Howard University, New York Medical College, and Harvard University, where he received a PhD in microbiology. His legacy at Pitt, says South-Paul, includes the talented minority students that Pitt attracts annually. —*CS*



Wiener

EUGENE S. WIENER

FEB. 28, 1940–JUNE 29, 2006

Eugene S. Wiener was known as a tough taskmaster and star surgeon whose greatest passion was the health of children.

The University of Pittsburgh School of Medicine professor of surgery and chief medical officer at Children's Hospital of Pittsburgh came to Pitt in 1973 as a pediatric surgical resident, after serving as a commander and deputy chief health officer in Vietnam.

Wiener guided multiple research projects directed at improving pediatric cancer treatment, particularly in the area of surgical oncology. He published more than 85 articles in peer-reviewed journals and contributed 18 book chapters.

He was among the best in the surgical suite, colleagues note. Henri Ford (Fel '93), former chief of pediatric surgery at the University of Pittsburgh and current vice president and surgeon-in-chief at Children's Hospital Los Angeles, called him "the Michael Jordan of surgery."

Wiener helped Children's implement a computerized physician order entry system designed to cut down on errors engendered by illegible handwriting and provide instant access to medical records.

Children's president and CEO Roger Oxendale said Wiener was pondering retirement but intended to remain involved with the hospital in a development role as it moved to its new location in Lawrenceville.

—*Joe Miksch*

HOWARD RABINOWITZ COUNTRY STYLE

BY JENNIFER DIONISIO



COURTESY RABINOWITZ

Rabinowitz signs his book *Caring for the Country* for Senator Jay Rockefeller (left) of West Virginia.

Say a patient broke his leg. As a young doctor at Sacaton Indian Hospital, 30 miles outside Phoenix on the Pima reservation, Howard Rabinowitz (MD '71) would find himself loading the x-ray film, taking the picture, developing the film, casting the limb, running to the pharmacy for pain medicine, counting out those pills, affixing the label, and passing the bottle to the patient. There wasn't anyone to delegate to, and he was one of only four doctors serving a rural population of 10,000.

"We basically did everything," Rabinowitz recalls 30 years later, sitting in his Philadelphia office. The Thomas Jefferson University professor of family medicine spent two years at Sacaton as a doc-of-all-trades before translating his knowledge of the issues surrounding small-town health care into a position as director of Jefferson's Physician Shortage Area Program. The program supports med students planning to work in underserved rural areas.

"Most people think of Pennsylvania as Pittsburgh and Philadelphia," Rabinowitz says, shaking a head covered in silver hair that contrasts with his youthful face. Although half of the state's doctors work in these two cities, almost 75 percent of the population lives in Pennsylvania's other 65 counties, he notes.

Rabinowitz took a year sabbatical to follow 10 of his graduates and document their experiences in his book *Caring for the Country* (Springer-Verlag, 2004). From direct observation in doctors' offices and 150 hours of taped interviews, Rabinowitz reveals a workforce and patient population as diverse as that of any bustling metropolis. These doctors—many are the only practitioners within a 20-mile radius—are certainly generalists, giving checkups, delivering babies, performing surgery, and, yes, sometimes making house calls.

Rabinowitz was raised in Pittsburgh's Squirrel Hill neighborhood and attended New Jersey's Rutgers University. As a med student, Rabinowitz says, "I had never been out of an urban area in my life." At least until his senior year at Pitt. At the urging of a fellow student, Rabinowitz signed up in his fourth year for professor of community medicine and pediatrics Ken Rogers' elective that took students on a nine-week rotation as researchers in the Navajo Nation. "It sounded fascinating culturally, geographically, and also medically," he says.

He was so impressed by the experience, he returned to work at Sacaton after his residency—many of his fellow students also sought positions in Native American communities.

Rabinowitz was driven to write *Caring for the Country* by his concern that medical students don't realize that practicing in such areas is even an option. What a shame, he says now, considering that rural doctors he observed seemed much happier than many he knows in urban areas. Far from considering their extra responsibilities a burden, they take pride in being such integral members of the community and enjoy raising their families in close-knit towns. And despite the assumption that rural doctors work longer and get paid less, all those Rabinowitz interviewed felt a few extra hours in the office equal an urban doctor's commute time—and cost-of-living differences assure financial security.

Small-town living isn't for everyone, Rabinowitz acknowledges. He can tell which students will be successful in the program just by asking if their hobbies lean toward opera or fishing.

But his own early experience in the Navajo Nation was deeply satisfying. He's since found that patients in small towns receive a kind of intimate care often lacking in big cities like Philadelphia.

"I wrote the book for students to get a sense of this," he says. ■

MEDICAL ALUMNI ASSOCIATION OFFICERS

MARGARET LARKINS-PETTIGREW (MD '94)
President

JOHN F. DELANEY (MD '64)
President-elect

GRAHAM JOHNSTONE, (MD '70)
Secretary

PETER FERSON (MD '73)
Treasurer

ROBERT E. LEE (MD '56)
Historian

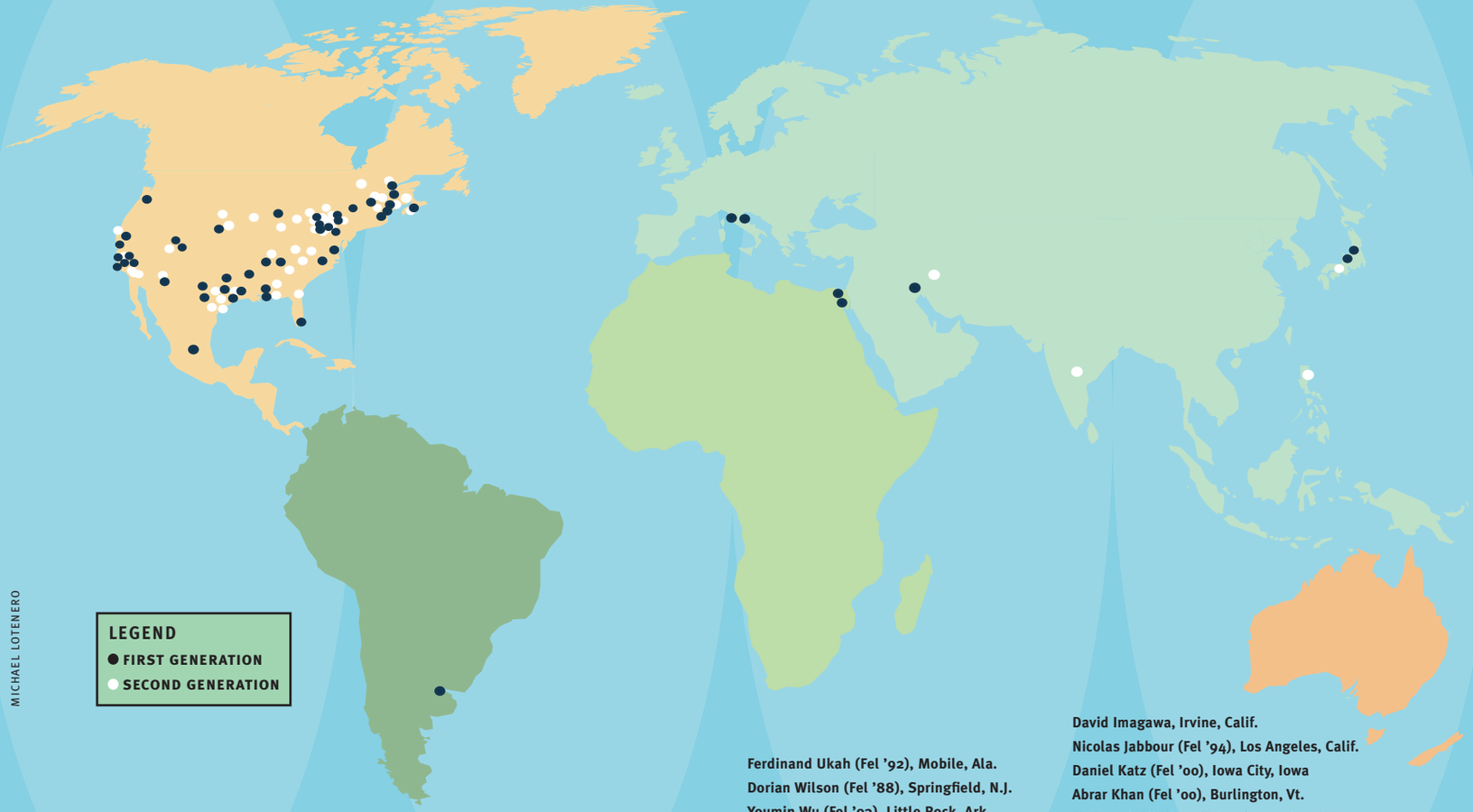
DALE ADAIR (MD '85)
PATRICIA CANFIELD (MD '89)
JOHN KOKALES (MD '73)
DONALD MRVOS (MD '55)
BRETT PERRICELLI (MD '02)
DAVID STEED (MD '73)
Members at Large

SUSAN DUNMIRE (MD '85)
Executive Director

M-200K Scaife Hall
University of Pittsburgh
Pittsburgh, PA 15261
tel 412-648-9090; fax 412-648-9500
medalum@medschool.pitt.edu

TRANSPLANT TRANSPLANTS

In case you were wondering how influential Thomas Starzl has been in the world of transplantation, have a look at this map. The dots mark where his first- and second-generation trainees run or most recently ran programs.



MICHAEL LOTENERO

PROGENITOR:
Thomas Starzl, Pittsburgh

FIRST-GENERATION PROGENY PROGRAM DIRECTORS:

Kareem Abu-Elmagd (Fel '91), Pittsburgh, Pa.
Mario Alessiani (Fel '89), Pavia, Italy
Giovanni Ambrosino (Fel '87), Vicenza, Italy
Ronald Busuttil (Fel '85), Los Angeles, Calif.
Joseph Cofer (Fel '89), Charleston, S.C.
Waldo Concepcion (Fel '89), Loma Linda, Calif.
Frank Darras (Fel '92), Stony Brook, N.Y.
S. Forrest Dodson (Fel '93), Chicago, Ill.
Caren Eisenstein (Fel '89), Fort Worth, Texas.
Carlos Esquivel (Fel '85), Palo Alto, Calif.
Paulo Fontes (Fel '91), Pittsburgh, Pa.
John Fung (Fel '86), Cleveland, Ohio
Timothy Gayowski (Fel '92), Pittsburgh, Pa.
Robert Goldstein (Fel '88), Dallas, Texas
Franklin Greif (Fel '91), Tel Aviv, Israel
Glenn Halff (Fel '89), San Antonio, Texas
Todd Howard (Fel '88), St. Louis, Mo.
Zakiyah Kadry (Fel '93), Hershey, Pa.
Igal Kam (Fel '85), Denver, Colo.
Frederick Karrer (Fel '86), Denver, Colo.
Baburao Koneru (Fel '87), Newark, N.J.
Ignazio Marino (Fel '92), Philadelphia, Pa.
Maureen Martin (Fel '91), Bakersfield, Calif.
Jorge Maza (Fel '90), Mexico City, Mexico
Hadar Merhav (Fel '89), Tel Aviv, Israel
Luis Mieles (Fel '86), Houston, Texas
Akimasa Nakao (Fel '90), Nagoya, Japan
Paul Nakazato (Fel '88), Tucson, Ariz.
Mark Nelson (Fel '89), Cumberland, Md.
Hector Ramos (Fel '91), Los Angeles, Calif.
David Reich (Fel '92), Philadelphia, Pa.
Jorge Reyes (Fel '89), Seattle, Wash.
Kerri Robertson (Fel '87), Durham, N.C.
Mahmoud Sakr (Fel '89), Ahmadi, Kuwait
Eduardo de Santibanes (Fel '83), Buenos Aires, Argentina
Velma Scantlebury (Fel '88), Mobile, Ala.
Robert Selby (Fel '89), Los Angeles, Calif.
Ron Shapiro (Fel '88), Pittsburgh, Pa.
Timothy Shaver (Fel '88), Farmville, Va.
Byers Shaw (Fel '83), Omaha, Neb.
Linda Sher (Fel '88), Los Angeles, Calif.
Rodney Taylor (Fel '82), Burlington, Mass.
Lewis Teperman (Fel '88), New York, N.Y.
Andreas Tzakis (Fel '85), Miami, Fla.
Ferdinand Ukah (Fel '92), Mobile, Ala.
Dorian Wilson (Fel '88), Springfield, N.J.
Youmin Wu (Fel '93), Little Rock, Ark.
Katsuhiko Yanaga (Fel '89), Tokyo, Japan

SECOND-GENERATION PROGENY PROGRAM DIRECTORS:

George Blessios (Fel '98), Buffalo, N.Y.
Rafael Botero, Houston, Texas
Adel Bozorgzadeh (Fel '99), Rochester, N.Y.
J. Stevenson Bynon, Birmingham, Ala.
Pradip Chakrabarti (Fel '00), Allentown, Pa.
Steven Colquhoun, Los Angeles, Calif.
John Daller (Fel '99), Rochester, N.Y.
Cataldo Doria (Fel '97), Philadelphia, Pa.
Douglas Farmer, Los Angeles, Calif.
Thomas Faust, Philadelphia, Pa.
Ermenegildo Eldo Frezza (Fel '01), Lubbock, Texas
Jonathan Fridell (Fel '02), Indianapolis, Ind.
Joseph Galati, Houston, Texas
David Geller (Fel '98), Pittsburgh, Pa.
David Gerber (MD '89, Fel '98), Chapel Hill, N.C.
John Goss, Houston, Texas
Hans Albin Gritsch (Fel '94), Los Angeles, Calif.
Frederick Grover, Denver, Colo.
William Hecker (Fel '97), Philadelphia, Pa.
Sayed Ali Malek Hosseini (Fel '92), Shiraz, Iran
David Imagawa, Irvine, Calif.
Nicolas Jabbour (Fel '94), Los Angeles, Calif.
Daniel Katz (Fel '00), Iowa City, Iowa
Abrar Khan (Fel '00), Burlington, Vt.
M. Farouk Ali Khan (Fel '95), Camden, N.J.
Ajai Khanna (Fel '95), San Diego, Calif.
Milan Kinkhabwala, New York, N.Y.
Alan Langnas, Omaha, Neb.
James Lim (Fel '96), New Brunswick, N.J.
Jeffrey Lowell, St. Louis, Mo.
Patrick Luke (Fel '00), London, Canada
Mario Magnone (Fel '95), Mobile, Ala.
James Markmann, Philadelphia, Pa.
Luis Santiago Marsano-Obando, Louisville, Ky.
George Mazariegos (Fel '94), Pittsburgh, Pa.
J. Michael Millis, Chicago, Ill.
Ernesto Molmenti (Fel '98), Tucson, Ariz.
Kim Olthoff, Philadelphia, Pa.
Thomas Peters, Jacksonville, Fla.
Santosh Potdar (Fel '01), Danville, Calif.
Ruben Quiros, Houston, Texas
Carlo Ramirez (Fel '95), Manila, Philippines
Dinesh Ranjan, Lexington, Ky.
K. Rajender Reddy, Philadelphia, Pa.
Steven Rudich, Cincinnati, Ohio
Abraham Shaked, Philadelphia, Pa.
Craig Smith (Fel '96), Los Angeles, Calif.
James Spivey, Atlanta, Ga.
Debra Sudan, Omaha, Neb.
Atsushi Sugitani (Fel '97), Fukuoka, Japan
Ngoc Thai (MD '97, Fel '04), Pittsburgh, Pa.
Phillip Thomas (Fel '95), Bangalore, India

—Compiled by Jaclyn Madden

CALENDAR

OF SPECIAL INTEREST TO ALUMNI AND FRIENDS

Unless otherwise noted, for information on an event contact the Medical Alumni Association: 1-877-MED-ALUM medalum@medschool.pitt.edu.

WHITE COAT CEREMONY
AUGUST 13
3 p.m.
Scaife Hall, Auditorium 6

CLEVELAND HEALTH SCIENCES ALUMNI RECEPTION
SEPTEMBER 20
Cleveland, Ohio
For information:
Pat Carver
412-647-5307
cpat@pitt.edu

HOMECOMING WEEKEND
OCTOBER 19–22
Pittsburgh v. Rutgers
Saturday, October 21
For information:
www.alumni.pitt.edu

MUSGRAVE LECTURESHIP
OCTOBER 27
5:30 p.m.
Scaife Hall, Auditorium 5
James W. May Jr., MD, Speaker
OCTOBER 28
10 a.m.
Scaife Hall, Auditorium 5
Surgery Grand Rounds

AAMC PITT RECEPTION
OCTOBER 29
6 p.m.
AAMC Annual Meeting
Grand Hyatt Seattle
Seattle, Wash.
For information:
Office of the Vice Dean
412-648-9000
vicedeanstaff@medschool.pitt.edu

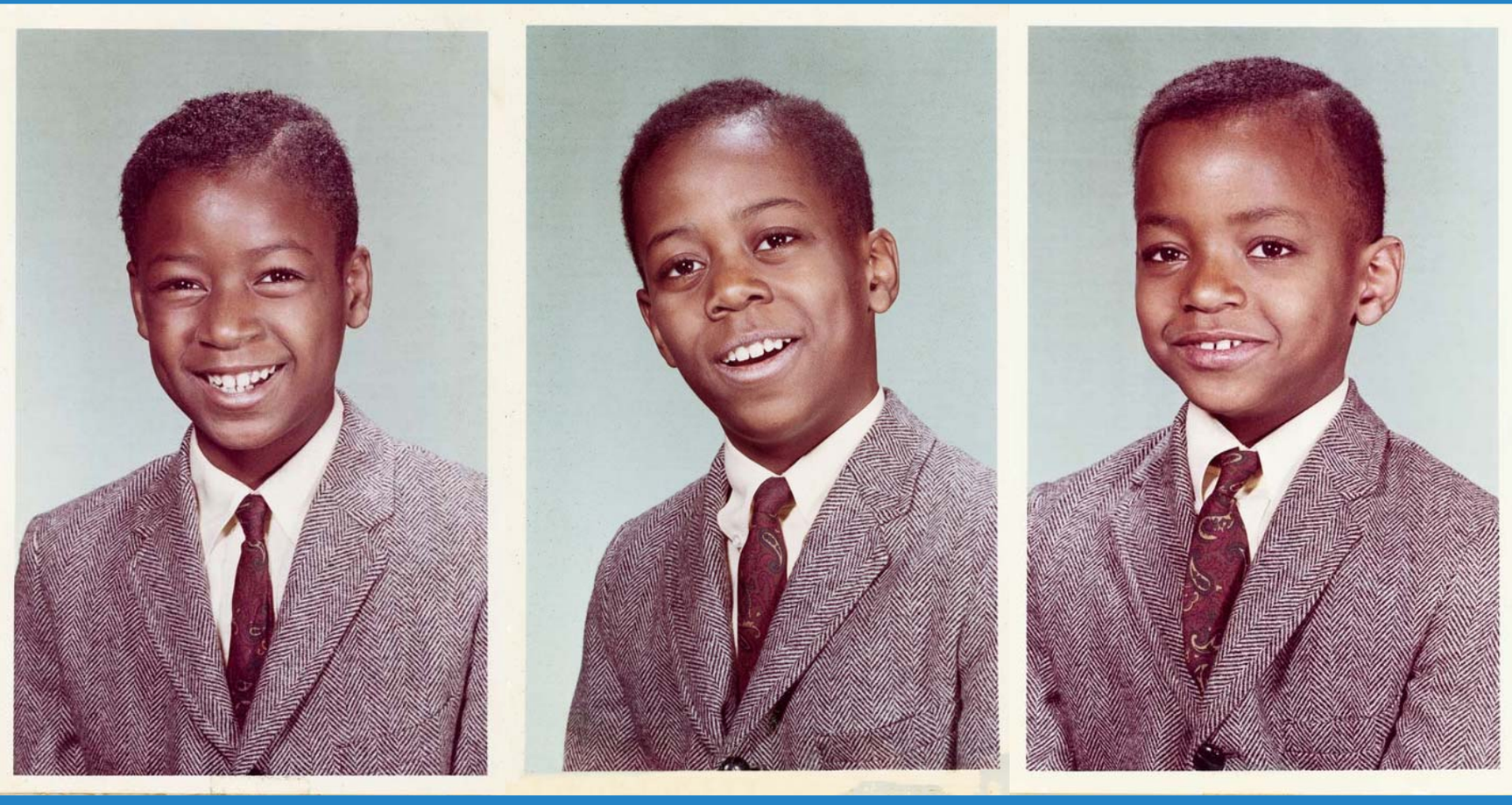
WINTER ACADEMY SCHOOLS OF THE HEALTH SCIENCES
FEBRUARY 2007
Naples, Fla.
To request an invitation:
Pat Carver
412-647-5307
cpat@pitt.edu

MEDICAL ALUMNI WEEKEND 2007
MAY 18–20, 2007
Reunion Classes:

1947	1952
1957	1962
1967	1972
1977	1982
1987	1992
1997	

Upcoming health sciences alumni receptions—
October: Dallas, Texas
November: Philadelphia, Pa.
March 2007: Raleigh/Durham, N.C.
May 2007: Erie, Pa.
For information:
Pat Carver
412-647-5307
cpat@pitt.edu

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



WELL SUITED

When Pitt is the best fit for terrific applicants, don't let concerns about costs squelch their dreams. A planned gift to the School of Medicine can be directed toward scholarships or other meaningful projects to keep the best and brightest gracing the halls of Scaife. In the meantime, it can provide an annual income stream for you or a loved one. (If the School of Medicine is already in your will and you haven't let us know, please contact us so that we can make sure your gift is used as you intend it to be.)

FOR MORE INFORMATION: School of Medicine, University of Pittsburgh,
Kathleen Helling, Medical Arts Bldg., Suite 400, 3708 Fifth Ave., Pittsburgh, PA 15213
412-647-4220, hkathleen@pmhsf.org

LEFT TO RIGHT: C. 1963, ROZELL, EZELL, AND JEWELL PENDLETON, BROTHERS OF ROBERT HILL, PITT VICE CHANCELLOR FOR PUBLIC AFFAIRS

UNIVERSITY OF PITTSBURGH
SCHOOL OF MEDICINE
SUITE 401 SCAIFE HALL
PITTSBURGH, PA 15261

CHANGE SERVICE REQUESTED