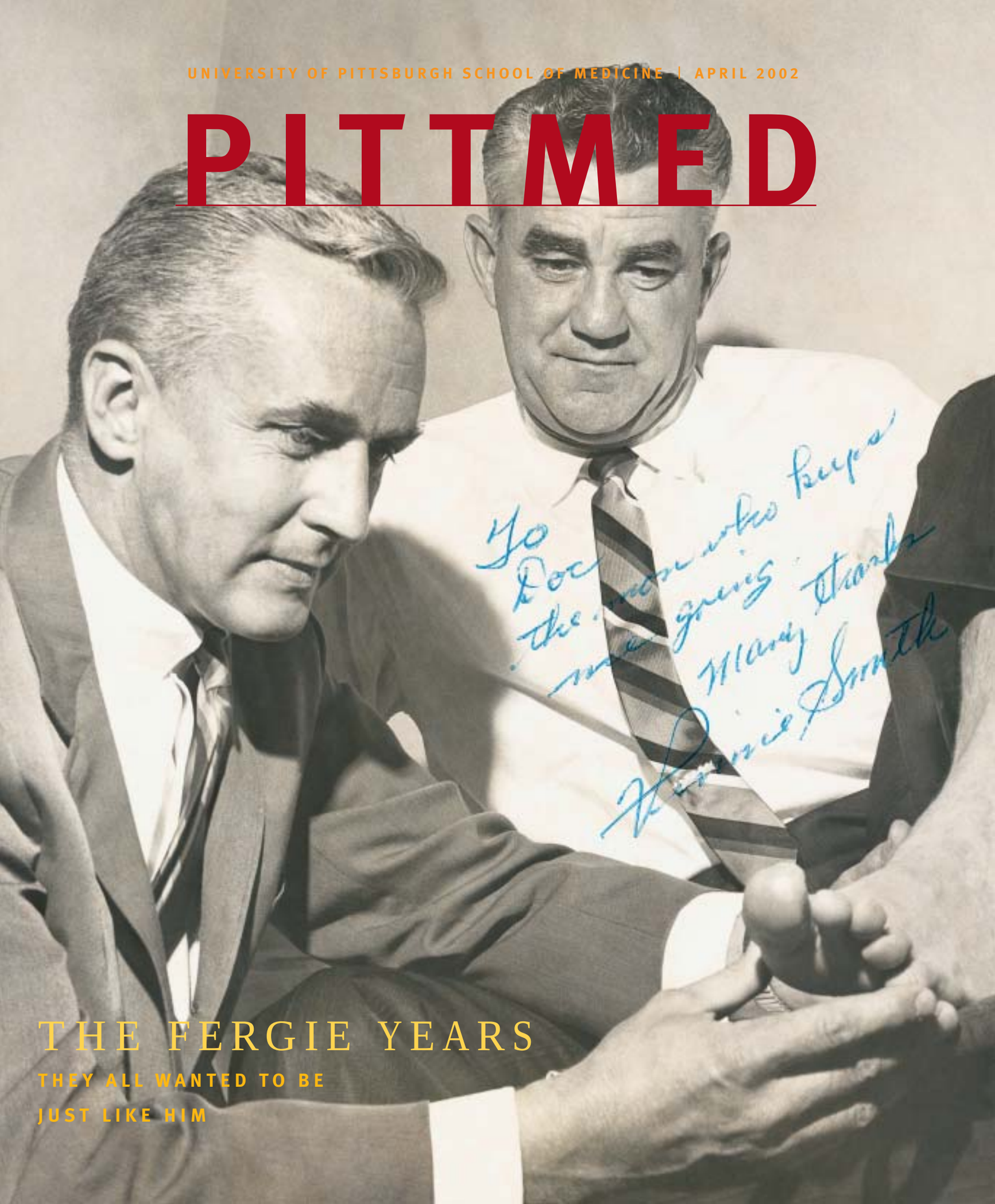
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | APRIL 2002

PITTMED



THE FERGIE YEARS

THEY ALL WANTED TO BE JUST LIKE HIM

DAYS OF LINE AND HOSES

I enjoyed your article entitled "Give My Grand Rounds to Broadway." It illustrated the importance of an activity [producing the annual graduating class' show, Scope and Scalpel] not often viewed as central to medical training. To the contrary, this is just the type of activity that allows students to explore areas that are critical to their development such as teamwork, communication, and creativity. I think this is good for morale and wonderful memories in the future.

Thanks again for a wonderful article.

Jeffrey S. Upperman, MD
Assistant Professor of Surgery
Children's Hospital of Pittsburgh

UNSORTING THE SORDID

A very interesting article regarding previous Scope and Scalpel productions.

However, to Sally Ann Flecker, the 1966 production (in which I played a large role) was entitled "The Sordid Life of Wally PMSTEN," a play on PMS IV. It was about a student in his tenth year of medical school who finally passes because he one-ups the professors regarding a certain [faculty member's] rectal bleeding. Pimpstein makes no sense.

Arlington G. Kuklinca, MD '66
Warren, Ohio

Gotcha.

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

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RECENT *PITT MED* HONORS

2002 Council for Advancement and Support of Education (CASE), District II

Gold Award, General Interest Magazines

Gold Award, Best Article of the Year ("House of Butterflies," by Rebecca Skloot)

Silver Award, Periodical Staff Writing (specifically Dottie Horn, Mark Jacobs, Robert Mendelson)

CORRECTIONS/ CLARIFICATIONS

Our apologies for misspelling Alfred Perfett's (MD '55) name in a caption in our January issue.

BANK IT

If you're familiar with the Pro-Am, think of this as the Pro-MD. Without the pros. But what's better than having Tiger Woods in your foursome? Knowing that your entry fee to the Annual Pitt Med Golf Outing helps heavily indebted students who are active in the community. And this year's outing *will* be held at one of the nation's premier courses, just 30 minutes from Pittsburgh. The student-run event begins with a shotgun start so that everyone can enjoy the buffet dinner and award ceremony together afterward. (Students $65, Others $100) April 27, Quicksilver Golf Course.

To register or make a donation, 412-648-9090 or pittmedgolfouting@yahoo.com

PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE | APRIL 2002, VOL. 4, ISSUE 2

DEPARTMENTS

CONTRIBUTORS

MEGHAN HOLOHAN—["The Natural" and other stories] Meghan Holohan once hung around sidewalk preachers for three months, turning her curiosity into a 5,000-word expose on the dynamic between evangelicals and the passersby who heckle them. Her talents lie not just in her writing. Last summer, after working on the research magazine for Ohio University (OU) as well as *Computerworld* and earning a bachelor's in journalism from OU, she joined the Public Affairs staff as an editorial researcher. The understanding around the office is that bin Laden would have been located months ago had Holohan been on the case. CHUCK DINSMORE—When a magazine staff hands over an issue to the printer, it's like sending a kid to college. You hope for the best, but need to accept, your role just became drastically limited in the life of your child. Every issue of *Pitt Med,* however, has a strict chaperone in Chuck Dinsmore. He oversees production of more than 400 University print projects each year and knows as much about varnishes, binding, and the like as anyone you'll meet. The coolest thing about his job, he says, is checking on a publication while the presses are running. *Pitt Med* is printed on a "behemoth" machine which, despite its size, lays minuscule dots of ink with the utmost precision. As it does, Dinsmore is there with art director Elena Gialamas Cerri to recommend fine adjustments, making sure the skin tones in a distinguished doc's photo, for example, don't come out too red or green.

COVER

Albert Ferguson, chair of orthopaedic surgery for three decades, kept many people going, including National League umpire Vinnie Smith (seated). (Photo: Paul Slantis/*Pittsburgh Post-Gazette,* reprinted with permission)

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FEATURES

PITTMED

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JULIA MAROUS STRAUT

Since Fracastorius' 16th Century writings, physicians have recognized that early detection and intervention limit the morbidity and mortality in a community exposed to a contagious agent. The earlier the detection, the less harm. Early detection is the goal of a computer-based system that has been developed by our school's Dr. Michael Wagner and his colleagues. The "Real-time Outbreak and Disease Surveillance System" (RODS) sets off an alarm during a surge of reported symptoms in emergency rooms throughout this region that might reflect a bioterrorist attack; RODS was also installed in Utah during the Winter Olympics. The system allows us to determine, on an instant-by-instant basis, unusual increases in flu-like symptoms, respiratory illnesses, diarrhea, skin rashes, encephalitis, etc. A graph showing the incidence of each symptom is updated as soon as patients present themselves in a clinical setting, and a map on a computer screen demonstrates the number of such events reported within any given zip code. Soon, RODS will be linked to cash registers in drugstores, so we can be instantly aware of a run on aspirin, Kaopectate, and the like. On February 5, President Bush visited Pitt to learn about RODS, and he used this forum to inform America of his intention to spend $6 billion in FY2003 for programs to defend the nation against biological terrorism.

While we were pleased indeed with the president's visit, and the international recognition which we received as a consequence (this was the first visit to Pitt by a sitting president), the fact is this country's infrastructure for protecting the public health, whether assaults on that health are man-made or natural, has been woefully insufficient. The president's budget proposes expenditures to support medical communications and training programs, strengthen health systems, build up the pharmaceutical stockpile, upgrade CDC labs, and increase the FDA's capacity for ensuring food safety. The budget also proposes very significant funding for NIH and DOD research. Yet the weaknesses in our public health infrastructure are only partly addressed by this proposal. Consider the 45 million in this nation with no health insurance. These people ultimately become sicker than they would with proper access to care, and impose a significant financial burden on academic medical centers, which deliver more than half of all the uncompensated care in this country. Consider the extraordinary debt that most med school graduates now face, and the constraining effect that this debt (ultimately $250,000 for indebted students) has on career choice, i.e., the unlikely choice of a career in primary care, or in a rural area or inner city, or in academia as a physician-scientist.

These threats to our public health infrastructure occur when health care delivery has become increasingly complex because of an aging population as well as increased ethnic and racial diversity and the health disparities implicit in this diversity. Perhaps a welcome side effect of our focus on bioterrorism will be that, as a nation, we begin to address these many politically and fiscally daunting issues.

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 http://www.health.pitt.edu

JEN URICH

Ford

Ford Presides over Academy

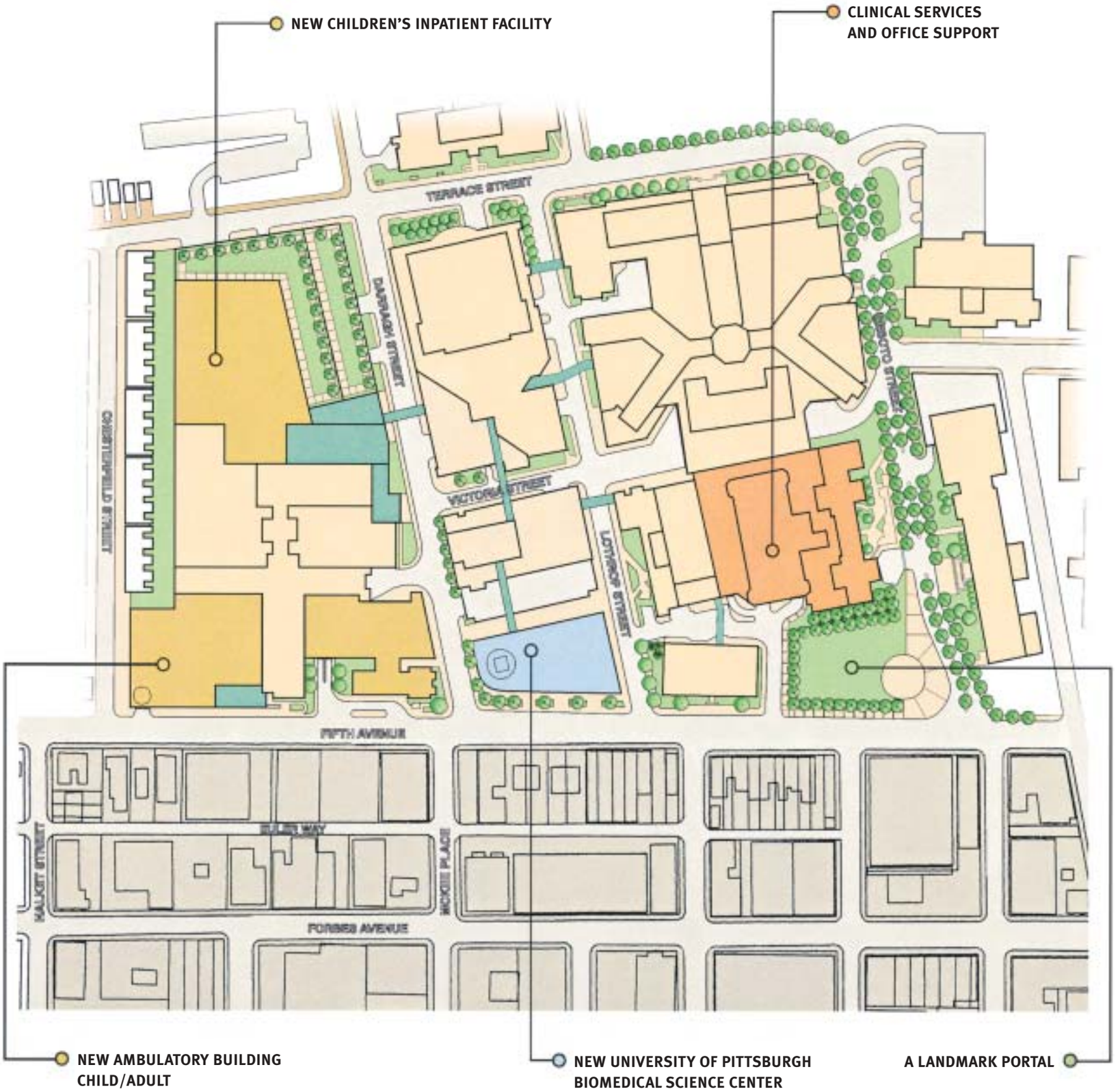
Henri Ford's typical 14-hour-days may get a bit longer now that he has been elected president of the Association of Academic Surgeons. During his term, Ford (Fel '93) aims to build greater ties to other academic surgical societies, to give the groups more leverage in terms of advocacy. (That proposal is made more realizable, perhaps, with Ford's boss, Timothy Billiar, chair of surgery, having just stepped down as president of the other major academic association for surgeons, the Society of University Surgeons.) Ford, who is chief of the Division of Pediatric Surgery at Pitt, will continue his research on necrotizing enterocolitis, a disease affecting premature infants. He will also help set up a model injury-prevention program at Children's Hospital of Pittsburgh, supported by a grant from the Robert Wood Johnson Foundation. *—DH*

FOOTNOTE

Okay, you can't couple "transplant" and "routine," but after almost 6,000 liver transplants at Presby, it's not exactly news—unless the patient is AIDS activist and playwright Larry Kramer *(The Normal Heart* and *The Destiny of Me)*. Some see Kramer's operation as a test case for more transplants among HIV-infected patients. It's a bellwether that Pitt surgeon John Fung finds a bit uncomfortable: "I'd like to think one case doesn't make or break the whole thing."

THINK MOLECULAR

Gene therapy at Pitt is likely to move forward more quickly with the recent creation of the Molecular Medicine Institute, headed by Joseph Glorioso, the William S. McEllroy Professor of Biochemistry. The institute will bring several existing facilities at Pitt under a single umbrella, including Pitt's Human Gene Therapy Applications Laboratory (which is the only approved site in the country for producing vectors used in clinical gene therapy studies funded by the National Heart, Lung, and Blood Institute). The new Pitt institute will make it easier for campus researchers to access services needed for gene therapy trials. It will also support other areas of molecular medicine, including research on the use of peptides to deliver proteins into cells and the exploration of genes whose activities have not yet been defined, in the hopes of finding potentially therapeutic genes. *—DH*



An Oakland medical campus renaissance will bring more greenery as well as "intelligent" buildings that conserve energy and meet the demands of modern care and new biological research.

A Campus Renaissance

"It's a once in a lifetime opportunity"—Ron Forsythe, a UPMC Health System official, has good reason to be genuinely enthusiastic about what's in store for the Oakland medical campus, as does Pittsburgh.

The recent UPMC merger with Children's Hospital of Pittsburgh has given these institutions and the University the occasion to rethink the use of the acres they occupy. The institutional partners saw a number of pressing challenges facing the crowded urban campus: Children's had determined that its current facility was woefully small and inappropriate for meeting the demands of future care. The University itself is maxed out in terms of modern, experimental biomedical lab space. And anyone who has traversed the "Cardiac Hill" area knows that getting around can be terribly confusing.

The $600 million plan:

Construct a new Children's Hospital—a 10-level, 500-thousand gross-square-foot facility, to be housed on the Terrace Street side of UPMC Montefiore. Among other improvements, all patient rooms will be private and include accommodations for parents to stay with their children.

Build a 14-story, 480-thousand gross-square-foot Child and Adult Ambulatory Care Center on Fifth Avenue with easy access to Montefiore's imaging and lab services.

Erect another 14-story building, also on Fifth, to house new biomedical lab space as well as shared core facilities that are key to recruiting and retaining top faculty. Still, some aspects of the plan—huge magnets, intense vibrations, and other attributes of today's cutting edge structural biology tools—impose severe architectural constraints. "This building is being defined by the biology of the future," notes one Pitt official.

The University and its partners are determined to put all this together in a way that makes the campus feel welcoming and, well, well put-together. So they'll add structural cladding around lower floors of existing buildings to lend architectural harmony, wayfinding and "interior streets" to link buildings and help patients and others get around, and greenery—including a parklet that will serve as a clear gateway to the medical campus.

The major facelift is expected to take a total of seven years. *—EL*

FOR MORE INFORMATION:
http://www.upmc.edu/newsbureau/director/campus/campus.htm
Don't miss the video!

COURTESY UPMC NEWS BUREAU

NO BABY STEPS

David Perlmutter makes it clear—the campus improvements coming out of the Children's Hospital/UPMC merger are, by no measure, baby steps for the University's pediatric program: "I call it a quantum leap." The chair of pediatrics, who came to Pitt last year from Washington University in St. Louis, is thrilled about the unexpected windfall. He notes the expanded and modern facilities will put Children's in a unique position for attracting other top faculty, especially in pediatric subspecialties. That bodes well for Pitt's chances to garner more federal funding; it also bodes well for the depth of expertise available to care for the region's children.

The big picture for pediatric education at Pitt as he sees it: "We'll have the most talented clinicians and researchers teaching the most talented students." *—EL*

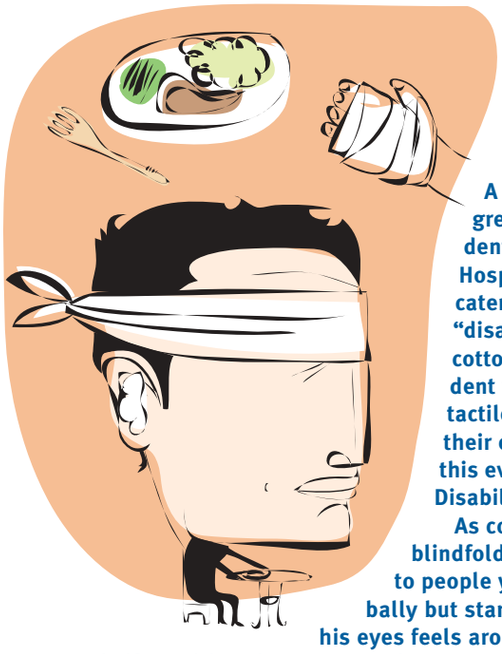
Faculty Snapshots

Professor of emergency medicine **Donald Yealy** (Res '89) often encounters residents who want to order tests for patients: "I usually ask, 'Why is it that you want that x ray? That blood count? That set of electrolytes? What are you going to do with the information?' My view is to teach people how to think through what they're doing." Yealy, who recently received the American College of Emergency Physicians Award for Outstanding Contribution in Education, calls these five- to 10-minute conversations "teaching moments." He uses them frequently when he is in the emergency department or lab, and believes they are largely responsible for his success as an educator. Clifton Callaway (Res '96), an assistant professor of emergency medicine who trained with Yealy, remembers the decision-making skills Yealy passed on and how reluctant his mentor was to make any patient-care decisions out of habit. "Yealy was teaching evidence-based medicine before it was a fad," he recalls.


Yealy

Jonas Johnson wants to reach out to the nearly 40,000 otolaryngologists outside the United States. "I'd like to educate physicians worldwide by providing access to educational materials electronically," says Johnson, considering his goals for his upcoming term as president of the American Academy of Otolaryngology, Head and Neck Surgery. (Johnson follows the trail of Eugene Myers, chair of the Department of Otolaryngology, who served as president of the academy from 1994 to 1995.) The professor speculates his own election was due to a number of factors: He is the editor of the *American Journal of Otolaryngology,* has published 15 books and more than 300 articles, and led the academy's continuing education program. It also helps that Pitt's department was ranked fifth in the country in 2001 (according to *U.S. News and World Report)*. Johnson's research at Pitt focuses on a new vaccine designed to help patients with head and neck cancer and the evaluation of surgical methods for the treatment of snoring and sleep apnea. *—DH*


Johnson



AN EYE-OPENING DINNER

A homey fragrance, reminiscent of casserole, greets the small group of first-year medical students gathering in a basement room at Children's Hospital of Pittsburgh. Before they dig into this catered dinner, however, each student will don a "disability." A young woman stuffs wads of thick cotton in her ears until she can't hear. Another student wears two pairs of plastic gloves to simulate tactile impairment. Others place pads or gauze over their eyes. Eventually, everyone sits down to eat at this evening meeting of the medical school's Disabilities in Medicine Interest Group.

As conversation travels around the table, one of the blindfolded students notes that it's interesting to talk to people you can't see: "A person could be so nice verbally but staring you down." One of the men with pads over his eyes feels around his plate with his fingers, looking for his knife. Neither the gauze nor latex seems to have impaired the guests' sense of humor tonight. Fumbling is mixed with self-deprecating chuckles. When the prospect of seconds comes up, a blindfolded student admits he would love another helping but fears that would necessitate a trip to the bathroom—a complication he's not ready to take on right now.

At one point, when laughter suddenly erupts at the table, Kendra Papson, whose ears have been insulated with cotton, doesn't know why. She raises both hands in a "What?" gesture. Later, when the gauze and gloves are taken out or off, Papson talks about her frustration: "I wanted to express myself, but couldn't."

Rob Oliver, a community coordinator at Children's Hospital, and Betty Liu, assistant professor of physical medicine and rehabilitation, direct the postdinner discussion. If someone wanted to offer help, how would you like to be approached? One student comes back with a thoughtful suggestion. Still Oliver, who relies on a wheelchair to get around, closes the discussion with this parting caution: The simulation can provide insight, but the nondisabled can never fully know what it's like to have a disability. —DH

A Therapeutic Circulatory System

Treatment for metastatic tumors typically has limited success: Only 15 to 20 percent of the time does a tumor shrink to less than half its size and remain stable for about six to 12 months. David Bartlett, who left the National Cancer Institute in October to become chief of the new Division of Surgical Oncology at Pitt, wants those numbers to improve. To date, he has treated 160 patients with a new therapy he helped develop for metastatic liver tumors. Seventy-five to 80 percent of the time, his patients' tumors shrank to less than half their size and remained stable for about 12 to 18 months.

Bartlett

The therapy involves, in effect, temporarily creating a separate circulatory system for the liver alone. For one or two hours, blood laden with high concentrations of chemotherapeutics circulates through the liver—but can't reach the rest of the body. After the treatment, normal circulation is restored.

The technique, which has yet to be tested to see whether it prolongs life, is called regional perfusion therapy. It has been used to treat cancers in body regions other than the liver, but is not frequently performed. One of Bartlett's goals as division chief is to teach the technique to other surgeons so that its effectiveness can be tested in larger clinical trials. —*DH*

TRY THIS LASER

Visitors to the Zap! Surgery exhibit might play a super-size Operation game, then watch a video—nothing from Disney's studios, though, only real-life drama. They can tune in as Deepinder Dhaliwal, professor of ophthalmology, performs laser vision-correction surgery and learn what she and her patients had to say about the procedure afterward. Dhaliwal, nine other physicians, a scientist, and an engineer affiliated with the School of Medicine or UPMC Health System served as advisers for the $2.2 million Zap! Surgery exhibit, created by the Carnegie Science Center. The exhibit educates the public about minimally invasive surgery, focusing on procedures involving a gamma knife, endoscopes, lasers, ultrasound, cryosurgery, and radiosurgery. Zap! Surgery debuted at the Science Center last year and now travels the country. —*DH*

TOP LEFT: MICHAEL LOTENERO; LEFT: COURTESY CARNEGIE SCIENCE CENTER

ALUMNI CHECKUP: KATE MCFADDEN

BY DOTTIE HORN

MARTHA RIAL

Anthropologist-turned-pathologist McFadden with Clare and Ernie.

One day, 9-year-old Clare—who is tall, has a full head of brown hair, and is autistic—was riding the bus to school. She took off all her clothes and lay down on the bus floor. The next day, her mother—who is a generous woman likely to arrange a ride home for a new acquaintance—called up government offices, saying: *You get an aide on that bus for Clare. If my daughter ends up coming to school without her seat belt on again, possibly distracting the driver, we're suing you, because you are endangering our child.*

"I was always a shy, retiring person, afraid of authority figures, and not a big social butterfly," says Kate McFadden, MD '01, Clare's mother. "I would never say 'boo' to anyone before, and now I'm a witch: *My daughter will go to summer camp, and you will pay for it.* I always thought people knew better than I did, and I would just go along with what people said. Not anymore."

McFadden's newfound assertiveness is not the only change that Clare has brought about in her life. In 1990, McFadden was in her first year of a PhD program in physical anthropology at Indiana University, planning a career examining ancient bones for disease. She took a pathology course as part of her work toward her degree:

"Three weeks into the course, I thought: *I love this!*" She considered going to medical school, but didn't want to go back to being an undergraduate—and didn't want to take "unspeakable" courses like chemistry and physics.

Two years later, in 1992, Clare was born. In 1993, McFadden completed her PhD coursework. When Clare was about 16 months old, she was diagnosed with mental retardation and, later, autism.

McFadden began to reevaluate her life. Uncovering ancient history suddenly seemed less important than doing something that would help people now. McFadden realized she would have to support Clare long after her own death, and jobs in anthropology didn't pay well. *Chemistry and physics,* she thought, *no problem. I can do them if I have to.*

"It was Clare that made me decide. Medicine was a much better idea for our family, and for her, and for me. I learned that a little suffering now is worth doing what you want to do—because I do like the medicine more than the anthropology, or I wouldn't have done it."

McFadden didn't abandon her PhD, though. While she was taking premed courses she also spent three months examining 5,000-year-old Egyptian skeletons (87 of them). She wrote her dissertation during med school and is putting the final touches on it now. As part of that thesis, she's arguing that bent bones on some of the skeletons were caused by rickets—though most experts believe that in sunny Egypt rickets wouldn't have been a health problem. McFadden suggests that pale skin may have been associated with status, leading some ancient Egyptians to avoid the sun.

At home in her cozy Squirrel Hill duplex, where her six-month-old son, Liam, (who is not autistic) is sleeping upstairs, McFadden sits in an armchair, her brown hair swept back from her face. She talks about anthropology, which she hopes to pursue as a hobby. Most skeletons, she says, have one or more distinctive traits—like extra sutures in the skull or a round hole in the breastbone.

"The skeletons feel like people you know," she says. "They're individuals in my mind, now, people with characteristics, like my friends."

She often wondered what life was like for those she studied—the woman buried with an infant, for instance. Similar questions creep up in her first year of a pathology residency at Pitt, where she also lectures in a history of medicine elective for fourth years. In the lab, she finds herself rooting for people whose specimens she's examining, hoping she doesn't "find something." She plans to subspecialize in neuropathology and research autism.

"That's another reason to be in medicine," she says. "What you do is try to make life more fair, for other people if not yourself."

WELCOME VALENTINE

"I was very up-front in my AMCAS essay: *I am 33. I am a mother of an autistic child. I am an anthropologist.* There are medical schools that didn't even ask me to interview, even though I did well in my premed courses and on the MCATs. I think they were worried about somebody like me. Whereas Pitt wanted me, not in spite of my background, but because of it. I interviewed on Valentine's Day, and I really felt loved that day because Pitt set up an extra interview for me, with a medical student who had an autistic brother, so that she could tell me about the services available in Pittsburgh."

—Kate McFadden, MD '01

RHYTHMS OF THE COSMOS

AN ASTRONAUT'S SLEEP DIFFICULTIES PARALLEL THOSE IN ELDERLY MEN | **BY ROBIN KRIEGER MEJIA**

Early this morning, while you were still asleep, your brain ramped up production of the hormone cortisol to raise blood sugar levels. At about the same time, your body temperature began to rise. These changes were part of a complex set of daily cycles controlled by your biological clock. They occur, explains Timothy Monk, professor of psychiatry, so that when you wake up, you "hit the ground all warmed up and ready to go."

A bundle of about 10,000 neurons, the biological clock, or endogenous circadian pacemaker, orchestrates the activity of the signals that make us sleepy at night, wake us up in the

PAGE 8: PHOTODISC; PAGE 9 TOP: COURTESY NASA; BOTTOM: COURTESY REYNOLDS/RINTOUL

morning, and keep us alert during the day. To get a feel for the magnitude of the changes your body makes to get ready for a solid night's sleep, think about how you would deliberately prepare to forgo eating, drinking, or using the restroom for eight hours.

But what exactly affects the signals that drive circadian rhythms? It may help you rest easier just to know that scientists are looking at this question from a number of perspectives—including some that are way out there, in a manner of speaking.

In a study published in the December issue of *Psychosomatic Medicine*, Monk examined what happens to the biological clock under the extreme conditions found in outer space. On the space station Mir, which completed an orbit every 90 minutes, astronaut Jerry Linenger saw 16 sunrises and sunsets every 24-hour "day" (though he kept a regular daily schedule based on Moscow time in order to be in sync with his earth-bound counterparts). Monk wondered: How would the astronaut's body respond to the lack of regular scheduling cues such as day and night?

To answer this question, Linenger monitored his own temperature, alertness, and sleep for three two-week blocks during a nearly five-month stay on Mir in 1997. He recorded when he went to sleep, when he got up, and if he'd awakened during the night. Five times each day, he took his temperature and used a computer program to rate his alertness.

After about three months in space, Linenger's biological rhythms flattened. His normal flux in body temperature became less pronounced. He slept more fitfully. And by the end of the voyage, he felt less tired at night and less alert during the day. (Though, after three months in space, the astronaut scored about as well on the computer-based alertness assessment as at the beginning of the trip. Monk explains that Linenger's subjective baseline for alertness may have moved over the months, or he may have been able to focus for the 10-minute test even if he wasn't feeling his best throughout the day.)

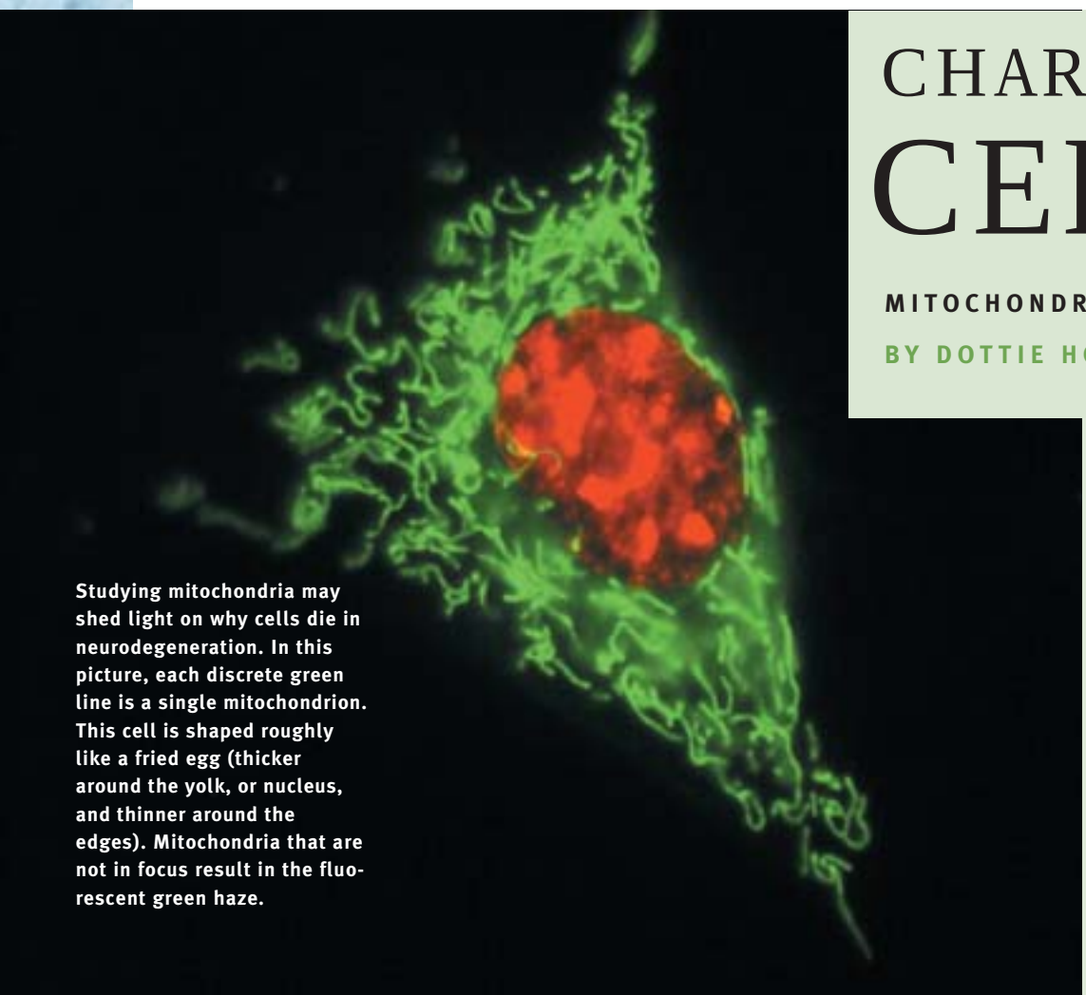
Finding a way to keep the biological clock working will be key to the future of extended space missions, be they on space stations or a trip to Mars. Accidents can quickly become emergencies in space. Staying alert can mean staying alive.

On Mir, Jerry Linenger saw 16 sunrises and sunsets every 24 hours.

Bright light therapy might help keep the clock on track in the cosmos. We know that on earth, when people are removed from the influence of light and other daytime signals, the biological clock cycles over a slightly longer period, about 24.2 hours, and people sleep less effectively, with more bouts of lighter, interrupted sleep, instead of one solid chunk of shut-eye. Exercise might also help astronauts sleep better. In the weightless environment of space, they expend little energy performing regular duties.

Monk, who is affiliated with the University's Clinical Neuroscience Research Center, notes that this research may also offer benefits to those of us content to stay put on this planet.

"The flattening that I saw in Dr. Linenger towards the end of the mission is very similar to the flattening of the alertness mechanism that I've seen in older men, men in their 70s and 80s," he said. "If we found ways of tricking the circadian system into solving this problem, it might work for older people." ■



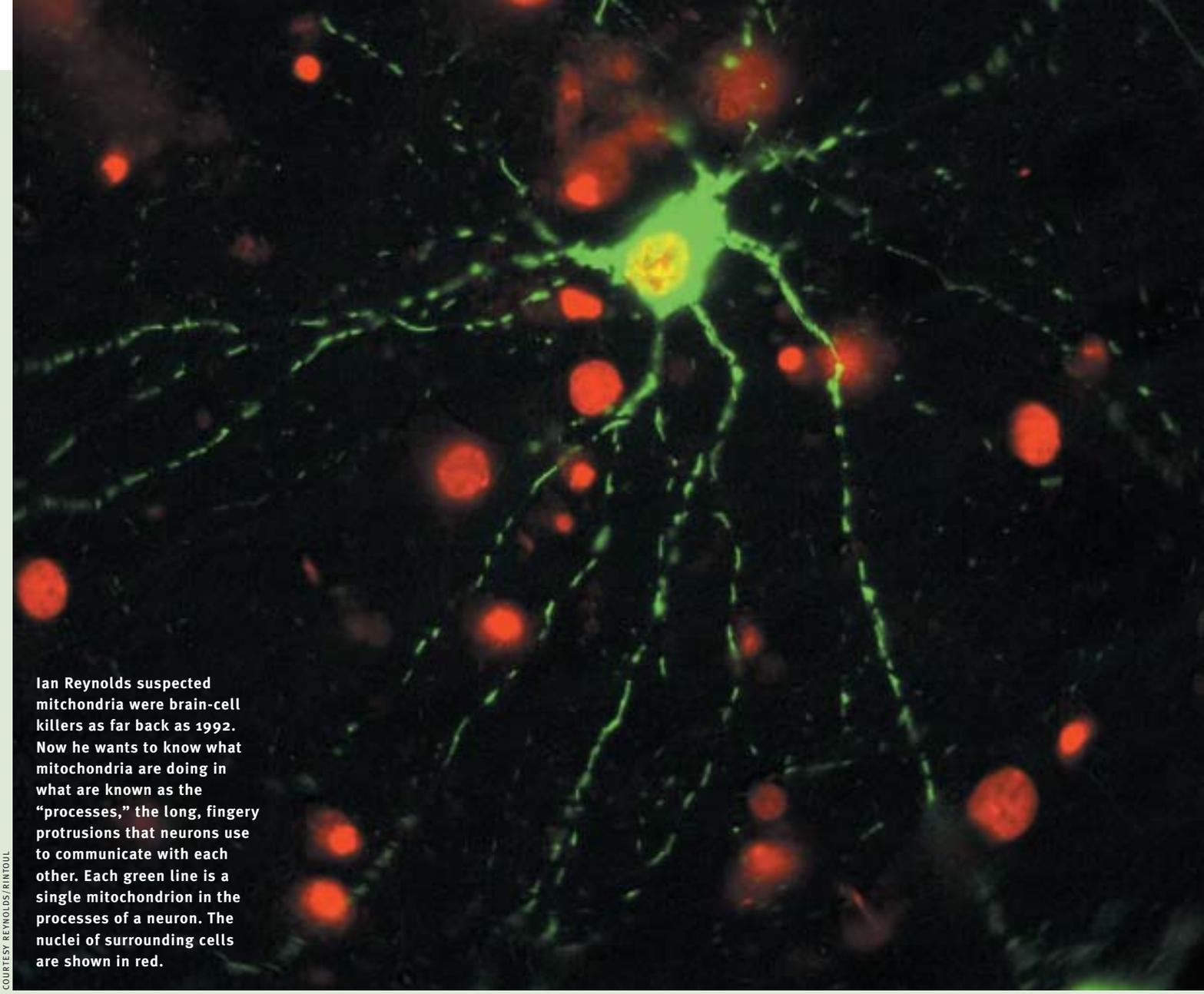
Studying mitochondria may shed light on why cells die in neurodegeneration. In this picture, each discrete green line is a single mitochondrion. This cell is shaped roughly like a fried egg (thicker around the yolk, or nucleus, and thinner around the edges). Mitochondria that are not in focus result in the fluorescent green haze.

CHARGED WITH CELLICIDE

MITOCHONDRIA SEEMED UNLIKELY CULPRITS

BY DOTTIE HORN

Inside brain cells, mitochondria wiggle and wend. One, looking like a short pencil, bends into a horseshoe, then straightens again. Sometimes, one will split in two; other times, two will fuse together. One mitochondrion, moving at a speedy clip, zips up one of the slender tendrils, called "processes," by which nerve cells communicate with each other. When the process splits into two divergent paths, the mitochondrion



Ian Reynolds suspected mitchondria were brain-cell killers as far back as 1992. Now he wants to know what mitochondria are doing in what are known as the "processes," the long, fingery protrusions that neurons use to communicate with each other. Each green line is a single mitochondrion in the processes of a neuron. The nuclei of surrounding cells are shown in red.

COURTESY REYNOLDS/RINTOUL

chooses one fork over the other as it rushes on its hurried way.

Ian Reynolds, professor of pharmacology, watches the antics of mitochondria on videos he makes using fluorescence microscopy. He points to one as it squirms: "It's almost like a worm trying to figure out which way it wants to crawl off to next." His videos have raised many questions for which, as of yet, he has no answers: Why do some mitochondria travel and how is their movement controlled? Why do they break into two and fuse? Why do some cells have lots of mitochondria, while neighboring cells may have only a few? The answers, Reynolds hopes, will reveal clues to why cells die in neurodegenerative diseases like Parkinson's and Huntington's. The organelles certainly appear to be a factor in those disorders as well as in cancer.

The raison d'être of mitochondria is not straightforward, however. Once scientists think they understand the importance of these organelles, another function seems to wiggle and wend into the picture.

Using microscopes early in the last century, scientists noticed parts moving inside cells. Later, during the 1950s and 1960s, they were able to observe these moving parts with new technologies—these were mitochondrial boom times. In 1961, the University of Edinburgh's Peter Mitchell published a paper delineating the mechanisms by which mitochondria use oxygen to convert sugar into ATP, the form of energy the cell uses. (Mitochondria's need for oxygen is why we have to breathe—they consume 95 percent of the oxygen we take into our bodies.) Mitchell's hypothesis was initially met with skepticism. By 1978, the year he won the Nobel Prize for Chemistry, it was accepted widely.

In the years that followed, many researchers abandoned mitochondria to study intercellular signaling, second messenger function, protein kinases. Then in 1997, mitochondria made an extraordinary comeback among investigators. Scientists, notably Xiaodong Wang, associate professor of biochemistry at the University of Texas Southwestern Medical Center in Dallas, realized that one kind of programmed cell death, or apoptosis, is triggered by the mitochondria's release of cytochrome c into the cytoplasm. The idea that an organelle so important for maintaining cell functioning could also routinely offer a protein that causes the cell to die—*that* seemed to come out of left field. It was, notes Reynolds, very unexpected.

The discovery has heralded a second wave of boom times for mitochondrial research. However, the organelles commanded

Reynolds' attention years before this second mito-boom.

In 1992, he was gathering evidence that mitochondria were killers. Reynolds was using a simplified model of stroke, in which he gave neurons in culture high doses of glutamate, an excitatory neurotransmitter, which killed a fair portion of them. He knew that the way glutamate caused damage was by stimulating excessive calcium to enter the cell. But where in the cell was the calcium going? He discovered the answer—into mitochondria.

Reynolds wondered what would happen if he put calcium into cells but prevented the element from entering mitochondria. When he did the experiment, he found that calcium had no detrimental effect on the cells, as long as it didn't enter the mitochondria.

From what Reynolds has gathered, mitochondria are killing brain cells, and not just through the process of apoptosis. They seem to take on the role of executioner in some other way as well—yet another function to be elucidated. ■

WHEN OUR OTHER DNA MUTATES

The woman had high cholesterol, but otherwise had always been healthy since a bout of irritable bowel syndrome 10 years earlier. She started taking medicine to control her cholesterol and, within a few months, developed weakness and muscle aches. Her grandson had some of the same symptoms and was dying from a rare inherited mitochondrial disease called MELAS. Her brother had died after showing similar symptoms years before. When the woman stopped taking the cholesterol medicine, her symptoms went away.

Carolyn Bay, assistant professor of pediatrics, has heard similar stories from other family members of children with inherited mitochondrial disease. The children become sick because in a large percentage of the cells in their bodies, there are mutations in the mitochondrial DNA. Bay suspects that apparently healthy family members on the maternal side (mitochondrial DNA, which is different from the nuclear DNA, is inherited from the mother only) may also have defects in their mitochondrial DNA, but at lower levels. The family members may develop symptoms of mitochondrial disease if they come down with a serious illness or take medications that affect mitochondrial function like statins and some HIV drugs.

"We are just at the beginning of our understanding of how mitochondrial diseases work," says Bay. "We know the glaringly obvious cases. As we get more sophisticated, we're going to learn the more subtle cases." —*DH*

DOUBLE TAKE

The scientific community did a double take five years ago when it learned that mitochondria, long understood as vital for converting oxygen into energy the cell needs, also play a role in apoptosis. As it turns out, the organelles set off a process of programmed cell death by releasing cytochrome c into the cytoplasm.

Hannah Rabinowich, a professor of pathology, says that since 1997, scientists have largely uncovered what happens in cells *after* mitochondria release cytochrome c. However, they have yet to understand what happens *inside* mitochondria *leading up to* the release of cytochrome c.

"Within the mitochondria, it's a black box," she says.

Rabinowich is determined to understand the mitochondrial events that trigger the release of cytochrome c and other apoptotic proteins. Her experiments utilize a cell line, cloned from leukemia cells, which is deficient in two mitochondrial proteins—Bak and Bax. A couple of years ago, she wondered: Are the proteins essential players in stimulating the release of cytochrome c? To get at the answer, she exposed the cells to chemotherapeutic drugs. (Like many common chemotherapeutic drugs, the ones she used kill cells by inducing apoptosis.) The cells were left unscathed by the drugs—suggesting that without these proteins, apoptosis cannot occur.

She's now working on further experiments using the deficient cell line. If she puts Bak into the cells, so that they are deficient only in Bax, will that deficiency alone protect them from apoptosis? What if she turns the tables so that there's a Bak deficiency instead? The answers, she believes, will give researchers more insight into how cells set in motion their own death. —*DH*

HOT FLASHES

When Ian Reynolds, professor of pharmacology, used a fluorescent dye to light up mitochondria in astrocytes (a type of brain cell), he didn't expect to see the mitochondria flashing—getting dimmer and brighter and dimmer and brighter again. Instead, he expected to see them steadily illuminated. The dye he uses, based on tests by former postdoc Jennifer Buckman, he explains, works because it is drawn to a negative charge. Mitochondria are negatively charged on the inside of their membrane and positively charged on the outside. This difference in charge, called the membrane potential, is what allows the mitochondria to do their job of converting sugar into ATP. When the mitochondria become dimmer, they are losing the negative charge on the inside of the membrane, and thus losing their membrane potential. "All these spontaneous changes in membrane potential—we had no idea they were occurring," says Reynolds. He believes that, as membrane potential is lost, mitochondria are unable to produce ATP. But he has no idea why the membrane potential changes. And he doesn't know why he has seen the flashing in astrocytes, but never in neurons.

"Every time you do one of these experiments," he says, "you bump into something different, some things you don't expect." —*DH*

Albert Ferguson built an orthopaedic dynasty in his three decades as chair at Pitt—a dynasty that lives on today. During his career, he trained about 30 other orthopaedic department heads. He's shown here with an x ray of a patella, created with an imaging technique that he developed. Behind him, in more ways than one, are (from left) William Green, Mark Goodman, Edward Hanley, and Dana Mears (circa 1980).

SCORES OF DEPARTMENT CHAIRS ASPIRED TO BE "JUST LIKE HIM" | BY EDWIN KIESTER JR.

PLEASE DON'T CALL HIM DR. FERGUSON

When Robert D'Ambrosia was a young flight surgeon with the 497th Tactical Fighter Squadron in Ubon, Vietnam, the jumping-off place for bombing raids into the North, he found himself surrounded by orthopaedic cases. Seeing those shattered and broken bones clarified for him how he was meant to spend his postdischarge days. He placed an international call to Albert B. Ferguson, the David Silver Professor and Chair of Orthopaedic Surgery at the University of Pittsburgh, and applied for a residency. The two had met during D'Ambrosia's brief orthopaedic rotation in medical school at Pitt, but it took only a few minutes of conversation over a crackling line, as both men remember 30 years later, before Ferguson responded, "Sure. I'll save a place for you." Somehow the busy chair determined, during a short, very-long-distance phone call, that this candidate wouldn't let him down. He was right: The Ferguson-trained D'Ambrosia has been chair of orthopaedic surgery at Louisiana State University (LSU) in New Orleans for 26 years and is the immediate past president of the American Academy of Orthopaedic Surgery.

PHOTOGRAPH | COURTESY UNIVERSITY OF PITTSBURGH ARCHIVES

COURTESY FERGUSON

When Ferguson needed a partial-knee replacement, he asked Pitt's Chris Harner to do the job. "A great honor," notes Harner. The patient was pleased with the results—except it didn't help his golf handicap. Shown here (from left) with David Bahnson (MD '73) and his father, Hank Bahnson, another icon of surgery at Pitt with bad knees.

Then there was Ed Hanley (Res '80). Hanley graduated from medical school at the University of Vermont at the top of his class and had a choice of prestigious residencies at Harvard or Johns Hopkins universities. A friend suggested visiting Pitt, because "there's a great guy there who's a Dartmouth man like you." Hanley says, "I had never thought of Pittsburgh, never been there in my life. But the minute I walked into Ferg's office I was enthralled by him. I knew I wanted to go there and try to be just like him." Hanley is now chair of orthopaedic surgery at Carolinas Medical Center in Charlotte, North Carolina.

When Harry Rubash (MD '79, Res '84) was a third-year medical student at Pitt, he hadn't a clue to what medical specialty he might choose. Then he signed up for a three-week elective in orthopaedics. "The minute I scrubbed with Ferg," he says, "I thought, 'Wow! I want orthopaedic surgery!' I saw the sheer joy he got out of restoring mobility to people." Rubash is now chief of orthopaedic surgery at Massachusetts General Hospital and professor of orthopaedic surgery at Harvard. (See p. 39 story.)

You can hear similar stories all over the world. Former Ferguson residents now head academic orthopaedic surgery departments in Britain, Turkey, Japan, and Korea, and at plenty of American schools, including the universities of Wisconsin, Illinois, and Kentucky—and at Pitt, where the incumbent of Ferguson's old chair, Freddie Fu, was Ferguson's chief resident in 1982. No one seems to keep precise statistics on such things, and you won't find an entry in *Guinness*, but "Fergie"—"No one but telemarketers calls me Dr. Ferguson"—must hold the world's record for training department heads. The current count seems to be around 30. (See p. 40 for a genealogy of the dynasty.)

What explains this remarkable record? Ferguson, with the infectious laugh that seems to punctuate his every sentence, professes not to know. He can hardly even remember what he did before 1986, when he retired, he says—almost believably. Plenty of others remember though. The white-haired 82-year-old spent 33 years not only training several generations of orthopaedic surgeons but also repairing baseball pitchers' balky elbows and ballerinas' damaged knees, and replacing literally thousands of worn-out joints—a field in which he became nationally heralded. He now divides his time between a high-rise in Fox Chapel and a farm in Upper Turkeyfoot Township in Somerset County, Pennsylvania, where he paints and plants furniture trees like red oak and cherry. But if he is gone from the academic surgery scene, his influence is still felt. When D'Ambrosia (MD '64, Res '70) was installed as president of the academy, he chose Ferguson to escort him to the podium.

"Trying to lead physicians is like trying to herd cats," says Rubash, considering what made his mentor stand out. "But Ferg could do it, and he picked people just like him." Moreover, his former residents agree, once he chose his trainees each year, he gave them his full confidence and encouraged their independence.

"Ferg picked the best horses," Hanley says, "and then he *let 'em run!*"

Rubash was a resident under Ferguson, learning the Ferguson techniques of hip replacement, then he received a fellowship to further his study at Mass General. There, he trained under William Harris, another noted joint-replacement expert, before returning to Pitt. "Bill's method was a little different from Ferg's," Rubash recalls. "So when I came back, here was my chair, who had a well-deserved national reputation in the field and had spent most of his career doing it a certain way. But he never once told me what I should do, what type of operation. He never, ever, told me what *he* would do. He'd just bring me the x ray, introduce me to the patient and say, 'I want you to take care of this patient. Do what you think needs to be done.' He was like that when you were a resident, too. He gave you a challenge and let you work out how to meet it."

Certainly, as Fu says, judged by current protocols, which involve tests, academic records, letters of recommendation, and a commitment to equal opportunity, the Ferguson method of choosing candidates for residency, standard for its time, wouldn't fly today. Each year hundreds of medical-school graduates vie for admission to the Pitt residency program; the field must then be winnowed down to fill eight or nine openings. (Last year, Pitt received 600 applications.) Ferguson's strategy was to rely on eye-to-eye, person-to-person judgment. And his own gut instinct.

"My model was Worth Hale, who was the admissions guy at Harvard when I applied," he says. "I walked into Hale's office as a 23-year-old and sat down; he said, 'You're in!' I said, 'I am? Why?' He said, 'You sold yourself when you walked toward me. I could see you had your motor running. You didn't need someone telling you what to do.' That's the same principle I used.

"Mind you, I did make some mistakes. Some were lollapaloozas. But that's the way it goes."

Of course, there were other elements in the choices. Ferguson admits he's partial to athletes, believing that athletics fosters the kind of quick decisions, self-reliance, and all-out energy that surgery requires. Would-be female surgeons were rare in those days, but Ferguson picked some standouts. Lynn Scovazzo now has a private practice in Fox Chapel; this Fergie-pick was a record-holding swimmer at Pennsylvania State University. "Competitive," he says admiringly.

Mary Cosgrove, who was his assistant for all 33 years, laughingly claims she had a voice in recruiting, too. "I always picked the good-looking ones," she says. "And I told him I was usually right."

When Ferguson came to Pitt as chair during the "brace-and-buckle days" of orthopaedics in 1953, there was no residency program in orthopaedic surgery. "Zero," he says. In fact, there was no department to speak of. "I was it," he says. Although he was only 34 and just a few years out of residency, he had already established a national reputation. After his undergraduate years at Dartmouth, he got his MD at Harvard. He spent two wartime years in the marines, then returned to Harvard to train in pediatric orthopaedics. There, his innovations made him, he says matter-of-factly, "the fair-haired boy."

His specialty was children with dislocated hips. The joints were frequently pushed out backward at birth, especially in feet-first breech deliveries. The dislocation often did not show up until the child was old enough to stand and walk. "No matter when it was discovered," says Ferguson, "the prevailing attitude among surgeons was, 'We can't do anything when he's so young. Bring him back when he's five.' But of course the delay caused all kinds of damage to the kid, not just in terms of mobility, but psychologically, socially, and every other way. He couldn't play with other kids, couldn't walk right, was left out. And even when it was done, the surgery often did as much damage to the hip as leaving it alone."

The maverick doc began operating—successfully—on children as young as 2, applying a new approach through the inner thigh that minimized scarring and didn't involve cutting through muscle. The procedure was soon widely copied.

His first practice in Pittsburgh was at Children's Hospital, but as his reputation spread, physicians began referring adult patients, too. He moved to the Falk Clinic for adult cases. Ferguson had played baseball at Dartmouth and still adored the game. Before long, Pirates general manager Joe L. Brown recruited him—as the team's orthopaedic surgeon, that is. He attended spring training, taught conditioning, and introduced several reforms, insisting, for instance, that teenaged rookie pitchers not be allowed to throw sharp-breaking major-league curves during training. He said the strain on the still-maturing shoulder could tear the small muscles around the shoulder joint. The Ferguson dictum is still followed by several major-league clubs.

The players loved him and listened to him, says Brown, now retired. Many of the great names of Pittsburgh sports passed through his Falk Clinic office—the late Hall of Fame outfielder Roberto Clemente, for instance. "He was a very high-strung guy," says Ferguson. "Most of my treatment wasn't orthopaedic; it was psychological. He was always complaining about neck and back problems that could not be pinned down. One time he could not move at all. He was brought to the hospital by ambulance, flat on his back. I sat and talked to him, and after a while he sat up, and then I persuaded him to try to stand and walk. We walked up and down the hospital corridors together, and finally I said, 'I think you're fine. I think you could play tonight.' He agreed, so I took him down and put him in a cab." Instead of going to the ballpark, however, Clemente went to the airport and boarded a plane to Puerto Rico. There he visited a relative who practiced a form of folk medicine. He stayed 10 days and came back "cured." "And he never played better," Ferguson says.

Fu is now "the major ballet guy in the US," Ferguson brags. But he himself once served as orthopaedic surgeon for the Pittsburgh Ballet, which gave him a lifelong respect for the athleticism of ballet dancers—"beyond question the best-conditioned athletes of all."

Speaking of conditioning: Working with scientists from the Mellon Institute, Ferguson found ways to fashion metals like titanium and the highly durable space-age materials used in rocket nose cones into replacements for the hip, knee, and other joints. He developed standards for the use of metals in the body, which are still used—"although they've gone far beyond what we did." This work is what he looks back on most proudly. Throughout his career, the surgeon has collaborated extensively with basic scientists and insisted that his residents do the same.

"When I came back from Vietnam, he put me in the lab for a year," D'Ambrosia says. "One of the best things I ever did." One result was D'Ambrosia's book on how orthopaedists could use the lab in evaluating patients; he wrote it as a resident.

In the OR, Ferguson was known for performing five operations in the time other surgeons might perform three. After an operation he would grab a mop and begin to swab down the floor rather than wait for the cleanup crew. "It wasn't that he was impatient," Cosgrove says. "He was a very patient man. He just wanted to get on with it."

After an operation, he would grab a mop and begin to swab down the floor rather than wait for the cleanup crew.

Today, he is a little slower; the man who performed thousands of joint replacements now has a partial artificial knee of his own, courtesy, of course, of Pitt's Department of Orthopaedic Surgery. He himself has not operated since his retirement, but retains an abiding interest in the health sciences. "I am in awe of what they're learning about the human body in recent years." He keeps in touch with his former residents, dropping them occasional cards (usually hand painted) and giving them advice—"words of wisdom," Rubash says. A recent card reminded Rubash to be good to his staff: "It will pay off many times."

He also continues to take a hand in the Orthopaedic Research Foundation, which was established by friends and colleagues after his retirement to give seed-money grants for small pilot projects by residents and private physicians. The fund began with $1 million in pledges; now it totals $2 million. "My sole role is to decide who gets the money," says the surgeon with a smile.

Loyalty runs deep among the Fergie crowd. When it is pointed out to D'Ambrosia that at 26 years as chair at LSU, he's approaching his mentor's epic tenure as department chair (33 years), the thought of surpassing it takes him aback. He's clear—that distinction, too, should always belong to Fergie. ■

Five students head to an impoverished village in Honduras—after Tropical Storm Michelle, no less. After some time there, it becomes hard to shake the thought, *We're only here for two weeks; what can we do?*

THE BEST INTENTIONS AND A HONDURAN VILLAGE

BY JESSICA MESMAN

GOLDEN HEARTS

Even when the rain abates, the air is so thick you can almost move it with your hand. It's November, seven months into Honduras' marathon rainy season. A guide leads Taji Yazdany and her University of Pittsburgh School of Medicine classmates Suzanne Atkinson, Michelle Dorsten, Rachel Eash-Scott, and Stacey Walter to a battered Toyota pickup outside the San Pedro Sula airport. They sit on wooden slats in the truck bed, gripping their luggage and the steel rails that have been installed for cargo. It's a rough ride from the city to the village of San Jose—where they'll be administering care and getting a crash course on community health assessments with the nonprofit health-care partnership Shoulder to Shoulder. As the driver turns off the two-lane highway and onto a muddy trail slashed through the woods, the passengers hang on even tighter. San Jose is just a tiny cleft in a mountainside, accessible only by this dirt path sliced into the green of the rain forest. The road is perpetually new, the red silt slick as potter's clay. Still, the driver maintains speed at a swerving, lurching chop.

PHOTO: ERIC SHELTRA

PHOTOGRAPHY | SUZANNE ATKINSON, RACHEL EASH-SCOTT, ERIC SHELTRA, STACEY WALTER

LEFT: RACHEL EASH-SCOTT; RIGHT TOP: STACEY WALTER; BOTTOM: ERIC SHELTRA

LEFT: An abandoned schoolhouse playfully known as "UPMC San Jose." TOP: Away from mud for a few minutes: from left, Taji Yazdany (Class of '02), Stacey Walter (Class of '04), Michelle Dorsten (Class of '03), Rachel Eash-Scott (Class of '03), and Suzanne Atkinson (Class of '02). BOTTOM: The entrance to the village of San Jose. The building that housed the clinic is to the right.

Atkinson is thrilled. Navigating this exotic, rough-hewn terrain in the back of a rattletrap pickup, she feels like the heroine of some adventure novel. But while she revels in the excitement, Yazdany is busy not looking over the guardrails at the earth flashing by on either side of her. By the time the truck reaches the village more than an hour later, she is carsick.

Most of the village is made up of mud and stick houses over the hillsides, accessible only by foot. Near the road sit simple cinder-block houses capped with rusting, corrugated tin roofs. Children, chickens, and pigs wander from plot to plot. Tropical Storm Michelle didn't cause the devastation that Hurricane Mitch did in 1998, but there have been some complications. Washed-out roads kept the translators away and stalled the delivery of meds and glass slides for the microscope.

No electric lines reach here. Anyone with a TV or a radio powers it with a car battery. A handful of *pulperías*—market stands that sell cold drinks and basic groceries—have generators. The few solar-powered refrigerators and telephones in the village are useless from June to December, the rainy season.

And then there's the mud. It oozes and attacks as if alive. When Yazdany jumps down from the truck's bed, queasy but still eager, she sinks a few inches. For days, no matter how carefully she treads, the mud finds its way to her ears, her hair, her last clean pair of scrubs. "How did I get mud *here*?" becomes her mantra. The locals seem immune. Students in expensive hiking boots slide and stumble behind a local woman in backless, high-heeled sandals gliding up the slippery clay inclines. This aggressive, coffee-colored paste is worse than the homesickness and the diarrhea. Worse than the respiratory infection they'll pass to each other and worse than the cold, concrete floors they'll sleep on each night. Above almost anything else, the Honduran experience will leave them with a greater appreciation for one simple luxury—a clean cotton T-shirt.

Days before she was due to leave for San Jose, 25-year-old Yazdany heard reports of a tropical storm in the Caribbean. Her parents called her in Pittsburgh, panicked by the memory of Mitch—the worst natural disaster to strike the Western Hemisphere in modern memory. *You're not going*, they insisted. But Yazdany didn't waver. Instead, the fourth-year student continued to pack her bag according to the list the program's coordinator, Pitt professor William Markle, distributed to his students: stethoscope, latex gloves, scrubs, sleeping bag, headlamp. Her own list was a little different—she wasn't taking any chances. She packed everything in her medicine cabinet, every over-the-counter drug she could find. Then she collected toys and money for impoverished families. And once a week, as a safeguard against malaria, she took her dose of chloroquine, despite what she heard from friends: *It may cause hallucinations. Nightmares. Cardiac arrhythmia.*

Besides violent tropical weather and harsh topography, social and economic challenges plague the mountainous interior of Honduras. San Jose villagers face all the usual problems of being Honduran—insufficient health care, malnutrition, poverty—plus the complications of isolation. Even in big cities like Tegucigalpa and San Pedro Sula, the ratio of doctors to residents is approximately 8 to 10,000. San Jose doesn't have a doctor, and the nearest clinic is in El Progresso, more than an hour away in good weather, inaccessible otherwise. A single Honduran nurse helps village midwives deliver babies and immunizes the children. The inroads she has made convinced Markle, an MD and an assistant professor of family medicine at the School of Medicine, that San Jose would be a place where a well-meaning group of American providers could make a difference—knowing also that such a proposal is not an easy thing to carry out.

Shoulder to Shoulder is devoted to assisting communities in Honduras to improve their own health care. Markle, a member of the

Days before she was due to leave for San Jose, 25-year-old Yazdany heard reports of a tropical storm in the Caribbean.

CLOCKWISE FROM TOP: **Yazdany and attending physician Maria Matsudo in the clinic. Markle treats an emergency case. Atkinson and family-practice resident Jon Maier talk to parents of children who have *grippe y tos* (cold and cough). A hammock serves as a stretcher.**

THIS PAGE ALL PHOTOS: ERIC SHELTRA

left: Short stature is common among San San Jose children, an indicator of chronic malnutrition. right: Cincinnati nurse Jenny Dornhagen and Dorsten shampoo a child with lice.

THIS PAGE ALL PHOTOS: ERIC SHELTRA

International Health Medical Education Consortium, joined with the organization hoping to partner with a village like San Jose—a place whose residents were looking for a long-term relationship with an organization to help them meet their goals. Shoulder to Shoulder had visited the village a few times—it provided training for a nurse for San Jose, helping to pay her salary. Some of the local women had formed a nutrition committee to develop programs for the village's malnourished children. Markle, with colleagues Mark Meyer, a private practice physician, and Randall Kolb, who practices family medicine at UPMC Shadyside, recruited a Pitt/University of Cincinnati team of family physicians, nurses, residents, students, a nutritionist, and an engineer. The students' rough truck ride marked the beginning of the Pittsburgh chapter's first mission. For two weeks, surrounded by the broad leaves of the Honduran rain forest, they slept, ate, studied, and saw patients in an abandoned shell of cinder block, a former kindergarten classroom.

Their days start with 7 a.m. breakfast. Rather than their using the limited food available in the village, groceries and bottled water were brought up to San Jose from El Progresso and stored on ice for the Shoulder to Shoulder team. Cooks wash dishes in an outdoor wash basin; the toilets and showers are open-air, concrete stalls outfitted with PVC pipe. Shoulder to Shoulder taught the local women to wash fruits and vegetables in a bleach solution, but they make the solution so strong that the entire kitchen smells like a swimming pool. The portions they dole out (homemade corn tortillas and oatmeal in the morning; tortillas, beans, rice, and chicken in the evening) aren't enough for the students, who easily could eat seconds. Maybe even thirds. The Americans seem about twice the size of their Honduran counterparts.

After breakfast, the children drift in, at first for a look at these strangers, and later to play with the toys they know are stashed in the clinic. They would come even earlier, but the doctors send them away if they show up before 7 a.m. They run in packs, barefoot. Most of their fathers leave the village to work in the *maquilas*—American apparel factories in the cities—while their mothers cook, clean, tend livestock, and dry out raw coffee cherries to sell to the roasters. It's almost impossible to identify which child belongs to which family. They just seem to belong to the village.

These children are tiny, easily mistaken for three to four years younger than their age by the doctors and students. They are dressed in ill-fitting, American hand-me-downs—an oversized Pittsburgh Penguins T-shirt, a too-small Looney Tunes hooded sweater. And their giggles and shouts fill the village air until the sun sets. To them, oranges plucked from trees are soccer balls; flats of mud are for etching circles that you throw marbles into.

Most of the children have worms. In fact, almost everyone in the village has a parasite of some kind. Mothers bring children into the clinic, complaining of worms in stool, worms crawling out of mouths. There's no plumbing in San Jose, and those who don't have a latrine or an outhouse relieve themselves in the forest. In the rainy season, excrement flows down the sides of the mountain, collecting in the yards of the poorer homes, where the children play barefoot.

But the worms don't seem to bother them. They're so accustomed to being hungry, to filling up on handfuls of rice and maybe some chicken or eggs once a week, the constant depletion of nutrients caused by the parasites probably goes unnoticed. More serious are the asthma attacks, the respiratory diseases caused from cooking fires in the home and burning trash in the yard. More painful are the tropical diseases, like leishmaniasis, sandfly bites that become pitting, ulcerated lesions all over the body. Worms they can treat. But all Yazdany and her colleagues can do for a young girl with leishmaniasis is scrub her sores clean and give her a referral to the clinic in El Progresso. When Yazdany finishes, she asks the girl to pose for a picture. She dutifully raises her raw, oozing arm and turns her big brown eyes to the camera.

The women complain of headaches, indigestion, fatigue, symptoms the students recognize as anxiety. Atkinson sees a 17-year-old girl whose brother raped her and whose mother threw her out of the house. Yazdany helps a bruised and bloody woman who tried to throw herself off the mountain when she found her husband in bed with his mistress. In Pittsburgh, they would refer these patients to the women's shelter or a mental health professional. In San Jose, Yazdany watches helplessly from the doorway of the clinic as the patient gets back in the truck with her husband and drives away.

And sometimes . . . "It felt like paradise. A weird mix of paradise and poverty."

But when the clinic closes at 4:30, the army of children floods the dirt yard behind the clinic for games of Monkey in the Middle and soccer. The students join them, plucking new oranges from the trees when they clumsily crush the makeshift soccer balls underfoot. Students struggle to remember each child's name, but limited Spanish and the sheer volume of small faces make it almost impossible. Instead, they're remembered as an eager huddle, a single entity clutching the chain-link screen of the pharmacy window, waiting with equal patience for a clinic visit or a turn with the jump rope. These children are sick—they don't need an exam to prove it—but in the backyard of the clinic, their stoicism relents to constant, pealing laughter. *A sound that makes you want to laugh and cry at the same time*, as Yazdany says. And sometimes, when the rain stopped and skies cleared over the orange trees, "It felt like paradise," says Atkin-

orange trees, "It felt like paradise," says Atkinson. "A weird mix of paradise and poverty."

After dinner, the students attend lectures by attendings and residents, where they discuss worms, tropical diseases, and malnutrition. Some take their second cold shower of the day in a futile attempt to be rid of the mud. Some actually find the energy to study. Others play cards in the clinic. Before bed, they try to maneuver bedding away from the leaks in the tin ceiling but soon give up. They learn to sleep pelted by cold raindrops in a pitch so black that when Atkinson waves her hand before her eyes, she sees nothing but darkness.

I'm going to turn on the lights now. Atkinson's running joke. At 6 a.m., she opens the windows.

The students have been in San Jose more than a week. Every day, they split into three groups. One group works the pharmacy window, dispensing medicine through a gash in the chain-link. Another sees patients in the clinic. The third goes out in the field to conduct nutrition surveys.

In the clinic, second-year student Stacey Walter translates the medical history of an elderly man who complained of trouble swallowing. Just a quick oral exam with the tongue blade revealed masses of distorted tissue, a carcinoma.

"I tried to explain that this was serious, that he needed to go someplace else, that it was cancer," she reports back. "But he didn't seem hugely concerned about it. He just wanted to swallow." All that could be done was send him away with a small bottle of children's Advil for the pain, a couple of doses. Not even a drop in the bucket from Walter's point of view. But the old man was appreciative, even chipper.

Another day, out in the field, Yazdany followed members of the local health committee into the barrios, down those steep and slippery slopes to mud brick homes stuck to the side of the mountain like magnets. (The cinder-block homes on the main road are for the wealthy.) When Yazdany visits, many families are busy repairing the damage caused by Tropical Storm Michelle. The children she wants to measure and weigh for the survey are naked, and it's hard to tell where they actually live. "You just have kids wandering in and out of people's houses," she tells her schoolmates, exasperated.

Distributing parasite medication to cancer patients and cleansing surface wounds for the mentally abused seemed futile. It was hard for Yazdany and her peers to shake the thought: *We're only here for two weeks; what can we do?*

With each evening's lectures, and each day's patients, the students came to realize that all their efforts might not change life in San Jose if their priorities didn't come closer to the community's. Markle tried to warn them from the start, but they couldn't hear it until they actually lived it, notes Atkinson. They came to this village, as Yazdany puts it, with "golden hearts"—deep pockets of good intentions. But they were hindered by the urge to do too much. In the end, maybe the most important thing they had to give was hope.

It was time to reassess their goals.

The mothers of the village might not recognize the need for a women's shelter, but they knew their children were hungry. Their nutrition committee hoped to serve all the local children one full meal each day. The med students' surveys reported the missing elements in the local diets and the severity of the malnutrition. With Shoulder to Shoulder, they could offer the knowledge and even some of the resources for villagers to help themselves. Here was the true beginning of the San Jose mission. And it was time to go.

But not for good. By the time the students scrambled back onto the pickup truck to leave San Jose, many had committed to returning in April. With Markle and the other Pittsburgh doctors, they intend to raise $18,000 to provide training and materials for the village's nutrition committee. The next time they visit, they'll also administer care from a mobile clinic donated by a Texas charity. These are smaller victories than they had dreamed when they landed in San Pedro Sula, but at least now it was clearer how to build a solid foundation that golden hearts could sustain and supplement, even from Pittsburgh.

"Going there, we had no perception, no idea, of what this trip would mean," says Yazdany a month later, stacks of snapshots from the trip fanned on the table in front of her. Her clear, olive skin is naturally flushed in the warmth of a coffee shop. She's not the tired, muddy young woman in the pictures, the one with the red nose swollen from congestion and the eyes underlined by bruise-colored circles. But she's not quite the student she was before, either. The chloroquine diminished her appetite and left her a few pounds lighter. And after being in the trenches, she admits *it feels a little weird to be home.* Part of her is still in San Jose, mud in her ears, wringing the rainwater from her scrubs. ■

BELOW: **Outdoor basin for dish washing.**
BOTTOM: **The Shoulder to Shoulder team dining.**
RIGHT: **Yazdany with village children.**

THIS PAGE ALL PHOTOS: ERIC SHELTRA; EXCEPT FAR RIGHT: SUZANNE M. ATKINSON

Lucky for Pitt, Dennis Swanson finds regulations governing human subject research—the same regulations that are likely to drive investigators to shake their fists at the ceiling—*interesting*.

MINIMAL RISK WITH DENNIS SWANSON

BY DAVID R. ELTZ

THE SECOND IN A SERIES

TRIAL RUNS II

Inside the cylinder, sweat beaded on Dennis Swanson's brow. His pulse quickened. His breathing hitched. Swanson, then the inquisitive director of radiology pharmacy services at Henry Ford Hospital in Detroit, was losing control.

A researcher who'd been testing diagnostic imaging agents for a decade, Swanson was evaluating whether a certain drug combined with magnetic resonance imaging (MRI) could be used to study four pea-sized nodules in the neck that regulate the body's calcium levels, the parathyroid glands. He had volunteered to crawl into the MRI himself, figuring, *What was the risk*? Soon, Swanson was tuning out the MRI's annoying banging and clanging sound only to realize that he was lodged inside something that resembled a coffin. It wasn't long before the constricting panic of claustrophobia wrapped around him.

PORTRAITS | TOM ALTANY

"They had to pull me out," Swanson says, some 20 years later.

Once outside the tube, he recovered and thought his way around the paralyzing feeling. Swanson theorized that he could tolerate the MRI's confines if he kept his brain occupied. So, he slipped back inside, taped a magazine article where he could comfortably see it while lying in the machine's bore, and, for the next two hours, read whenever fear slithered in. His psychological experiment worked; the scientific one did not.

Today, Swanson, director of the University of Pittsburgh Institutional Review Board (IRB) office—the IRB is the oversight body that approves or rejects every formal plan for human subject research at Pitt—forgets what the article was about. It is the claustrophobia he remembers. "It was interesting," he says, pointing out the merits of distracting the mind from fear. He says that again—*It was interesting*—about his brazen act of sailing recently in the Caribbean during a squall, warning himself he might fall off and drown but just the same hanging off the stern to keep the sails from tangling.

Swanson drives his lumbering black Dodge van down a Pennsylvania highway at the 65-mile-per-hour limit. (Okay, maybe just a bit faster.) At 55, he bears a striking resemblance to Jerry Garcia, a slight paunch beneath his navy-blue suit coat, metal-framed glasses riding high on his bearded face, a mane of white hair brushing his collar. (A three-foot-tall pencil sketch of the late Grateful Dead musician hangs in Swanson's office.)

In an hour he'll tell researchers at Pitt's Bradford campus about human subject research and federal regulations and IRBs and research conduct and compliance. He'll watch some, say, social work profs who are conducting sensitive questionnaires, raise their hands with questions, a bit hesitantly, because, well, they don't know all of the rules. That's okay; he wants to help. He finds the regulations—regulations that often drive investigators to shake their fists at the ceiling—*interesting*.

Swanson refers to himself as a child of the '60s: "I like to question federal authorities," he says, eyes on the road. "There's nothing I like better than to quote a federal agency's regulations back to them when they tell me I can't do something.

"I do that a lot. I think we need to question their interpretations of the regulations often. Because, frankly, they aren't the people out doing the research."

Donna Medich

PHANTOMS WHO KEEP DATA STRAIGHT

In 2000, Donna Medich got a phantom in the mail. In Medich's world, a phantom is a clear rectangular box containing a synthetic lumbar spine surrounded by liquid. She ran 10 scans of the phantom on her densitometer, measuring the bone mineral density (BMD) of the artificial vertebrae. Then, she sent the phantom, along with the results, to a central data collection site for a study that tests the use of parathyroid hormone for osteoporosis treatment. Once the central site got the phantom back from Medich, it mailed it off again. Eventually, the phantom was sent to more than 100 study sites, including some outside the United States. This allowed the central facility to compare phantom readings and adjust data if needed—ensuring that differences are not merely due to equipment aberrations.

Medich, a radiologic technologist, gets phantoms in the mail several times a year. They are used for quality control in several of the 11 trials for which she collects data. Her job is running BMD scans and body composition scans (which measure the percentage of body fat) for the 11 trials. Nine of the studies focus on osteoporosis. (Susan Greenspan, professor of medicine, is the principal investigator for eight of these.) Two trials, headed by David E. Kelley, professor of medicine, focus on diabetes.

"For a lot of the studies, it comes down to the BMD numbers that you get [in determining] whether a therapy works or not," says Medich. In the world of Medich and other technologists who support clinical trials at Pitt, accuracy and precision are everything. *—DH*

Swanson never was *radical*. Sure, he visited the scene at Haight-Ashbury in 1971, on break from a meeting of pharmacists in San Francisco, but by then the scene had become irrelevant. The most radical thing he has done, from his perspective, was to become the first member of his family to leave Iowa for good.

In 1975, Swanson quit his job, sold the house, and packed his wife, kids, cat, dog, and all worldly possessions into his station wagon. The wagon headed west so that Swanson could earn a master's in nuclear pharmacy from the University of Southern California (USC). Having been reared in Iowa, educated in Iowa (graduating in 1971 with a bachelor's in pharmacy from the University of Iowa), and in the process of raising a family in Iowa, Swanson never planned to leave

Swanson refers to himself as a child of the '60s: "I like to question federal authorities."

Iowa. But the lack of variety in being a community pharmacist in Burlington (population 27,500), at the same pharmacy for which he'd delivered prescriptions as a teenager, had grown tiresome. When the local Veterans Administration hospital offered to pick up tuition at USC, Swanson "escaped" into nuclear pharmacy as the field was just taking off.

"It was a minimal risk to do something different," he says in the parlance of his current position.

Whatever risks there were soon paid off. A year later, master's in hand, Swanson landed a faculty appointment at the University of Michigan Medical Center. In six months, he was the center's director of nuclear pharmacy, developing new radioactive drugs for diagnostic imaging.

Pharmacists often say they have the most regulated profession in the world, with oversight from the likes of state pharmacy boards, the federal Drug Enforcement Administration, and the Food and Drug Administration (FDA). Nuclear pharmacists, you can imagine, are regulated even more. At Michigan, Swanson's work necessitated he interact with regulatory agencies. He wrote his team's IRB applications for approval to conduct human subject research. He submitted applications to the FDA for approval to test investigational drugs. He studied the rules of the Nuclear Regulatory Commission.

In the '70s, Swanson came face-to-face with federal investigators. Michigan was one of several sites in a study of a new agent for imaging the flow of bile through the liver, gall bladder, and intestine. It was (and still is) typical, upon asking the FDA to approve a drug, for some of the trial sites to be audited. The FDA picked Swanson's site. Auditors discovered "documentation issues" in the research. In other words, when Swanson's team inadvertently wrote down data incorrectly, they would cover it with typewriter correction fluid and jot the new value over top—a no-no. Per FDA rules, investigators were supposed to cross out the old value, enter the new one, and initial it. Luckily, the auditors pointed out the deficiency without issuing penalties.

Swanson notes that neither he nor the physicians he was partnering with were familiar with the requirement—touching on an ongoing problem with such research. People who become clinical researchers do so because they have an interest in science, in solving the riddles of the body, in helping people. Often they're not trained in the details and seeming vagaries of regulations. (They also have plenty else on their plates, between performing research, seeing patients, teaching, preparing grants, writing articles for publication in peer-reviewed journals, managing research data and staffs, and other administrative duties.) Pitt has made it a priority to alleviate the pressure on investigators, recently creating a master's in clinical research program and establishing the Office of Clinical Research to manage educational efforts and help investigators navigate the regulatory process. The University also has made it mandatory for clinical research faculty to certify in research practice fundamentals.

Swanson filed away the lesson—to learn the regulations before something intractable happened—and continued his research.

His Michigan team developed two radioactive imaging agents. One is still used today to find pheochromocytomas, tumors particularly adept at hiding—even from CT scans. The incidence of such tumors was so low that no pharmaceutical company would carry the agents; so Swanson distributed the drugs to nuclear pharmacies around the country. As such, the university was required to register with the federal government as a "manufacturer," and Swanson added another body of regulations to his understanding. Later he would help Michigan set up a positron emission tomography (PET) laboratory before moving on to Henry Ford Hospital.

In 1988, Randy Juhl, who'd been dean of the School of Pharmacy at Pitt for two years, recruited his old friend and colleague. The two had known each other in school at Iowa and had golfed together since. Juhl, still dean today, brought in Swanson as his assistant dean for a variety of special projects.

Word about Swanson's knowledge spread. He was drafted into the Department of Radiology in the early 1990s to help Pitt set up a PET center and to get federal approval for using radioactive agents in humans. (While at Henry Ford Hospital, Swanson chaired a group that wrote the PET standards that Congress incorporated in the Food and Drug Modernization Act of 1997.)

THE HUMAN FACTOR

It takes a lot of people to make a clinical trial happen. What follows is a list of those involved in the Pitt segment of a multicenter Phase I clinical trial, led by Ramesh K. Ramanthan, director of the University's Gastrointestinal Cancer Center, for the new cancer drug Gleevec. The other nine sites in this study have similar staffing requirements.

Volunteer patients: 7

Primary investigator: 1

Coinvestigators: 7

Institutional Review Board (IRB) committee (which checks the primary investigator's protocol for ethical efficacy to protect the rights of all trial participants): 1 committee, 18 members

IRB office staff: 11

University of Pittsburgh Cancer Institute (UPCI) protocol review committees (which approve the protocol for scientific relevancy): 2 committees, 15 members each

UPCI regulatory staff (maintains files of correspondence with all regulatory agencies granting approval of the study): 9

General Clinical Research Center (GCRC)—where blood samples and data are gathered from trial participants—review committee: 16 members

GCRC staff—

- **nurses:** 12
- **clinical technicians:** 6
- **administrative staff:** 3
- **dietary staff:** 3

UPCI clinical coordinator: 1

UPCI clinic nurse: 1

UPCI investigational drug pharmacist (who prepares Gleevec): 1

UPCI outpatient pharmacists (who dispense the Gleevec and provide patient education): 3

Data manager: 1

Phlebotomist: 1

This particular trial requires the participation of patient volunteers whose health is often very fragile. Sadly, Leslie Levendosky, profiled in our last issue, was not physically able to continue with the Gleevec study. *—DRE*

By 1996, when Pitt wanted to expand the size of its IRB and create a director's position, Swanson was the logical choice. The nuclear pharmacist is perfect because he strikes a balance between, says Juhl, "the rigidity of federal regulations and the free-flowing characteristics of biomedical research." He knows what researchers do, what they're up against, and how to get them through it while maintaining the integrity of clinical research at Pitt.

It wasn't until the 1970s that the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research recommended that academic research centers establish IRBs. And not until the late '70s were researchers required to obtain written "informed consent" from a patient participating in federally funded experimental therapy (see "Bond of Trust"). Before then, clinical trials were guarded by ethical codes established at individual institutions as well as some nonbinding federal guidelines. Still, sometimes patients received pills yet were told nothing about them. During the early days of the Cold War, researchers working for our own government conducted radiation experiments on citizens, primarily soldiers in the US military, again without their consent.

Even today, IRBs don't always catch every potential problem. This was dramatically demonstrated at the medical research powerhouse Johns Hopkins University last summer. On June 2, 2001, a volunteer in a clinical trial at Hopkins died after inhaling a chemical that caused her lungs to fail. Ellen Roche was 24. She also was healthy when she enrolled in the trial. Investigators had given her the drug hexamethonium hoping to understand what happens during an asthma attack. After Roche's death, the federal government shut down some 2,800 human subject tests at the university for four days. For four days bills weren't paid, some therapies were halted, and a family waited to learn why they'd lost their daughter.

The story of what went wrong long before Roche took the drug emerged after an internal audit by the university and external investigations by the FDA and Office for Human Research Protections. Researchers allegedly had failed to properly warn volunteers of the risks involved, the Hopkins panel reported. What's more, federal investigators charged, the researchers didn't read far enough into the history of the drug; peer-reviewed research from the 1950s—not included in the protocol the IRB approved—suggests that hexamethonium could cause respiratory problems. Moreover, the FDA accused the IRB of not forwarding questions from some board members to the trial researchers, and concluded that, overall, Hopkins' IRB process was so overwhelmed that research protocols often were reviewed by only one IRB member. The finding sent shivers through the academic medical community, which holds Hopkins in such high regard. (November brought more concern. That month, Hopkins disciplined a faculty investigator who was conducting a clinical study in India, charging that the researcher did not seek university or government approval before testing a chemical derived from the creosote bush on the oral cancers of 26 people. The investigator countered that she was never told she needed university approval to conduct a trial in India.)

A clinical trial's investigators have a responsibility to keep their trials safe and ethical. Investigators are required to search scientific writ-

Julie Wagner (left) with Jodi Ribich

FINDING VOLUNTEERS IN HAYSTACKS

They needed 73 women to participate in a clinical trial, and it was the job of Jodi Ribich and her colleagues to find them. Ribich, nurse coordinator for an ongoing study at Pitt's Osteoporosis Prevention and Treatment Center, and company sent brochures to every woman older than 55 in greater Pittsburgh. They advertised in the Sunday paper. They took an ultrasound machine to local supermarkets, offering free screenings. They visited health fairs. Every Friday for a year, the study's primary investigator, Susan Greenspan, and her team brainstormed about finding more volunteers—all methods which would be approved by Pitt's Institutional Review Board (IRB). They went to the trouble of purchasing small incentives—jar grippers and magnetized memo boards for refrigerators—to give volunteers when they came in for a series of visits, such as an initial screening and a three-month checkup, with Ribich and Julie Wagner, Greenspan's physician assistant. Later, they simplified their incentive system, offering trial volunteers $5 gift certificates from a local supermarket for each visit. But this required them to resubmit the research protocol to the IRB *all over again* for approval. In the end, though, the best incentive for volunteers turned out to be the altruistic one—the opportunity to contribute to a better understanding of how to prevent and treat a debilitating disease. *—DRE*

He knows what researchers do, what they're up against, and how to get them through it while maintaining the integrity of clinical research at Pitt.

ings well enough to determine whether there are risks to the subjects' health, to inform volunteers of those risks, and to report any occurrence of "adverse effects" to the IRB as soon as possible. At the same time, the IRB is accountable should anything go wrong. At Pitt, the IRB committees protect the welfare of those enrolled in roughly 3,000 human subject investigations under way at any given time. "When something bad happens . . . the federal agencies hold the institution accountable, because it's the institution that's a recipient of the federal grant money [funding the study]," says Swanson.

Hopkins' immediate response to Roche's death was to double its number of IRB committees to six.

Swanson said he was already thinking about boosting Pitt's number of committees prior to the incident. He had done so in 1996, when he came on board as director of the IRB office. Within Swanson's first year on the job, the number of IRB committees at Pitt went from one to four, each comprising some 20 people ranging from research faculty members to everyday citizens (who are especially valuable for making informed consent documents understandable for the average research participant). That accelerated expansion reflected the University's mushrooming research enterprise.

It's a good bet, Swanson says, that Pitt's IRB will add several more committees this year—in part to avoid having to battle anything like what Hopkins just endured.

Passing through the IRB office each week are something like 35 new research protocols, 40 studies back to the IRB for review after one year, 20 protocols from investigators petitioning to add changes, and 20 coming back after changes have been added. Really, Swanson's job is straightforward: Interpret incredibly complex, constantly changing regulations written by people who don't do clinical research, and make sure they're followed by people who do often incredibly complex research but who don't necessarily know those regulations. Not a match made in heaven. Were he a marriage counselor working under such conditions, the outcomes might not be as solid—knock on wood—as they've been at Pitt. The secret? Swanson, current IRB chair Philip Troen, and the IRB are always looking ahead. They watch for coming changes, notes Swanson, before problems occur.

Despite this success, perhaps because of it, the research community sometimes refers to the IRB as the Dark Side, a frustrating fact of Swanson's work. But the frustration cuts both ways. Investigators tend to see the IRB as interfering with their research. When the IRB sends a protocol back to an investigator with questions about medical jargon in the summary, a researcher might say, "Who are you? You don't understand this disease!" notes Clifford Schold, head of Pitt's Office of Clinical Research. Such dissatisfaction among some faculty exists, he adds, because their business is science—not regulations.

That said, Schold, whose office helps investigators to write protocols that pass muster with the IRB, praises Swanson and his office. "I can tell you I've been at two other major academic institutions, and this is by far the best IRB I've ever seen.

"This is the most efficient and the most attentive."

The regulations aren't going away, Swanson says. Biomedical and surgical device research will continue to increase. The regulations will grow accordingly. To handle the glut, he would like the oversight structure at Pitt to become a "one-stop shopping office." (What he'd also like to do someday is open a bar, but that's another story.) Today, one research protocol might need approval from three different University offices other than the IRB—perhaps the Radiation Safety Committee, the Investigational Drug Service, and the General Clinical Research Center—with none of those offices necessarily working in sync. Swanson believes an investigator should be able to hand a protocol to a research analyst, who then sends it simultaneously to all those offices.

"That's where I really think we need to get to if we're going to continue being a major research player down the line," he says. "If we keep building our own bureaucracy [to meet federal regulatory measures], it's going to reach a point where investigators aren't going to comply with all the things we put in front of them, or it's going to be so difficult to comply they're never going to get their research done."

There is no such model in the country, but to suggest that much to Swanson would be like telling former National Football League commissioner Pete Rozelle that Super Bowls will never make money. And after all, this is a minimal risk opportunity. ■

This is the second of a two-part series on people who play often unsung roles in advancing new therapies.

BOND OF TRUST

"Informed consent" is the bond of trust between a clinical investigator and a patient volunteer. In each clinical trial, participants are required to sign an informed consent document, which states clearly, in common language, the purpose of the research, what will be asked of and done to the patient, and what potential risks could endanger the patient's health. The document must first pass muster with an Institutional Review Board (IRB). The IRB, under the guidance of the federal Office for Human Research Protections, takes even greater care to ensure that studies involving children, prisoners, and people with cognitive impairments are held to the highest ethical standards of consent. For instance, the federal government asks IRBs to consider that people with cognitive impairments who are institutionalized—because of their complete dependence upon that institution—might be vulnerable to requests for their "cooperation" in studies, for fear of being denied services or privileges.

Informed consent is more than a piece of paper. It is a process through which the research volunteer can ask the doctor about the research. The doctor, in turn, has an obligation to make sure the patient understands, say, in a Phase I cancer drug trial, that it is designed to test dosage levels and determine possible side effects, not necessarily to cure that person's disease. Pitt's new Office of Clinical Research was created to help investigators write such documents—and navigate the rest of the complex world of clinical research. Without informed consent, when research is conducted on people unknowingly or when a treatment is altered without a patient's consent, human subjects feel betrayed, as if they were guinea pigs, says Clifford Schold, assistant vice chancellor for clinical research and director of the new office.

More fundamentally, as Schold says, "It's the right thing to do." —*DRE*

The winter of a Freudian discontent and happier chapters in the life of Western Psychiatric Institute and Clinic.

FREUD, BIOLOGY, AND THE HISTORY OF A PSYCHIATRY POWERHOUSE | BY EDWIN KIESTER JR.

DRAMATIC LANDING

When Harry Mehalic was a University of Pittsburgh psychology major in the late 1940s, the highlight of his abnormal psychology class was a visit to Western State Psychiatric Hospital to view firsthand the unfortunates whose illnesses he had studied in class. One by one the professor brought out the patients, after first identifying them as "simple schizophrenic" or "manic-depressive" and listing their symptoms. "Our next patient is hebephrenic schizophrenic," he would say, describing her delusions and what he called "inappropriate emotional responses," then usher out a young woman in a shapeless gray hospital garment who would giggle out answers to simple questions like, "What is your name?" and "How old are you?"

No other university comes close to Pitt in NIMH funding.

COLOR PHOTOGRAPHY | JEN URICH
BLACK AND WHITE PHOTOGRAPHY | MERVIN S. STEWART

Ward rounds, 1962

Some patients were clearly disturbed, their answers obvious fantasies, Mehalic recalls, while others gave rational answers and appeared "as normal as you and me." One student asked how long a patient had been hospitalized. A matter of months, the professor said, but she had actually returned several times. What treatment was the patient receiving? another asked. Not much, it seemed. Electroshock was almost the only treatment available for some conditions; it succeeded temporarily, but patients often relapsed. For extreme cases there was lobotomy. Otherwise the profession couldn't prescribe much except patience—and confinement. Patients' prospects looked bleak; you didn't need to be a health care professional to see that. (In fact, Mehalic's career took him into the cosmetics industry.)

A great deal has changed at the 11-story, buff-brick building on O'Hara Street since those days of limited treatment and what Thomas P. Detre, Pitt's former senior vice chancellor for health sciences, termed "descriptive psychiatry" in a recent interview. The hospital has been renamed the Western Psychiatric Institute and Clinic (WPIC), and the building itself has become Thomas Detre Hall. Pitt is now a powerhouse of modern psychiatry. Today, no university in the country comes close to its $60 million in grants from the National Institute of Mental Health (NIMH). A torrent of research now pours out of WPIC, covering areas from psychopharmacology to neurobiology to the genetics of mental disorders. And the history of WPIC in the second half of the last century mirrors the marked transformation of the field of psychiatry itself in that time.

The idea of establishing a state mental hospital associated with the University for research and training purposes was born in 1924, at the emphatic suggestion of the state's Department of Welfare. The world was just beginning to acknowledge mental illness as a diagnosable and potentially treatable family of disorders, influenced by the remarkable theories of Sigmund Freud and his disciples in Vienna and the earlier writings of William James. Pennsylvania had already opened several mental hospitals, but the state did not actually authorize WPIC until 1931, even though Pitt willingly offered the land. In the depths of the Depression, the state had little money for constructing, let alone outfitting and supporting, a hospital. Not until 1938 was ground broken for the hospital; four years passed before it was equipped and staffed, with Grosvenor B. Pearson serving as the first director. The initial 160 patients were admitted in November 1942.

Those early years were difficult, according to a remarkable WPIC history written as a doctoral dissertation by Marcia Kramer Schachner in 1986. "There was not a book in the library, not a dinner knife nor fork in the dining room, not a piece of wood nor a tool in the carpenter shop," Pearson said of those beginnings. The professional staff was primarily part-time, and the few trained psychiatrists were rapidly being swept into the military.

With many soldiers suffering from shell shock, the war's end revived interest in mental illness and the need to seek and understand its causes as well as treat it. Psychology and psychiatry became recognized as academic disciplines. Dean William S. McEllroy launched an effort to elevate Pitt academic medicine to the front rank of medical research. He asked William Menninger of the Menninger Clinic to evaluate the university's offerings in psychiatry. Menninger endorsed the WPIC/Pitt affiliation, and recommended a strong emphasis on research. In 1951, the University leased the building for a token $1 and took over operations while the state continued to provide funds. The University and the institute were charged with missions in psychiatric research, training, and clinical services. Almost simultaneously, Pitt announced the appointments of three prominent scientists to lead the hospital and department into a bright new era. On Menninger's recommendation, the well-regarded psychiatrist Henry Brosin was hired from the University of Chicago to be department chair and director of the hospital; Arthur Mirsky, a noted psychiatrist, one of the first also to be an expert physiologist, would become head of research; and Benjamin Spock, the renowned author of *Baby and Child Care*, came from the Mayo Clinic to direct the child psychiatry program.

Freud's ideas had spread like wildfire. Psychoanalysis became popular, even chic. WPIC went right along with the trend.

"It [psychoanalysis] was fashionable and attracted the better minds," Brosin told Schachner years after he left Pitt. The way to recruit the best students and faculty, he reasoned, was to organize an institute and become a leader in the field. Francis Sargent Cheever, who held the position then known as vice chancellor for health professions from 1967 to 1974, agreed. He told Schachner, "Psychoanalysis was very much in the saddle, and that seemed to be the way to get to the top."

WPIC thus became a bastion of psychoanalysis and psychoanalytically informed (psychodynamic) psychotherapy training. (For example, residents were trained to support and talk with very psychotic patients in order to build their trust and treat them.) When the Pittsburgh Psychoanalytic Institute was officially established at WPIC in 1964, the faculty included about 10 psychoanalysts. "I would say 80 percent of the faculty were psychoanalysts, and their thinking was predominant," Detre says today of that earlier period. Much of the nursing staff was also psychoanalytically oriented, along with Spock (who left in 1955 after a lengthy clash with Brosin).

In some circles beyond O'Hara Street, however, psychoanalysis gradually was becoming less "fashionable." In 1952, the drug chlorpromazine had been introduced for treatment of schizophrenia; later, about 1971, US doctors began to prescribe lithium for manic-depressive illness, but it already had been found to be effective abroad. These new ideas began to make headway at WPIC, too, recalls Mervin S. Stewart, MD '53, now a volunteer clinical associate professor of psychiatry. Stewart was an intern from 1953 to mid-1954 at Montefiore Hospital, finished out 1954 as a resident at WPIC, served two years in the army, then returned to Pitt to complete his psychiatric residency from 1956 to 1959. He recalls that drugs were already in use at WPIC in 1955, when he left, and were in greater use, along with newer forms of psychotherapy, during his residency. He himself conducted family and group therapy for multiple sclerosis patients as a research project.

Still "The basic orientation remained psychoanalytic," Detre says of the period before his arrival at Pitt in 1972. "The psychoanalysts had a strong belief that all mental illness was basically caused by some serious psychological disturbance, and the therapy had to be psychotherapy. . . . There were here at that time very, very few people interested in the biological aspect of psychiatry, and few or no experts in psychopharmacology."

A great deal has changed since those days of limited treatment and what Thomas Detre terms "descriptive psychiatry."

Although these psychoactive drugs did not "cure" the disease, they often alleviated symptoms. The new treatments allowed patients to be released from custodial care, eventually, by the mid-1970s, emptying many of the mental hospitals. And, while the exact mechanisms by which these medications achieved their effect were not completely understood (and in the case of lithium, still are not), their effectiveness obviously pointed to some underlying chemical and biological component to illnesses once thought primarily psychological. Research began to focus on identifying the neurobiologic and biochemical roots of mental illness. The shift to treatment by medication also gave rise to a new specialty, psychopharmacology.

At the same time, psychiatrists were developing new forms of psychotherapy—short-term approaches, targeted to patients' immediate problems. Doctors often used these therapies in combination with drugs.

One result of the psychoanalysts' convictions was that promising students and potential researchers went elsewhere, Detre says. Annual reports showing dwindling enrollments seem to confirm his view. Another was that the state legislature trimmed or failed to raise WPIC appropriations. Brosin, who had been president of the American Psychiatric Association in 1967, and had steered the hospital and department through some difficult financial times, stepped down in 1969 at age 65, making it clear in an interview that it was not his idea. (Two years later, Mirsky retired, too, after a long period in which he and Brosin ignored each other. Mirsky's retirement closed his semi-independent Division of Clinical Research.)

WPIC's Jack Wolford, who directed teaching programs in other state hospitals, was among those who served as interim director—"or some such title," says Wolford, now professor of psychiatry emeritus.

Enter Thomas Detre—lured from Yale to become director of the hospital and chair of psychiatry. Detre had been struck by the future of psychoactive drugs back in 1954 during his first residency, at Mount Sinai Hospital in New York. Soon after arriving at Yale a few years later, Detre introduced the concept of psychopharmacological management of patients. By the late 1960s, he had risen to chief of psychiatry at Yale-New Haven Hospital. When four consultants—prominent academic psychiatrists who included Fritz Redlich, Detre's dean at Yale—recommended that Pitt choose someone immersed in biological psychiatry to lead its psychiatry department, Detre was at the top of the list of candidates. As the new chair, Detre brought with him other like-minded academics, notably David Kupfer, who would direct research efforts, and 26 other researchers; the lot was soon nicknamed "the Yale Mafia."

Detre has famously recalled a conversation with a Yale colleague when he announced he

LEFT: **Frederick Weniger taught ward management as well as group and individual psychotherapy during the Brosin years.** ABOVE: **(from left) Jack Wolford, Henry Brosin, and Robert Vosburg**

"Planes fly over Pittsburgh," the colleague said. "They don't land there."
"They will land when ***we*** land," Detre answered.

was going to Pittsburgh. "Planes fly over Pittsburgh," the colleague said. "They don't land there." "They will land when *we* land," Detre answered. And land he did, with an impact still being felt 30 years later.

Detre and Kupfer can be caustic about the WPIC situation they inherited. One of Detre's first moves was to go to Harrisburg to prod the state into raising its contribution.

"They told me we were not doing anything of value to the state in terms of clinical services and training," Detre says, "that we were locked into an Ivy League mentality and only concerned about research. I said they were right about us not being very useful, and I regretted to report to them that we weren't doing much research either. I said, 'Give me a little time, and the change will become obvious.'"(It should be noted that one WPIC publication from Brosin's era does list several research projects, most in clinical research.)

Detre's plea got the budget restored, even increased. He and Kupfer began to shift the hospital and department in new directions, and it was only a matter of time until they clashed with the psychoanalysts. "When we came here," Kupfer said recently, "the principal prevailing faith was the psychoanalytic one."

In the hospital's 1973 annual report, the author of the section on the psychoanalytic institute referred to time under the new leadership as "the winter of our discontent." Things came to a head in 1974 with the death of M. Royden Astley, who ran the psychoanalytic institute. It followed the death of another prominent psychoanalyst, Bertram Lewin, and left the institute without an heir apparent. Psychoanalytic faculty wanted one of their own to be elevated, or for an outsider with impeccable psychoanalytic credentials to be named. Detre agreed that the director should be a certified psychoanalyst, but also wanted the recruit to have an established track record in research. He also wanted to set up a program to rigorously evaluate the outcomes of psychoanalytic treatment: "I thought if a person spent three to four hours a week for four to 10 years on a psychiatrist's couch, and spent a fair amount of dollars, that treatment should be evaluated."

The psychoanalysts protested; evaluation, they said, might jeopardize the integrity of the patient-therapist relationship. What patients would be forthright and honest about their innermost feelings if they knew their progress would be monitored and measured? Worse, such evaluation could sabotage treatment efforts.

A long standoff ensued. Finally 20 psychoanalysts left to establish a new independent Pittsburgh Psychoanalytic Institute. Each contributed $600 to get the entity up and running. Some psychoanalysts remained to teach and offer psychotherapy at WPIC, though the hospital would no longer offer psychoanalytic training.

"Analysts Split as Pitt Puts Freud on Shelf," the *Pittsburgh Press* announced. The exodus touched off other defections. A group of psychiatric nurses also resigned, and the Staunton Clinic, a psychoanalytically oriented clinic associated with Pitt, gradually severed ties.

As can be expected, not all WPIC veterans agree with the "Yale mafia's" take on history. Brosin, for his part, answered complaints by one prominent psychiatrist that WPIC was "too monothematic."

"We do not preach a monolithic religion," Brosin said in his farewell message.

"We steadfastly avoid all dogmatism and maintain an empiric, pragmatic approach to mental health. We use drugs and shock therapy where it is indicated, but only where it is indicated. We have experimented with all the newer forms of psychiatry, such as family therapy, group therapy, marital pairs, and so on, and adopt those methods which seem to work."

Brosin himself was known for his broad interests, which ranged from information theory and evolution to the psychological aspects of organic brain disease. Stewart, who is still affiliated with the psychoanalytic institute, has nothing but praise for the Brosin period. Under Brosin, hospital stays were reduced from "one, two, three, four years to a few months," he notes.

Regarding the psychoanalysis controversy, he says, "The most important thing in any form of medical practice is to take a very thorough, very careful patient history, not simply go down a checklist of symptoms. One must learn how to listen and to talk."

Wolford, who had been at WPIC since the '40s, notes, "Hank Brosin was very solid, very broad in his outlook, and very much in favor of somatic therapies and general psychotherapy. He attracted a lot of people, and helped the institution to grow. And he did this during harsh financial times. Dr. Detre was an excellent administrator, gifted in the recruitment and utilization of top people. His coming gave a tremendous boost to WPIC. As for his

emphasis on research, well, that's what a university program ought to be about, isn't it? I would say that before Dr. Detre, WPIC enjoyed a good reputation. Under Detre, it got a great reputation. That's why they named a building for him."

Behind the hubbub, which gradually subsided, there were physical and structural changes in those 50 years, too. Most notably, the University built a 10-story addition to the original building; it was completed in 1982.

As new and intriguing knowledge about the origins of mental illness unfolded, Detre was quick to capitalize on NIMH's increasing budget for basic research. Before he became senior vice chancellor in 1983, his leadership brought hundreds of millions of dollars in basic and clinical research grants.

"I was absolutely convinced that what I was doing made perfect sense, that biologic treatments would take the upper hand in psychiatric management of patients," Detre says.

Under Detre, the Department of Psychiatry linked research with other programs across the University, including anesthesiology, neurology, pediatrics, pharmacology, and surgery, thereby earning the NIMH's favor. Detre suggested that evaluative research was necessary for good clinical care, and grants from the NIMH soon supported lab studies in metabolism and neurophysiology, animal studies to define more accurately the biochemical systems involved in mental disorders and their interaction with psychoactive drugs, and studies in sleep and motor activity. By 1977, the NIMH declared WPIC a Clinical Research Center for Affective Disorders.

He is careful to point out, with a smile, that psychopharmacology can become a religion.

Several among the first wave of recruits under Detre would grab the NIMH's attention. Israel Hanin joined the faculty in 1974, becoming director of the psychopharmacology program. His arrival coincided with the start of an NIMH grant used to purchase a gas-chromatograph mass spectrometer, which Hanin used to analyze levels of antidepressants in plasma from depressed patients. Through his research, Hanin, now chair of pharmacology at Loyola University in Chicago, helped classify subtypes of depression and opened the path for further research on biochemical, physiological, and neurotransmitter mechanisms altered by mental disease.

Among many major players of the Detre era were Seymour Antelman and Zaven Khachaturian. Antelman, still with the department as a volunteer professor of psychiatry, discovered a unique, stress-dependent interaction between the neurotransmitters norepinephrine and dopamine. He also demonstrated that anorectic agents such as amphetamine were relatively ineffective in counteracting stress-induced eating. Khachaturian helped improve treatments for hyperkinesis in children and developed a computerized method for analyzing and collecting clinical electroencephalogram data. He would leave Pitt in 1981 for the National Institute on Aging. Kupfer notes that Khachaturian now is credited with developing the notion that Alzheimer's research centers were needed across the country.

The psychiatry program's scope and prestige have ballooned since Pearson was at the helm of a fledgling hospital. In 2000, the hospital and department had a budget of $125 million; 200 faculty, two-thirds of whom were psychiatrists; and 1,800 other employees. It served 250,000 outpatients a year; inpatient stays ranged from seven to 20 days. A bibliography of WPIC research papers published from 1998 to 2000 covers nearly 500 works. Current research encompasses biological factors related to mental illness ranging from the effects of naturally occurring brain chemicals to structural changes in the brain to changes in the body's circadian rhythms.

"The advent of psychopharmacology permitted physicians and mental health professionals to deal directly with psychoses and depression in a way that was not possible before," Kupfer said recently. "The ability to restore functioning, adequate for living outside of the hospital, in the case of schizophrenia, and the restoration of complete functioning, in the case of depression and manic-depressive disease, shortened the length of hospitalization and profoundly changed our understanding of these diseases. We now understood that many of these problems were recurrent."

The recognition that depression must be treated for the long term to prevent acute episodes, as one might approach heart disease or diabetes, ranks as one of WPIC's major contributions to the history of psychiatry in the last 30 years, Kupfer says. That also led to a focus on understanding depression and bipolar disorder across the entire life span.

Many of the key initial studies in treating childhood depression and geriatric depression have come from WPIC, along with the beginnings of biological understanding of early onset depression. The department has also been at the forefront of the use of imaging technology to peer inside the brain and understand its subtle workings. And rapid advances in psychopharmacology have deepened our understanding of the brain's fundamental chemistry.

Still, Kupfer cautions, much about the brain remains a mystery, if less so than in Harry Mehalic's day. He is careful to point out, with a smile, that psychopharmacology can become a religion.

"There is a belief that we would be able to understand all the behavioral factors if we simply understood the biological underpinnings of disease, and we would then be able to develop medications and drugs that would treat those diseases and cure them," he says.

"To us, that is a reductionist way of thinking because it says the brain doesn't have to think very much and you can treat it as you would liver disease.

"I think the contribution this place has made over the years—and we were not the only ones—was the recognition that these diseases would not be treated necessarily just by psychotherapy nor necessarily just by giving drugs." He pauses for a moment, savoring the irony of what he is saying, considering WPIC's past.

"What has evolved here is an integrated, combined way of thinking about disease and treatment that might involve both drugs and the so-called 'talking' psychotherapies." ■

COURTESY DETRE

David Kupfer (left) and Thomas Detre brought Pitt's psychiatry department into a new era. (Photo c. 1990)

People and programs that keep the school healthy and vibrant

COURTESY ZEIGLER

Donald Fraley, center, with his son and a train-collecting friend

THE NATURAL

DONALD FRALEY

BY MEGHAN HOLOHAN

As head of the intensive care unit at UPMC Montefiore for 14 years, Donald Fraley, MD '68, encouraged his staff to talk to comatose patients, to avoid dehumanizing the unconscious. On the happy occasions these patients awakened, he made special arrangements to welcome them back. Once, he purchased a bottle of wine for a woman and her husband after she awoke from nine months in a coma. He pulled the curtains shut and instructed the staff to bother the couple only if the life-support buzzers wailed for an hour. Fortunately, the buzzers didn't interrupt.

When Fraley, a professor in the School of Medicine's renal division, volunteered for a mentoring program, he was likely to ask for students who needed "extra attention." "I hope you're up to the task," he might tell students charged with helping him mentor their more junior counterparts, at the same time instilling confidence that they were in fact up to the task at hand. All they had to do was look at his record. In one program, Fraley was known to take on 25 mentees at a time.

Fraley, who died November 14 following a struggle with a brain tumor, had a way of taking people under his wing. He invited students to dinner at his home, showing off his Lionel train collection, which twists through tiny villages in his basement. He took them to observe his wife at work (she is a hematologist and oncologist). He met with them one-on-one to help mold their futures.

Zella Zeigler, MD '68, Fraley's wife, finds it hard to explain what motivated him to devote himself completely to everything he pursued, "It's just the way he was; it was a God-given talent. I don't have it. Not a lot of people do."

So it's no surprise to many that the School of Medicine is working with Zeigler to establish a lectureship to honor her husband's memory. The annual lecture will focus on nephrology, featuring noted experts in the field. The lectureship seems a fitting way to memorialize a great mentor who was also a gifted physician. (His own doctor recalled how one of Fraley's patients survived what's normally a fatal condition because of his meticulous care.)

James Johnston, MD '79, also a professor in Pitt's renal division, says Fraley always questioned students and trainees, making them think, forcing them to answer. It didn't matter if students said the wrong thing. He would steer them in the right direction. Further, he was likely to encourage them to take on tasks they might, at first, think they could never accomplish. This was his modus operandi.

As part of a train-collecting group, Fraley partnered with eight men who were writing a collectors' guide about toy trains. The men began to think the feat impossible, then Fraley swooped in, taking notes and photographs, typing and editing, encouraging them so much, they found themselves occasionally chipping away at the project until 4 a.m. At the time, Fraley knew little about trains. It didn't matter; he was just doing what came naturally.

FOR MORE INFORMATION: Call Jennifer Rellis at 1-877-MED-ALUM.

ARRESTING BREAKTHROUGH

PNC FOUNDATION FUNDS GENE THERAPY RESEARCH

BY DAVID R. ELTZ

This year 20,000 Americans will be diagnosed with glioma, the most common form of brain cancer. Their tumors will grow rapidly, shoving aside healthy brain cells, blocking their ability to function. The patients might develop dizziness, exhibit uncharacteristic behaviors, become paralyzed. They will see doctors, undergo surgery, and most will discover that their tumors have returned, stronger than ever. Some 18 months after diagnosis, more than half will be dead.

Pitt's Shi-Yuan Cheng, assistant professor of pathology, and Xiao Xiao, assistant professor of molecular genetics and biochemistry, believe they can arrest that process. Along with Hsin-I Ma, a postdoctoral fellow, the two scientists are testing therapies involving the angiostatin gene. Angiostatin is a protein that stops blood vessel growth in tumors. The researchers hope to stifle tumors by choking off their blood supply.

In a recent study, the scientists injected an adeno-associated viral (AAV) vector carrying the angiostatin gene into the thigh muscle of mice. Soon after, high levels of angiostatin were circulating in the animals' blood—and the levels remained high over time. The researchers then injected glioma cells into the mouse brains. All the control mice, who did not receive the angiostatin gene, died within six weeks, while 40 percent of the mice who received the gene therapy lived more than 10 months.

The scientists' efforts have been recognized with the first PNC Foundation Innovation Award. The three-year, $150,000 gift will fund two other research projects at the University of Pittsburgh Cancer Institute in 2003 and 2004.

Cheng envisions AAV, in combination with existing cancer treatments, effectively triggering tumor cell death. "The advantage is that this inhibitor will reach, in theory, every tumor in the body and prevent metastasis," says Xiao. ■

Giant pandas Hsing-Hsing and Ling-Ling in 1974

HE SHOULD HAVE BEEN A PANDA

BEFORE A BROTHER'S HEART QUIT PUMPING

BY BARRY R. BERKEY, MD '61

A version of this story first appeared in the American Journal of Psychiatry, *157: 1941-42, 2000.*

AUTHOR'S NOTE: Hsing-Hsing and his mate, Ling-Ling, arrived at the National Zoo in 1972—a gift from the Chinese government. Immediately they became the zoo's most popular attraction and perhaps the most loved and photographed giant pandas in the world. Ling-Ling died at age 28 in 1992 of heart failure, and when Hsing-Hsing died in 1999, an acute outpouring of public sorrow and communal mourning gripped the nation's capital.

My brother, Floyd, lay in a coma for six years before his heart quit pumping on October 28, 1999. This was about the same time that Hsing-Hsing, the National Zoo's remaining panda, began a steep decline from a fatal kidney disease diagnosed that May.

Like Hsing-Hsing, Floyd was cared for at home, with expert care—and loving attendants. Not a single bedsore. Spoon fed only the most nutritious, pureed foods. No trace of urine or feces on his waxy skin. Each day since the series of devastating strokes shattered an active and productive life, a caretaker read to him from the *Pittsburgh Post-Gazette:* book reviews and sports, Floyd's favorites. Of course, he never heard a word. Never responded. Just lay there motionless. Except he was rolled over every two hours—which was why he had no bedsores.

"When I started with Floyd six years ago," the caretaker told me upon my arrival for the funeral, "I never thought I could get so attached to nobody who couldn't talk back. But I did. I really did, and I talked to him all the time. I'd say, 'Floyd, it's time to clean you up now, so help me roll you over' or I'd tell him, 'Swallow,' when I'd bring the spoon up to his mouth."

"You think he understood?" I asked.

"I ain't sure. But you know, there's a funny thing. Every night, long about two in the morning, he'd start screaming. Real loud screams. Scared me the first time I heard it. And he wouldn't stop 'til I'd hug him. I'd hold him like he was a baby; and in a little bit, he'd quiet down. Then the next night, same thing all over again."

This kind man told me how he worried about Floyd when he wasn't on duty and how he got to know him through others. The neighbor next door told him about Floyd being a World War II hero, a flyer on a B-26, and that he had a heck of a sense of humor. "Like that time—it was about three in the morning—and the neighbor was working in his garage, running his band saw. Floyd's bedroom was right next to the guy's garage. Well, Floyd opens his window and yells, 'Hey, John, knock it off! How do you expect me to count my money with all that racket?'

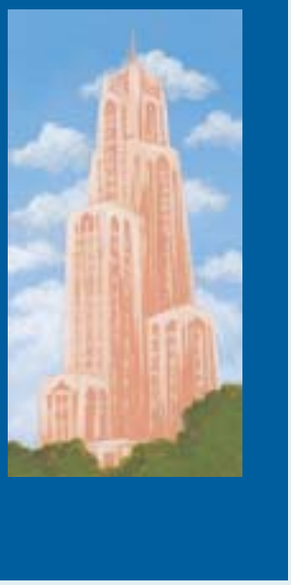
"Your brother was something else," the man who held my brother like a baby told me. "A real fighter, I can tell you that. Almost every time I was feeding him, I'd say, 'Floyd, why do you keep on swallowing? You'd last no time at all if only you'd stop swallowing.' You see, he weighed maybe 75 pounds at the end."

Through my sadness and foggy emptiness, I thought about the "real fighter" comment. As a physician, I had many times heard the "fighter" phrase spoken in consolation by doctors or caregivers to surviving relatives about the long but losing battle of a loved one.

But I know my brother. And I know he "swallowed" not to prolong his vegetative limbo, but merely from a gag-like reflex that he had no control over. Floyd would never have voluntarily put his family through the anguish and sorrow of seeing him this way. Nor would he have prolonged the hellish indignity he himself suffered.

Which brings me back to Hsing-Hsing who, like Floyd, suffered mightily, but unlike Floyd, briefly. Until shortly before his death, Hsing-Hsing had been fairly healthy for an old bear. He had recovered from surgery for testicular cancer in 1997, but several months ago he was found to have a fatal kidney disease. His condition worsened, and zoo officials became concerned about the panda's quality of life. Ordinary life activities had become very difficult for him. With Hsing-Hsing's rapidly worsening kidney failure, complicated by arthritis, poor vision, nosebleeds, anemia, weight loss, and loss of appetite, the officials and caregivers at the zoo decided he had suffered enough. He was given a lethal intravenous injection. Is there anyone who would argue this?

Regarding my brother, there is no doubt that his suffering was light years greater and also years longer than the celebrity bear's. I realize that condoning euthanasia in human beings is a slippery slope that arouses widespread concerns of heinous abuses. Yet, as a loving brother who mourned Floyd's six years of indignity, how I wish that someone had the authority to show the same compassion for him that Hsing-Hsing received. ■



CLASS NOTES

'20s

Paul Greenlee, MD '24, who is probably the School of Medicine's oldest alumnus, retired in 1982, after nearly 60 years as a general surgeon. He paid only $500 a year for tuition to medical school. The physician made house calls in Waynesburg, Pennsylvania, with his eldest daughter as late as 1948; and in exchange for his services, he accepted items like chicken, cattle, or hams. Greenlee, who turned 100 in March and still lives in Waynesburg, likes to spend his time watching the Steelers and the Pirates and reading books about cattle.

'40s

Harvey Lincoff, MD '48, professor emeritus of ophthalmology at the Weill Medical College of Cornell, has been named Newhouse Clinical Scholar and was awarded $1 million from the Samuel L. Newhouse Foundation, Inc. to support his clinical research. A current project focuses on testing anti-angiogenic substances and photodynamic therapy to diminish the visual loss that occurs from age-related macular degeneration.

'60s

David D. Madorsky, MD '62, recently completed a term as president of the Texas Dermatological Society. He still is active in the organization, lobbying Congress for patient advocacy legislation and the NIH for funding for research on skin cancer and other association priorities. In his spare time, he dons a red nose, big shoes, and a funky wig as a clown for the Shriners.

Mark Orringer, MD '67, professor of surgery and head of the section of thoracic surgery at the University of Michigan, recently finished a term as president of the Society of Thoracic Surgeons. During his tenure, he helped hire a new executive director and find the organization new headquarters in Chicago. In July, Orringer represented the group in discussions with President George W. Bush regarding a patient's bill of rights. Bush also sought Orringer's advice about stem cell research. Orringer was the 1998 winner of the Hench Distinguished Alumnus Award.

Martin Plutzer, MD '68 (Internal Medicine Intern '69), is an associate professor of psychiatry at MCP Hahnemann University and has a private practice in Philadelphia. He enjoys teaching medical students the fundamentals of psychiatry to help them better communicate with and understand patients. His work has paid off. Over his career Plutzer has won about 10 teaching awards.

The Owl, 1968

Fred F. Ciarochi, MD '69, **Michael Savin**, MD '69, **Charles "Terry" White**, MD '69, all practicing in the Dallas area, are among that city's best doctors, according to *D Magazine*. Ciarochi, an endocrinologist, and Savin and White, both hematologists and oncologists, were pals in med school. Savin recalls the three dedicated a lot of time to *Medic Hair*, their class' production of Scope and Scalpel. Savin and White spent a significant amount of time helping to craft the script about "Spaz," a med student who always tried to best his classmates. Ciarochi played several roles, including a chimp, in the musical, which Savin claims was one of the first Scope and Scalpel productions to have a story line.

'70s

Michael Johnston, MD '71, chief medical officer and director of the division of neurology and developmental medicine at Johns Hopkins University's Kennedy Krieger Institute, recently published an article showing that use of the drug diazoxide, traditionally used to treat high blood-pressure, prevents brain damage in patients who undergo cardiac surgery (*Annals of Thoracic Surgery,* December 2001). Patients whose hearts are stopped for a long period of time often suffer brain damage, but animal models show that diazoxide may protect against this, notes Johnston.

John Blenko, MD '79 (Anesthesiology Internship '80, Anesthesiology Resident '80–'82, Pediatric Anesthesiology

HUGH PRATT | FROM FINANCE TO SURGERY

BY MEGHAN HOLOHAN

Almost a decade ago, Hugh Pratt (MD '00) sat in his home in Winnipeg, Canada, sadly contemplating his comfortable life. Even though he had a secure job as a finance professor at the University of Manitoba, he was miserable.

He'd always dreamed of learning to fly, so he began taking lessons. After a year, Pratt decided he wanted to leave finance and become a full-time pilot. But he realized his partial color blindness would prevent him from obtaining a job as a commercial pilot. Rethinking his position in life, Pratt recalled his first love, the love he once abandoned because a family crisis diverted his attention from school, forcing him to change his career goals. And at age 31, he began a new career—as a medical student.

Now a second-year surgery resident at Tulane University Hospital, Pratt admits the only time he even thinks of finance is when he figures out how much money he owes in student loans.

"Surgery is more interesting to me because I enjoy working in three dimensions," he says. "I think human anatomy is beautiful. I think it's a huge privilege that I can have a job where I work with [the human body]. That's something I think about a lot."

COURTESY PRATT

and Critical Care Medicine Fellow '83), is an assistant professor of anesthesiology at the University of Maryland Medical Center in Baltimore. Blenko recently cowrote a chapter on the management of pain following acute trauma. The chapter is featured in *Textbook of Acute Pain Management,* which Pitt's Paul Paris, MD '76, professor of emergency medicine, is coediting. Blenko wrote the original chapter in 1987 when he was affiliated with the Center for Emergency Medicine of Western Pennsylvania.

'70s RESIDENTS AND FELLOWS

Paul Nelson (Neurosurgery Resident '74–'79), former vice chair of neurological surgery at Pitt ('84–'85), has served as chair of neurosurgery at Indiana University in Indianapolis for the past 10 years. In the last five years, Nelson has helped the medical school rank third in placing students in the field of neurosurgery. He also is conducting research on the use of stem cells in spinal-cord injury. Nelson was the 2000 winner of the William S. McEllroy Award.

'80s

Ronald N. Roth, MD '82, recently was appointed medical director of the Pittsburgh Emergency Medical Services (EMS). Roth, a member of Pitt's faculty since 1987, is an associate professor and chief of the School of Medicine's EMS division. While his responsibilities include tasks like evaluating ambulance equipment, he also serves as a command physician, advising paramedics in the field via radio. He enjoys the challenge of treating patients using paramedics as his "eyes, ears, and hands."

John France, MD '86, an associate professor of orthopedics and neurosurgery at West Virginia University in Morgantown, has published an article in the December issue of *Spine*. France's research reveals that a low electrical charge administered onto the spine will encourage host cells to make more bone, thus allowing faster and stronger healing when two vertebrae need to grow together.

Robert F. Heary, MD '86, is an associate professor of neurological surgery at the University of Medicine and Dentistry of New Jersey–New Jersey Medical School in Newark. For the past several years, Heary, also director of the Spine Center of New Jersey, traveled to Chile and Lithuania to lecture at neurosurgery conferences about advanced spinal surgery techniques. He says his work overseas helps him realize how lucky he is to use high-tech equipment back home: "The doctors are very smart and hard working, but they don't have the technology we have."

'80s RESIDENTS AND FELLOWS

Laura E. Riley, MD '85 (Obstetrics and Gynecology Intern and Resident '85–'89), is an assistant professor of obstetrics, gynecology, and reproductive biology at Harvard Medical School. She specializes in high-risk pregnancies and treating women with HIV. Recently, Riley served as the American College of Obstetricians and Gynecologists' representative to the Centers for Disease Control and Prevention, helping to create national guidelines for pregnancy and HIV testing.

'90s

David Kaufman, MD '90, director of neonatal respiratory therapy at the University of Virginia Health System in Charlottesville, recently published an article in the *New England Journal of Medicine* (December 6, 2001), noting that the drug fluconazole prophylaxis effectively prevented preterm infants from contracting fungal infections. (The fungus tends to cling to intravenous lines, creating a critical problem. Though the infants generally need the IVs for life support, the lines must be removed. If the fungus gets into the blood, it will stick to organs, causing septic shock.) The fungus, which affects 10 to 15 percent of infants under two pounds, is fatal in 30 to 40 percent of cases. In this limited, double-blind trial none of the 50 infants taking the drug contracted an infection or suffered side effects. Kaufman plans to replicate the study with a larger sample.

Adam J. Gordon, MD '95, recently was awarded the American Medical Association's Young Physicians Section Community Service Award for his work as medical director of the Salvation Army's two drug and alcohol abuse centers in Pittsburgh. Gordon coordinates all the volunteer doctors and students, and is available 24 hours a day for medical emergencies in addition to working as an assistant professor of internal medicine at Pitt. —*MH*

COURTESY PRATT

For a while, Pratt flirted with the idea of becoming a full-time pilot.

THE WAY WE ARE: CLASS OF '57

BY MEGHAN HOLOHAN

It was hot. The sticky heat of July. Murray Sachs (MD '57), a first-year resident, thought he'd be more comfortable if he wore his scrubs to the Veterans Administration hospital in Oakland. He joined Jack Myers, chair of medicine, for rounds. Myers barely said anything; Sachs would later learn Myers was not pleased with the resident's attire. That evening, Sachs got a scolding call from his chief resident: Don't ever wear scrubs on rounds again. You're a resident now, and you wear white slacks, a starched white shirt, and a tie. Myers, it seems, had called Sachs' superior about his break from protocol.

Despite the admonishment, Myers influenced Sachs' career. Sachs, who today has a private practice in Pittsburgh, wanted to be a pulmonologist because of a childhood bout with tuberculosis. Working with Myers, a thorough practitioner, helped solidify Sachs' decision.

Sachs' colleague from the class of '57, Robert Hartsock, now retired, also credits a School of Medicine professor with guiding him toward a successful career. He recalls the teachings of Edwin Fisher (MD '47),

COURTESY FU

LIGHTING THE WAY: Last summer, Freddie Fu (MD '77, Res '82) tumbled across the hood of a Chevy Blazer, his bicycle having been struck. Fu, Pitt's chair of orthopaedic surgery, became a patient, his wrist and fibula broken. He was back in form December 19 carrying the Olympic torch as it passed through Oakland on its way to the Winter Games.

Well dressed members of the Class of '57

a pathologist with a keen eye for detail. Hartsock followed Fisher's example, eventually becoming a distinguished pathologist himself. He spent his career helping to advance the understanding of lymphoma, serving on projects with the National Cancer Institute and the World Health Organization.

Classmate Morton Berkowitz (MD '57) found guidance in med school from William Earley, then director of training at Western Psychiatric Institute and Clinic. Currently, Berkowitz is in private psychiatric practice in Great Neck, New York, and is on the teaching faculty of New York University Medical School.

Along with other members of the Class of '57, these three hope to reminisce about their mentors in May, during their 45th reunion. The group plans a full weekend: lunching with the Class of '02, attending the Annual Alumni Dinner Dance, and maybe touring Phipps Conservatory.

COURTESY HARTSOCK

Hartsock

HOWARD R. SLOAN
SEPTEMBER 5, 1937—DECEMBER 24, 2001

When Howard R. Sloan's oldest son, Michael, was 10, he approached his father about playing football. Sloan, who'd become a pediatrician after earning his MD in 1962 from the University of Pittsburgh, knew all about the permanent damage the game could cause to growing bodies. "Why don't you try soccer?" he suggested, and his son did.

Later, Sloan helped start a league for his younger twin sons and coached their team. He was so popular that he was asked to coach a team of older children as well—always making time for those who wanted to learn. Meanwhile, he was leading the genetics and lipid biochemistry section of the National Heart, Lung, and Blood Institute.

Sloan

As a researcher, Sloan helped to increase the understanding of carbohydrate metabolism. His mid-1960s work in the lab of Donald Frederickson, who would head the National Institutes of Health in the late 1970s, helped to introduce a system for identifying blood abnormalities. Later, at Ohio State University, Sloan was part of a team that developed a carbohydrate additive found today in many baby formulas.

Still, his curiosity about the world impressed others most. Sloan was, all at once, a scientist, clinician, educator, and mentor known to take "troubled" residents under his wing. "You couldn't walk into his office and not learn something," remembers Steven Schwarz, chair of pediatrics at Long Island College Hospital. Whether the topic was jazz or genetics, Sloan was expected to have the answer.

Sloan's career took him eventually to Long Island College Hospital, where he taught and made hospital rounds until last Thanksgiving, a month before he died of lymphoma at 64. *—DRE*

COURTESY ERIC SLOAN

IN MEMORIAM

'30s

FREDERICK A. MILLER (MD '33)
JANUARY 8, 2002

HERMAN L. SCHMITT (MD '35)
JANUARY 26, 2002

'40s

RUBEN SNYDERMAN (MD '40)
DECEMBER 2, 2001

ALBERT W. CORCORAN (MD '44)
JANUARY 29, 2002

DANIEL E. NATALI (MD '46)
JANUARY 22, 2002

GEORGE M. DULABON JR. (MD '47)
JANUARY 29, 2002

DAVID B. JOHNS (MD '48)
MARCH 28, 2001

'50s

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NOVEMBER 18, 2001

EARLE R. DAVIS (MD '53)
DECEMBER 15, 2001

DONAL C. PARKER (MD '57)
DECEMBER 1, 2000

'60s

HAROLD E. MUSSER JR. (MD '62)
DECEMBER 3, 2001

HOWARD R. SLOAN (MD '62)
DECEMBER 24, 2001

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HARRY E. RUBASH: HEADS ABOVE

BY E. DOUGLAS BANKS

PAUL BATISTA/MGH PARTNERS

Mass General's Rubash put himself through school working as a mechanic.

The outbreak of infections in Minnesota made headlines everywhere, and Harry E. Rubash was well aware of them.

Last November, orthopaedic surgeons nationwide were talking about the three Minnesota patients who died within a week of having knee surgery. Such surgeries, along with hip replacements, are Rubash's specialty. Even before he became chief of orthopaedic surgery at Massachusetts General Hospital and the Edith M. Ashley Professor of Orthopaedic Surgery at Harvard, Rubash (MD '79, Res '84) had conducted landmark research at Pitt on major joint replacement surgery and the complications arising from them.

One weekend that month, Rubash received a telephone call about a patient. Recovering in a rehabilitation facility on Cape Cod, about 75 miles south of Boston, the woman seemed to be suffering from an infection. Rubash was concerned it could be from contaminated artificial graft tissue, the problem in at least one of the deaths in Minnesota. Rather than having the patient brought to Boston, or calling a doctor closer to the Cape, Rubash jumped in his car, drove to the patient, and examined her knee. Only after he was certain that she was out of danger did Rubash return home.

That devotion seems inborn. David L. Steed, who was the administrative chief resident in surgery at the University of Pittsburgh School of Medicine in 1979 remembers Rubash as an intern. "I'm sure he went home that month, I just don't remember when he wasn't here," recalls Steed, now a professor in Pitt's vascular surgery division.

Rubash studied articles about orthopaedics before he chose the field as his specialty, because he wanted to know as much about medicine as possible. When he had residents of his own, he encouraged them to do the same.

This surgeon is often more than a head above everyone, at almost 6-foot, 8-inches tall. During surgery, some of his fellow practitioners stand on stools. Indeed, at that stature, personally and professionally, Rubash might seem intimidating. But though he applies muscle in the operating room, he's a gentle giant outside.

Rubash was reared in Turtle Creek, a humble town east of Pittsburgh. His family has lived in the area for four generations, and Rubash is the first doctor in a long line of engineers and mechanics.

"At first, I wanted to be an engineer, because I like to build things," says Rubash, sitting in his office along the Charles River in Boston. "I put myself through college working as a mechanic. I started out building things that are inanimate and then said, 'Why not build things and make things that are alive?'"

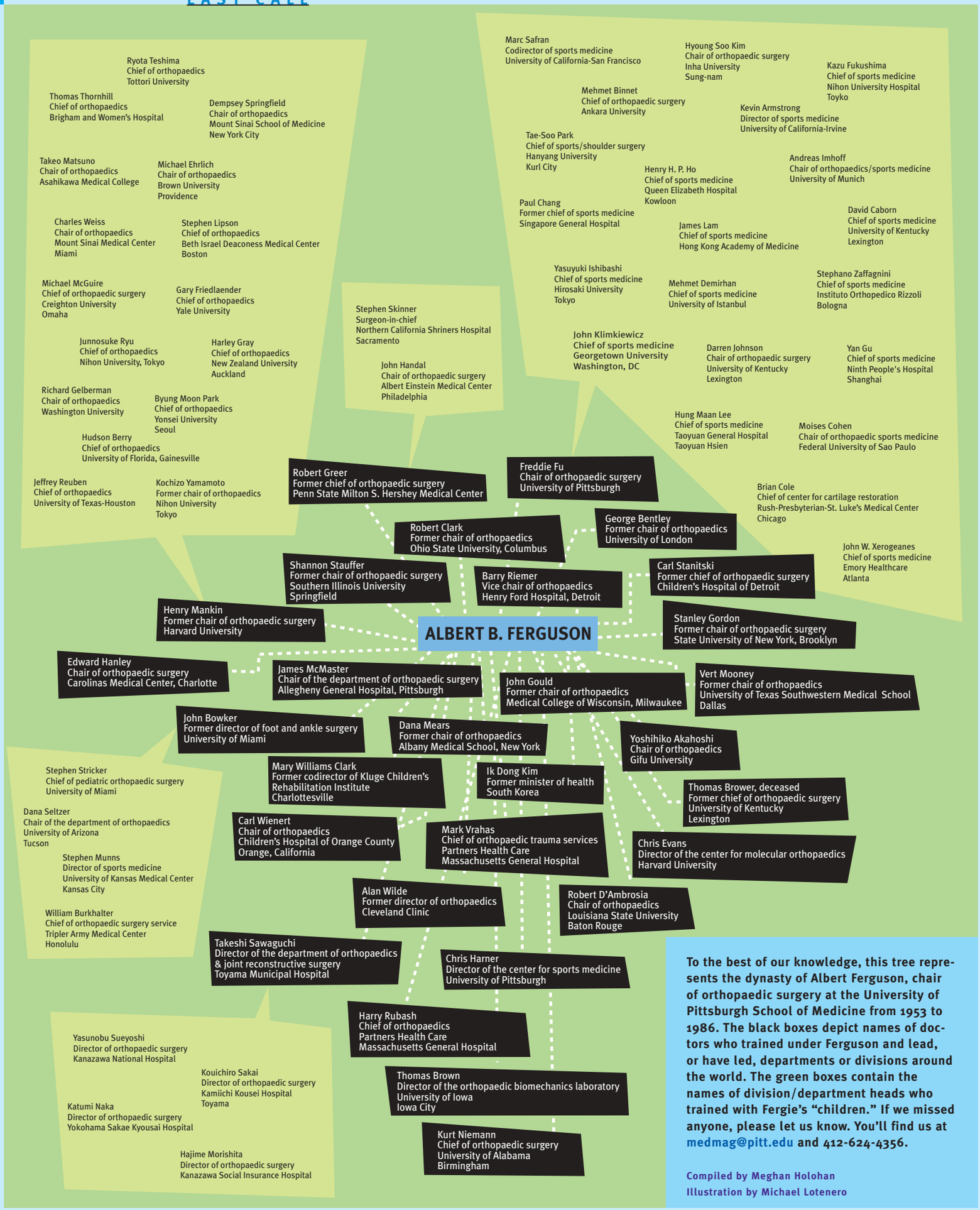
"When you injure heart tissue, or have a heart attack, you form scar tissue. When you break a bone, you form bone."

It didn't take long for Rubash, now 48, to make orthopaedic surgery his specialty. And though he has worked on his share of celebrities and professional athletes, his attraction to the field is bone—"the only tissue that, when it heals, forms healthy, native tissue. That's not true of any other tissue we know of. When you injure heart tissue, or have a heart attack, you form scar tissue. When you break a bone, you form bone."

Rubash's devotion to bone led to his research into the causes of total hip and knee replacement failures. His work has revealed a better understanding of the biochemistry of artificial joint loosening and the wear-debris particles that cause inflammation and bone dissolution where living tissue and prosthetics make contact. His current research is on the genetic causes of those wear-debris particles.

James H. Herndon, chair of orthopaedic surgery for Partners HealthCare, the parent organization of Mass General, Brigham and Women's Hospital, and other hospitals, brought Rubash to Mass General in 1998. Rubash was recruited from Pitt's Department of Orthopaedic Surgery, where he was clinical vice chair and chief of adult reconstructive surgery. The two men have known each other for 15 years. In fact, one of Herndon's hips was replaced under Rubash's steady knife.

"He's an excellent surgeon," says Herndon. "Otherwise, I wouldn't have let him work on me." ■



To the best of our knowledge, this tree represents the dynasty of Albert Ferguson, chair of orthopaedic surgery at the University of Pittsburgh School of Medicine from 1953 to 1986. The black boxes depict names of doctors who trained under Ferguson and lead, or have led, departments or divisions around the world. The green boxes contain the names of division/department heads who trained with Fergie's "children." If we missed anyone, please let us know. You'll find us at medmag@pitt.edu and 412-624-4356.

Compiled by Meghan Holohan
Illustration by Michael Lotenero

CALENDAR

OF SPECIAL INTEREST TO ALUMNI AND FRIENDS

STARZL LECTURE
APRIL 20
Scaife Hall, 10 a.m.
Lecture Room 5
For information
Kathleen Haupt
412-647-5314
http://www.surgery.upmc.edu

THIRD ANNUAL PITT MED GOLF OUTING
APRIL 27
Quicksilver Golf Course
8:30 a.m.
Midway, Pennsylvania
For information
412-648-9090
pittmedgolfouting@yahoo.com

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SCOPE AND SCALPEL
Crouching Patient, Hidden Finger
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SENIOR CLASS LUNCHEON
MAY 17
The Twentieth Century Club
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DEAN'S BREAKFAST MEETING
MAY 18
University Club, 9 a.m.
Pittsburgh
For information
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GRADUATION CEREMONY
MAY 20
Carnegie Music Hall, 10 a.m.
For information
Student Affairs Office
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SEPTEMBER 20
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OCTOBER 26
Pitt vs. Boston College
For information
Ross H. Musgrave, MD '43
412-648-9090
medalum@medschool.pitt.edu

SCHOOL OF MEDICINE HOMECOMING BREAKFAST
OCTOBER 26
University Club, 9 a.m.
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Bring back your moves and grab fine food and good cheer while you're at it. Don't miss the University of Pittsburgh School of Medicine's Annual Alumni Dinner Dance on May 17. (Remember, attire is semiformal.) The event will be held at the Pittsburgh Athletic Association, the center of attention being the 2002 Hench and McEllroy award winners, the Pitt Alumni Dance Band, and many of your old friends. Call the Medical Alumni Association for details: 412-648-9090.

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