UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | FEBRUARY 2005

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ONE CHILD AT A TIME

FIFTY YEARS AFTER PITT'S SALK VACCINE TRIUMPH, WILL WE WITNESS THE END OF POLIO?

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

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- Robert G. Fenley Writing Award

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- Award of Honor, Magazines
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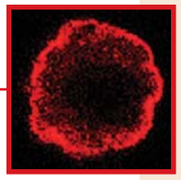

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By studying very short lives, a Pitt researcher may have found a mechanism at work in aging.
BY CHUCK STARESINIC

CONTRIBUTORS

Born in Brazil as the son of a cattle rancher, SEBASTIÃO SALGADO [cover, "The End of Polio"] was 29 with a PhD in economics when he decided to become a photographer. Within four years, he was elected to membership in Magnum Photos, a prestigious international cooperative. Subjects of the acclaimed documentary photographer include Latin American peasants, refugees, migrants, and Doctors Without Borders. All his photographs are "about human beings fighting for their dignity and trying to live better together," Salgado revealed to one reporter.

LEAH KAUFFMAN ["The King of Peptides"], the former managing editor of the journal *Genetics*, is a freelance science writer who's been instrumental in bringing a European phenomenon called Café Scientifique to Pittsburgh. Their slogan says it all: "Eat. Drink. Talk science." About once a month, the public is invited to a Pittsburgh brewpub to join a lively scientific discussion. Kauffman and her co-organizer line up speakers on topics like stem cells, quantum theory, and genetically modified foods. Kauffman hopes it will help "break down the invisible wall of authority between scientists and the public."

COVER

Will 2005 be the year of polio's worldwide eradication? (©2001 Sebastião Salgado/Amazones Images/Contact Press Images.)

PITTMED

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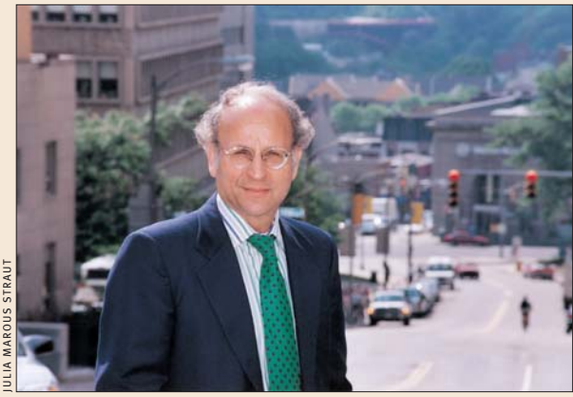
JULIA MAROUS STRAUT

Months before walls of water washed away whole communities in South Asia, visitors to the Carnegie Museum of Art's 54th Carnegie International were offered a peephole view of epic disaster. *Magma Spirit Explodes. Tsunami Is Dreadful*, a 40-foot long-mural by Chiho Aoshima, is impossible to ignore, like a premodern Japanese print brought to life by an animé hallucination.

Aoshima shapes what would otherwise be gruesome into a hauntingly flat narrative. Volcano, fire, war, and tsunami are spawned by a giant pretty-eyed cartoon priestess belching flames and fury. Atop the monster waves crashing down, drawn very small, is a girl bobbing adrift in a boat. Just one oar in the oarlocks. She doesn't fight the waves, but instead lies languorous, staring down the viewer. Is her struggle over? I don't know what the prescient Aoshima had in mind when she created this character, but the girl seems a metaphor for those we so easily forget.

Tsunami is dreadful, indeed. The groundswell of support for relief efforts heartens: Here's proof that people really do care about the suffering of others. It's also useful to note, as Nicholas Kristof did in a recent *New York Times* op-ed, that many times more people die each year of malaria than did in the recent tsunami. (Estimates range between 1.5 and 3 million, depending on the year.) How might we respond to these quieter calamities that befall millions as a matter of routine health circumstance? Four million children born each year don't see life beyond one month. In the developing world, millions suffer from neglected diseases such as tuberculosis, leishmaniasis, and encephalitis. If they're treated at all, it's often with old, ineffective, and sometimes toxic drugs. Yet, the pipeline of drugs for these diseases is just about empty. Merely 3 percent of all health research dollars are spent on the global disease burden. For instance, from 1975 to 1999, of the 1,393 new drugs marketed, only 13 were for tropical diseases.

In some cases, more money is spent to treat pets with such afflictions (namely, leishmaniasis). How does it feel to watch loved ones die knowing resources exist elsewhere? It must seem that there is, to borrow the great poet Fernando Pessoa's words, "out there a great silence like a god asleep."

Our system for drug research and development has failed these patients. Why? The price tag of discovering and developing a new drug has reached $1 billion, so the industry focuses on diseases that will yield the highest profits. We see the repercussions at home. More than 6,000 "orphan diseases" affect 25 million Americans. (An orphan disease is one that afflicts fewer than 200,000 people). Nearly one in every 10 people in this country has been diagnosed with a disease for which there is little hope for a cure.

Academia can position itself to respond to these issues in ways that commercial pressures don't allow. I'm pleased to report that Pitt is establishing a Drug Discovery Institute, to be housed in the new Biomedical Science Tower. This novel institute will be dedicated to unearthing small molecules that can heal. One of our major focuses in this effort will be the discovery and development of drugs for the treatment of orphan and neglected diseases.

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

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

A Futuristic Fin

Recently, Stephen Badylak, research professor of surgery, got a phone call about a dolphin named Liko.

"Even though I'm a veterinarian, I don't know that much about dolphins, in fact next to zero, except that I used to watch *Flipper,*" he says.

The dolphin's life was in danger because it had repeatedly injured its dorsal fin. Another injury and Liko was likely to lose the fin, which is essential for temperature regulation and steering. The veterinarian who called Badylak knew that the Pitt professor had developed a "bioscaffold" used in some 250,000 human patients to repair small bits of tissue. (Once placed in a person, the scaffold, which is made of animal products, degrades, summoning cells and other factors to rebuild the damaged human tissue.) The vet wondered: Was there a tissue engineering solution for Liko? Badylak thought he could make one work.

Using pig bladder, Badylak made a scaffold to fill in the hole in the fin; the scaffold was approximately 8 by 4 inches.

"It's probably the biggest piece of tissue that we've ever tried to regenerate," says Badylak, an MD/PhD, as well as a DVM. A few months after the scaffold was implanted, Liko had regrown about 90 percent of the missing piece of fin and was no longer in danger of losing it. For Badylak, the success went beyond saving the dolphin: "Now we know we can grow a blood supply into an area that's very big. We know that we can grow nerves into it. That's pretty significant, because it says it's possible to [accomplish this] in a mammal. … The real application is to extend this finding to human patients who need a new heart or a new esophagus." *—Dottie Horn*

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FOOTNOTE

Ask Pittsburghers when they became Steelers fans, and they probably won't understand the question. People are born that way, right? That was true this winter at Magee-Womens Hospital, where newborns donned the black and gold right out of the womb. A 74-year-old fan crocheted tiny gold hats with black and gold tassels for babies born on Steelers' playoff game days. Alas, she'd planned to have enough for the Super Bowl, too.

C.E. MITCHELL

A&Q

On the Peace Corps/Pitt Med Connection

In 2000, first-year student Peter Syré (above, right) and his wife arrived at Pokigron, a village of about 200 people in Suriname. As Peace Corps volunteers, their task for the first few months was to visit with people in the village. They'd sit in a family's home for an hour or two; they'd go back to visit again and again. The couple wanted to get to know people, to gradually learn about what the community needed, to build trust. Only later would they implement projects, including educating villagers about health issues, especially malaria and AIDS; teaching small children; and creating a 300-book library for children in the school. Giving children access to books beyond school hours was "a pretty huge thing," says Syré. His classmate, Jessica Robb (above, left) spent two years as a Peace Corps volunteer in Guinea, West Africa, where she implemented several health education projects in a village of 1,000. Two other members of the Class of '08 (not pictured here), Brandi Swanier and Andrew Fisher, are also former Peace Corps workers. What's the connection between the corps and medical school? For Syré, working in a village clinic made him first consider a career as a physician; seeing babies born and helping to vaccinate children intensified Robb's interest in medicine.

On the challenges of the Peace Corps experience:

Robb: I was put in a place with no support network. I didn't have the language skills I needed. I saw all this poverty and people suffering. And the customs were different. Before any conversation, you go through a five-minute string of greetings that includes asking about the person's family—whether or not you've ever met them. There were many difficult aspects. But now I think, "If I could deal with that experience, I can deal with most things that will come my way."

Syré: Two years seems like an enormous amount of time in your life, because you could be doing something else. But it's such a small, small amount of time. You're leaving, and you're still just figuring out what's really going on at the place where you live. You're just skimming the surface of the whole culture, the whole dynamic in your village.

On the impact they had:

Robb: Personal interactions and relationships may have had the biggest impact, just working with a little neighbor girl and helping her with her homework to promote education for women, since two-thirds of women in the country had never even been in a school.

Their question for us:

For others who've had this type of experience, did they ever do it again?

—Interview by Dottie Horn

WE'D LOVE TO HEAR YOUR RESPONSE: **medmag@pitt.edu**

Faculty Snapshots

One secret of outstanding mentoring, from an expert: "You have to make it clear to people that your mentorship extends beyond the straightforward part of their professional and academic life, that you're there to help them with other issues that might come up. ... People don't live in a vacuum. They've got families and children and responsibilities outside their home," says **James Roberts**, professor of obstetrics, gynecology, and reproductive sciences. He recently received an award for mentoring, the Duane Alexander Award for Academic Leadership in Perinatal Medicine (given by the National Institute of Child Health and Human Development). A leading researcher on preeclampsia and a member of the Institute of Medicine, Roberts has mentored close to 50 MDs and PhDs, most of whom are still academics.

Roberts

Coronary artery bypasses might be more effective if stem cells were transplanted into the heart at the time of the bypass, according to pilot data from **Amit Patel**, director of clinical cardiac cellular therapies, McGowan Institute for Regenerative Medicine, and **Robert Kormos**, professor of surgery. The researchers recently conducted a randomized trial in South America with 20 patients—half received the bypass alone, half received the bypass as well as a transplant of approximately 20 million stem cells. (The cells were from the patients' bone marrow.) Patients who received the stem cells and a bypass experienced better heart function and fewer symptoms of heart failure than those who received the bypass alone. In another study, the researchers used a stem cell transplant as a treatment for 10 patients with idiopathic heart failure (the reason for their heart failure is unknown, but it is unrelated to coronary artery disease—a bypass won't help these patients). The transplants improved heart function. This year, the researchers anticipate getting FDA approval to repeat these studies in the United States.

Two million people die each year from tuberculosis, the second leading cause of death from infectious disease worldwide. **Joanne Flynn**, an associate professor of molecular genetics and biochemistry and TB researcher, recently received a Senior Scholar Award from the Ellison Medical Foundation. The award will enable her to use a monkey model of TB to explore why some monkeys get active TB and others contain the infection and have latent TB. (Ninety percent of infected people develop the latent form of the disease.) She will try to find markers in blood that could predict whether someone, once infected, will develop active or latent TB, and whether a person with latent TB will end up with the active form of the disease. *—DH*

Flynn

SIMMONS GETS MEDAWAR PRIZE

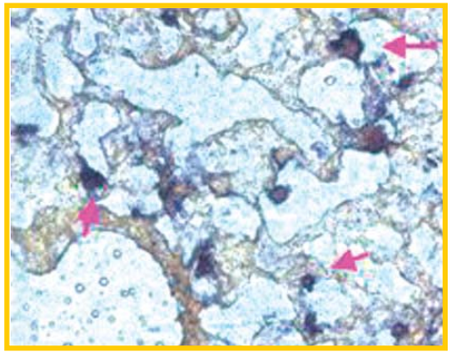
Forty years ago, in the early days of organ transplantation, when immunosuppression was first used, organ recipients began developing infections. These infections previously had been very rare, so they were largely unrecognized by surgeons, their clinical presentation and course were uncertain, their cause was unknown, and treatments didn't exist. One infection, which was often fatal, later turned out to be caused by cytomegalovirus. "What I did with colleagues was to describe this illness, so that you could recognize it from across the room," says Richard Simmons, Distinguished Service Professor of Surgery and emeritus chair of that department. Simmons also uncovered the clinical pattern of a condition in transplant recipients caused by the Epstein-Barr virus. Before that, no one knew that the Epstein-Barr virus could turn into a cancer-causing agent under immunosuppression.

For these discoveries, Simmons was recently awarded the Transplantation Society's Medawar Prize, which he shared with his mentors, John Najarian and Paul Russell (of the University of Minnesota and Massachusetts General Hospital, respectively). The prize is the world's highest honor for contributions to the field of transplantation. ***—DH***

A PROTECTIVE MIST

Esophageal cancer has a grim prognosis—less than 25 percent of people diagnosed survive five years. In some cases, doctors cannot treat the patient with enough radiation to eradicate the cancer, because the treatment would destroy the lungs. Matthew Carpenter, a radiation oncology resident, and Joel Greenberger, professor and chair of radiation oncology, have developed a gene therapy that might one day be used to protect lungs during radiation. Under normal circumstances, the cells' small reserves of antioxidants (some from food or vitamins and some produced internally) are no match for the large numbers of destructive free radicals that form in irradiated tissue. But the new Pitt therapy delivers a gene that boosts cellular production of an internally produced antioxidant called MnSOD. There's good news: The treatment works in animals. The researchers have shown that injecting the gene therapy into the windpipes of mice before irradiating them prevents some lung damage. However, using a windpipe injection in humans would be painful and could lead to infection. So the researchers took another approach. Carpenter recently showed that the mice can also derive lung protection by inhaling a mist containing the gene. For the aerosol research, the American Society of Therapeutic Radiation and Oncology awarded him the Resident Clinical/Basic Research Award in biology.

The researchers are now awaiting approval from the FDA to begin human testing of the MnSOD therapy. *–Corey Ballantyne*



COURTEST EPPERLY

After gene therapy, these lung cells are producing more of an antioxidant (dark blue), which helps protect against radiation.

Film Treatments

As a med student, Jim Basinski (Class of '05) has interviewed more than 40 patients with schizophrenia. One said that while she was sitting in a restaurant, everyone was staring at her because her food was poisoned. Another heard the voice of Satan telling him to kill himself. The first few times patients described their delusions to him, Basinski was shocked. Soon, however, hearing about psychotic visions became routine, business as usual. Basinski wonders how often doctors imagine what it is like to experience what are often terrifying hallucinations. (Medication can help a patient's visions subside.) Basinski is interested in how doctors keep from becoming "emotionally and intellectually numb" to patients.

One recent Friday night, he watched *Donnie Darko—The Director's Cut*, as part of the Film Interest Link for Medical Students (FILMS), a group formed for medical students interested in meeting periodically to watch and discuss movies. Some of the movies are related to medicine and some aren't; regardless, the conversation about the film usually turns in that direction: "Medicine is everywhere, once you look for it," says Alana Iglewicz (Class of '05), the group's founder.

Darko tells the story of Donnie (Jake Gyllenhaal), a teenage boy who sees and takes orders from a 6-foot-tall talking rabbit demon. The boy shows the classic symptoms of someone with paranoid schizophrenia, and *Darko* viewers see Donnie's demon as he does. Since watching the movie, Basinski, an aspiring psychiatrist who especially likes fantasy and science fiction films, sometimes finds himself making up a movie in his head about the delusions a patient has described. Watching the movie made him think that you could make a film out of every life—and reminded him to view each patient not just as a collection of symptoms or a diagnosis, but as the subject of his or her own personal story.

"Movies remind us of the drama, emotions, and mysteries of life that are happening all around us, but sometimes we're not sensitive [enough] to see," he says. *—CB*

C.E. MITCHELL

THE SMILE ZONE

The glimpse of a stuffed menagerie sometimes entices strangers—visitors to the med school or lost patients—into the Scaife Hall office of Robin Hammonds and Judy Schantz, who are both curriculum specialists. In just three years, Hammonds and Schantz have collected more than 150 Beanie Babies, mostly bears, but also the odd crab, pelican, monkey, and snail. When frazzled med students come to the office—looking, say, for help with lost keys, emergency messages from family, or replacements for lecture notes—they often smile or laugh at the extensive array of animals. "They help you to not take yourself and life so seriously," says Schantz. "If you look around, how can you stay upset?" Even so, the collection isn't the office's main attraction. "We have a candy jar that draws more people than the Beanies," adds Schantz. *—CB*

Appointments

W. Allen Hogge is the new chair of the Department of Obstetrics, Gynecology, and Reproductive Sciences. The field of obstetrics and gynecology is most often associated with pregnancy and menopause, but it's also concerned with diseases, like gynecologic cancers, many of which occur in postmenopausal women. In light of the aging population and Pitt's strengths, Hogge will expand the department's Division of Gynecologic Oncology. He also will develop an entirely new focus in the department, creating a prenatal medicine program, which will study ways to treat fetal problems prior to birth using medical rather than surgical approaches. Hogge, an MD who has been at Pitt since 1992, plans to recruit approximately 10 faculty members in the next three years. His own research has focused, in part, on evaluating an early, noninvasive method of prenatal testing for birth defects.

Hogge

Greenamyre

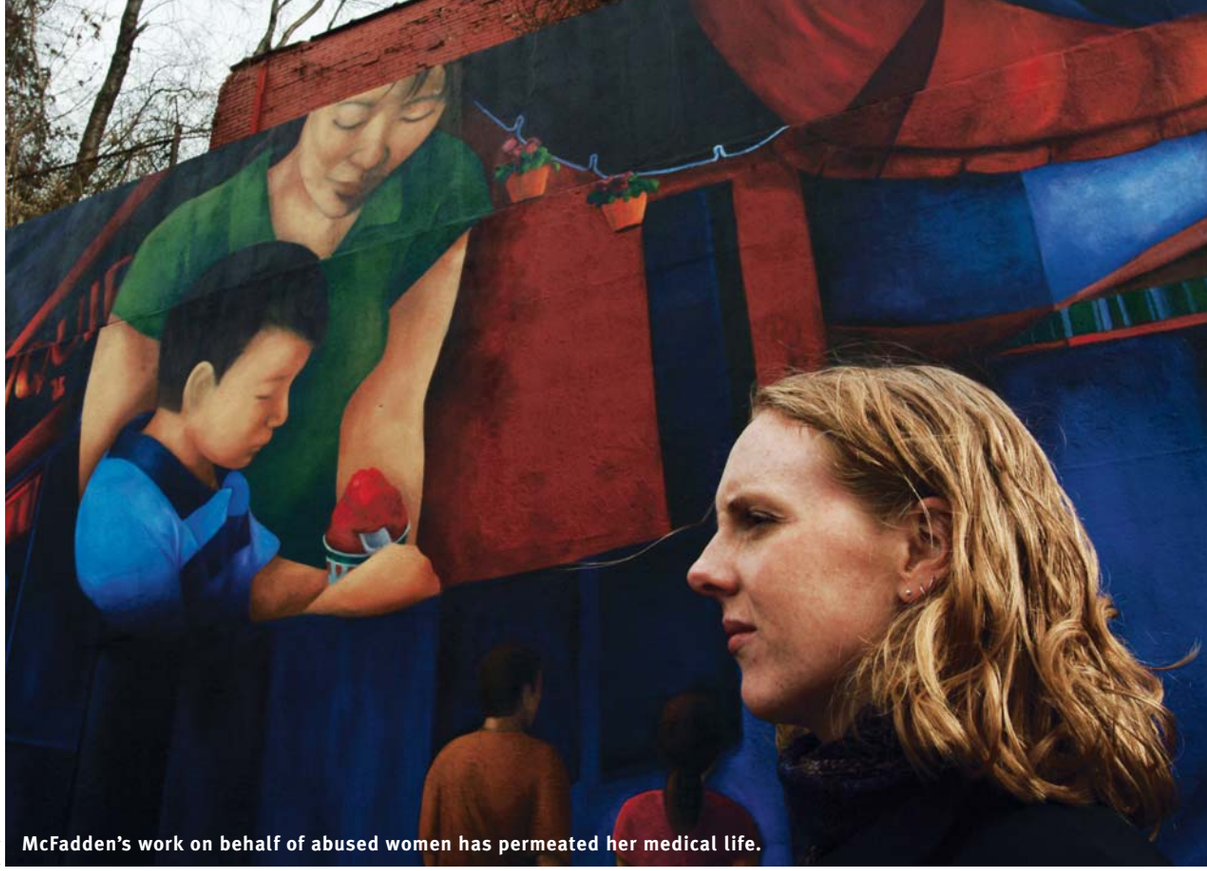
In a paper published in *Nature Neuroscience* in 2000, **J. Timothy Greenamyre** showed that when rats receive chronic, low-level exposure to the pesticide rotenone, they develop the features of Parkinson's disease. The paper offers strong evidence that environmental factors can cause the disease. "Although rotenone is not a widespread pesticide, there are many other much more commonly used pesticides that have the same mechanism of action as rotenone," says Greenamyre. "If we look at cells in a dish, some of [these other pesticides] are much more toxic than rotenone." Greenamyre is investigating the effects of these other pesticides in animals; he also recently showed that exposure to rotenone causes monkeys to develop features of Parkinson's. Greenamyre, an MD/PhD, came to Pitt in November from Emory University; he will direct the Pittsburgh Institute for Neurodegenerative Diseases and the movement disorders division within the Department of Neurology.

Ivet Bahar, until recently a professor in the School of Medicine's Department of Molecular Genetics and Biochemistry, is the chair of the school's new Department of Computational Biology. Pitt is one of the first medical schools in the country to establish a computational biology department—giving the new discipline the same status as more traditional fields. *—DH*

"YOU SAVED ME"

A DOMESTIC VIOLENCE CRUSADE

BY DOTTIE HORN



JIM JUDKIS

McFadden's work on behalf of abused women has permeated her medical life.

Sandra Mills' boyfriend was threatening her. He had a gun at home. She and her two children had escaped, to a friend's house, but she couldn't stay there. She called the domestic violence crisis hotline. Padi McFadden (Class of '05) answered the phone.

McFadden listened to Mills (not her real name) and gradually began to assess the situation: Was the woman in immediate danger? What was her greatest need? Was she an appropriate candidate for the women's shelter? McFadden helped Mills develop a plan for how she could stay safe until she came to the shelter.

"It's always horrible to hear about situations, but it's really rewarding to be on the phone with somebody and to help them. I just fell in love with the hotline," says McFadden, who has volunteered at the hotline since her first year of medical school. "Domestic violence has made itself my little crusade."

In March 2003, McFadden became a leader in the American Medical Student Association's domestic violence advocacy project, a yearlong initiative. For that project, she put together brief guidelines on domestic violence screening that med students could download onto their Palm Pilots and take into the clinic. "The thing I always thought, especially in the beginning, was, *What do I say? I need words.* I wanted to give people words to say," she recalls.

As part of a women's health area of concentration project, she's now working to put volunteer domestic violence advocates into the emergency departments of local hospitals. But the core of her advocacy has been the hotline—the one-on-one interaction with women in crisis.

She's learned not to tell those women, *I think you should do this.* "That was a really difficult thing for me to learn," she says.

Her well-honed listening skills and the hotline's philosophy of empowering women to make choices for themselves will prove invaluable, she believes, when she interacts with her own patients and helps them make behavioral changes.

But the work can sometimes be overwhelming. She remembers the man who beat his quadriplegic wife. He'd threatened to kill the woman and her adult daughter if she left. She remembers crying after she got off the phone with a woman whose boyfriend had repeatedly raped her 8-year-old daughter. "My heart went out to her," says McFadden.

Some days, she wonders if there's any good left in this world. "And then," she says, "it's very hard to not be suspicious of everyone's relationship around you."

Even so, the chance to bring about change makes her involvement worthwhile, McFadden believes: "I have a view of the world that some people do bad things, but it's the result of bad experiences they were brought up in or exposed to.

"Maybe it's idealistic, but if we can change circumstances, we can make the world better."

Sometimes the impact of her work is tangible. A few days after she spoke to Mills on the hotline, McFadden was at the shelter. That night, Mills and her children arrived to move in. "She just had this incredibly big, warm smile on her face and was so happy to meet me," says McFadden. "She said, 'You saved me.'

"I didn't save her, but that's what she said. That was so rewarding." ■

FOOTNOTE

"There have been some medical schools in which, somewhere along the assembly line, a faculty member has informed the students, not so much by what he said but by what he did, that there is an intimate relation between curing and caring."

—Ashley Montagu

American scientist, 1905–1999

DOES THAT HURT?

SOMETIMES, IT'S ALL IN YOUR HEAD, AND THAT'S REAL, TOO

BY KRISTIN OHLSON

When Stuart Derbyshire was 10, a teacher played a mean, if enlightening, trick. The teacher sent Derbyshire and a few of the boy's friends out of the classroom and also left the room himself. He returned with a pot of boiling water, which he lugged past the children

into the classroom. While Derbyshire and his friends waited in the hallway, wondering what was happening, another boy crept out of the room. *The teacher is going to plunge your hands into boiling water!*, he warned them. In a few minutes, everyone was summoned back into the classroom. The teacher pointed out the pot of water, blindfolded Derbyshire and his friends, led them across the room, and one by one, dunked their hands into the pot. The children screamed and yanked out their hands, yet the teacher had replaced the hot water with tepid water before they'd returned to the room.

"I distinctly recall that the water felt hot, even though it was actually tepid," says Derbyshire, now a Pitt assistant professor of anesthesiology and radiology. "I really perceived it as hot." His teacher had taught them a lesson about how sensations are not absolute but can be influenced by context.

Ever since, Derbyshire has been interested in pain, especially in the relationship between pain and perception. "Pain is capricious," he says. "If you're playing football and get kicked in the shin, it won't hurt much, but if you say something inappropriate at a dinner party and your partner kicks you in the shin, that hurts a lot. Pain has many layers of context and subjectivity. That's what makes it fascinating but also hard to understand."

Derbyshire has cast some light on what is known as functional pain, which is pain that has no discernable physical cause. An estimated 5 to 20 percent of the population suffers from mysterious ailments that involve functional pain. One such ailment is fibromyalgia, characterized by widespread, chronic pain, fatigue, and sleep problems; researchers believe abnormal sensory processing causes the condition. One fibromyalgia patient told Derbyshire that it hurt just to put on her clothes. Sometimes, these patients become frustrated, because they feel no one believes they are in pain. Derbyshire's study lends credence to their claims. He and researchers at the University College London have shown, for the first time, that the brain can generate the experience of pain on its own, without any physical cause.

In the study, eight healthy young adult volunteers with no history of functional pain were hypnotized while they were inside a magnetic resonance scanner. Derbyshire scanned their brains functioning under three circumstances. First, the volunteers were told to hold a thermal probe in their hands, and, after they were alerted to the beginning of the experiment by a tap to the foot, the researchers heated the probe to 119 degrees Fahrenheit for 30 seconds. Nearly all the volunteers found this to be painful. In a second scenario, researchers told the volunteers that their probes were going to be heated to the same level following another tap to the foot, even though the probes actually were turned off. In a third scenario, volunteers were asked to imagine the pain caused by the hot probe after the foot tap but were informed that the probe would not be turned on.

During the first two circumstances, the volunteers reported similar levels of pain. If they were warned that the probe would be hot, people believed that their hands hurt even when the probe wasn't heated.

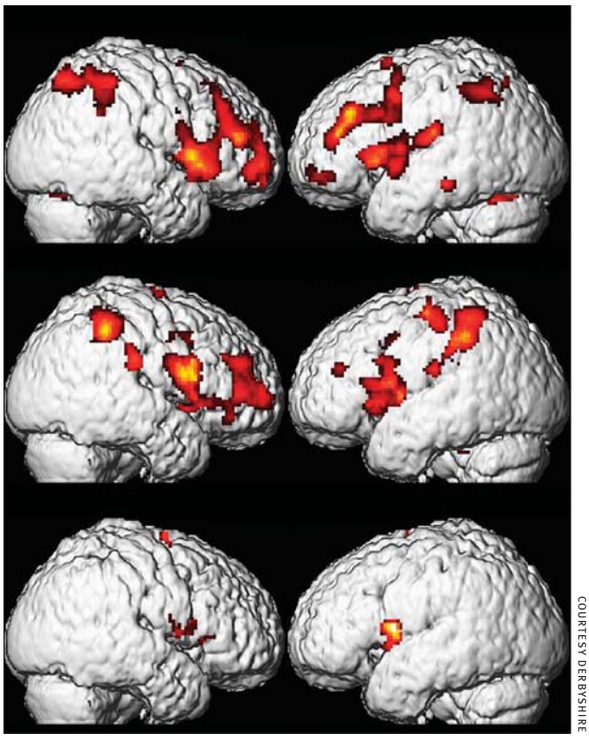
And when Derbyshire and his colleagues examined the scans from the first situation, they found activity in areas of the brain that are already known to be associated with pain. In the second situation, they found similar activity. The brain had actually created the experience of pain in the absence of physical stimulus.

(There were fewer reports of pain from the third situation, when the volunteers knew the probe would not be hot. The brain scans of imagined pain were not similar to the scans from the first two situations.)

The study results have been independently replicated by a group in Finland and will be published in the journal *NeuroImage*.

Hypnosis was useful in this study, because it does not alter the perception of reality but makes people more open to suggestion. Derbyshire wonders if the same psychological mechanisms may be involved in both hypnosis and functional pain. In an upcoming study, he will use hypnosis to try to decrease the pain experience of fibromyalgia patients while they're in the MRI scanner, then examine scans to see which brain areas are affected when the patients feel better. In another study, he'll compare brain scans from healthy people who can be easily hypnotized and are able to lessen the amount of pain they feel to scans from people who are not able to alter their pain experience during hypnosis.

"It's intrinsically fascinating to get someone to experience something out of nothing," says Derbyshire. "Now when we say that the brain can generate an experience of pain, we're not talking hot air—we've shown it. And, hopefully, that will get us closer to understanding functional pain." ■



COURTESY DERBYSHIRE

Sometimes doctors can find no physical cause for a patient's pain. Magnetic resonance imaging may help explain the brain's role in experiencing such pain. Composite scans from volunteers holding painfully hot probes (top) look a lot like scans from volunteers who are holding probes they've been told are hot, even though they really aren't (middle). But when volunteers just imagine touching a hot probe (bottom), their brain activity looks very different. Volunteers were hypnotized in all three circumstances.

GETTY/ HULTON ARCHIVE

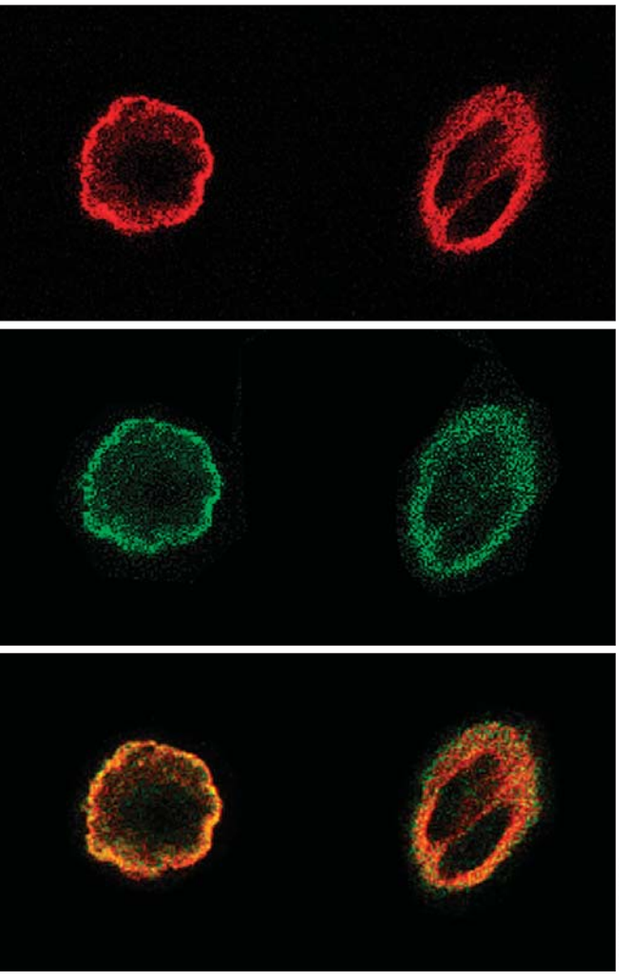
RAMPANT RECEPTORS

NEW STRATEGIES FOR HEAD AND NECK CANCER

BY SUSAN GULLION AND DOTTIE HORN

An imagined patient, Ronald, has a malignant tumor removed from the wall of his throat. The surgery is followed with chemotherapy and radiation, but two years later, cancer reappears. The first time, his vocal cords were free of cancer, but now, his voice has become gravelly. If his vocal cords have tumors, he'll probably have his voice box removed.

New drugs have shown promise against head and neck cancer—but the interplay between two protein receptors (EGFR and GPCR) may limit the effectiveness of those drugs. This image shows that two proteins involved in communicating between the EGFR and the GPCR are located in the same part of the cell. (The bottom image is the digital overlay of the first two images, each of which shows a separate protein. The areas where the proteins overlap are orange.)



COURTESY GRANDIS

Ronald is fictional, yet his story is not unlike that of many patients with head and neck cancer. The recurrence rate is high, and only 50 percent of patients with the disease survive five years. The treatment can be disfiguring and make it difficult to swallow, talk, or breathe. There has been no improvement in the cure rate in the past 50 years.

However, work by Jennifer Grandis (MD '87), professor of otolaryngology, and Jill Siegfried, professor of pharmacology, may offer new hope for treating this devastating disease. Gene therapy is one treatment strategy that looks tentatively promising.

The researchers are testing a new treatment that involves epidermal growth factor receptor (EGFR), which is found on the surface of epithelial cells, like skin cells and the cells that line the esophagus and the gut. This receptor's role in normal cells is unknown. In 1998, Grandis and Siegfried showed that EGFR is overproduced in tumors from patients with head and neck cancer. The patients with the highest EGFR production died from the cancer, and those with the lowest production levels survived. What if they could inhibit EGFR?

The researchers then demonstrated that in animal models of head and neck cancer, inhibiting EGFR resulted in decreased tumor size. That work helped set off a flurry of research activity into ways of manipulating EGFR.

Recently, the FDA approved the first EGFR-inhibiting drugs. In 2003, Iressa (manufactured by AstraZeneca) was approved for treating lung cancer; in 2004, Erbitux (manufactured by Imclone) was approved for use against colon cancer. A recent paper in *The New England Journal of Medicine* showed that certain lung cancer patients—those with a specific EGFR mutation—responded well to Iressa.

Erbitux has been tested against head and neck cancer with mixed results. One study compared head and neck cancer patients who were treated with chemotherapy to those treated with a combination of chemotherapy and Erbitux. The addition of the drug did not improve patient outcomes. In another study, Erbitux proved beneficial when combined with radiation therapy. Many new trials are under way that will test the addition of Erbitux to more typical treatment protocols.

What if doctors were to deliver a gene into the tumor cells that would inhibit EGFR? Siegfried and Grandis are in the early stages of a phase I clinical trial designed to evaluate such a gene therapy. Although they've only enrolled three patients so far, their anecdotal evidence has been exciting: One patient's tumor, which was too large for surgical removal, completely disappeared after gene therapy. (However, the patient had another tumor that was positioned too deeply to be injected with the therapy.)

Despite the possible value of the gene therapy and new drugs, Grandis believes inhibiting EGFR is unlikely to be sufficient as a primary or adjunct therapy for head and neck cancer. Even when EGFR is inhibited, another receptor, the G-protein coupled receptor (GPCR), can be a source of trouble. Think of GPCR as a generator waiting in the wings—shut down EGFR, and GPCR can take over—stimulating the same sequence of events normally set into motion by EGFR. (These events ultimately lead to unrestrained cell growth.) So it may be necessary to inhibit both receptors. Fortunately, GPCR inhibitors exist. Grandis and Siegfried are planning a clinical trial that will look at the effectiveness of combining EGFR and GPCR inhibitors in treating head and neck cancer.

In another effort, they're searching for a means to predict how a given tumor will respond to a given therapy. They'd like to not only develop better treatments, but also help physicians choose which treatment option is best for a particular patient. ■

TOO MUCH OF A GOOD THING?

IN CYSTIC FIBROSIS, QUALITY CONTROL GETS OUT OF HAND

BY DOTTIE HORN

Destroying mutant protein sounds like a good thing, and often it is. Many diseases result when mutant proteins aren't destroyed. However, in the case of cystic fibrosis, the mutated gene that causes the disease results in a protein that, even though it is abnormal, isn't completely dysfunctional. It can still do its job—it's just less efficient than the normal protein. The cell's quality-control system, however, sees the mutant protein and destroys all of it. None is left to perform the critical role of forming an ion channel at the cell membrane. If only the protein weren't completely destroyed, studies suggest, a person with CF might have enough functional protein to cure or curtail the disease.

In the case of CF, the mutant protein wouldn't cause any damage to the cell, says Jeffrey Brodsky, associate professor of biological sciences and medicine. "That's the whole problem, the quality-control mechanisms are overzealous, hyperactive," says Brodsky. "That's what makes it so frustrating, because the cell's doing too good a job."

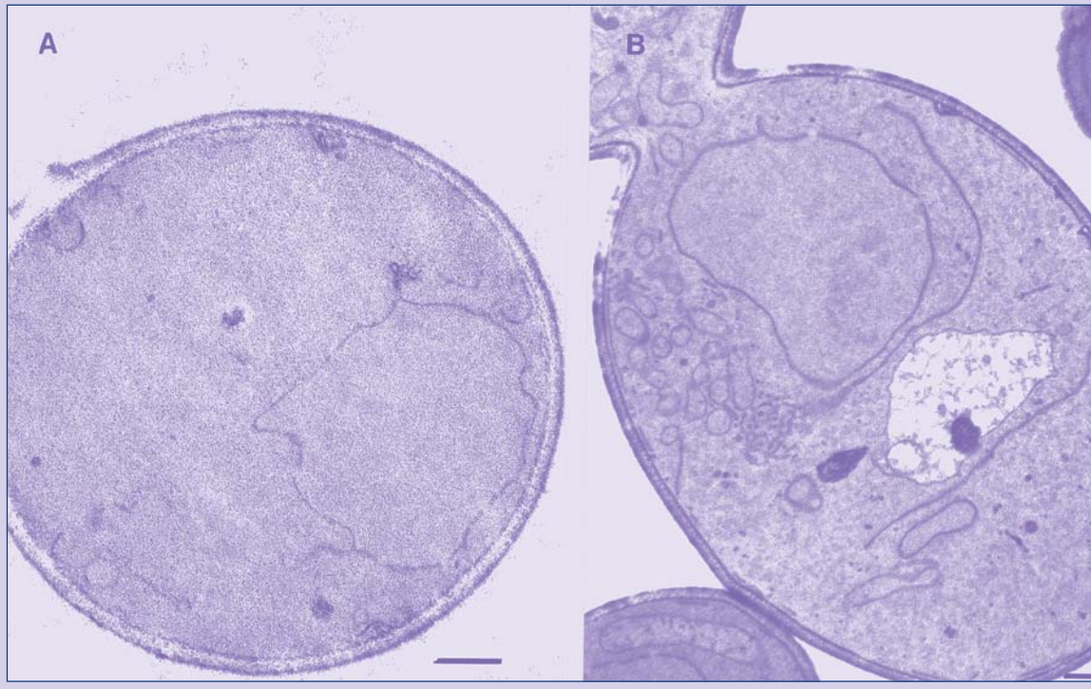
He wonders: If we could modulate the quality-control mechanisms, make them a little less ardent, could we change the course of CF? To study this question, he uses yeast, the same yeast used to make bread and beer. Although yeast is a single-cell organism (simple compared to multitrillion-cell people), it shares many proteins in common with humans.

Brodsky starts with healthy yeast, which he grows in a nutrient-rich broth in glass flasks. (His microscopic yeast cells are cannibals—as part of their diet, he feeds them extract derived from other yeast.) He puts into the yeast the mutated gene that codes for CFTR, the protein that's defective in CF. The cells start making the abnormal CFTR protein. But they also destroy it as soon as it's made, and the cells remain healthy.

Then Brodsky applies microarrays to the yeast; this tool allows him to look at the expression level of every single gene in both the normal yeast and the yeast with the CFTR gene. He looks for differences, genes whose expression changes dramatically in the yeast with the mutated CFTR gene. His finding: "Whoops, a few things go up, big time."

One of the "things" that goes up is the expression of what's known as a molecular chaperone, Brodsky explains. Chaperones are key players in the cell's quality-control system; they pick out the damaged proteins that should be eliminated. Brodsky tried knocking out the gene for this particular molecular chaperone; when he did, the CFTR protein was no longer destroyed. It was this chaperone, then, that was condemning the mutated protein to destruction.

A clinical trial is under way at Johns Hopkins University, looking at whether curcumin, an agent derived from the spice turmeric, might be effective against CF. Curcumin is believed to inhibit the action of some molecular chaperones. It's not yet known whether inhibiting these chaperones might allow other malformed proteins, which really should be degraded, to go unchecked. ■



If the cell's policing of mutants was not so diligent, people with cystic fibrosis might fare better. The yeast cell on the left is normal. The cell on the right is working overtime to destroy a protein that is mutated in cystic fibrosis patients.

Before Klaus Hofmann came along, most hormone chemistry was hypothesis.

KLAUS HOFMANN GAVE HIS STUDENTS AND SCIENCE AN ADRENALINE RUSH

BY LEAH KAUFFMAN

THE KING OF PEPTIDES

It's a graduate student's anxiety dream come to life. You're working in the department chair's lab, where it's standing room only: Every spot at every bench hosts a colleague hard at work. Then your chemistry experiment with a known explosive—the one that's so dangerous that a postdoc must closely supervise your work—detonates in a shower of glass.

It happened to Robert Wells (PhD '64) the summer after his first year of grad school, though he'd followed all the protocols, done nothing wrong. The explosion knocked Wells to the floor, stunned. By the time he realized what had happened, the room was filled with smoke. Wells made for the door on hands and knees, but just as he was about to clear the threshold, he was stopped by a pair of immaculately polished Bally shoes. Wells' eyes tracked up the sharp crease of a trouser leg, up a well-cut suit jacket and stylish tie, to the eyes of the chair of the biochemistry department, Klaus Hofmann,

DRAWING BY HENRY KOERNER

standing resolute at more than 6 feet. Loud noises didn't alarm Hofmann. As a boy, he'd gleefully exploded nitroglycerin-soaked bits of paper; as a young man, he'd commanded a corps of heavy artillery in the Swiss militia.

Hofmann looked down at Wells, whose face seeped blood from dozens of small cuts. "Bobs," Hofmann counseled, "I think you better take the rest of the day off." Although Hofmann had a nickname for everybody—Noboru Yanaihara, the postdoc supervising Wells' work, was called "Nobby"—no one in the lab dared reciprocate.

Hofmann knew the chemistry at work within Wells' body during those fearful moments: He was one of the world's experts on the molecular structure of hormones. Hormones, secreted by one set of tissues and circulated to another, tell cells what to do, when. Hormones are what guide our bodies to make the myriad small adjustments that keep us functioning within our changing environment, adjusting our metabolism to respond to hot, cold, night, day, hunger, and satiety. And when things get tough, hormones guide the mechanisms of self-preservation. Hurting? The hormone endorphin will secrete from your pituitary gland and circulate through the brain, reducing the perception of pain. Just explode something in front of your department chair? Your body will let loose epinephrine, also known as adrenaline, and norepinephrine, which will circulate to the heart, causing it to pump faster. These two hormones open the passages of the lungs to increase respiration and direct blood toward the brain and muscles—all to help fuel the ability to flee, or in the direst situations, to keep the brain oxygenated enough to survive.

Sixty years ago, most hormone chemistry was hypothesis. It was understood that there were two main classes of hormones: steroid hormones, which are derived from cholesterol, and peptide hormones, which are composed of amino acids. But their molecular structures were just beginning to be teased out. In long-drawn, step-by-step experiments, hormones were purified from animal extracts to analyze their structure, then synthesized to understand their function.

These days, the job of peptide hormone synthesis is automated. For the price of a faculty member's salary, your lab can have a peptide-making machine of its own, or you can call up and have your made-to-order peptide hormone delivered. But in the early days of hormone biochemistry, peptide synthesis was a laborious, meticulous process of stringing molecular beads, all within a set of narrow conditions that encouraged new chemical bonds without breaking the extant ones. It required quiet hands, patience, discipline, and rigor. It required someone like Klaus Hofmann, who spent 51 years at Pitt investigating peptide hormones and other proteins, chaired the biochemistry department from 1952 to 1964, and helped a generation of first-year medical students, when faced with his notoriously demanding biochemistry course, master their epinephrine-fueled urge to flee.

Hofmann was recruited to the University of Pittsburgh's College of Arts and Sciences in 1944 to help elevate its research program. His reputation as a chemist was already well established. His postdoctoral work with Leopold Ruzicka and Vincent du Vigneaud, who would both become Nobel laureates, placed him in a fine pedigree. After his tightly run laboratories and courses established his reputation as a leader, Hofmann was invited to chair the new biochemistry department in the School of Medicine.

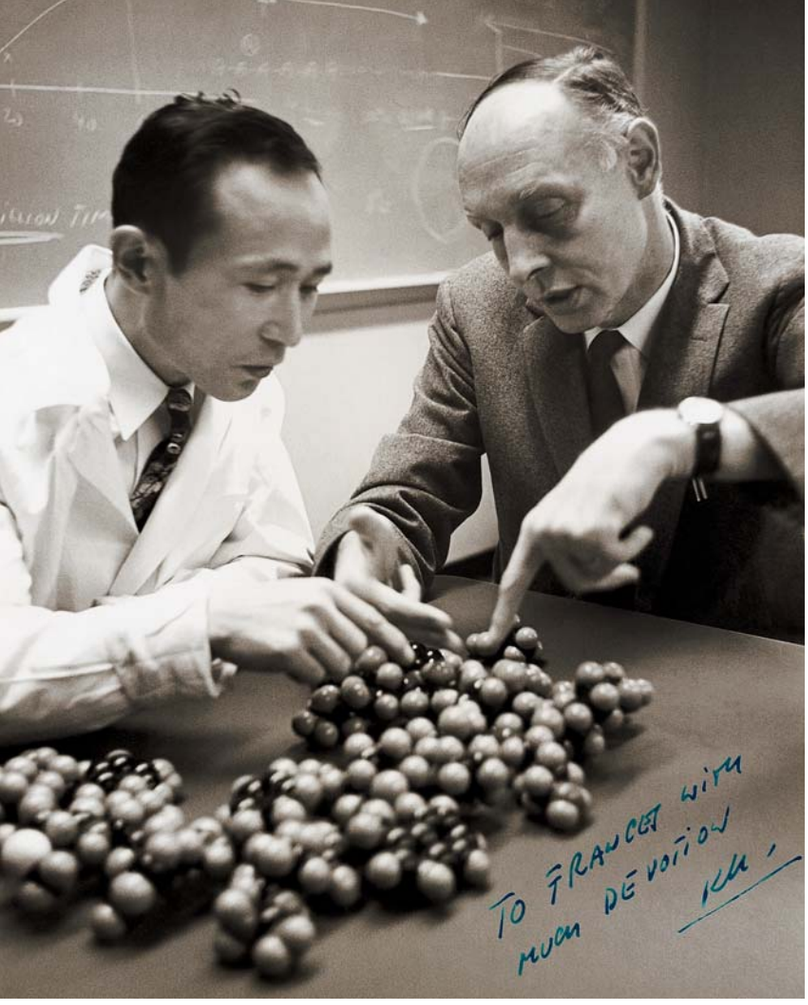
It was about this time that Hofmann became an American citizen (though he would later serve as an honorary Swiss consul) and fell in with European expatriate Patrick Laing, a British orthopaedist at Pitt. Laing got to know Hofmann because of the biochemist's precise scale, the only one like it in the medical school. Laing had sought out such a scale to further his studies on the degradation of metal implants. Their friendship, in which they shared a world of ideas outside science, would span the next 40 years (and a dozen-and-a-half metal implants—all of them, unfortunately, in Hofmann).

First-year medical students expecting Hofmann's course to be a breezy refresher of their undergraduate labs blanched at its demands, for it detailed the whole of biochemistry. Hofmann took his teaching obligations seriously and expected his faculty to do the same. To keep his perspective and the material fresh, he reinvented the course each year. His blackboard notes were no incidental asides, but carefully storyboarded in advance. His destruction of each lecture's preparatory notes ensured that he never delivered the same talk twice. Once a month, he observed surgery, to better understand how basic science affected clinical practice. In the company of Hofmann and his similarly precise colleagues—Jack Myers (chair of medicine), Frank Dixon (chair of pathology), and Hank Bahnson (chair of surgery)—Pitt's star rose.

Hofmann took delight in his fearsome reputation, yet he was equally and secretly pleased with the accomplishments of his trainees, many of whom now lead biomedical research. Barry Brenner (MD '62) of Harvard University rewrote the book on kidneys. Robert Wells of Texas A&M has challenged paradigmatic notions of DNA. Bert O'Malley (MD '63) of Baylor College of Medicine earned a special place in Hofmann's heart by remaining in the hormone field and by bringing good scotch to conferences. According to O'Malley, Hofmann "didn't mix in a lot of polite tact. But, on the other hand, he loved his students, and he wanted them to do well, and he wanted them to learn."

He loved the finer things. (He played violin in string quartets and with critical care medicine giant Peter Safar on piano. And he'd often take a midday repast at the Pittsburgh Athletic Association.) That appreciation came at the knee of his grandfather, who amassed an early fortune manufacturing silk ribbons, then treated himself to retirement and a castle at the age of 36. Yet whatever sense of entitlement Hofmann had was lost along with the family fortune, squandered on a bad business deal when he was a teenager. He would have to make his own way.

At the Swiss Federal Institute of Technology Zurich, he trained as a chemical engineer, then spent several years working on the structure and synthesis of steroid hormones. His success is archived in a set of 13 papers, astounding prolificacy for a trainee, but he'd had enough of the crowded steroid field. Knowing that steroids' cousin molecules, peptide hormones, were relatively unexplored, he arranged a fellowship with protein chemist Max Bergman at the Rockefeller Institute and, later, with Vincent du Vigneaud at Cornell University. There, Hofmann purified and revealed the structure of biotin, also known as vitamin H. His training was then complete, but it was wartime, and universities were reluctant to hire foreigners, so Hofmann accepted refuge as a guest scientist in industry, at what's now Ciba Pharmaceutical Products in New Jersey. Eventually, Arts and Sciences Dean Herbert Longenecker invited him to the University of Pittsburgh. News soon came that du Vigneaud had isolated and synthesized the posterior pituitary peptide hormones vasopressin and oxytocin. Seeking undeveloped real estate, Hofmann decided to go after adrenocorticotrophic hormone (ACTH), an anterior pituitary hormone.



In 1960, Hofmann discusses ACTH synthesis with Haruaki Yajima, a fellow investigator in his lab. The hormone helps preserve crucial brain function during difficult times.

ACTH is an intermediary in a complex cascade caused by physiological stresses like infection or trauma. The hormone helps preserve crucial brain function in difficult times.

Early work by Armour & Company in Chicago showed that ACTH was rich in the amino acid arginine, but no one had yet developed a way of inserting arginine into synthesized peptides. Looking ahead, Hofmann developed a new method. When another group finally purified ACTH and determined its structure, Hofmann was ready to synthesize it, the gold standard experiment for proving that its biological effect was attributable to the hormone alone and not something unrecognized in the mix of animal brains from which the natural purified form was derived.

No one had synthesized a molecule as large as ACTH, which is 39 amino acids long. The task was made less onerous when another group showed that when purified ACTH was limited to just the first two-thirds of its length, it was still biologically active. Hofmann synthesized a sequence corresponding to the first 23 amino acids and showed that the molecule had biologic activity. But now he had new questions to answer. For instance, how does the hormone influence its target cells? What do those other 16 amino acids do?

And who is that new graduate student? Frances Finn arrived in the Hofmann lab in 1961. It's hard to believe that Finn was, like everybody else, terrified of Hofmann, at first. Later, cooking for guests in their home, the two would raucously compete for top chef honors, poking fun at each other and everybody else, their pet parrot joining in, sometimes cursing a blue streak. (Hofmann tried to blame that on Finn, but the parrot's Swiss accent gave him away.) Finn jokes that Hofmann married her as an anchor for the lab, a counter to the students who cycled through every few years.

"I certainly stayed there for 30 years," says Finn (now Frances Finn Reichl). "That worked."

It was a heady time for Hofmann. He was a newlywed in his 50s. He had recently been elected to the National Academy of Sciences—the first Pitt medical school faculty member to be so honored. He received the first Chancellor's Medal, and was the first—and last—Jonas Salk Professor named by the Commonwealth of Pennsylvania (renamed the Commonwealth Professorship). While the accolades, lecture invitations, and faculty position offers poured in, Hofmann maintained that in science, "you're wrong if you go after prizes; the only real way to do science is for the fun of it." By then, he craved more time for his studies. Chancellor Edward Litchfield obliged, accepting Hofmann's resignation as chair and granting him space on the 12th floor of Scaife Hall. Hofmann took delight in applying his engineering education to the design of his new Protein Research Laboratory, then devoted himself full-time to answering the remaining ACTH questions. Finn, an adept protein chemist, had a place at the lab bench and co-authorship on all of Hofmann's papers. (In addition, Finn, now faculty emeritus in the Department of Medicine, taught biochemistry for three decades.)

Those extra amino acids? Scientists still are unclear as to what they do, says Finn. But Hofmann was able to zero in on how ACTH influences its target cells.

His studies led him to believe that some of the molecule's first 23 amino acids represented sites that were recognized by a receptor on the target cell. They allowed the hormone to "dock" at the right place on the cell surface. This was an important process to understand, for if a synthetic hormone was going to be of any practical use, it had to be able to initiate a response after binding to target cells, and only the correct target cells. (You don't want your ACTH docking in your thyroid gland, after all.) But measuring such minutiae in animal models was too uncertain. Hofmann, who insisted his work be correct rather than first, needed a new model.

An enzyme called ribonuclease, a string of 124 amino acids, showed promise. By swapping out amino acids, Hofmann determined how a peptide binds to a protein—a fundamental discovery. He reasoned that this must be the way a peptide hormone binds to a protein receptor on a target cell. Hofmann considered this breakthrough, rather than the synthesis of ACTH, his most important contribution to science.

In 1977, while hosting a party in his role as Swiss consul, Hofmann tripped on the dance floor and refractured a hip he'd broken some 20 years before. As party goers rushed to his assistance, he called out, "Get me two things: a bourbon and Patrick Laing!" Laing put Hofmann's hip back together with 18 screws. Once the hip was knit, and Laing removed the screws, Hofmann weighed himself to see if their absence made a difference. It didn't, but then he wasn't using the very precise scale over which he and Laing met.

Hofmann isolated the receptor for insulin in 1984. He'd hoped to use the same method for ACTH, but identifying that receptor would have to wait. At the time, it was too difficult to purify enough of the target cells from the adrenal glands.

By the time the rest of the ACTH field caught up to Hofmann, he had inoperable liver cancer. As Hofmann's world contracted to home and hospital, Laing helped Finn keep him company. In their 40 years of companionship, the two men had always been able to talk about anything at all. Hofmann died in 1995.

Remembering him, Laing says quietly, "He was my friend." ■

The polio vaccine did not reach these good-humored Indian children in time. This photo and the others by Sebastião Salgado on these pages document polio's modern legacy and pending eradication. The work appears here courtesy of Salgado and PixelPress, curator of *The End of Polio* international traveling exhibition, which Pitt is bringing to the Carnegie Museum of Natural History this March 5; the exhibition will run through May 15. To build awareness about the polio eradication effort, PixelPress has published *The End of Polio,* which features Salgado's work and has been released in both hard- and soft-cover editions. For more information, or to donate to the eradication effort, see www.endofpolio.org.

SEBASTIÃO SALGADO | PHOTOGRAPHY

EDWIN KIESTER JR. | TEXT

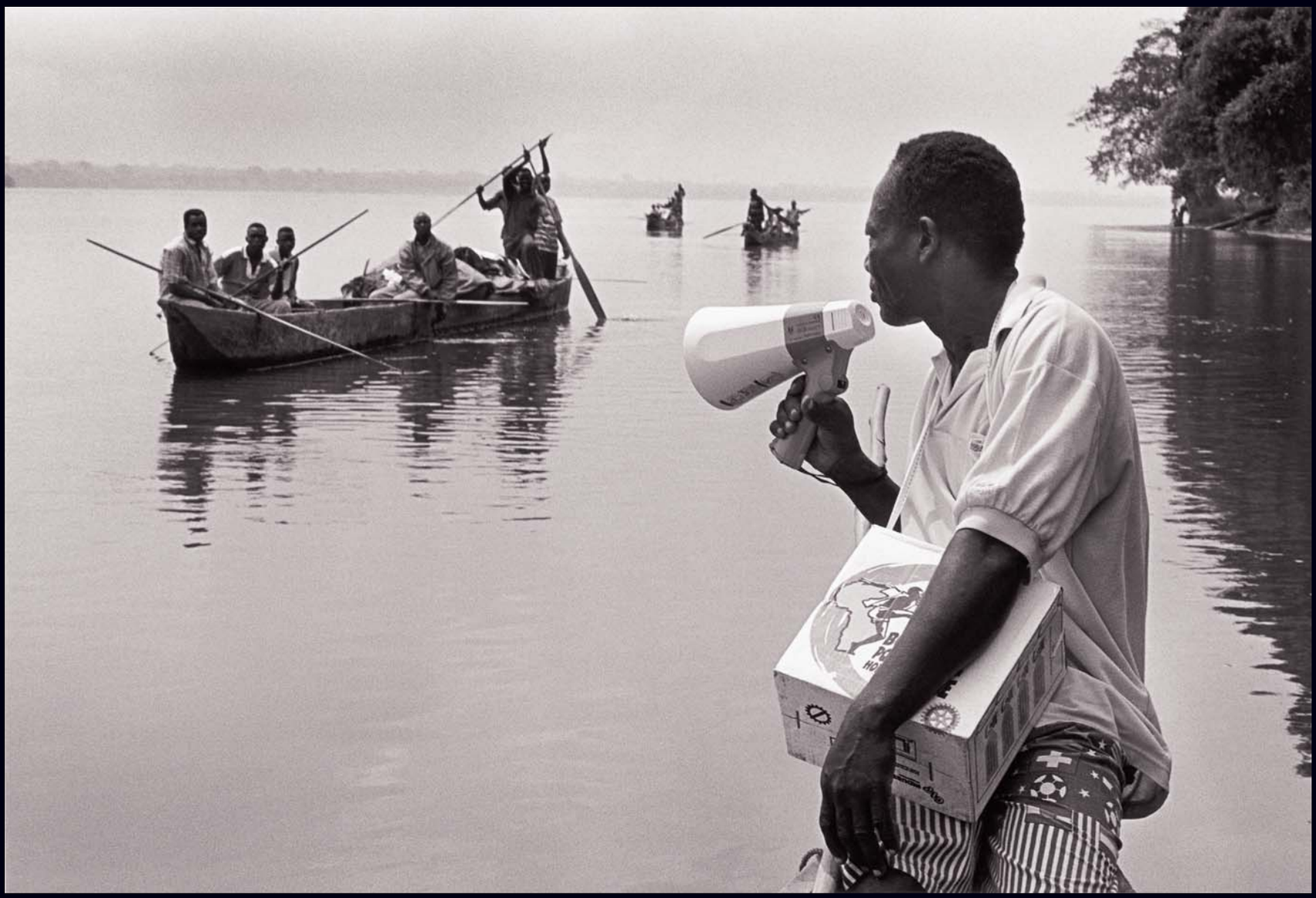
THE END OF POLIO

When the guerrillas arrived, brandishing weapons, the immunization volunteers in Somalia did not flinch. Two of their colleagues from the Global Polio Eradication Initiative had already been taken hostage by a similar band. Yet this time, the mission came with armed guards. A firefight ensued, but even as bullets were flying, the volunteers proceeded with the task at hand: to completely wipe polio from the face of the earth.

Fifty years ago, on April 12, 1955, news that the polio vaccine developed at the University of Pittsburgh was "safe, effective, and potent" electrified the world. In 1988, an international campaign began to eradicate the poliovirus everywhere, as had been done with smallpox. Volunteers traveled by canoe on unmarked rivers, climbed untracked mountains, traversed deserts, and survived deadly gunfire. In 2001 and 2002, at least 500 million children under 5 were immunized each year thanks to worldwide efforts. Today, stubborn polio pockets remain only on the Indian subcontinent and Africa. The photographs on these pages (which will be exhibited at the Carnegie Museum of Natural History beginning March 5) document the Eradication Initiative's heroic work. Brazilian photojournalist Sebastião Salgado traveled with the health workers, recording how a scourge is wiped out, one child at a time. The photos also capture polio's prevaccine legacy, in twisted limbs and damaged lives.

The drive to protect every child in the world goes on. World Health Organization (WHO) officials hope the disease will be eradicated this year.

INDIA Yoga stretches damaged limbs and improves mobility for children with polio (shown above). Their state, Uttar Pradesh, has been hit hard. Of 2,000 new cases worldwide in 2000, two-thirds were from there. Muslim areas were particularly afflicted. Vaccination teams now include at least one woman to ensure access to all members of each family. Young people (shown right) learn vocational skills, attend schools, and practice music at New Delhi's Amar Jyoti Rehabilitation & Research Centre. Although India has a burgeoning pharmaceutical industry, most of its polio vaccine must be imported.



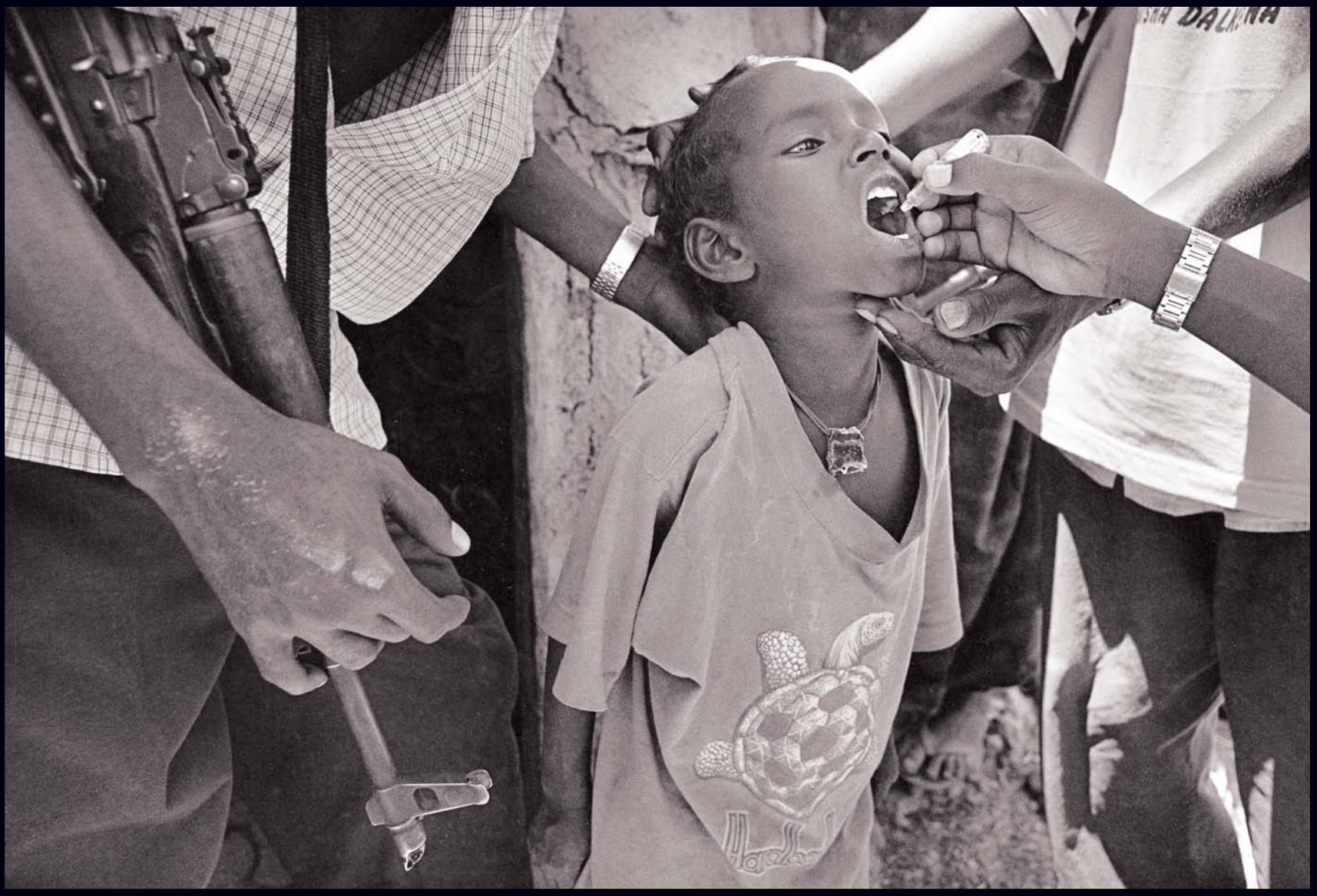
CONGO A vaccine volunteer (above) on National Immunization Day summons river traffic ashore. Canoes will not be permitted to proceed until all children aboard under 5 have been vaccinated.

PAKISTAN What became known as the "Salk vaccine" utilized a killed virus and required three injections. The Salk vaccine is now routinely included in U.S. childhood immunizations. An orally administered live-virus vaccine, effective in areas where sanitary conditions are poor, is used by WHO and others. (Otherwise, the polio virus might be transmitted through fecal matter.) Here, families in the Thar Desert wait as a volunteer administers "just two drops."

PHOTO NOT AVAILABLE

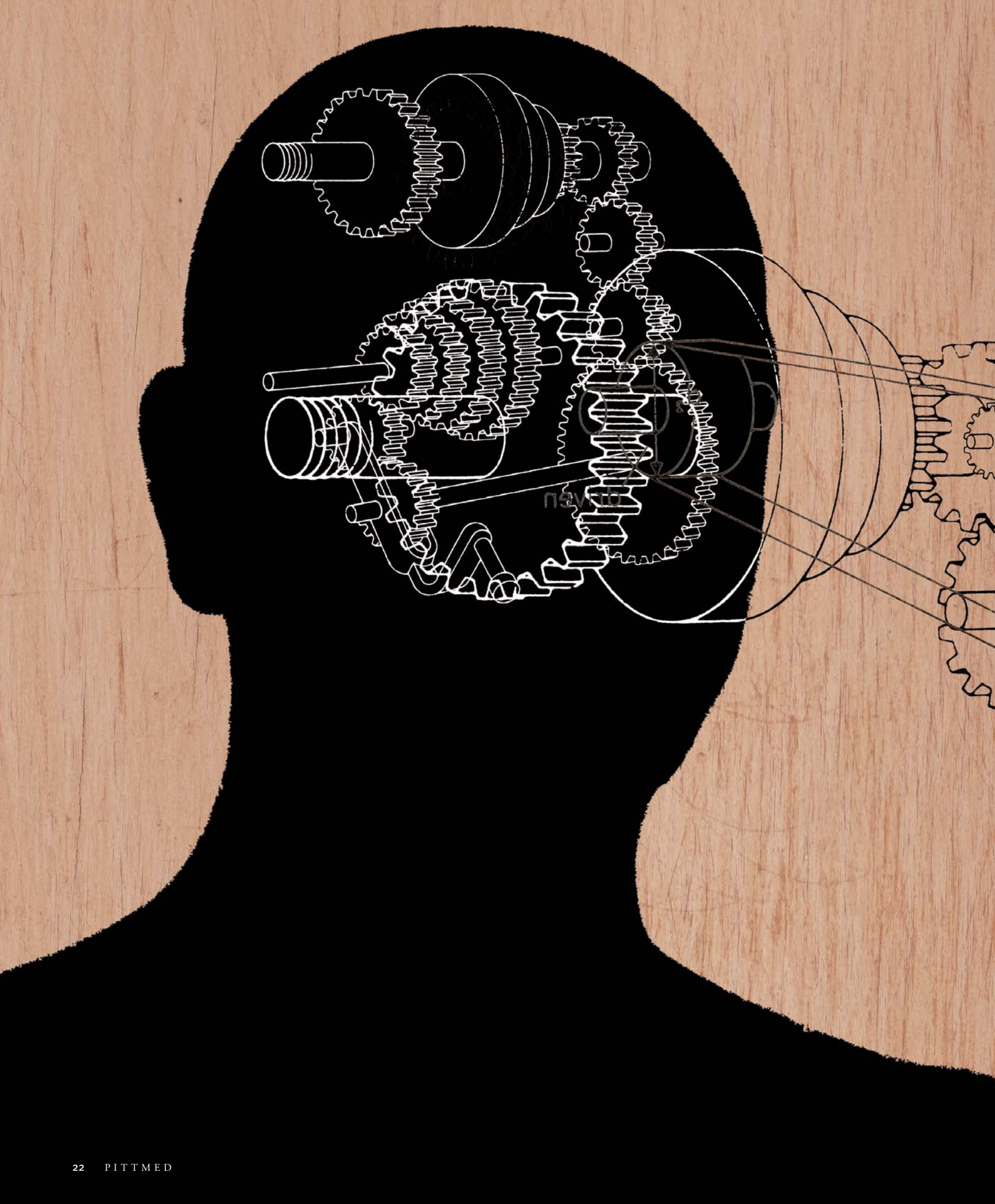
SUDAN A cattle-raising community (upper photo, this page) marches forward to welcome volunteers. Below, a child opens wide for the prescribed drops. Sudan reported no new polio cases in 2001, a landmark year. Then last May, a Darfur child was found paralyzed by the virus. The virus had migrated from Nigeria, where eradication efforts had been interrupted by a rumor the vaccine was a ploy of the West to make Muslim women infertile. Epidemiologists warned Africa was on the brink of another epidemic—but the vaccine campaign has now made up for lost time.

SOMALIA Armed men (opposite page, above) stand guard as a girl receives her dose of lifelong immunity. Below, vaccine teams use singers to attract villagers.



WHERE IT BEGAN Pitt will celebrate the Salk vaccine's golden anniversary April 10–12 with a series of commemorative events, in addition to the Salgado exhibition. A community celebration April 10 in the Commons Room will bring together Salk family members, pioneers from the pilot project and national trials, and prevaccine polio patients. A two-day symposium, "The History and Future of Vaccine Development," will feature international health experts, among them Julius Youngner, Distinguished Service Professor Emeritus and a key member of the Pitt research team that created the Salk vaccine.

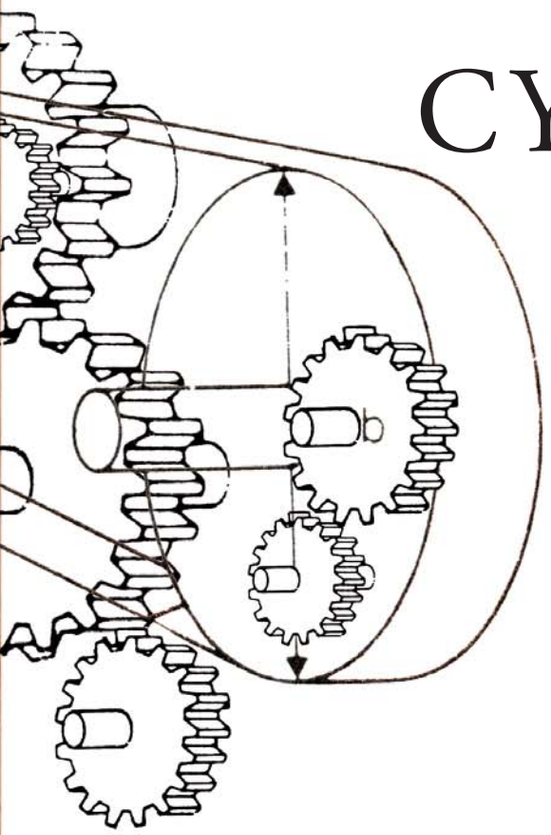
FOR MORE INFORMATION:
www.polio.pitt.edu



COMPUTER-BRAIN INTERFACES

AND OTHER PRAGMATIC VISIONS

BY ERICA LLOYD



CYBORG MEDICINE

"That's good. What's that? Is that internal rotation?" asks Andrew Schwartz, who's standing next to a workstation outfitted with Yamaha speakers, a recording system, and a lode of computer and video screens.

A crackling electronic noise is his object of intense interest. With each crackle, a wave trips on a screen, like a seismograph detecting a tremor of the earth. Each crackle is a clue to what's happening in the brain of a monkey sitting in a room next door.

"Right there!" says Schwartz, as white-coated technician Ingrid Albrecht records each hit.

More crackling.

"There."

Crackle!

"There," he says.

Crackle.

ILLUSTRATIONS | DAVID POHL

"Okay, that's good. All right. What's that now?"

"Abduction," says Albrecht after getting up from her chair at the workstation to peer through a cracked open door. She is relaying the answer to Schwartz's question from Edgar Ycu, another technician here at the University of Pittsburgh McGowan Institute for Regenerative Medicine. Ycu is just out of earshot, in the neighboring room, moving a monkey's arm in different ways. The crackling is the result of neuronal firings, what are called spikes, from the monkey. The spikes are made audible to Schwartz and the others by eight microelectrodes that Schwartz has surgically implanted in the monkey's brain through a quarter-size incision in its skull.

"AB or AD?" Schwartz asks Albrecht. He wants to clarify whether the movement is abduction or adduction, that is, whether Ycu is guiding the monkey's arm away or toward its body.

"AD?" Albrecht asks Ycu. Nope.

"AB. Abduction," Albrecht reports back.

"Okay, that's about it. That's good, Edgar. We're going to let him rest for a while. Can we give him some food? Give him monkey chow."

the cursor ball just by thinking about it.

The monkey seems to be doing pretty well. Its cursor ball starts in the middle of a cube and then "reaches" to the corners. When it hits a target, the monkey is rewarded with a drink of water.

Monkeys that play this game in Schwartz's lab usually have graduated from using their actual arms in the 3D environment. (In this version of the game, the cursor is tied to the back of the monkey's hand.) They play the game this way for about four weeks. Eventually, Schwartz's techs restrain the monkey's arms and, with microelectrodes in place, see what happens. The monkey always learns to manipulate the cursor with no hands. And, as it turns out, even when the monkeys don't start playing the game by using their hands to move the cursor ball, they figure out how to move the cursor with mere thoughts.

As a monkey plays these 3D games, Schwartz's team records the firings emitted by neurons that are in contact with the microelectrodes.

While he gives a tour of his lab, Schwartz notes that he started these studies with one electrode; now he can use as many as 16. As

questions," Schwartz says.

Neuroscientists carry some baggage regarding the motor cortex, though. For some time, it was thought a given neuron moved a given muscle. This is not the case. Many neurons are involved in moving any one muscle. And a given neuron is likely to be involved in moving lots of muscles. "It's not a push-button switchboard hypothesis, where you turn on one cell and you get a muscle twitch," says Schwartz.

But some would still rather study one cell at a time instead of populations, says Apostolos Georgopoulos, who has at least six prestigious titles at the University of Minnesota, including the McKnight Presidential Chair in Cognitive Neuroscience. Georgopoulos was Schwartz's postdoctoral fellowship adviser in the '80s at Johns Hopkins University, where the senior investigator first got neuroscientists talking about neuronal activity in terms of cell populations. He would liken investigators who disregard the population approach to those who were duped by one of the most notorious pranks in collegiate history.

On January 2, 1961, a capacity crowd in Pasadena, Calif., filled the Rose Bowl Stadium. They were there to watch the University of

This monkey is not using its hands. This monkey is sitting in a chair and moving the cursor ball just by thinking about it.

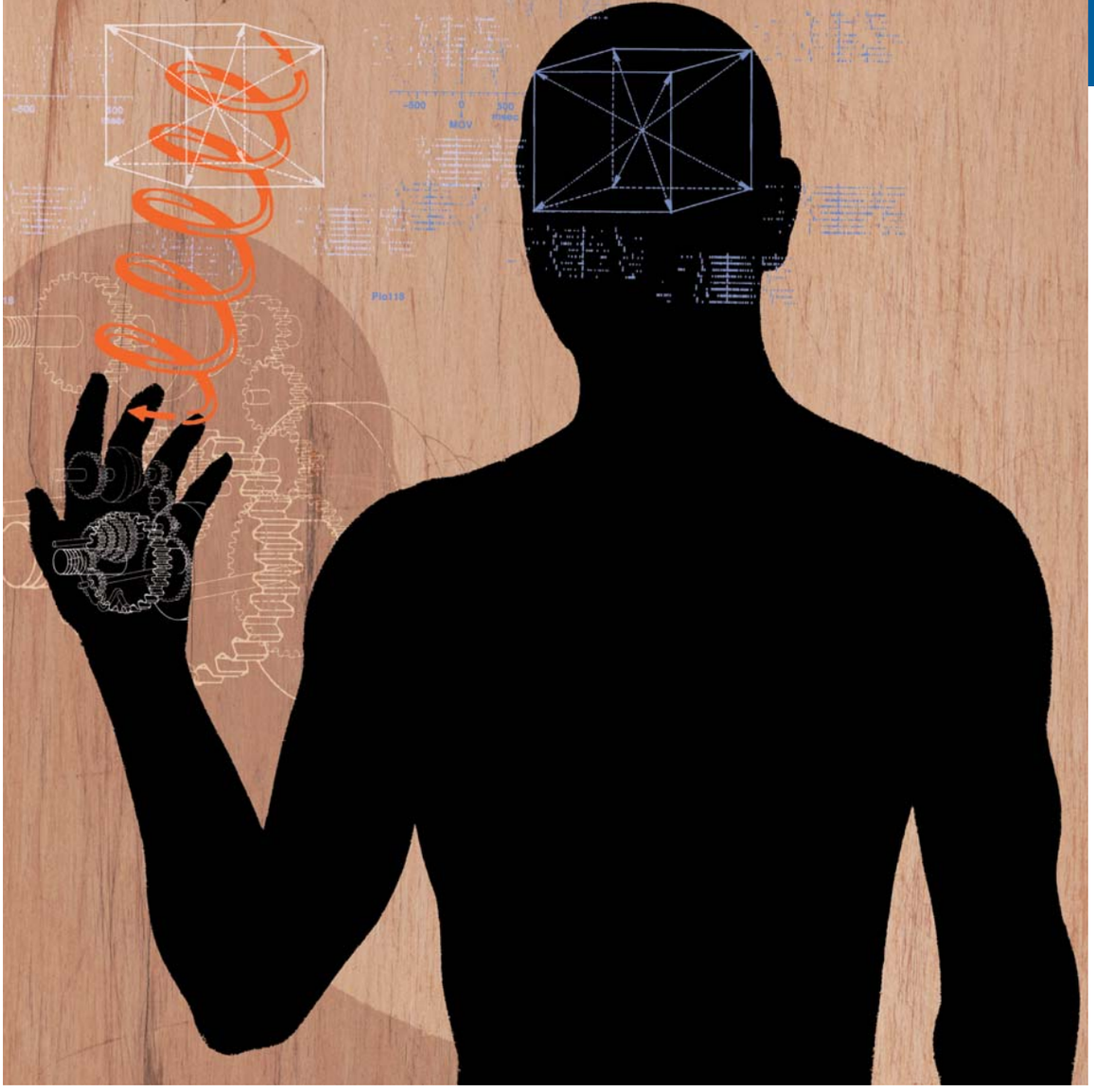
This is their second day exploring the topography of the monkey's primary motor cortex (so called since scientists in the 1800s discovered that electrical stimulation to that area of the brain produced movement). So far, the crackles have told the researchers that the electrodes are in the region that controls the shoulders and elbows, which is where they want to be. This process allows them to find the hot spots of interest in the brain, before Schwartz—a neuroengineer, Pitt professor of neurobiology, and faculty member in Pitt and Carnegie Mellon University's Center for the Neural Basis of Cognition—implants an array of permanent recording microelectrodes.

Around the corner, at another workstation, a technician monitors the ability of a monkey in a neighboring room to control a cartoon cursor ball in a virtual reality 3D environment. Monkeys are pretty clever; it's not so strange that you can teach one to play such a game. But this monkey is not using its hands. This monkey is sitting in a chair and moving

he reports this, he walks with more spring in his step. The combination of Schwartz's runner's build, high forehead, and small wire glasses conveys energy most of the time. And the possibility such microtechnology holds gets the 48-year-old more charged. "It took a long time to get to this point," he says. His lab has been working on this for more than 10 years. (The first time neuroscientists implanted an electrode to monitor the activity of a brain cell in an active monkey was in the '60s.) By using an array of microelectrodes, Schwartz's lab is monitoring the activity of several groups of neurons at once.

Miniaturized technology used by his and a few other labs has allowed scientists to see more than one part of the brain at a time, leading to new insights on fundamental issues like causality. Scientists hadn't the tools before to determine, for instance, what influence one neuron might have on all the other parts of the brain. "We're within the range of being able to answer these

Minnesota Golden Gophers take on the University of Washington Huskies. At the signal of the Washington cheerleaders, the Husky fans had been instructed to lift colored cards. The plan: They would spell WASHINGTON in letters a few stories high across the stands, making their school pride evident to the opposing team as well as millions of NBC television viewers. In the first half, the Huskies charged ahead, gaining 17 points while Minnesota failed to score. The ebullient Huskies in the stands rejoiced during halftime and, at the cheerleaders' signal, raised their cards to spell, unwittingly, the name of the nearby engineering college that had never been invited to the Rose Bowl, CALTECH. In an elaborate hoax, a gang of Caltech students had studied and infiltrated the card cheer plans. But the Washington fans were too busy holding their individual cards as directed to realize what had happened. They kept smiling while the Washington cheerleaders, who could, of course, see all the cards



from the field, stood in shock.

To understand how any part of the brain works, you need to pay attention to a lot more than one card at a time—and you need to keep watching.

"You want to know what combines with what and how things interact," says Georgopoulos. "The biochemistry changes. Behavior, emotion, these are time-varying conditions. That's the essence of the brain."

Figuring out the roles of neurons involved in motor control gets even more complicated if you think about the intricacies of how we move in space. Consider the small spatial acrobatics an arm performs when doing something as simple as reaching for a glass of water (or raising a card in a Pasadena stadium). Consider how the shoulder reaches, the arm extends, the wrist twists. Schwartz's kingdom is the nuance of such everyday feats.

Yet Schwartz says that scientists can't tell you much of anything with precision about how the brain makes such actions happen.

"There really isn't anything we can point to and say, 'We understand how the brain does this.'" Even in the heavily studied visual cortex, he insists, "you cannot point to a single thing in the brain and say, 'Oh, we understand how the brain creates an image or how you see something.' We don't." After 20-plus years of study, Schwartz doesn't pretend to understand how the motor cortex functions, either. (And these operations must be small potatoes compared to how "higher-level" operations like thinking happen, he points out. As he sees it, anyone who tells you neuroengineers are on the brink of enhancing memory or math skills or other cognitive functions is serving up pure bunk.)

But how could he understand the motor cortex's precise role in 3D movement when no one knows all the muscles engaged during a seemingly simple movement like a bicep curl, he asks, demonstrating a curl himself with his arm extended. "It may be 90 percent bicep, but what else?

"Now let's say you're doing *this,* okay?" he says, making a similar movement with his arm next to his body. "Where you're flexing your shoulder and your elbow at the same time—it could be a completely different set of muscles."

He intends, however, to find out which muscles are involved in certain activities. His lab is refining a study in which the arm movements of human subjects in a virtual reality 3D setting will be tracked with highly sensitive sensors.

"If we want to do this for a paralyzed person, to activate their arms," he says, "we should understand what the natural way is of doing it so we can replicate that."

Schwartz spurs his lab on to accomplish a whirlwind of nonpedestrian feats. Need a virtual 3D environment? Build one. Need to understand the muscles in the arm like no one has before? Figure out how.

"He delivers," says Georgopoulos, who believes Schwartz is "just ramping up."

Last year, he delivered, in the form of a paper in *Science,* his finding that the illusion of movement and actual movement are governed by different parts of the brain. (See "It's an Illusion," on p. 27.)

Computer-brain interfaces may one day help people with disabilities; that work has already begun in experimental stages. Such technology will also tell us a great deal about the human brain.

His studies have also shown that what happens in the motor cortex when a primate performs a task (like the virtual reality game) using thought control is not necessarily the same as what happens in the motor cortex when the primate uses its own limbs. The same neurons may be employed, but to a greater or lesser extent.

In the '80s, when Schwartz was graduating with his PhD in physiology from the University of Minnesota, he appealed to Georgopoulos, who was then at Hopkins, to let him train in his lab. Georgopoulos asked the would-be postdoc to describe himself.

The answer: "I'm just an honest guy from Minnesota." Georgopoulos laughs about that today. Schwartz has great integrity, he confirms; in fact, he says, his "star fellow" is so honest, he can get himself in trouble. Schwartz, who considers himself an experimentalist, has been known to tell a dinner table full of theorists, "It must be nice not to be bogged down by data." Then he'll chuckle, and others will join in. Besides being an honest Minnesotan, he's also a pragmatist. Yet he's a pragmatist with real vision. Georgopoulos credits him with bringing their field into the 3D realm, seeing the potential for how this science might one day help people with paralysis, and taking the steps—in particular, applying microelectronics—to begin to make that happen.

Schwartz may be a pragmatist, but his is a world without the boundaries you and I are used to.

Using thoughts to control objects, that's old hat around his lab. The dialogue here sounds almost spooky: "I want to implant electrodes in people's brains to help them," says one of Schwartz's graduate students, Marshall "Chance" Spalding. He may be able to realize that dream one day, but on this September day, he's working with postdoc Meel Velliste to refurbish a robotic arm that a monkey will use to feed itself just by thinking about it. Schwartz has already succeeded in getting two monkeys to manipulate a robotic arm in this way.

Watching a video of a monkey feeding itself with the robotic arm, it's striking how natural the movements appear. There's little jerkiness that you might expect from watching robots featured in popular media. The robot arm doesn't make choppy movements like the arms of one of George Lucas' battle droids. Instead, its extensions and contractions are fluid, reminiscent of how a monkey might actually grab a piece of orange and place it in its mouth. By capturing the spikes created by populations of cells at regular millisecond intervals and interpreting them, Schwartz's team has translated the monkey's brain firings into fluid prosthetic movement.

In fact, the robotic arm seems to adhere to what are known as the invariant rules of movement. Invariant rules explain why we tend to, for example, slow down when we come to a sharp curve as we draw an oval. They explain why my arm movement is slow as I begin to reach out for a glass, then reaches maximum velocity halfway to the glass, then slows down on my approach a couple of inches from the glass.

All animals follow these invariant rules, Schwartz points out, even octopi—who get around using propulsion, rather than manuvering joints.

The monkeys successfully fed themselves with the robotic arm, yet they can do better, Schwartz believes, with a better robotic arm. The arm, handmade in China, had a lot of play around the joints and some questionable wiring. It didn't respond with precision. After refurbishing, the arm will have better cables, new sensors, and other updates. Although there may be a few kinks to work out, it is shaping up nicely, says Schwartz, as he proudly displays the newly installed cables and moves the elbow joint.

In the past, the monkey managed half the job of feeding itself. A human placed the orange in its robotic gripper. (The prosthesis has three simple nonbending digits for gripping rather than a full set of fingers.) With a more precise robot arm, the hope is the monkey will be able to grab the orange itself. And getting the human out of the room will be less distracting. Monkeys are fascinated by human facial expressions and like to interact with us.

There's some healthy anxiousness about having the robot arm ready in a month or so for a conference in San Diego, where Spalding and Velliste are expected to make a poster presentation and star in a press conference.

"Will it be ready?" they're asked.

The answer might not satisfy their boss, yet it is in line with his pragmatism.

"There's working, and there's working better, and then there's working well, and then there's working real well," says Velliste.

Using thoughts to control objects, that's old hat around his lab. The dialogue here sounds almost spooky: "I want to implant electrodes in people's brains to help them."

Johnny Ray, of Carrollton, Ga., played the guitar and made a living installing drywall before he suffered a devastating stroke at the age of 52. Though his intellect was intact, the stroke left him unable to move or communicate with the world. He became locked in his own body.

One thing Ray had in his favor was living not far from Philip Kennedy, a Dublin native, MD/PhD, and CEO of Neural Signals in Atlanta, who believed he could help Ray. He'd developed a miniature electrode, encased in glass, which had won FDA approval for implantation in human brains. (His microelectrode was the first, and now is one of perhaps three, to be so approved.) Kennedy hoped that by implanting electrodes in Ray's brain, the man would be able to communicate through a tailor-made computer interface.

For the first three months after implantation, fibrils from Ray's nervous system grew into the electrode. (Kennedy's electrodes are designed to become one with the brain in this way.) Then Ray spent about a month of daily 20-minute training sessions learning to control the cursor. One day, Kennedy asked him to spell his own name. By moving a cursor across a screen of letters, Ray managed to spell JOHN twice in just four tries.

He took a break and tried again.

JOHLQQQ.
GYUVWABDN.
HIJJROHNLN. JOIH.N.

When he began moving the cursor over to the P, Kennedy thought he'd let him rest.

But then, Ray spelled PHIL, Kennedy's first name.

"It was very exciting," says Kennedy.

Ray has been called one of the first cyborgs. His architect, Kennedy, is visibly humbled by accolades sent his way for his achievements, like *Discover* magazine's award for assistive technology. Kennedy had hopes that, through the computer, Ray might be able to create music again, perhaps even run an Internet business. Ray's activities didn't progress beyond spelling and clicking icons (designed with locked-in patients in mind, so that a patient could control the heat in his room or convey other complex ideas quickly), yet the electrodes continued to serve Ray for more than four years, until he died of a brain aneurysm in 2002. (The basilar artery at the base of his brain was weak from his stroke, causing a blockage of fluid and fatal swelling.)

Since Ray was implanted, four other Kennedy patients have been as well. (One other patient used the brain-computer interface before Ray.)

As this story was finalized, Schwartz and Kennedy were about to embark on a collaboration that would combine their technologies. They plan to use Kennedy's FDA-approved microelectrodes in a locked-in patient who will experiment with Schwartz's virtual reality 3D environment. After that, they'll consider giving such a patient access to a robotic arm.

Schwartz divulges news of the collaboration without grandeur, as though this were simply the logical outgrowth of his efforts. He's clearly pleased, but expects more from himself and the field. If such prostheses are to be used widely by quadriplegics, they'll need to offer finger dexterity, he believes. "And why not work toward using a patient's own limbs?" he asks.

The field of neural engineering is fraught with dashed hopes. So Schwartz proceeds with discretion. It's easy to see how such projects can capture our imagination. This is the stuff of made-for-TV movies, literally. In the '80s, CBS ran a docudrama about an Ohio undergraduate who was paralyzed from the rib cage down. Working with Jerrold Petrofsky, a physical therapy researcher then at the same university, she learned to use a computer-driven interface that sent a pattern of electrical pulses to her legs. With Petrofsky and another professor at each side, she eventually "marched" a few tentative steps in her commencement ceremonies using the technology.

The docudrama and other media reports of the woman's march brought the National Institutes of Health a flood of letters from paralyzed people and their families wanting to know how they could benefit from this technology. The woman marched before an audience again, down the aisle at her wedding, years later, yet these and similar feats by other patients have still not translated to anyone tossing aside her wheelchair for good. (Though some patients were eventually able to walk miles with another evolution of the technology.) Petrofsky, the inventor who is now at Loma Linda University in California, says that it would have cost millions to get FDA approval for his walking system, so he decided not to pursue it. The application of this technology he's most proud of developing—has FDA approval—helps people with disabilities lift weights and ride exercise bikes. (These systems build endurance, strength, and cardiovascular health and combat atrophy.)

The flurry of press around that undergraduate's commencement march resulted in a group of neuroscientists issuing a joint statement cautioning the public on the experimental nature of such technology.

The Schwartz/Kennedy collaboration will be experimental as well, and Schwartz prefers to focus on the implications for fundamental discovery that we can expect in the long term from such research in humans:

"I think the really powerful part about what we are doing is we're coming up with new technology to record neural activity.

"I don't believe you can study cognition in any other animal besides humans. People have all of these theories about cognition and how it takes place, so now we're going to have all these opportunities to [actually test them]. I think we'll be able to do, in conjunction with this prosthetics work, some really interesting basic science experimentation that we've never been able to do before.

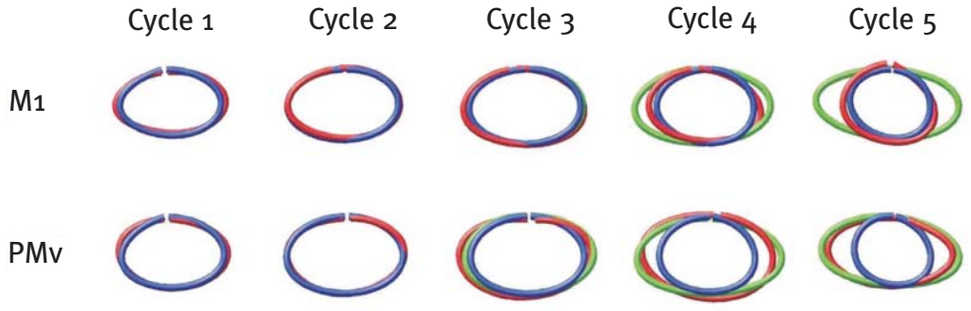
"I think the benefit to society from those scientific observations will far outweigh anything we do in prosthetics."

That said, it's hard not to be captivated by what his and Kennedy's efforts could do for people like the late Johnny Ray, for whom such technology means finally being able to communicate with the world again, or for others with less severe disabilities.

One possible candidate for the study is a man in his 20s whose movement, since a brain-stem stroke six years ago, has been limited to directing his eyes upward.

Both researchers are eager to push ahead. When Kennedy is asked in an e-mail if he has a timeline for when a patient will be confirmed for the collaboration, his one-sentence reply imparts a sense of urgency:

"I am working hard to implant as soon as possible." ■



IT'S AN ILLUSION

Andrew Schwartz can get you to move in a way that's different from how you think you're moving. This illusionist is a neural engineer at Pitt. In virtual reality experiments, Schwartz had people draw ovals and circles. When he presented volunteers with an image of the path of an ellipse, but subtly required their hands to move in a circular path, they still reported that they were drawing an ellipse. Time after time, people reported that they drew what they saw, rather than what they were actually drawing.

Schwartz did similar studies with monkeys whose neurons he monitored. You can't ask a monkey to report what it's doing, but data collected from brain firings show that the monkeys perceived they were drawing what they appeared to be drawing as well, even when they were drawing something else. The above figure demonstrates Schwartz's results. Blue represents the actual path of a monkey's hand. After the first two cycles, Schwartz makes slight changes in the gain of the cursor (shown in green), so the monkey must make more circular (and less elliptical) movements to keep the cursor on track. Yet throughout the experiment, the path the monkey is supposed to follow appears the same on the computer screen. By the final round, the monkey appears still to be drawing an ellipse—from what it sees on the screen—yet it has made the movement of drawing something much closer to a circle.

What do the brain firings tell us? Action and perception of action seem to be represented by different parts of the brain. The monkey's motor cortex (see M1) captures the impression of drawing a circle when the monkey actually draws a circle. (The neural trajectory is shown in red.) The monkey's ventral premotor cortex (PMv, its trajectory is also in red) stubbornly senses that an ellipse is being drawn. So it seems that vision is dominant compared with proprioception. And, it seems, you can't believe everything you see. —*EL*

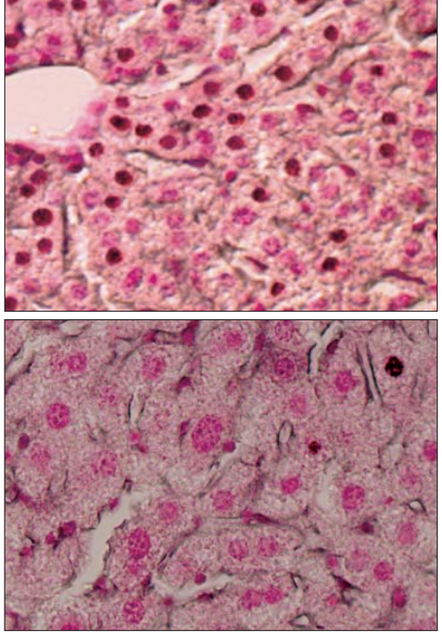
Jeanne Calment celebrates her 120th birthday in Arles, France, in February 1995. If you had been able to ask Calment, who is now deceased, "What's the secret to a long life?" she would most likely have said, "Laughter." Scientists are still trying to answer that question and a more fundamental one—that is, what makes us age?

A PITT RESEARCHER SUGGESTS SHE'S FOUND A MECHANISM AT WORK IN AGING | BY CHUCK STARESINIC

WHY DO WE AGE?

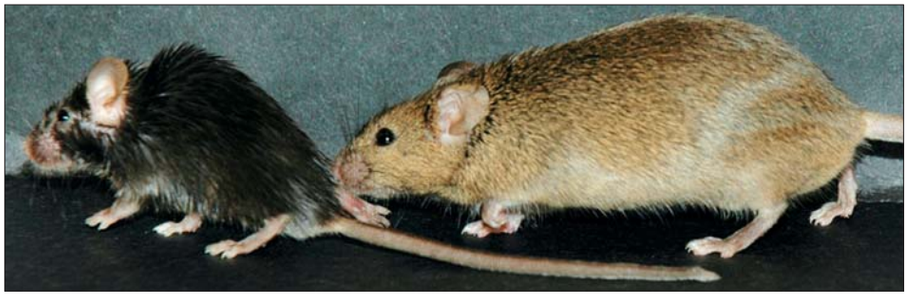
On February 21, 1875, a girl was born in the town of Arles, in Southern France. She began life like any normal baby—working her tiny limbs and fighting for breath in this strange new atmosphere. Her parents named her Jeanne.

She grew as expected and eventually lived a comfortable adult life, marrying at 21. Her husband, Fernand Calment, was prosperous, and she did not need to work. Jeanne Calment swam, played tennis, bicycled, and especially liked to go along on hunting excursions. She bore one child, a daughter, who eventually gave her a grandson. For the first 90 or so years of her life, the details of her day-to-day existence were no more and no less noteworthy than those of most women, but by the time she turned 100, she was a local celebrity. At 110, her notoriety extended beyond the borders of France.



COURTESY NIEDERNHOFER

Healthy tissue regenerates through cell proliferation, as shown with these liver cells from a young mouse (top). Proliferative cells are stained dark red. An engineered mouse fails to repair DNA damage, leading to cell senescence (bottom) and outward signs of premature aging. Only one proliferative cell can be seen.



A mouse that lacks a DNA-repair protein (left) wastes away, loses muscle mass, and develops osteoporosis and neurodegeneration in a matter of weeks, while its normal sibling (right) ages normally.

In 1995, newspapers around the world reported that Jeanne Calment had become the oldest living person the world had ever known. She was 120 years and 239 days old, and still she lived. Readers around the planet sifted through the details of her life, looking for the secrets to longevity. They learned that she treated her skin with olive oil, sometimes ate two pounds of chocolate a week, and rode a bicycle until she was 100. She favored port wine and reportedly quit smoking cigarettes when she was 117. But which, if any, of these nuggets were the gems that helped to explain her long life?

There are many theories of aging and no consensus on which is closest to the truth. Some argue that aging is the result of gradual damage to our cells, particularly DNA that goes unrepaired. Others believe that, though such cellular damage has significant health consequences, it is just a symptom of the overall aging process. Aging itself, they say, is probably orchestrated at a level higher than the cell, perhaps by the winding down of some sort of master biological clock. Uncovering the basic science of aging could dramatically change the way we live, not to mention the number of years that we live. To do so, some researchers are taking a counterintuitive approach: To learn more about longevity, they study those with short lives.

When Jeanne Calment was a mere 110, a 17-year-old woman in Afghanistan gave birth to her first child, a boy, fathered by her cousin. The boy, whom we'll call Kahlil, seemed healthy at birth, with one peculiar trait: He developed sunburns very easily, despite having the normal dark skin of an Afghani boy. By the age of 6, he showed mild learning disabilities and suffered some hearing and vision loss. At 10, Kahlil began to look old beyond his years. His features narrowed. The bones of his face protruded. By 12, he was a wizened boy, who not only failed to grow taller but began to lose weight. His spine curved, and he lost muscle tone. Desperate, his parents brought him to Germany for help, where doctors diagnosed him with an undetermined form of progeria, or premature aging. Kahlil was 15 then. His case didn't fit any of the known progerias neatly, but his face was like that of a grown man with a small head. He was 47 inches tall and weighed 39 pounds. He moved with an unsteady gait, and his knobby knees seemed to knock together. In a matter of months, he developed severe pneumonia complicated by acute respiratory distress syndrome. He died of multisystem organ failure at the age of 16.

What happened to Kahlil? His family had come to Germany for a cure. When that failed, they hoped to find some comfort in a simple answer. Uncovering the mechanism underlying their child's physical deterioration has led researchers to ask other, profoundly important, questions: Is the syndrome that this child experienced physiologically the same as natural aging, or does it only resemble aging? If it is analogous to natural aging, is it possible that this young man, by aging in fast-forward, could point the way toward slowing the aging process?

In a lab at the Hillman Cancer Center, Laura Niedernhofer pops open a shoebox-size "caging unit." She reaches in with a latex-gloved hand and gently grasps the tail of a mouse between her thumb and index finger. "Good morning," she chirps. "See how old they look?" she says to her visitor. Her eyes peer out from between a surgical mask and a sort of shower cap as she demonstrates the proper way to pick up a mouse. When momentarily held by the tail, she explains, most mice will spread their legs wide for balance and wait to be put down. But this one, when held for an extra second, curls its limbs asymmetrically and trembles. She sets down the mouse and watches it walk. It's unsteady on its feet.

They seem a little arthritic, she points out with wonder. "They have trouble getting up in the morning, but once you get them moving, they do okay." Niedernhofer turns to the lab tech, Andria Robinson, who is also clothed head to toe in sterile garb, and asks, "Do we have some soft mush?" referring to the food prepared for the mice as they grow older.

The arthritic-seeming mouse is small and squinty. It appears almost disheveled next to its sturdy, svelte companion sniffing about the same enclosure.

The curious thing about these two very different mice is that they are the same age; they are littermates, in fact. Although the living arrangement looks like that of an aging parent stuck with a grown child, it is more like that of Kahlil, who seemed to grow old before his time, and a normal sibling. By studying the two side-by-side, Niedernhofer, a University of Pittsburgh assistant professor of molecular genetics and biochemistry, expects to learn about more than premature aging syndromes. Niedernhofer believes that her observations are revealing something new about natural aging and cancer, as well. As Robinson goes about the process of weighing and observing dozens of mice being studied, Niedernhofer explains how she came to work with these engineered mice.

She never set out to study aging or progeria. She was more interested in cancer when she walked into Kahlil's case almost by accident. As an MD/PhD student at Vanderbilt University, she was interested in the ways in which our cells contend with damaging compounds that result

Is the secret to how and why we age linked to DNA damage? Laura Niedernhofer thinks so.

MARTHA RIAL

from normal cellular metabolism. When she exposed bacteria to one such compound (malondialdehyde), the bacteria mutated. Our bodies are making gobs of this stuff, she thought, and if it causes mutations in human cells, it's a potential cause of cancer. Sure enough, when she exposed human cells in the lab, they mutated. With her PhD adviser, Larry Marnett, she showed that this natural byproduct of our metabolism causes a devastating kind of DNA damage called interstrand crosslinks. No one had demonstrated this before. These crosslinks are strong bonds that form across the two strands of DNA. They can kill the cell if not repaired: For our cells to do anything with DNA, the strands have to be pulled apart and read. That's how DNA is replicated to produce daughter cells and transcribed to produce the proteins that are the workhorses of cells. If the genome is the book of life, crosslinks can be thought of as drops of spilled glue pasting whole pages together and rendering them unreadable.

Niedernhofer found this fascinating: When she exposed cells to their own byproduct, they developed crosslinks. Yet, spontaneous crosslinks are almost impossible to find in people. A lab in the Netherlands offered Niedernhofer a chance to explore this puzzle further. She went to Erasmus University in Rotterdam for a postdoctoral fellowship because Jan Hoeijmakers' lab there had engineered a mouse with a missing DNA-repair gene. This mouse could not repair crosslinks and died very young. Normally, to study crosslinks, researchers would have to induce them by treating an animal with a chemotherapeutic agent, but they had not treated these mice with anything, providing evidence that crosslinks form spontaneously. Around the time that Niedernhofer arrived, the lab discovered a connection between the engineered mouse and the boy with the unknown progeria.

A year earlier, Kahlil's doctors in Germany had sent a living sample of his cells to this same lab for diagnosis. They found that Kahlil had a mutation in a gene called Xpf, which was intricately linked to Ercc1, the gene they had knocked out of their mouse. The proteins these genes produce are like a pair of figure skaters spinning with all four hands locked together. As long as they hold on to each other, they are stable; take away one protein, and everything breaks down. In other words, if you don't have Ercc1, then you don't have Xpf, and vice versa. This protein duo is called Ercc1-Xpf, and, letter by letter, its name rolls trippingly off Niedernhofer's tongue, with the ease of a 10-year-old talking about R2-D2 and C-3PO. Ercc1-Xpf was known to be involved in DNA repair as a molecular switchblade that snips the ends of damaged strands of DNA after other proteins have identified them. But Niedernhofer and her colleagues had found something new: The protein duo appeared to be related to accelerated aging, too, possibly by virtue of its connection to crosslinks. Kahlil had a mutation in Xpf and had progeria. The Rotterdam mouse lacked Ercc1; it developed spontaneous crosslinks and lived only three weeks.

"It's difficult to study a mouse that only lives three weeks," says Niedernhofer, so she began experimenting with different versions of the Ercc1 knockout mouse. She came up with two knock*downs,* as she calls them, because they are able to produce drastically reduced but detectable amounts of the protein. One produces 10 percent the normal amount and lives six months. The other produces 20 percent the normal amount and lives 18 months. (Normal lifespan for a laboratory mouse is about two years.) As she and her colleagues watched these mice, they began to think they had more than a model for studying a rare genetic disease.

The knockdown mice hobbled around, their spines became a little hunched, they lost weight and muscle tone, and the collagen in their faces began to degrade, so they had bags under their eyes. Then they started showing solid tumors, spontaneously, which is unheard of in young mice. The mice looked like a model of human aging.

Human cells are bombarded daily with insults to our DNA, including ultraviolet light, cigarette smoke, and other environmental toxins. But some of what damages our DNA arises spontaneously as natural byproducts of our own cellular metabolism. Our cells use oxygen to create energy, for example. Wayward rogues among those oxygen molecules pick up loose electrons in the cell, become highly reactive, and scoot around the cell damaging DNA.

Scientists used to believe that metabolic rate could predict longevity, both in species and in individuals, because high metabolism seemed more likely to result in rogue oxygen molecule activity. Mice owed their short lives to high

metabolism, went the logic. Elephants were at the other end of the scale, and humans were somewhere in the middle. Birds, however, fell off the curve; they had exquisitely high metabolism and longevity. It turns out that birds have a very efficient metabolism that doesn't result in oxygen wreaking much havoc. So it appears that the amount of destructive, or reactive, oxygen that cells produce is a better predictor of longevity than metabolism.

Niedernhofer's hypothesis goes one step further. She's suggesting that the cell's proficiency at avoiding and repairing specific kinds of DNA damage is the real mechanism at work in these comparisons of longevity versus metabolism. In her model mice, she and her colleagues have made a strong case that what makes the mice look old before their time are interstrand crosslinks, those messy drops of DNA glue. Niedernhofer believes this process is directly related to natural aging, too, in mice and in humans. To strengthen that case, she'd like to find spontaneous crosslinks in living organisms, which is a challenge. As Niedernhofer has learned, the crosslinks appear to be so toxic that cells with unrepaired crosslinks don't stick around long—they simply die.

In the coming months, Niedernhofer will watch her engineered mice and their normal littermates to see how well they are able to repair crosslink damage, and how this ability relates to signs and symptoms of aging. In collaboration with Pitt biochemist Shivendra Singh, she's feeding some of her mice special diets—one high in fat and another high in phytochemicals from broccoli and garlic—to see how these variables might affect aging.

Don't expect to see antiaging pills that include DNA-repair proteins. It's not that simple. First of all, a large number of proteins work together in complex ways to repair our DNA. Second, DNA-repair proteins are very destructive; that's why the body destroys them when they aren't needed. To leave them in place, or to supplement them with a pill or an injection, would be like leaving several power saws running in your house at a time when you didn't even need any repairs. Niedernhofer says we're probably better off preventing DNA damage in the first place—by eating intelligently, for example.

In many ways, Niedernhofer still feels like her work is just getting off the ground. It takes time to raise and observe a colony of mice, some of which live two years, and she's been at Pitt only a year since completing her postdoc. She's tall, outgoing, and she laughs when anyone calls her Dr. Niedernhofer. (A security guard at the cancer center has been known to meet her halfway with "Dr. Laura.") She spends part of every workday down in the "mouse house"—not because the colony would fail to thrive or the study would lose data otherwise, but because she knows the mice have more to teach her, and she'll never know what that is if she's upstairs in her office. "When you come downstairs and see a mouse that looks old, that is just overwhelming. ... That takes it one step closer to home for me."

One of the possible problems with Kahlil's disease, or any progeria, as a model of natural aging is that neither mice nor humans with these syndromes mimic the process of aging exactly.

Richard Miller, a gerontologist at the University of Michigan, says progeria syndromes in general may look like aging, but they are probably just another illness. The way he sees it, animals with progeria simply remind us of what old animals look like.

Niedernhofer says Miller is a critic of her work, but one with whom she has an open dialogue and who offers his best advice in the interest of advancing the science. Her team has created a long list of physical and behavioral characteristics found both in natural aging and in her mouse models, but it's not extensive enough for Miller. The exceptions, she says, are partly because of the nature of aging—different tissues age through different processes.

"We call it segmental aging or tissue specific," says Niedernhofer. "It doesn't happen throughout the body, but just in certain tissues." Her mice are deficient in one particular aspect of a very elaborate system of DNA repair pathways. "I think it's reasonable to imagine that the DNA damage you get in your liver is different from that in your heart," says Niedernhofer. So a progeria like Kahlil's may not be a complete picture of aging but is still very relevant to aging, she and others hold.

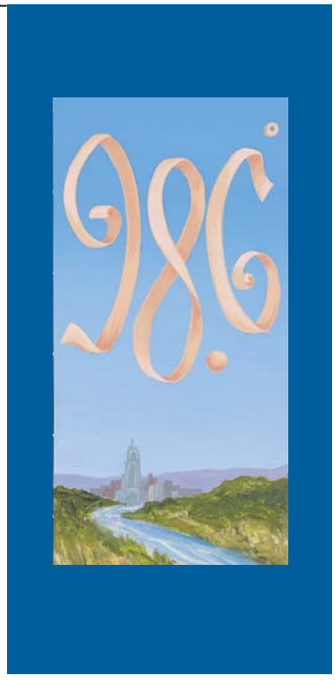
Miller says that no theory of aging has been demonstrated to be correct, but he doesn't find the segmental hypothesis compelling. He imagines an underlying mechanism keeps time for a wide range of processes in the body:

"If I tell you, for instance, that I've got someone in my office right now who has got some cataracts, thinks a bit more slowly, reflex speed is down, they have broken blood vessels in their skin, and bones are a little bit porous, you know that's an old individual, but it could be an 80-year-old person, a 15-year-old dog, a 30-year-old horse, or a 3-year-old mouse. All of those factors change together. All of those systems decline together at a pace that is specific for the species' own aging range. And it's very hard to see how that might come to pass if all of these symptoms were all aging in an unsynchronized fashion. Similarly, a calorie-restricted diet slows all of those things down in mice and rats—all of them together. And that's almost impossible to imagine how that might occur by chance unless there's some common underlying timing mechanism."

Niedernhofer and others who believe in using mouse models of accelerated aging have their supporters. They contend that natural aging in humans is segmental. We all age a bit differently; various tissues age quickly in some people and slowly in others. Two researchers (Paul Hasty and Jan Vijg of the University of Texas, San Antonio), responding to Miller in *Aging Cell* last year, wrote that, though Miller "believes the scientific community does not yet have a sound idea of what causes aging... in our opinion there is such an idea and it is based on damage accumulation." They point out that more than 100 genes are involved in DNA repair and many more in overall maintenance of the genome. Therefore, knocking out one or two mechanisms of DNA repair should be expected to result in an animal that shows segmental aging, and certain progerias could model the way specific parts of our body age. Niedernhofer's knockdown mice are particularly promising in this respect, because they seem to age in so many different tissues and because the crosslinks they suffer from had never been shown to be related to aging before.

Science advances slowly, methodically, and rationally, yet scientists themselves are a bit like speculators. They stake out what looks like promising ground, commit to it wholly, and see what will come of it. Such a gamble might someday be seen as a paradigm shift or just a historical footnote. But unexpected outcomes will always occur in science as well as real estate. Back in the mid-1960s, for example, a lawyer in France made a deal with an elderly woman: He would pay her 500 francs a month for the rest of her life. In return for this regular income, he would take possession of her grand apartment in town when she died—a common transaction in France. He was in his 50s and she was already 90, so it might have seemed that he was taking advantage of her. "Sometimes in life, one makes bad deals," said Jeanne Calment, 32 years later. By then, the lawyer had paid her three times the apartment's worth and finally died without ever taking possession. His family was obligated to continue the payments until 1997, when Mme. Calment died, at the age of 122. ■

People and programs that keep the school healthy and vibrant



ABLE AND INCLINED TO

PEDIATRIC RHEUMATOLOGIST HONORED

BY COREY BALLANTYNE

Aldo "Vinny" Londino was a bearded and jovial figure, and the similarities with Santa Claus didn't stop there. Every holiday season, the late pediatric rheumatologist and associate professor of pediatrics and medicine used to arrive at Children's Hospital of Pittsburgh with shopping bags full of gifts for his patients. He selected the neediest patients, and his wife, JoAnne Londino, shopped for the gifts with help from their two sons.

Londino knew many of his patients and their families well, because rheumatoid diseases like arthritis and fibromyalgia are chronic. Growing children with these conditions came to see him regularly for help in controlling the joint and muscle swelling, stiffness, and pain that could dramatically limit their abilities. Londino talked with them about the physical and social challenges that came with their diseases. As one who suffered from cystic fibrosis, and therefore lived for years with chronic pulmonary disease, Londino knew about overcoming physical limitations.

People remember Londino for playing with Barbies to keep a little girl calm, for bringing his own sons to play Nintendo with another patient during his weekend rounds, and even for giving patients' families his own money to buy groceries. "He just never hesitated to help people out," says Sara McIntire, associate professor of pediatrics.

One patient, whom we'll call Joey, first came to see Londino when he was about 5. When Londino learned that Joey had never had a birthday party, he arranged for one in the nurses' station. After Londino's death, hospital staff continued to hold birthday parties for Joey, as Londino had requested.

Coworkers could sometimes hear Londino coughing from down the hall; cystic fibrosis, a hereditary, terminal condition, produces thick mucus in the lungs. Once, when he had pneumonia, Londino went about his work with an IV needle in his arm, pausing between patient visits to reconnect to his IV bag of antibiotics and other fluids. He counseled his patients' parents never to discourage their kids from doing as much as they were able and inclined to. Londino fought off the fatigue associated with his illness for years. He stopped working six months before he died in December 2000 at the age of 48.

In Londino's 15 years at Children's Hospital, he was the only pediatric rheumatologist in Western Pennsylvania. (Pediatric rheumatologists are scarce—there are only a few hundred in the United States.) By 2001, Pitt was ready to support a major recruiting effort in this field. Raphael Hirsch, the new head of pediatric rheumatology, has quickly developed one of the top pediatric rheumatology programs in the country, with six faculty members and one fellow thus far. Collaborating with Carnegie Mellon University researchers, Hirsch is developing novel methods for measuring inflammation in arthritis patients. This year, Children's created, and awarded to Hirsch, the Aldo V. Londino Jr., MD, Endowed Chair in Pediatrics. ■

COURTESY LONDINO FAMILY

Londino was once the only pediatric rheumatologist in Western Pennsylvania. He treated patients even when he had pneumonia.

BOOSTER SHOTS

For almost three years, **Andrea Katz McCutcheon** suffered flashes of excruciating facial pain. She had been diagnosed with trigeminal neuralgia, a disorder of the fifth cranial nerve, but treatments failed to bring relief. Then, doctors in Pitt's pain medicine program implanted a pump to deliver medicine directly to the receptors in her spinal cord. It relieved her pain. McCutcheon, who says she'll wear the pump for the rest of her life, recently donated $50,000 to establish an educational endowment for Pitt's pain medicine fellows.

Gregory Davies, the tall and charismatic president and CEO of Wabtec Corporation, was credited with steering his company through an economic downturn while others in the rail industry went bankrupt. Those in the company were stunned last year when Davies, at 57 years old, was diagnosed with a brain tumor in March and then died at home four months later. Wabtec has created an endowed fund for brain tumor research and physician education in Davies' name through the University of Pittsburgh Cancer Institute. The company and its directors contributed $300,000 and will match its employees' contributions toward a goal of $1.5 million. —*Chuck Staresinic*

FOR MORE INFORMATION ON THESE FUNDS OR OTHER GIVING OPPORTUNITIES:
1-800-MED-ALUM or mhsf@ia.pitt.edu

OUT OF CONTROL

HOW THE FEDS HAVE GRAPPLED WITH CONTROLLED SUBSTANCES, WHILE KEEPING THE MEDICAL COMMUNITY AT BAY | BY EDWIN KIESTER JR.

HARRY J. ANSLINGER COLLECTION, COURTESY OF HISTORICAL COLLECTIONS AND LABOR ARCHIVES, EBERLY FAMILY SPECIAL COLLECTIONS LIBRARY, THE PENNSYLVANIA STATE UNIVERSITY, UNIVERSITY PARK, PA.

ABOVE: Drug czar Anslinger with confiscated drugs. A recent book by a Pitt historian chronicles the feds' unhealthy tension with doctors and others over control of illicit substances.

He was a nice young man, a student from a good family in St. Louis. But then, Federal Narcotics Commissioner Harry Anslinger told horrified legislators in 1937, the young man began smoking marijuana cigarettes. Before long, the boy had been driven insane and confined to a mental hospital, his once promising future in tatters. Anslinger went on to other scary stories of a young woman raped, a boy who'd murdered his entire family—all because of marijuana.

"Those were lies," Jonathon Erlen says. "Anslinger basically made things up to serve his purposes. He created horror stories about marijuana causing insanity or worse, and people believed them. Our drug policy today is directly based on his myths of 60 or 70 years ago."

Erlen is history of medicine librarian for the University of Pittsburgh's Health Sciences Library System and teaches in the School of Medicine and the Graduate School of Public Health. With Joseph Spillane of the University of Florida, Erlen coedited the newly published *Federal Drug Control: The Evolution of Policy and Practice* (Haworth Press). The book traces 100 zigzag years of the U.S. government's war against illicit drugs, highlighting what Erlen calls "the unhealthy tension" between those who believe substance abusers should be punished and those, including many physicians, who emphasize treatment or a combination of both. (Erlen falls in the latter category: Both carrot and stick are needed, he says.)

Millions of Americans are addicted to powerful and illegal drugs, and prisons bulge with those convicted of drug-related crimes. "Every one of us is impacted every day by the drug question," says Erlen, "if only in the taxes we pay to build more prisons." *Federal Drug Control* shows how America's

political history has further crippled its ability to deal with drugs as a health menace. How did we get to this point? Erlen and Spillane have taken it upon themselves as historians to wonder aloud.

Drugs were a back-burner issue in America until 1914, when Congress passed the Harrison Narcotics Act, requiring those who dealt in opiates and cocaine to register and pay a tax. Some federal officials interpreted the act as supporting drug clinics, where doctors treated addicts with maintenance doses to keep their habits under control. This view became less popular as government became more conservative; by 1923, the last public clinic closed. In 1930, a Prohibition-minded Congress passed a new antidrug law and established a Federal Bureau of Narcotics (FBN) to enforce it. Anslinger was a native of Hollidaysburg with a two-year Penn State certificate in agriculture; he'd stair-stepped his way up the bureaucracy to assistant commissioner in the Prohibition Bureau and was named FBN's first chief. He quickly built an empire that lasted 32 years.

Anslinger saw drugs as not only a criminal but a moral issue and campaigned for stiffer sentences both for users and dealers, says Rebecca Carroll, of St. Mary's College of California, who earned her PhD in rhetoric and communication from Pitt in 1991. Carroll's dissertation topic, with Erlen as an adviser, was on the rhetoric used by Anslinger. Her two chapters in *Federal Drug Control* scathingly review the Anslinger years. In session after congressional session—encouraged by politicians who believed being tough on drugs paid off at the polls—Anslinger warned that drugs threatened the very fabric of society. He fed the legislators a fanciful, nonstop litany of bogus tales, including the assertion that most crimes could be traced to criminals high on illicit drugs. He said that marijuana was, as Erlen puts it, "a mandatory force drug—one joint and you were 100 percent certain to go on to cocaine or heroin."

During World War II, he claimed that the widespread use of marijuana in U.S. Army camps involved 20,000 FBN man-hours, with 3,000 investigations pending, and required the full-time attention of 25 agents. (He offered this at a time when Congress appeared ready to divert part of the FBN budget to the war effort. The money was quickly restored.)

Musicians were violating marijuana laws, Anslinger said in Senate testimony: "And I don't mean good musicians. I mean jazz musicians." He wanted to arrest them in large numbers to make an example of them.

Anslinger "discovered" marijuana, *Federal Drug Control* reports, only in 1935. Before that, he had considered pot smoking benign. But then use of hard drugs stabilized in the population, and FBN agents risked becoming irrelevant. So Anslinger found a new target.

Doctors and others respectfully raised objections to Anslinger's more extreme claims. They noted, for instance, that no scientific study had ever found a link between drug use and violence. He quickly silenced them—"he beat them bloody on the floor of Congress," Erlen says. Physicians had earlier recognized the palliative properties of cannabis, and sometimes prescribed it for terminally ill patients. FBN threatened, and most gave it up. The New York Academy of Medicine proposed a rigorous experimental clinic where heroin and cocaine addicts would receive maintenance-level drugs. Anslinger publicly condemned the academy for proposing free drugs to criminals, and the idea died. A joint committee of the American Bar Association and American Medical Association undertook a major study of the legal and medical aspects of drug policy. Anslinger attacked it as "full of glaring inaccuracies." The chastened groups withdrew.

Musicians were violating marijuana laws, Anslinger said in Senate testimony: "And I don't mean good musicians. I mean jazz musicians." He wanted to make an example of them.

In 1937 Congress passed the Marihuana Tax Act, punishing even first-time or mild offenders. It was the first of three increasingly "draconian" (Erlen's term) and fiercely enforced measures adopted during Anslinger's tenure. When Anslinger retired in 1962, he was hailed as the world's leading expert on illicit drugs and drug trafficking.

More psychoactive drugs, "designer" drugs, amphetamines, and barbiturates hit the streets. As drug wars and murders demonstrated the violent, million-dollar international interweaving of drugs and crime, the Controlled Substances Act, which still governs, was passed. One effect of the 1970 legislation was to incorporate Anslinger's old agency into a new Drug Enforcement Administration.

Conflicts about policy continued. As medicine began to look more closely at pain control and palliative measures, a movement sprang up to allow patient access to marijuana. In 1996, voters in California overwhelmingly approved the use of marijuana as medicine—10 other states followed suit—allowing clinics to be established where marijuana could be procured with a doctor's recommendation. Subsequently, the Institute of Medicine undertook a lengthy study. Its carefully measured report, *Marijuana and Medicine: Assessing the Science Base,* declared: "The accumulated data suggest a variety of indications, particularly for pain relief, antiemesis, and appetite stimulation. For patients such as those with AIDS or undergoing chemotherapy, who suffer simultaneously from severe pain, nausea, and appetite loss, cannabinoid drugs might offer broad spectrum relief not found in any other single medication." The report cautioned, "Marijuana is not a completely benign substance, but a powerful drug with a variety of effects." Meanwhile, federal agents raided the clinics and medical marijuana gardens, claiming patients were retailing their doses on the streets.

Anslinger's horror stories were fictional rubbish, according to Erlen, yet researchers have long suspected a link between heavy pot smoking and mental disturbances, and recent European research indicates that a fraction of those who use marijuana as youth may be susceptible to the development of psychoses, such as schizophrenia, later in life. (Those with a family history of schizophrenia are particularly at risk.)

What's the future of federal drug control policy? Will doctors be included in its evolution? Erlen doesn't foresee any changes soon. He has just this to offer: "What history tells us is how frustrating are efforts to properly control drug use." ■

CLASS NOTES

'50s

As a resident at the Mayo Clinic, **P. Kahler Hench** (MD '58) was treating a woman with a history of rheumatoid arthritis, a chronic inflammation of the lining of the joints. Hench saw her several times during his time in Rochester, Minn., and each time it seemed that her condition worsened. Soon, she was diagnosed with the autoimmune disease lupus, then she was diagnosed with systemic sclerosis, another autoimmune disorder. Hench was intrigued. Normally, he would see a patient with only one of these conditions, not all three. Hench decided to pursue a career in rheumatology, spending much of his career collecting histories of patients who suffered from multiple rheumatoid conditions, like the woman he treated as a resident. He spent most of his career at the Scripps Research Institute in La Jolla, Calif. Hench's father, **Philip S. Hench** (MD '20), also a rheumatologist, won the Nobel Prize in Physiology or Medicine in 1950 for his discovery of cortisone. The younger Hench had a distinguished career himself and was named a master of the American College of Rheumatology last year. He and his wife are enjoying retirement and their grandchildren in La Jolla.

'70s

Barry Riemer (MD '75, Orthopaedics Resident/Teaching Fellow '77–'80) is the chair of orthopaedic surgery at Louisiana State University Health Sciences Center in New Orleans and has been chief of surgery at Charity Hospital since 2003. With his residents, Riemer strives to impart wisdom that they won't learn from textbooks—the sort of things Riemer learned from Pitt legend Albert "Fergie" Ferguson. Riemer trains residents to run an efficient practice, for example, believing a surgeon must maintain order in the office as well as in the operating room.

'80s

We last covered Pitt sleep researchers in January '03, and they keep churning out findings that will elicit few yawns. **Daniel Buysse** (Intern '83–'84, General Psychiatry Resident '84–'87, Clinical Research Fellow and Clinical Polysomnography Fellow '87–'89), professor of psychiatry, along with **Eric Nofzinger** (Intern '87–'88, General Psychiatry Resident '88–'91, Clinical Research Fellow '91–'93), associate professor of psychiatry, published a paper in the November issue of the *American Journal of Psychiatry*. In this study, they report that if you have insomnia, your brain is probably more active while you're asleep and also while you're awake compared to those who find it easy to get a good night's sleep.

In 1989, **Lisa Cibik** (MD '83) became friends with a couple whose 26-year-old daughter had just died from complications of cystic fibrosis. Cibik saw their grief and the emptiness in their lives where their daughter had been. In 2003, Cibik was one of the Cystic Fibrosis Foundation's 50 Finest, becoming the top fundraiser in the history of this event. In September 2004, the Audia

C.E. MITCHELL

Rosenberg helps her patients age well.

CYNTHIA ROSENBERG

SPREADING HEALTH LITERACY

The patients who come to Cynthia Rosenberg's new practice in Fox Chapel, Pa., aren't usually looking for the typical exam or bloodwork, so the rooms don't look like those in a typical doctor's office. There are no counters with glass jars of cotton balls or tongue depressors. One room, with four chairs at a round table, looks like a kitchen. Another has rows of chairs for small groups to attend presentations. Rosenberg (MD '82) has practiced geriatrics for 20 years at West Penn Hospital, UPMC St. Margaret, and the Benedum Geriatrics Center (following a Pitt internship in pediatrics and child psychiatry and a residency in family medicine). But in these rooms, she's providing a different sort of geriatric assessment, which won't be covered by Medicare—probably not by a private insurer, either.

Her elderly patients and their concerned family members will come in for anywhere from three to six visits of about 90 minutes each. If a patient is unable to leave home, Rosenberg will make a house call. Her goal is not just to diagnose, but to help people do everything they can to age well. She coaches patients to prepare specific questions for their physicians that will give them the information they need to make informed health decisions. She'll help families figure out whether a particular elderly adult can continue to live alone, discussing the risks and strategies for living as independently as possible. "People get older and their families need to understand how to cope with some of the changes that happen as they get older," says Rosenberg.

She isn't modeling her practice on others that she's seen or heard about. She's simply providing what she has found lacking in the healthcare system: personalized and thorough health education.

"Is it a risk? Everything's a risk," says Rosenberg, who describes herself as "mission driven." She sums up her mission best in the phrase, "combating health illiteracy." Rosenberg has given presentations to physicians on how to do this through the media. And many know her through her column, "Dear Dr. Cynthia," where she answers readers' health questions in the *Pittsburgh Post-Gazette*. —*Corey Ballantyne*

Caring Heritage Society, which provides medical equipment and services in needy communities around the world, recognized Cibik as Woman of the Year for her service to the foundation, for which she is a trustee. Cibik helped woo Frank Sinatra Jr. and Tony Bennett to Pittsburgh for two benefit concerts for the Washington County organization. She practices ophthalmology in five offices in Western Pennsylvania, specializing in cataract surgery.

Lisa Cibik (MD '83, shown right), with Amber Brkich, who won CBS's *Survivor* competition. They're mugging for the camera at a fundraiser for the Cystic Fibrosis Foundation.

'90s

When **Maria Simbra** (MD '93) was an intern, she spent a lot of time fetching papers and answering phones. She realized her boss was observing how she would react to routine administrative tasks. But it wasn't an attending keeping close eye on the neurologist. Rather, it was a news producer from KDKA-TV. In 2001, Simbra entered Point Park University to earn a master's degree in journalism and mass communications. Her gophering paid off when the news director sent her to complete her first assignment as an on-air medical reporter. Simbra has worked at KDKA since her debut there in 2002, reporting on everything from hormone replacement therapy to the trend of young men taking Viagra recreationally. She enjoys reporting and feels that her background as a physician prevents her from overplaying the fads. Dr. Maria, as regular viewers know her, also plans to work part-time in private practice as a neurologist.

As a first-year med student, **Glenn Updike** (MD '98) became friends with classmate **Daniel Bensimhon** (MD '98). One day, Bensimhon invited Updike to go running—a seemingly innocuous invitation to get a little exercise, which he accepted. But Bensimhon had a little advantage his friend didn't know about—he had completed several marathons and an Ironman Triathlon. Although Updike says that he has never been able to keep up with Bensimhon, his friend must have inspired him, because he now has successfully completed six marathons. As a Pitt assistant professor of obstetrics, gynecology, and reproductive sciences on staff at Magee-Womens Hospital, Updike is broadening his horizon in different ways. Every Thursday he works at the Clinic for Women with Disabilities. When he returned to Oakland from his residency in Columbus, Ohio, Updike discovered that a nurse practitioner staffed this clinic without a physician. The nurse would often call Updike when she needed help; he would come to see patients if he could. Eventually, he started devoting part of his practice to seeing these women, many of whom have never had a gynecological exam.

'00s

Robert Denshaw (MD '00) missed many Monday night football games and dates with his girlfriend as he spent hours sequestered in Scaife Hall with friends writing about nephrology. The sophomore wasn't writing a paper for a class. With almost 40 other med students in his class, he was writing a nephrology textbook. For three years, these students wrote, revised, wrote, and revised, while running between classes and rotations. They churned out 17 chapters by graduation. Yet, the book wasn't complete. The pages sat in a file cabinet in Professor **Jamie Johnston's** (MD '79, Internal Medicine Resident '79–'81, Chief Resident '81–'82, Clinical Fellow '82–'84) office for a few years. When Denshaw returned to Pitt for a nephrology fellowship, former classmate **Negin Noorchasm** (MD '00, General Surgery Resident '00–'03, Plastic Surgery Resident '04–present) gave him the manuscript in a paper shopping bag. Now, Denshaw is hoping to recruit current classes to finish the revisions, but first he needs permission from the original authors. Classmates are encouraged to contact him at denshawsoulliere@comcast.net so that he can dust off those manuscript pages and finish the book. *—CB & MH*

ONE STONE, TWO BIRDS

This year, it's not the same old reunion. In addition to the popular Dean's Breakfast, Senior Class Luncheon, and Saturday night dinner, you'll have the chance to earn CME credits.

To find out if your class is celebrating this year, check the calendar at the back of this magazine.

Medical Alumni Weekend
May 20-23
Sheraton Station Square, Pittsburgh

For more information:
1-877-MED-ALUM
medalum@medschool.pitt.edu

SCOTT SERBIN | CONCIERGE SERVICE

Scott Serbin's father was diagnosed with lung cancer in 2003. The son found himself sitting beside his dad in hospitals and doctors' offices for a year's worth of treatments.

As a pediatrician on Pittsburgh's North Side, Scott Serbin (MD '82) had been in health care for some time. Suddenly, he was seeing his profession from the other end, and he was shocked. Everybody was too busy.

The nurses and doctors were responsible for too many patients. There was no time for long talks explaining procedures. There were few moments for compassion. It's not that the health professionals didn't care—they just didn't have time. Serbin understood that. At his practice, he was seeing 25 children a day.

At some point during that year, Serbin read an article in *The New England Journal of Medicine* about concierge medicine that got him thinking. Concierge practices charge a periodic fee and give patients more access to their physicians. The first such practice started in Seattle in 1996 in response to insurance companies' restrictions on health care.

Serbin's father passed away in June. In December, Serbin opened the first concierge practice in Pittsburgh. He would not be surprised to learn it was the first pediatric concierge office in the country.

About five or six children a day visit his office now. They come at almost any time a parent wants an appointment. When a parent calls with medical questions, he—instead of a nurse—will answer them. He plans on being available for house calls after hours. (This will be convenient for parents and also reduce the overall cost of care. Most patients who go to the emergency room don't have true emergencies, Serbin says. They go there because needs arise after normal office hours, or because their doctors are simply unavailable.)

Serbin's new approach to practice will incorporate more of his interests, like sports medicine. He's creating exercise and nutrition plans for his patients. "We're going to attack pediatric obesity," he says with conviction. "I'd like to have the healthiest kids in the country." *—Meghan Holohan*

COURTESY SERBIN

Serbin won't be too busy for patients.

THE WAY WE ARE

CLASS OF '69

At the Class of 1969 reunion last year, from left: Edmund Petrilli, Michael Kiken, Anthony Gentile, Eugene Orringer, and Gerald Levine.

Lawrence Friedman (MD '69) says he's been doing his level best to keep a low profile. Apparently, it hasn't worked, because we found him anyway, and not a moment too soon. The acting deputy director of the National Heart, Lung, and Blood Institute expects to retire—if not by the time you read this, then soon after. He began at the National Institutes of Health (NIH) in 1972, after a residency in medicine. Through the years, he has been active in epidemiological research and clinical trails, including several large multicenter trials in cardiovascular disease. In 1998, the third edition of *Fundamentals of Clinical Trials*, which he coauthored, was published. He has been pleased to read in this magazine about Dean Arthur S. Levine's thoughts on clinical trials. "There is a disconnect between our interest in trials and the ease with which we enable them," Friedman says. The requirements and barriers that researchers encounter have laudable goals, he believes, but it must be possible to make patients safer while meeting the needs of research.

CANADIAN PAEDIATRIC SOCIETY

Sacks

His classmate Diane Sacks (MD '69) arrived at Toronto's Hospital for Sick Children during the height of the '70s drug culture. Much to her surprise, the staff began to call on her whenever a patient came in with drug problems. She explains: "They thought everybody from the States knew about drugs and overdoses, so they'd call me down to emergency to say, 'Do something—he's high!' And I'd say, 'What am I supposed to do? I've been studying. I haven't been smoking!'"

Those early patients fueled her interest in adolescent medicine and taught her a lot, she says. She finds adolescents open and honest when they feel they're with a doctor who listens and doesn't mind purple hair, tattoos, or earrings. "They want to have someone to answer their health questions honestly and without value judgments," she says.

Sacks displays her acquired Canadian accent regularly on a CTV health program called *Balance*. She also writes a magazine column for parents. Last year, she served as president of the Canadian Paediatric Society.

The curious thing about Eugene Orringer (MD '69) is that he has arrived at his own recipe for success by conceding that his personal successes aren't the end all. What he really enjoys, he says, is helping young people. To that end, he heads up the MD/PhD progam at the University of North Carolina, Chapel Hill. When he took over in 1995, there were 12 students in the program. Two years later, the training program was funded by NIH. It has since grown to include 62 students. In the dean's office at UNC, Orringer invests about half his time in junior faculty development, helping young investigators get their first grants and papers written. He's the principal investigator on two NIH K12 grants that allow him to support five or six junior faculty. If he has anything to say about it, they all will have secured future grant support before they are finished. Orringer, himself, has been funded by the NIH for more than 22 years and is currently working on novel pharmacological agents for treating sickle cell disease.

—Chuck Staresinic

IN MEMORIAM

'30s

HARRY A. BLACK JR. (MD '38)
OCTOBER 2, 2004

'40s

REUBEN STUTCH (MD '40)
OCTOBER 21, 2004

ROBERT J. SIDOW (MD '41)
APRIL 19, 2004

HARRY J. HECK JR. (MD '42)
NOVEMBER 27, 2004

EDWARD L. KEIM (MD '43)
NOVEMBER 3, 2004

'60s

LOUIE LINARELLI (MD '64)
NOVEMBER 8, 2004

'70s

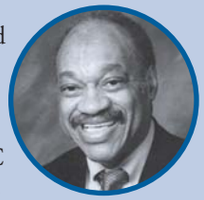
JAMES H. HARGER (RES '74)
FEBRUARY 5, 2004

'80s

SAMUEL W. GOLDEN IV (MD '80)
NOVEMBER 2, 2004

CHARLES M. HEFFLIN SR.

JULY 13, 1934 – NOVEMBER 9, 2004



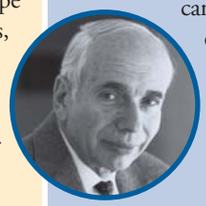
Hefflin

Charles Hefflin (MD '74) was featured in a recent television ad promoting the wisdom and experience of UPMC physicians. The reserved Hefflin, a family practitioner on staff at UPMC Shadyside, was known and beloved for his devotion to his patients and to his community. He was really honored to have been chosen for the ad, says David Blandino, chair of the clinical department of family and community medicine at Shadyside. "But you'd never know it from talking to Charlie," says Blandino (MD '78). "I found out by talking with his wife. He spoke with his actions."

Hefflin, who was the vice president of the Medical Alumni Association when he died, ran a private practice in Regent Square and served as medical director of Lemington Center, "the first and only Black nursing home in the area," says Levi Walker (MD '84), also of Lemington. Walker credits Hefflin with doing much more than was expected of a medical director, especially helping to ensure the home's survival through periods of financial distress. Through the years, Hefflin mentored many young African American physicians, several of whom gave testimony at his funeral about how much his example meant to them. *—CS*

HERBERT S. ROSENKRANZ

SEPTEMBER 27, 1933 – NOVEMBER 27, 2004



Rosenkranz

Herbert Rosenkranz helped make it possible to use computer models of mysterious chemical compounds to predict whether they were likely to cause or even cure cancer. In the 1980s, he and a colleague investigated how environmental pollutants cause cancer, then designed one of the first computer programs to identify carcinogens based on chemical structure. Rosenkranz came to the University of Pittsburgh in 1990 to chair the Department of Environmental and Occupational Health in the Graduate School of Public Health (he was interim dean there from 1998 to 2001), and he brought computational chemistry to the School of Medicine through a secondary appointment in pharmacology.

"His work was prescient," says Pitt professor and former chair of pharmacology John Lazo. "Those early programs harnessed the power of computers to search chemical libraries." Today, this technology can quickly characterize billions of potential drugs to identify the attributes that might make them useful or toxic. Rosenkranz retired with emeritus status in 2002. He was professor of biomedical science at Florida Atlantic University at the time of his death. *—CS*

JOSEPH BARBERA: ALL SYSTEMS READY

BY HATTIE FLETCHER

When disaster strikes in the movies—and sometimes in real life, too—health professionals swoop in to try to save lives, heedless of their personal safety. *Let me help*, they say with authority, *I'm a doctor.* Then they get to work.

"Disaster tourists," says Joseph Barbera (MD '80), and though he appreciates their willingness to help, he really wishes they would be a little less pushy. Whatever the crisis—hurricane, earthquake, biological attack, explosion, epidemic—Barbera and his colleagues have spent a lot more time thinking about and planning for the response than the average healthcare professional, no matter how well-intentioned. It's Barbera's job to put emergency management procedures in place that not only help save the lives of victims, but also protect responders.

Barbera has a history of traveling great distances on short notice to be at the scene of large-scale disasters, often departing within the hour. He's more than familiar with the aftermaths of hurricanes, earthquakes, mine collapses, and wildfires. In 1995, he was almost finished building a house for his family when he learned that a bomb had been detonated outside a federal office building in Oklahoma City. When FEMA called, he left the house unfinished and his wife and four sons in a rental property they were required to vacate in 10 days. (Barbera's wife said that if he was needed, he should go.) Following the September 11 attacks, he was at both the Pentagon and World Trade Center sites.

When he was a young emergency medicine physician working in a crowded ER in the Bronx, Barbera noticed that many adverse outcomes were caused not by poor practitioners, but by poor systems. An unfortunate patient might end up waiting 12 hours or longer for care. Thus began an interest in systems that would eventually lead Barbera far beyond the emergency room.

In Latrobe, he joined the Special Medical Response Team (SMRT), a group of physicians and paramedics who respond to emergencies in unusual environments. They go to places where EMTs usually don't—to the sites of machine entrapments in factories, deep mining accidents, and the like.

"I feel like I had a doctoral-level education from folks who wear fire hats and turnout gear on a regular basis," Barbera says.

Through SMRT, Barbera became involved with an alphabet soup of federal and international agencies. The team represented the United States in an international search-and-rescue coalition, and Barbera became the point person for the development of its medical component. He later helped FEMA develop the National Urban Search and Rescue Team.

CORBIS

The Alfred P. Murrah Federal Building in Oklahoma City after the bombing—one of many disasters where Barbera was called upon to assist.

There's no question systems are Barbera's primary interest—so much so that his present position at George Washington University is in the School of Engineering and Applied Science, not in the School of Medicine. He is codirector of GWU's multidisciplinary Institute for Crisis, Disaster, and Risk Management and the author of *Jane's Mass Casualty Handbook.*

When Barbera responds to disaster now, he supports those managing the response and makes sure that the response proceeds according to plans he helped develop.

"It's personally satisfying if you save lives," he says. He quickly adds with a pleased laugh, "It's also intellectually satisfying that you've had a chance to test the systems that you developed in very tedious committee meetings."

For Barbera, this preparation spills over into his personal life; by virtue of his profession, he says, he is "situationally aware."

He'll tell you not to sit in the first or the last car of a train, because they are more frequently destroyed in crashes. He pushes elevator buttons with the back of his nondominant hand, to avoid infection. He avoids his academic office at GWU when he doesn't need to be there. Its location, one block from the White House, is within "blast perimeter." He knows what that area would look like after an explosion. He fully expects—hopes, even—to be on site at future disasters. But he prefers to be at ground zero after time zero. ■

In the introduction to this 1943 book, Robert James Devine speaks of marijuana dealers as agents of Satan. He compares them to ancient Phoenicians and Ammonites who sacrificed children to the fire god, Moloch. Devine also notes, "Continued credit must be given to the faithful efforts of Mr. Harry Anslinger, Federal Commissioner of Narcotics, and the splendid men engaged with him in fighting this terrible menace. Anyone waging warfare against marihuana or any other dope evil will find in the Narcotics Division of the Federal Bureau of Investigation a strong and willing ally."

For more on Anslinger's drug policy legacy and dealings with the medical community, turn to page 34.

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ELVIS MAKES LIKE A PITTSBURGHER

Before Elvis Presley rolled up his sleeve for the Salk vaccine, before the 1955 announcement that the vaccine was ready for widespread use, Pittsburghers bared their arms in pilot tests. It's time they were honored.

The University of Pittsburgh is looking for anyone who participated in pilot field tests and national field trials of the vaccine in Pittsburgh in the early 1950s as well as polio patients from that era. They are invited to a reception on April 10 to commemorate the 50th anniversary of the licensing of the vaccine.

FOR INFORMATION: 412-383-SALK (7255) or www.polio.pitt.edu

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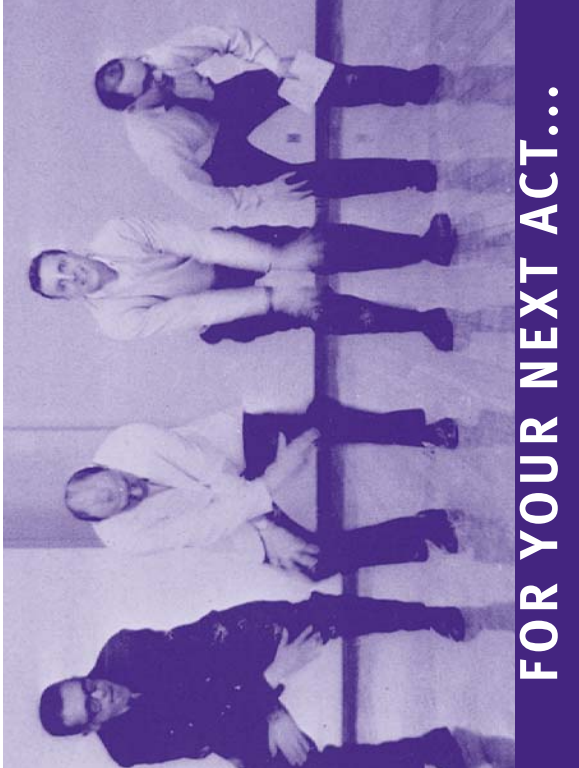

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