EVOLUTION OF FLU

SCIENTISTS CHART INFLUENZA’S MUTATIONS
TO SEE HOW A SNIFFLE BECOMES A SCOURGE
Astonishing Starzl

Was Chuck Staresinic living in my body in 1981? His article “Only Starzl Dared To” (May 2006) is written as if he were there with us all in the bloody trenches of liver transplants at Presbyterian University Hospital in 1981. How on earth did Mr. Staresinic get this factual and totally honest story about the first two years of liver transplants at Presby?

I was there, on the front lines, in 1981 as a critical care fellow in Ake Grenvik’s fantastic program when Dr. Starzl came to town. Dr. John Sassano’s recollections are correct. However, my view was very different from his. I was in the ICU; he was in the OR. I was an internist at the time, not an anesthesiologist, as I am now.

Here’s what happened as I saw it:

Dr. Starzl came to town. It was announced that “we” were “doing” liver transplants.

Dr. Starzl performed his first transplant. I have no idea how many units of blood, FFP (fresh frozen plasma), and platelets were used on this patient. I believe this transplant happened during the middle of the night, as most of the first transplants did. The transplant lasted, what, eight to 10 hours? Taxi drivers and radio stations reported, hourly, on the status of this patient.

I do remember that three out of four of the first transplants died. Most of them died after agonizing days and high-tech/high-price therapy in the ICU. These patients required isolation rooms in the ICU and 2-1 nursing (two nurses in the room with one patient).

While dying, these patients depleted the entire city of Pittsburgh of packed red blood cells, platelets, and FFP. Cardiac surgery was cancelled throughout the city, and leukemic patients went wanting for component therapy. The other hospitals went into an uproar.

Here’s what happened. Presby became full of jaundiced, comatose, liver-failure patients on the medical wards. These patients were transferred to Presby without question—by ambulance, helicopter, etc. The medical wards were truly overwhelmed with these patients, leading to the “boycott” by the internal medicine residents at the time.

Presby surgeons were called in the middle of the night to retrieve organs. When they went, they usually brought back a liver, a heart, two kidneys, and other body parts. These retrievals would require the OR to perform a liver transplant, two kidney transplants, and a heart transplant. The surgeries were emergent and unscheduled. They totally disrupted the elective surgery schedule and placed dire demands on the OR, anesthesia department, ICU, blood bank, and clotting lab.

I used to meet Dr. Starzl in the middle of the night, often in the hospital stairwells. He was tall, slim, and quiet (almost like a coyote, a fox, a Steppenwolf!) and used to bum cigarettes from me back then when I smoked.

I now realize that Dr. Starzl learned from his mistakes, and that Dr. Sassano stood his opposition. It was huge and vocal. I had no idea where his support came from. Now I know.

It was a great article.

H. D. Matthias (Fel ‘81)
M adison, M iss.

Chuck Staresinic responds

In addition to several hours of interviews with Dr. Starzl and his current and former colleagues, I relied on a sizeable stack of printouts from the scientific literature and a heavily bookmarked copy of Starzl’s memoir, The Puzzle People. Another book, M any Sleepless N ights, by Pitt English professor Lee Gutkind, provided background information and a view of the high-pressure atmosphere of Starzl’s first decade in Pittsburgh.

As a Starzl Transplantation Institute liver recipient (March, 29, 2004), I was much impressed with both the content and style of Chuck Staresinic’s fine articles, “Only Starzl Dared To” (May 2006) and “Break on Through” (Fall 2006).

In addition to recognizing Dr. Thomas Starzl as a medical genius, gifted teacher, and humanitarian, Staresinic covers well the basics of organ transplant art and science. Of particular interest to those personally involved, he clearly describes the continuing efforts in attempting to understand, adjust, and eventually control the body’s rejection process. He has given me another topic to explore during my next STI clinic visit!

Staresinic’s thoughts and words are so caring in regards to donors and recipients that one might suspect he is one himself.

Larry M ayer
O akmont, Pa.

Laughter and Tears

May be it is because I just finished five overnight shifts in a row and I’m tired. Or maybe it is because I dealt with four deaths in the ED this weekend. May be it’s because I am returning to Pittsburgh this weekend for a classmate’s wedding at which there will be a mini-Pitt med ’05 reunion. Or maybe it’s just because I had the best experience I could possibly imagine at Pitt med, and missing it makes me a little emotional.

Whatever it is, I just read Pitt Med ed to cover to cover and both cried and laughed, more than once.

I am proud to come from such a respected and incredible institution. And despite the trials of residency, I have never been so resolute in my career choice than I am right now.

Padi M cfadden (M D ’05)
Yale-New H aven H ospital

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

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Recent Magazine Honors

AAMC Robert G. Fenley Writing Awards of Distinction (2 awards)
IABC Best of Show
IABC Golden Triangle Award of Excellence Magazine Design
CASE Circle of Excellence Bronze, Special Interest Magazines
CASE District II Accolades Silver, Visual Design in Print, Covers
CASE District II Accolades Bronze, Best Article
CASE Circle of Excellence Bronze, Periodical Staff Writing
The White House honors Beatriz Luna.

Getting to know the Class of 2010.

Top reasons to see a therapist.

We're with the band.

There's more to addiction than that feel-good sensation, it seems.

Supervaccine?

Generations of Hamiltons look out for future medical scientists.

A small-town practice goes pharma-freebie free.

For one alum, Katrina brings up power issues.

The rations that may have saved the Union.

Everybody Hurts

A writer discusses the nature of physical suffering with Gerald Gebhart, probably the world's preeminent pain researcher and a new Pitt recruit, as well as with pain treatment specialist Doris K. Cope.

Evolution of Flu

Influenza reinvents itself at a dizzying rate. Scientists chart its new identities, tracking how a snuffle could become a scourge.

New Math

Menacing diseases like tuberculosis could be thwarted by mathematical modeling, researchers are discovering.

In the Timing

Ernst Knobil's research laid the groundwork for revolutionary treatments for dwarfism, infertility, and prostate cancer.
It helps to recognize when you’re in the right place at the right time. In the last issue, I described a moment of serendipity when scientists noticed a fruit-fly embryo with hedgehog-like spikes on its surface. They later learned the mutated gene (Hedgehog) that produced the spikes has been conserved in evolution. In higher animals, including humans, the loss-of-function mutation affects the formation of midline nervous system structures, producing a cyclops-like congenital anomaly. Not only has this very basic fly research illuminated our understanding of human nervous system development, but we’ve recently learned that excess expression of the normal Hedgehog gene is associated with some human cancers. Some companies are now developing drugs to inhibit this overexpression. All this good news is from the chance observation of a fly by the very keen eyes of superb basic scientists!

Here’s another short story—this one about a worm—that not only makes the same point (chance favors the prepared mind), but portends more happy endings. The related work has yielded the 2006 Nobel Prize for Andrew Fire and Craig Mello. (Fire was our 2003 Mellon Lecture awardee.) These scientists wanted to understand what regulates the expression of genes that produce muscle proteins in a small roundworm. They injected the worm with a mirror image of the single-stranded messenger RNA (mRNA) that normally encodes muscle protein, expecting to inhibit protein production. Simply as a control, they injected other worms with double-stranded RNA. Much to their surprise, the mirror-image RNA had no effect on the worms, but the double-stranded RNA made worms twitch—they could no longer form muscle protein. Fire and Mello had discovered “RNA interference” (RNAi), a phenomenon hinted at earlier by plant biologists who, trying to make pink petunias redder by injecting them with red pigment RNA, instead turned them white. This year’s Nobelists went on to explain interference: They found that double-stranded RNA activates a cellular enzyme-like machinery, conserved from plants to humans, that destroys mRNA with a code identical to that in the double-stranded RNA. (Those white petunias had lost the recipe for making color.)

Many viruses have a double-stranded RNA genome; when these viruses infect cells, RNAi destroys the viral RNA, thereby limiting infection. We also know now that some of our genes encode “micro” RNA As, which can degrade unwanted mRNAs from protein-encoding genes. Such a mechanism plays a role in normal human development, when proteins needed in embryogenesis are not needed later in life. RNAi also controls “jumping genes.” These unusual genes, which encode partially double-stranded mRNA, can move around within our chromosomes and are known to cause disease if they alight in the wrong place.

The discovery of RNAi has allowed us to “silence” genes at will, revealing the normal functions of genes that have been enigmatic or even unknown. RNAi as a research tool has spawned many new biotech companies, and we already see its clinical importance: RNAi has silenced a mutation that causes high cholesterol levels, suggesting itself as a treatment for cardiovascular disease. Many researchers and companies are exploring RNAi to treat viral infections, cancer, endocrine disorders, macular degeneration, and more. The worm has truly turned: Fire and Mello’s chance observation, first reported in 1998, has now led—within an incredibly brief time frame—to almost limitless research and clinical opportunities.
FBI Calling
A little more than a year ago, Beatriz Luna got a phone call from officials at the National Institutes of Health (NIH). They asked her a few questions, told her the reason for the call "might be very good," and left it at that. Shortly thereafter, she received a letter from the FBI, asking for permission to release her files.

At such times, she says, one doesn’t know what to think. This summer, the University of Pittsburgh PhD associate professor of psychiatry and psychology and director of the Laboratory of Neurocognitive Development at Western Psychiatric Institute and Clinic learned some good news.

The White House named Luna one of 56 recipients of the 2005 Presidential Early Career Award for Scientists and Engineers. The award provides her with approximately $1 million to continue her NIH-funded research into adolescent brain development. Luna’s work delves into the role an adolescent’s developing frontal cortex plays in executing cognitive tasks. Too much frontal cortex activity, she says, can essentially burn out that portion of a teenager’s brain, leading to impulsive behavior. Her work is helping scientists understand why adolescents tend to put themselves in precarious situations. —Joe Miksch

Luna won a Presidential Early Career Award for Scientists and Engineers.

FLASHBACK
[The president of Harvard University] actually proposes to have written examinations for the degree of doctor of medicine. I had to tell him that he knew nothing about the quality of the Harvard medical students. More than half of them can barely write. Of course they can’t pass written examinations.

—Harvard professor of surgery
Henry J. Bigelow, c. 1869

PITT AGAIN RANKS 7TH IN NIH FUNDING
The National Institutes of Health recently released data showing the University of Pittsburgh and its affiliates (such as Children’s Hospital of Pittsburgh and Magee-Womens Research Institute) were awarded $431 million in grants in the 2005 fiscal year. That makes Pitt the seventh highest ranked university for the agency’s funding a second year in a row. The University took in $396 million in fiscal year 2004.

“Almost 80 percent of the University’s total NIH funding is generated by medical school faculty,” says Arthur S. Levine, senior vice chancellor for the health sciences and dean of the School of Medicine at Pitt.

He notes that the University’s percentage increase is second among the top 15 institutions funded by the NIH and that Pitt ended fiscal 2005 almost $37 million ahead of the eighth-ranked institution, Washington University in St. Louis. Pitt has closed to within $560,000 of number six on the list, UCLA.

“The $560,000 represents one grant,” Levine says. —JM
Faculty Snapshots

Patrick Kochanek has often glanced with admiration at Peter Safar’s awards displayed at the Safar Center for Resuscitation Research.

This year, the American College of Critical Care Medicine recognized the University of Pittsburgh’s Kochanek as a Distinguished Investigator, an honor Safar received in 1995. Kochanek, a professor and vice chair of critical care medicine who now directs the Safar Center, studies acute brain injury.

Kochanek’s work spans a number of injury processes, including traumatic brain injury, blast injury, cardiac arrest, and hemorrhagic shock. His approach involves linking lab work to real human conditions so that doctors can better understand and treat head injuries.

The American Academy of Physical Medicine and Rehabilitation has named Ross Zafonte its Walter J. Zeiter Lecturer for 2006. Like Kochanek, he has fostered a reputation as an accomplished researcher of brain injury, particularly traumatic injury. Zafonte, chair of Pitt’s Department of Physical Medicine and Rehabilitation, says it’s not so much his individual accomplishments as a clinician and researcher that netted him the award. Rather, being named the Zeiter lecturer is a testament to the growth of Pitt’s physical medicine department.

“I've tried to grow the residency program and develop curious clinical investigators,” he says. “We're always trying to plow ahead in rehabilitation medicine.”

The human immune system remembers exposure to bacteria and viruses. Geetha Chalasani would like to make it forget sometimes.

Chalasani, an assistant professor in the renal-electrolyte division of the Department of Medicine at Pitt, recently won the John Merrill Transplant Research Scholar Award from the American Society of Nephrology and the American Society of Transplantation. The award, worth $200,000 over two years, will help her pursue her research.

Chalasani, an MD, is interested in the process by which B cells generate memory T cells that are necessary to mount rapid attacks against invaders. Understanding this mechanism, Chalasani says, could help develop a regimen to curtail immune system responses prompted by transplanted organs.

Speaking of transplantation, Thomas Starzl, Distinguished Service Professor of Surgery in the School of Medicine, recently earned the American Society of Transplantation’s highest honor, the Roche Ernest Hodge Memorial Award.

—Alicia Kopar & Joe Miksch

A&Q

Top 10 Reasons to See a Therapist

On orientation day, Lee Wolfson (above) stood before the University of Pittsburgh med school’s incoming Class of 2010 with a David Letterman–style top 10 list of reasons students should seek him out. Among those: Your girlfriend says, “We need to talk” (Reason Number 4).

Reason Number 1? You take Psychiatry and are convinced you have at least three Axis I diagnoses. Inevitably, med students come across academic and emotional detours en route to earning their degrees. When these moments arise, Wolfson is there to help. He directs the Medical Student Counseling Program, the first office of its kind, which was founded more than 25 years ago at Pitt. Wolfson, who received his master’s degree in education from the University in 1976 and worked at Western Psychiatric Institute and Clinic for 21 years, now tailors his interpersonal psychotherapy counseling to the specific needs of med students. He talked with us days before flying to Malaysia to speak before the World Congress of Psychotherapy.

Common issues students face

I see 50–60 percent of students at some point in their four years of [med] school. Their most common problems are depression and anxiety. Sometimes they’re having a hard time academically. They’re also carrying enormous debt. I try to give them support and help them maintain confidence. The stress of med school is unrelenting. Whatever vulnerability they might have already, med school is going to exacerbate that.

Advice for incoming students

It’s important to develop real self-compassion. These students are really driven, and sometimes that drive turns into feelings of worthlessness if they’re not achieving at the level they’re used to. My key point: Never lose sight of your original vision of yourself as an individual, a doctor, a healer. And if there’s a bump on the road—and there will be—give me a call. It doesn’t go on your record, and we don’t bill your insurance. It’s completely confidential.

His question for the world

One of my favorite quotes is from Rainer Maria Rilke’s Letters to a Young Poet: “Be patient toward all that is unsolved in your heart and try to love the questions themselves.” So I ask, what are the questions that you have learned to love? —Interview by Jennifer Dionisio

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—Alicia Kopar & Joe Miksch
Make Me a Match

Among the 20 or so scientists stationed in front of display posters in the William Pitt Union’s lower lounge one October night was Uddhav Kelavkar, nattily dressed in a black-and-gray checked jacket over a black mock turtleneck. This assistant professor of hematology and oncology at the University of Pittsburgh believes he has found a better way to detect prostate cancer. It has to do with a gene he has been researching for more than a decade.

Kelavkar was an exhibitor at Science 2006’s Technology Showcase. In a room full of people talking hard science—peptides, histones, epithelials—Kelavkar gave passersby an “elevator pitch,” a layperson’s explanation for why his work matters.

“If you live long enough, you’ll get prostate cancer,” he told one man, a scientist with salt-and-pepper hair clutching a Penn Pilsner. The conversation got more candid from there as Kelavkar brought up erectile dysfunction and urine collection bags, describing how quality of life “goes down the drain” with some prostate cancer surgeries.

“We men are really doomed,” the listening scientist responded with a chuckle and a shake of his head.

The University’s Office of Enterprise Development and Office of Technology Management sponsored the showcase. Its main purpose was pollination, by putting venture capitalists and scientists in a big, plush room with an open bar and buffet of roast beef and salmon for two hours. Exhibitors had promising early results. Firms represented had the know-how and licensing dollars to bring discoveries and inventions to real patients. The possibility of matchmaking gave the event an ambience somewhere between a middle school dance and Mensa gathering.

The exhibitors revealed new medical software, implantable technologies, and gene therapies while they dished on where to get the freshest tissue samples. A plurality were cancer researchers like Kelavkar, who, toward the end of the event, leached through the business cards he’d collected in his suit pocket. It had been a good night.

“This guy,” he said, tapping a card left by a venture capitalist, “he wants to see our manuscript.” —Reid R. Frazier
Name-Dropping

Pitt welcomed these scientific heavyweights to campus this fall for Science 2006, the University’s annual celebration of research in medicine, engineering, computation, and basic science:

Just before Stanford University’s Roger Kornberg left for Pittsburgh to give the Dickson Prize in Medicine Lecture, the Royal Swedish Academy of Sciences announced he’d be getting the Nobel Prize in Chemistry. Kornberg offered the world the first molecular picture of how information stored in the genes of organisms with well-defined cellular nuclei (like mammals and yeast) is copied and transferred to the parts of cells that produce proteins. A PhD professor of structural biology at Stanford, Kornberg’s recent discoveries include isolating proteins responsible for transcription and gene regulation. Kornberg is the 11th Dickson Prize winner also to be honored with a Nobel. His father, Arthur Kornberg, another genetics researcher, won the 1959 Nobel Prize in Physiology or Medicine.

Carla Shatz, chair of the Department of Neurobiology at Harvard University, delivered the Mellon Lecture. As the PhD has worked to understand the essential patterns of brain development, she has found that long before humans are capable of seeing, the retina generates waves of activity that establish cell pattern formation in the brain.

Klaus Hofmann lecturer Baldomero Olivera is into poisonous sea snails, but not because he’s a thrill-seeker. He has found that their venom contains peptides that hold potential for drug discovery. Olivera is a PhD, Distinguished Professor of Biology at the University of Utah, and adjunct professor at the Salk Institute for Biological Studies. —JM
Josh Dunklebarger (MD ’06) assembles his drum set. John Falcone (MD ’06) sets up his effects pedals. The growing crowd in Swissvale’s Pub in the Park mills about. Hunched over his cymbals, Dunklebarger drifts back four years, recalling his anatomy class. He and Falcone were paired up at a cadaver and, for a moment, the conversation turned away from the vascular system and toward music. Next thing Dunklebarger knew, Falcone was pressing the percussionist to bring his kit to Pittsburgh from his family home in York, Pa. Dunklebarger soon acquiesced, and he and Falcone, a former professional trumpet player and accomplished child soprano turned self-taught guitarist, became Pitt med’s own rock-and-roll darlings, Mercury Rising.

The lights dim and the two-man band roars to life. Accompanied by a smoke machine, Mercury Rising tears through a two-hour set, performing their own songs and covering staples from the likes of Green Day and Neil Young. Falcone, affecting rock star poses, nimbly fingers his axe. Dunklebarger pounds his skins. A swaying crowd becomes a dancing crowd, taking Mercury Rising back to its days as house band at Boomerang’s Bar & Grille in Oakland while the duo was in med school.

The pair considered the evening a welcome diversion from residencies at UPMC hospitals, where Falcone is learning the art of general surgery and Dunklebarger otolaryngology. Their performance was a fundraiser for the Susan G. Komen Breast Cancer Foundation’s Race for the Cure. Dunklebarger sported a pink oxford for the occasion. Why? His mom, a cancer survivor, told him to.

—Joe Miksch

PHOTOGRAPHY MARTHA RIAL
INVESTIGATIONS

Explorations and revelations taking place in the medical school
We’re “addicted” to chocolate, jogging, sex, and food because of a rise in the happy-making neurotransmitter dopamine that’s associated with pleasurable activity.

Or so the conventional wisdom goes. Something is satisfying to us. We see the opportunity to do it again, or get some more of it, and our brain releases dopamine. We feel good even anticipating the reward.

Charlie Bradberry’s studies of cocaine addiction, however, paint a different picture of real addiction. His work suggests that although dopamine plays a part in keeping people doing cocaine long past the time they find it enjoyable, it may be that many are unable to kick the drug habit because of changes in the brain’s decision-making center.

“It’s been thought that the only reason these things [like drugs] are enjoyable is because of dopamine,” Bradberry says. “The brain’s a much more complicated place.”

Particularly the brain of a primate.

Not surprisingly, a human brain is more like that of a monkey than that of a rat. Cocaine alters brain metabolism in humans and monkeys in ways not seen in rats. So Bradberry, a PhD associate professor of psychiatry in the University of Pittsburgh School of Medicine, has abandoned the rodent model often used to study the neurochemical effects of addiction for a primate model.

By allowing these monkeys to self-administer cocaine, then monitoring cognitive ability and neurochemistry, Bradberry follows his hunch that cognitive ability—in particular decision making—plays a significant role in addiction and relapse. His work in recent years has confirmed that assumption.

In Bradberry’s lab, monkeys were seated in front of a panel of lights indicating when cocaine was available. On that cue, they could choose whether to press a lever that would cause a dose of cocaine to be delivered intravenously. After the monkeys had become sensitized to cocaine, Bradberry examined their brain chemistry, looking for a rise in dopamine levels when the primates were given a visual cue telling them the drug was available. That’s the way it worked in rats.

“We were just not able to see any activation of dopamine by environmental cues,” he says. “It was kind of unsettling because you immediately worry about whether you’ve done something wrong.”

But as the results were repeated, Bradberry became convinced they were not evidence of a fluke or error, but were an indication that he should look elsewhere for the internal drive that prompted his monkeys to push that lever.

Since arriving at Pitt from Yale University in 2004, Bradberry has continued to try to divine the source of his monkeys’ desire for cocaine. Behavior in primates, he says, is the consequence of the dance between the cerebral cortex—which guides reasoning and control—and regions of the brain that pertain more to urges and appetite.

That led Bradberry to hypothesize that the cortex, the seat of cognition, was a good place to start looking for answers. Measuring cognitive ability in a control group and in cocaine-exposed monkeys confirmed he was looking in the right place. Bradberry found clear-cut cognitive deficits in the cocaine-exposed monkeys long after they’d last taken cocaine. They were slower to adapt to changing rewards and slower to formulate strategies to maximize the number of rewards they earned.

What changed in the brain that made these monkeys less able to make the right decisions? Had they lost the ability to be mentally active enough to remember which choices earned them rewards? Had they merely lost interest in rewards other than cocaine?

In humans, Bradberry says, one can raise the same sort of questions about an addict who is unable to change a pattern of drug abuse despite losing a job, spouse, friends, and family.

If addiction is more than a result of feel-good dopamine, Bradberry says, it’s vital to look beyond the dopamine system for explanations.

Perhaps, Bradberry says, a drug could be developed to enhance cognitive ability and, therefore, decision making. Cognitive behavioral therapy might be appropriate, too, he adds.

“You’ve probably got to do more than just try to regulate an appetitive urge,” says Bradberry. “What’s happening when people relapse is that they’re making a bad decision.”

ADDICTION

DOPAMINE MAY NOT BE THE ONLY REASON PEOPLE CAN’T KICK THE HABIT

BY JOE MIKSCH

Vin Mariani combined Bordeaux with cocaine and was a popular tonic in the late 1800s. Although cocaine use has been stigmatized for some time now, neurobiologists are still learning how it and other addictive substances make such a mess of people’s lives.
A boy is born too soon, and his parents wait and worry. He does well on a respirator for three days, then four. His lungs are gaining strength, a reason to exhale.

Then on day five, there's trouble—not in his lungs, where prematurely born infants are commonly known to have problems, but in his gut. His blood pressure falls, his belly swells, and he can't digest food. As he's rushed into surgery, the parents are told he has a terrible disease that's quite common among premature children, but this is the first they've ever heard of it. Inside him, a tiny tangle of intestine is breaking down, turning black, and dying.

This is an imagined story, but it's much like what tens of thousands of young families go through every year in this country. Fifteen percent of all preterm babies, both boys and girls, develop an inflammatory disorder called necrotizing enterocolitis (NEC). Among them, only half survive. If NEC isn't caught early enough, portions of the intestine must be removed. The more the baby loses, the more difficulty absorbing nutrients he'll face throughout his life.

Third-year University of Pittsburgh medical student Chris Rippel says that given the frequency and devastating effect of NEC, it's surprising how few people know about it.

"It seems the only people you'll find outside of the medical community who know about NEC are people directly affected by it," he says.

Rippel is on a team that plans to give premature infants a better chance. He's working with David Hackam, an MD/PhD, assistant professor of surgery, as well as of cell biology and physiology at Pitt, and principal investigator on an ongoing NEC study. Last fall, Rippel received the Phillips Award for his summer-research project on NEC. He's now continuing the same series of experiments for his scholarly research project. (Such multiyear projects are a new curriculum requirement for all Pitt med students.)

Rippel is not the first student to be recognized for work completed under Hackam's guidance. In recent years, Hackam's mentees have won awards from the Pittsburgh Surgical Society, the Eastern-Atlantic Student Research Forum, and the American Medical Association.

The primary cause of NEC is still unknown, but the presence of immune cells called macrophages in the intestines of NEC patients suggests that infection may play some part. It's not clear what kind of infection triggers the immune response, or whether this reaction helps or harms the intestines—it may do both.

Hackam is exploring the idea that NEC may be a result of cells being held incommunicado in the midst of an infection.

"Chris was fascinated by the question," says Hackam.

His lab is focusing on how intestinal cells called enterocytes communicate and what happens if and when they don't.

Throughout the body, certain pathways between cells—channels known as gap junctions—have been shown to act as cellular telephone lines. Cynthia Leaphart, a surgical research fellow in Hackam's lab, was the first to demonstrate the functional significance of the junctions in the intestine. She and Rahul Anand, another surgical research fellow in the lab, worked with Rippel to observe the effects of inflammation on enterocyte communication and to test the hypothesis that the presence of macrophages may be somehow responsible for disconnecting the phone lines.

Rippel found that the hypothesis was correct. As molecules secreted by the macrophage traveled along the cellular party line, the enterocytes stopped communicating with one another.

Next question for Rippel and the Hackam lab: Among the inflammatory molecules secreted by the macrophage, which one disabled the phone lines?

Based on studies by Pitt's former pediatric surgery chief Henri Ford that linked elevated levels of nitric oxide to NEC, Hackam's team thought nitric oxide was a likely suspect. Rippel introduced a nitric oxide blocker to the enterocytes, and sure enough, in the absence of this molecule, the phones started ringing again.

Rippel says that working with Hackam has not only fueled his interest in research, it has also benefited him as a surgeon-in-the-making.

"He really has an exceptional manner with patients," Rippel says.

Rippel is getting ready for the next phase of his scholarly project, which involves a series of imaging experiments, during which he will "tap" into the cells' communication lines.

Perhaps the secrets behind NEC travel this cellular grapevine.
An evil genius stalks the land, invading bodies and stealthily draining life from them.

Decades later, while the archvillain continues to lay waste to vast segments of humanity, its descendant—engineered in a university lab—takes on superpowers and races to the rescue. What the forefather wrought, the youth seeks to set right.

This intergenerational melodrama, worthy of a darkly illustrated superhero comic book, is playing out in a University of Pittsburgh dermatology lab.

There, researchers are exploring a new approach to vaccination that uses a modified virus. This test-tube baby is a third-generation scion of a family called lentivirus, which is better known for its most murderous member, HIV.

The researchers are finding that a souped-up lentivirus can deliver a vaccine that is both more potent and longer-lasting than existing vaccines. Eventually, they hope, it can be used to prevent a slew of infectious diseases, and even to treat cancer.

Strength and stamina aren't the only advantages of this brawny new vaccine-delivery system. Louis Falo, MD/PhD professor and chair of the Department of Dermatology at Pitt, lists others: It can be produced quickly in response to developing diseases. It's less expensive. It can probably be put into patch form so that it doesn't need refrigeration or even a needle.

Get this thing a cape and call it Supervaccine.

Falo notes that a problem with existing vaccines is the time it takes to make them. As a result, the flu vaccine you get this year is based on viruses in circulation last year.

Falo and other researchers around the country have been experimenting with an alternative. Instead of growing, say, measles or flu virus in fertilized chicken eggs, scientists extract a gene from the disease-causing agent, copy it, and multiply it.

"The production time would be greatly reduced," Falo says, "even to the point where you might be able to make patient-specific vaccines" from the patient's own body.

But there's a hitch. "DNA vaccines haven't been very effective," Falo says. "The problem, we think, is the delivery."

So scientists have been working on a new delivery system, using a virus to carry the antigen (that bit of the infectious agent) inside the patient. There, like any vaccine, it causes the patient to make antibodies and killer T cells.

Then there's another problem. "The cells that they infect are actually damaged by the virus, which makes perfect sense," Falo says. "It's a virus, after all."

In particular, the virus experiments seemed to impair the skin dendritic cells (DCs). These cells, front-line sentinels in the immune system, ordinarily snare an invader and take it to the lymph nodes, where the dendritic cells activate pathogen-fighting T cells.

For a virus-based vaccine that lets the dendritic cells do their job, you need a virus that can't reproduce, damage the immune system, or cause other bodily harm. You want it to simply deliver its load of whatever you're vaccinating against.

That virus should be able to lurk in the patient's system without alerting the immune system. Otherwise, the vaccine stops working after delivering its antigen load only once.

"One virus is very good at hiding," Falo says. "HIV."

"So what we did was take a member of the same family, lentivirus, and we took away all its ability to reproduce."

The results: In lab animals, the lentivirus vaccine produced several times the immune system response of conventional vaccines. A single injection also lasted longer.

In addition to its practical potential, the vaccine study contributes to the basic science of immunology. Based on experiments with other viral-vector vaccines, scientists had downgraded their view of the role that skin dendritic cells play in the body's immune response.

The success of the lentivaccine suggests that skin DCs are vital after all, says the study's first author, Yukai He, an MD/PhD and Pitt assistant professor of dermatology.

"It's the first evidence that the skin DC paradigm is working in the system in initiating the T cell response."

The researchers wonder how the vaccine will perform in human skin, for which no animal offers a close approximation.

FDA approval for clinical trials is, at best, 18 months to two years away, Falo estimates.
There must be better options for treating pain than opioids, which are the best medicine has to offer many people. Pittsburgh is building a new pain-research enterprise to pursue such a dream. In these pages, Doris K. Cope, Pitt’s expert on today’s remedies, and new recruit Gerald Gebhart, considered by many to be the world’s preeminent pain researcher, share their visions and insights. (Shown immediate left, Papaver somniferum, from which opioids are derived, with other flowers.)
Buddha thought pain was endemic to the human condition, a natural partner of desire.

Athletes wear T-shirts advising us that pain is weakness leaving the body.

Your little sister can be a pain.

The consideration of pain at the University of Pittsburgh School of Medicine is a slightly different animal, less a philosophical pursuit than one dedicated to alleviating hurt born of cancer, nerve disorders, or surgery.

On the clinical side of things is Doris K. Cope, Pitt professor of anesthesiology and division chief of the UPMC Pain Medicine Program. Cope came to Pitt in 1997 to found and lead the program. During the early years, the program saw hundreds of patients a year. Last year, with the program having grown to seven sites from one, program staff saw more than 22,000.

The tools of Cope's trade are nerve blockades, electrical stimulation, radio-frequency current, medication, and intrathecal pumps—which deliver medicine directly to the spinal cord. Physical therapy, psychological therapy (Cope has a master's degree in clinical psychology in addition to her M.D.), exercise, and nutritional and sleep counseling also are often part of the pain-treatment regimen.
In her office at UPMC St. Margaret, Cope—who speaks quickly, but with a gentle lilt true to her Georgia roots—explains that though pain has always been with us, pain medicine per se is a newly recognized subspecialty. Having a core group of physicians dedicated to treating pain, she says, improves care and, frankly, has become something of a necessity as humans live longer.

“Now, cancer patients with successful treatment can live decades,” says Cope. “People live until their bones wear out.”

She adds it only makes sense that those who live long want to live well:

“People want to function and be happy. They’re not content to sit on the porch and knit afghans and moan about their arthritis. They want to go to the beach. They want to go to the mountains. They want to fly fish. They want to entertain. They want to do things.”

On the flip side of the pain coin is Gerald Gebhart, basic scientist and new recruit for the School of Medicine. Gebhart hails from the University of Iowa College of Medicine, where he led the Pain Interest Group. (P.I.G., for short. Who says pain researchers in the heartland don’t have a sense of humor?) At Pitt, the PhD professor of anesthesiology, neurobiology, and pharmacology heads the newly established Pittsburgh Center for Pain Research.

It’s clever acronym-free, yet Gebhart has high aspirations for the center, which represents a collaboration of the anesthesiology and neurology departments as well as the gastroenterology, hepatology, and nutrition division.

“Simply stated, I want to make the University of Pittsburgh the preeminent pain research center in the world,” he says.

The achievement of this goal requires the recruitment of existing world-class pain research talent, bright young minds interested in pain research, and a balance between the clinical and the basic science sides.

“I’m kind of ambitious about that,” Gebhart concedes.

Gebhart, as one might suspect, is no slouch himself, having developed a reputation as one of the world’s most sophisticated pain researchers during his tenure at Iowa. Among his more recent honors is the $50,000 Purdue Pharma Prize for Pain Research, which recognizes a lengthy heritage of research, a dedication to training young researchers, and a deep and broad range of research interests.

If Gebhart is known for his work in any one area, it’s visceral pain, the kind of agony associated with damage or disease affecting the internal organs. Pancreatic cancer patients usually experience visceral pain. It’s difficult to treat. Finding the pathways and systems at the root of visceral pain has been his focus. His work may lead to new targeted drugs.

In an effort to tease out the nature of pain, Pitt Med sat down separately with Cope and Gebhart. In wide-ranging conversations, each spoke about where we’ve been and where we’re going in treating humanity’s common yet unwelcome companion. — JM

DORIS K. COPE

PM: What are the differences in types of pain?

DKC: Okay, when you pinch yourself, when you feel something, there are certain molecules, certain channels that are opened that cause a response, and it’s an appropriate response. You stop pinching yourself, and it stops hurting.

Chronic pain, a pinch that goes on and on for days or weeks or months, sets up entirely new pathways in the central nervous system. New feedback loops, new proteins are being synthesized. We think even new genes are being expressed, so it’s kind of a self-perpetuating abnormal state. Chronic pain is not warning you that, “Ouch, I touched the stove, and it’s hot.” We call it a wind-up phenomenon. It’s a rewiring of the central nervous system. It’s almost like a seizure of pain. A seizure is just out of control.

PM: How has treatment of pain progressed?

DKC: I think the options have changed. At one time, for surgery, for example, they didn’t have anesthetics, so they gave people whiskey and a bullet to bite on. ... They had the orderlies hold people down, and they would pin them to the table, operate as fast as they could without sterile technique, and hopefully the person survived the shock of it.

So we’ve progressed to better analgesics. In addition to anesthetic and analgesic drugs, we now have neuropathic pain medicine. We know that some of the antidepressants work for pain on some of the same neurotransmitters that are involved in both pathways. We have a lot of interventional options. We have radio-frequency [current], we have certain...
nerve blocks, injections. We have steroids; we have surgical techniques for implantation. If I give you an intrathecal pump, I’m literally giving you less than one-hundredth of a [standard opioid] dose, but it’s going directly to the spinal pain receptors, and it’s much stronger—with fewer side effects.

We also have more psychological understanding. People can be distressed, and it’s not a “pain problem.” It can be depression, anxiety. It can be opiate seeking, you know, “I want to feel euphoric, and I perceive this as pain.”

I sometimes see patients who had a very traumatic childhood, who have been abused or suffered, and it’s not okay to talk about psychic pain, it’s not okay to even acknowledge psychic pain, but [patients may be able to say], “I’m not quite right. I feel pain. My stomach. My pelvis is just not right.”

They feel they’re not right, but they can’t put [a] finger on it. It’s very diffuse, free-floating anxiety and pain. Because, to go back to the memory of what they went through—they’ve almost distanced themselves from that. So we talk about pain, but it’s not really a pain syndrome.

So, there’s pain, and there’s suffering.

Old people who live a long time, I tell them, “You live your life, and your body keeps score.”

People who have been active in sports, who’ve been steelworkers, who’ve been heavy lifting all their [lives], they come in at 75 or 80, and their [bodies] keep score. It’s not the same as the person who has been trim, exercised, not done heavy, strenuous things to [her] body.

**PM:** What’s the “next big thing”? Where is pain medicine heading?

**DKC:** Maybe gene therapy, targeting specific brain chemistry that we can change. Maybe we’ll be able to produce certain neurotransmitters in our own body. Maybe we’ll be able to diagnose genetic likelihoods, a tendency toward developing neuropathy.

If we were able to more specifically measure the ravages of pain, maybe [we could] target our therapy more specifically to those mechanisms. Right now, you take morphine—it gets the acute pain, the chronic pain, it gets the brain, it gets everything. So it makes you constipated, nauseated, and dopy, though it does take away the pain. If we could find more specific drugs and more specific receptors, [the therapy] would not make you constipated and confused and give you euphoria. It would just work with the pain changes molecularly. That would be a huge leap forward.

**PM:** If there’s one thing you could understand about pain and the treatment of pain, what would that be?

**DKC:** I would like to have some kind of objective measure of the changes that have happened in the brain chemistry or in the spinal cord from pain—some way to objectively quantify both the pain that’s there, the type of pain, and also the response to treatment. Right now, patients get some better, or some worse, or they stay the same. And we do multimodal therapy, so we’re not even sure if physical therapy is 10 percent [responsible for a success in treatment] and medicines are 20 percent and injections are another 20. If you put it all together, that’s a 50 percent reduction, which is significant. The function’s good. The pain’s better. But it would be nice to be able to do a blood test like you do for diabetes. You can follow that.

**PM:** How does what Dr. Gebhart is doing complement what you do?

**DKC:** I would like to see more interdisciplinary collaboration. Maybe we can come up with some cross-training opportunities. Maybe we can be present in each other’s clinics. I’m thinking we can really transcend boundaries here and work collaboratively with others. An institute without departmental boundaries.

**PM:** When did we start to understand pain?

**GG:** The actual study of pain mechanisms, Sherrington actually began to study reflexes to noxious stimulation. He’s sort of the father of pain experimentation. He provided for us a lot of the operational definitions of stimuli and responses that are still used today in the study of pain.

**PM:** Are there different kinds of pain, or is pain pain?

**GG:** Pain can be characterized in many, many different ways. So the simplest differentiation is acute pain as opposed to chronic pain.

But then there’s also pain that’s defined by its location. There’s cutaneous pain and deep pain, like muscle, joints, and viscera. And people categorize pain in that context because deep pain, particularly visceral pain, is organized anatomically in a different way and associated with greater emotional responses to the pain. So if you slam a car door on your hand and in the process you break a finger or two, you look at that—it’s bleeding, it hurts, but you know you’re not going to die from this.

If you get pain substernally in your chest that radiates up to the shoulder, the emotional import of that is [it’s] potentially life threatening. So pain that arises from the internal organs is almost always associated with greater emotional importance than other kinds of pain.

Then there’s other pain that’s associated with specific injuries. So there’s what’s called 

**GERALD GEBHART**

**PM:** When did we start to understand the mechanisms behind pain?

**GG:** The actual study of pain mechanisms,
neuropathic pain, which is pain due to nerve injury. There are many different ways in which pain is categorized. I guess [how you think about it] depends upon your medical specialty and discipline.

Interestingly, the mechanisms are different for deep pain, for cutaneous pain, for neuropathic pain, and understanding those mechanisms will potentially lead to better strategies for managing the treatment of pain. That's the reason why we study mechanisms of different kinds of pain.

**PM: What are these mechanisms?**

**GG:** Let me give you an example from visceral pain. Each visceral organ receives input from two separate nerves, whereas your finger receives input from one nerve. So, immediately, there's an anatomical difference between the internal organs and skin, muscle, and joints. Skin, muscle, and joints are all the same [in anatomical organization]. One nerve goes here, and that's it. If this were your bladder, there would be a nerve from here, and therein'd be a nerve from there. [Gebhart gestures to opposite ends of an imaginary bladder.]

This complicates things enormously. If you think about it. It makes visceral pain difficult to localize, so if you get a pain in your abdomen or thorax, because of the anatomical organization of the nervous innervation, it's hard to localize. So the mechanisms are different, because each nerve has a different function.

So it's easy to understand how the viscera are different from other tissues. And it's easy to understand that if you can understand the mechanism of visceral pain, it's going to be different than cutaneous pain, and it also may provide a different therapeutic target. It may have different receptors associated with it or different ion channels associated with the mechanism of the pain.

The same is true of neuropathic pain. When you damage a nerve, or sever a nerve, as opposed to cutting your skin, that nerve will heal, but even though it does there may be some permanent damage. So when the nerve is damaged, you get bizarre sensations: tingling, numbness. If you fall asleep on your arm, and you wake up, you can't move it. Then when it sort of begins to wake up it tingles a little bit. Neuropathic pain is sort of like that. You have incomplete sensory properties, but you have tingling, you have numbness, sometimes you have shooting pain associated with it.

**PM: How does that complicate treatment?**

**GG:** I think that acute pain and acute postoperative pain management [are] pretty straightforward. You go in for a surgical procedure, they cut into your belly and remove your appendix, and they sew you back up, and you've got pain. But it's treated with opioids and nonopioids very effectively. They make you walk around, and you're out of the hospital in three or four days. And you recover.

The other kinds of pain are very difficult to treat because they're associated with insults that don't heal properly or heal inappropriately and then lead to continuing pain. The usual strategies for management, like opioids, if they work, usually have to be given in high dosage. That's pretty undesirable, because opioids have unwanted effects. They make you drowsy and sedated and make you constipated. They can affect your breathing. And then long-term use of opioids is associated with development of tolerance and maybe dependence and maybe abuse.

So if you look at the drugs we have available for pain management now, we still rely on those that have been around for quite a while. The nonsteroidal drugs like aspirin ... there are many new aspirin-like drugs, but in terms of efficacy, they're not that much different than aspirin. There are new opioids, but an opioid is like a rose—it may differ in color, but it's still a rose.

Opioids are the most efficacious drugs we have for pain. Opioids are capable, in sufficient dosage, of relieving virtually all pain. But sometimes you have to be nearly unconscious for that to happen. And that's not good. So we're looking for new drugs all the time, and the molecular revolution in biology has permitted us to identify some specific molecular targets, such as ion channels and new receptors that are associated with pain mechanisms. The hope is that identifying these new molecules that are in neurons and are associated with pain will allow us to develop new chemicals, new drugs, that target those molecules.

The downside of identifying all of these molecules is you identify and target a single molecule, and you can very effectively block that molecule, but pain is not associated with activation of just the single molecule. It's multiple molecules. That's why opioids, for example, are so good. They do more than just a single thing. The drugs that have been developed that do just a single thing typically work just a little bit. We want to know what the molecules are, but targeting them has not been particularly fruitful in developing new drugs.

Presumably some very new strategies are effective in combining targets. The [drug] industry [has been] saying, “Let's develop..."
this specific drug that acts on a selected target." But now I think they know they need to develop a chemical that has selectivity for several targets, two or three targets. I think that's what's on the horizon.

**PM:** Any research into nontraditional forms of pain treatment?

**GG:** There's great interest in the pain community to understand why some of these things are effective in people. I take the view that some of these folk medicines and these nontraditional approaches are helpful and useful. It's part of our job to find out what is contained in those folk medicines or ... strategies that is the useful principle.

People drink green tea or they take some herbs ... and some of these things have been proven to be useful. And others have been shown to be totally nonuseful, though they may have a placebo effect.

If you look at the history of effective drugs, they were derived from natural sources. Opium comes from the poppy plant. We learned about aspirin [after realizing the analgesic effects of] salicylates, which are part of willow bark. So there are many, many natural products out there—some of them that come from toad skin, and others have come from plants, and venoms from snakes and spiders—which are complex things when you collect them. But you have to identify what the active principle is. There's [a new drug] that comes from a cone snail that's a poison that the snail uses to kill its prey. [It's] now used as an analgesic in certain pain states.

There are also toxins from snakes and spiders that have been extracted and purified that are being tested in a variety of circumstances. For example, some of these block sodium channels. [You're probably familiar with local anesthetics like lidocaine that your dentist might administer.] But they're sort of nonselective in that they block all sodium channels. There are like nine or 10 [channels]. So, you don't want to give a local anesthetic in great concentration directly into an artery because it will affect the heart and could kill you.

**GG:** But some of these things that people have gotten from snakes and spiders and whatnot have very selective actions on certain sodium channels. If you could, for example, develop a drug that was effective at one of the sodium channels that's called the NAV 1.8 channel, it could be useful, perhaps, in pain because neurons that express NAV 1.8 are uniformly associated with pain processing. I think it emphasizes again why it's important to look at these natural treatments people have used over the years, sometimes centuries, because some of them have active principles that might be extremely useful. And some of them are just hokum, just nothing. Still, I think it's incumbent on us to find out—to find out the truth.

**PM:** Is there one question regarding pain that you'd like to have answered? What would you like to know most that you don't know right now?

**GG:** Let me preface this by saying, one of the characteristics of many of the pains that are chronic and difficult is the fact that people are hypersensitive to normal stimuli.

So, if there was one question that I could answer and address, it's "What is the mechanism that contributes to the development and the current irreversibility of hypersensitivity in disorders like interstitial cystitis, low back pain, fibromyalgia?"

It may be naïve to think there's one mechanism, there may be multiple mechanisms, but if we could [ask] about the mechanism that causes the persistence and current irreversibility, that would be the question I would like to see answered. Because that would probably provide an efficacious strategy for management of many, many types of chronic pains.

**PM:** What problems do physicians face in treating pain?

**GG:** It's a complicated issue. First of all, to be blunt about it, most medical school curricula do not include sufficient education about pain and then about pain management. Most physicians, then, when they get out and practice, specialize in things where pain is almost always present in a subset of their patients, but is not their primary focus.

Pain management is poor because it is not emphasized in education. It's also poor with respect to the use of opioids because there are societal and legal restrictions against the use of opioids. In the current [federal] administration, the Drug Enforcement Agency is very aggressive in seeking out and punishing healthcare practitioners, principally physicians, who are prescribing huge dosages of opioids to patients.

There are many, many cases where physicians have been put away in jail for basically distributing opioids, as if they were drug dealers. And it's a very, very fine line physicians are walking these days in terms of efficiently and effectively managing pain and staying out of legal trouble. We're trying to do the best we can to educate law enforcement people about the difference between opioid abuse and opioid use at high dosages. But it's a difficult, difficult fight. And it is a fight. Physicians are under considerable legal pressure not to give prescriptions for high dosages of opioids to people in pain.

There's also the stigma associated with the use of opioids.

So, as bizarre as it may sound, there are families who are not happy that grandma is being treated with an opioid for her cancer pain, even though she may be terminally ill, because, "What are the people in the community going to think? Grandma's become addicted."

In some way, it makes them complicit in making grandma addicted and, in some way suggests that they're a bad family.

If you talk to cancer pain patients who have been told, "You've got a certain amount of time to live; it's inevitable that you're going to die [soon]," and you ask them, "What worries you most?" You might think they'd say, "I'm scared of dying." It's not that. They're scared of dying in pain. That's what it is. They're afraid of suffering.

Most of these people will accept the fact that their lives are going to come to an end. It's going to happen to all of us at some time, so you accept that once you get over the initial shock. But ... they don't want to die in pain.

"There are families who are not happy that grandma is being treated with an opioid for her cancer pain, even though she may be terminally ill."
Influenza diversity is staggering. In this chart, narrow columns represent a total of 207 influenza A viruses collected from 1998 to 2004. Each row represents an altered amino acid position in one viral protein. Amino acids are color coded, so that mutations can be seen as changes in color when scanning from left to right along a row. (The large image is a close-up; the inset shows the entire chart.)

Cover Story

EVOLUTION OF FLU

On April 24, a 37-year-old woman in a Sumatran village became ill. It is presumed she developed a fever, cough, and aches. She died 10 days later and was promptly buried, long before any distant authorities became interested in why she died. In the next three weeks, however, six of her relatives died of avian influenza, including her two sons, a sister, a brother, a niece, and a nephew. A second brother also caught the flu. He alone survived.

In this village of a few hundred households, chickens wander freely. Those that appear ill are often eaten. The woman is suspected to have caught the virus from live chickens in the market where she sold fruit and peppers or from chicken manure that she used to fertilize her garden.

At least 252 people have been infected by the H5N1 strain of avian flu in the past few years. More than half died. Fortunately, the virus is not readily transmitted from one person to another. Almost all victims caught the virus directly from birds or from another person who did. The Sumatran case set off alarms for two reasons: It was the largest cluster of cases ever, and it
marked the first time that the virus was known to have been transmitted from one person to another and then to a third person. It showed that avian flu might be adapting to humans. There is precedent for this.

In the winter of 1918, a doctor in Haskell County, Kan., alerted the U.S. Public Health Service that people in his wide, flat, wind-blowen patch of the Midwest were suffering from “influenza of a severe type.” The doctor, Loring Miner, had seen influenza many times before, writes historian John Barry in The Great Influenza. But this was different. The disease seemed to race through its victims with great speed. They were wracked by an unusually violent cough and terrible aches. They gasped for air. In the month of February, influenza consumed all of Miner’s time and energy. He grew deeply troubled as he crisscrossed the frozen prairie in a horse-drawn buggy. He saw people die that winter who had been in robust health and in the prime of their lives only weeks before. Many experts now believe that an avian flu virus—the H1N1 strain—jumped species in Haskell County.

When spring arrived, the flu seemed to depart with the wintry weather, even before Miner’s alert was published. This is typical of influenza, which is most readily transmitted through dry winter air when people spend long hours together indoors. It’s possible that this was the end of the line for Miner’s flu—an unusually nasty bug that appeared overnight, raced through much of the population, then fizzled out for lack of new hosts in this sparsely populated area.

But there is another possibility: The virus may have mutated enough to become less lethal and continue circulating. Influenza needs a regular supply of new hosts, because anyone who is infected and recovers becomes immune to that strain. A supply of new hosts was readily available that year. There was a war on, and young men who otherwise might never have left Haskell County traveled hundreds of miles to Camp Funston, where more than 50,000 soldiers lived crowded together like livestock. From there, they would disperse to yet more crowded military bases and, eventually, pack and plains. This is the adaptive landscape of influenza A. (Influenza A encompasses the typical flu viruses that become epidemics, the deadly avian flu that concerns us now, and the 1918 strain.) Every possible coordinate on this tumultuous landscape represents a different genetic variant of influenza A. Points that are close together are genetically similar; distant points are genetically varied. The mountains that represent fitness in the Darwinian sense—that is, the higher a point is on our landscape, the more successful that particular virus is at generating copies of itself. The lower slopes and valley bottoms are genetic variants that are unlikely to thrive.

The adaptive landscape of influenza A is vast. It’s like a relief map of Eurasia, largely unexplored. It has peaks of fitness like the Alps and Himalayas and large, blank regions of mystery that, even today, may as well be marked, “Here be demons,” because scientists do not yet understand all of the variations that make a virus lethal, transmissible, drug resistant, or the stuff of pandemics. A virus might have high fitness and remain relatively benign—causing symptoms that eventually subside as the immune system restores order. Others threaten to bring us back to 1918. A small but growing number of scientists are trying to map this world and learn how the viruses in circulation move about the map—how they scale the deadliest peaks, how they leap suddenly from one place to another, and what we can do to be ready when they do.

Some strains of flu virus are always circulating in the human population. Hippocrates is said to have described an influenza epidemic in 412 B.C.

When a virus crosses the species barrier and adapts to humans, a pandemic can result. The 1918 Influenza killed between 20 million and 50 million people as it ran its course through 1920; it was probably the deadliest outbreak of disease in human history. The Asian Flu of 1957—58 killed more than 1 million people, and the Hong Kong Flu of 1968—69 killed at least three quarters of a million people. Many experts say we’re due for another pandemic.

Scientists could not be certain influenza actually was caused by a virus until the virus was isolated in the 1930s. During the 1918 outbreak, suspicion had largely fallen on an opportunistic bacterium, which now bears the somewhat apocryphal name Haemophilus influenzae. (It often turns up in the lungs at autopsy, having caused pneumonia in people weakened by influenza.)

The virus didn’t get its due respect in the genomic revolution of the past decade—not until as recently as 2004, anyway. That’s when Elodie Ghedin, a molecular biologist working at The Institute for Genomic Research (TIGR), was given a new assignment. TIGR (pronounced tiger) is a nonprofit institute in Maryland dedicated to unraveling the genetic code of living organisms, especially important microbes. As a junior investigator at TIGR, Ghedin stood out as one of the few people who had time to take on a big, new project, she says, with a laugh. TIGR had a large grant from the National Institute of Allergy and Infectious Disease for sequencing human pathogens. With a small team of colleagues, Ghedin was tasked with figuring out influenza. She had worked extensively on the genomes of human pathogens, but never that of influenza virus.

Ghedin is now a Pitt assistant professor of medicine. Her first name rhymes with “melody.” She is quick to smile. A first-generation Canadian, Ghedin was pleasantly surprised to...
find that Pittsburgh reminds her of the Montreal of her childhood, with its working-class, closely built neighborhoods that are by turns beautiful, historic, a bit sad, welcoming, insular, pedestrian, and newly resurgent. She is the child of French immigrants, a product of Montreal’s public schools, and a PhD graduate of that city’s McGill University. She first came to the United States for a postdoc in molecular parasitology at the National Institutes of Health (NIH). There, she continued working on her thesis subject: Leishmania donovani, which causes visceral leishmaniasis in half a million people annually, mainly in Africa and Southeast Asia. (After a second NIH postdoc in parasite genomics, she and several collaborators would publish the complete genomes of three related pathogens, including Leishmania major, in Science in 2005.)

At the time she was given the influenza job, fewer than 10 samples of flu virus had been fully sequenced (with their genetic code transcribed molecule by molecule). The few sequences available were of viruses chosen because of unusual characteristics or rarity. For a virus as variable as influenza, this is like trying to learn about humanity by looking at the genomes of six people with unusual genetic conditions. Ideally, hundreds or thousands of random, complete genomes would be needed to begin to unlock the secrets of influenza. But sequencing was an expensive and painstaking process. Ghedin’s team had to create a new way to do it—faster, cheaper, and in higher volume.

Influenza is simple, in a way. It consists of a spiky ball made of two interlocking proteins. Inside are eight lengths of RNA that comprise the virus’ eight genes.

The genomics methods that work so well for sequencing human DNA would not work for an RNA virus like influenza. To sequence the human genome, scientists used what they call the “whole genome shotgun” approach. “You just shatter it,” says Ghedin. “Just break it up. Then you clone these pieces and you can get a whole genome [when you reassemble them]. You can’t do a whole genome shotgun on RNA. You have to reverse transcribe it into DNA. And when you do that, you are bound to lose pieces.” It was the ends of the pieces that were being missed, making it impossible to reconstruct a whole genome. Ghedin’s team’s solution?

“We just glued the pieces together. ... We got rid of the ends. Well, that was inefficient,” she admits, laughing.

In the end, they settled on a novel version of the whole genome shotgun. They copied the influenza genome into very tiny overlapping pieces—about 250 base-pairs long. By putting the overlapping pieces together, they could reconstruct the entire genome. The volume of work they managed to complete in short order was unprecedented in flu research. They employed robots to inoculate the large number of 96-well plates containing the viral RNA to be duplicated. Then the assembly line went to work.

“We built little teams of people,” says Ghedin, who retains an adjunct position at TIGR. “And that’s how it works, still. There is a team that does the reverse transcription and the amplification [duplication] of the pieces. Then it’s passed on to another team that will do the sequencing. Then another team—the informatic team—will pull all these sequences, clean them up, trim them, and assemble them. Then another team, called the closure team, are the guys that go through and make sure there are no holes in the genome. ... The product is then sent to GenBank [the public database of genomic information], which does the annotation. They have a team there that determines whether the coding regions are good. They would come back to the TIGR team and say, ‘There was this area that looks a bit strange.’ They are the ones that post all the data.

“The brunt of the project was really on the bioinformatics end,” says Ghedin. “And this type of project could not have been done 10 years ago, when we didn’t have the bioinformatics tools.”

“The folks at TIGR have a real institutional experience and understanding of how to wrap things up,” says David Lipman, director of the NIH’s National Center for Biotechnology Information, which manages GenBank. “And Elodie herself really was very central to solving a number of challenges there.”

In less than two years, the team has sequenced more than 1,500 flu viruses in circulation between 1996 and the present. Most have come from upstate New York, where that state’s health department conducts exten-
An RNA virus like flu evolves about a million times faster than humans, okay? So, a phylogeny of 10 years of influenza virus evolution is something like 10 million years of human evolution. That’s the difference. And what you see is buckets of diversity. You see lineages being born, dying out, replacing each other—a big sort of melting pot of diversity, with lots of various evolutionary processes: selection, drift, extinction, replacement, and reassortment (kind of a sexual thing) going on in single populations.”

Virus sex? Not exactly, but influenza evolves by two main mechanisms, one of which is analogous to sexual reproduction. Scientists sometimes refer to the mechanisms as “drift” and “shift.” Drift, aptly named, is a rather passive process. It’s the result of random errors in the virus’ RNA as it is reproduced inside infected cells. RNA is much more error-prone than DNA. In the case of viruses, this is an advantage, because random errors, or mutations, sometimes help the virus adapt. For example, a change to its surface protein might mean that the immune system doesn’t recognize it as flu. Other mutations can change the way the virus makes you sick or reacts to medication.

Shift, or reassortment, is a much more dynamic process, involving two flu viruses contributing a portion of their genes to create one dramatically new virus—sort of like how your parents created you. It occurs when a cell is infected with two different influenza viruses simultaneously. The cell’s machinery is hijacked so that it produces many copies of influenza’s eight genes. But with two viruses infecting this cell, there are actually 16 influenza genes being copied. They mix and mingle and come together in various new combinations. Then, they are enclosed in a new capsid—the spiky shell of interlocking proteins that completes the construction of the new virus.

“I think they found a whole new way of looking at influenza diversity and evolution that had been missing before,” Holmes says. “We found the virus was much more diverse in single populations than we had thought before. We found lots of reassortments.”

“It was thought that drift mutations—just the little sequence mutations—were a major component of the way influenza evolves,” says Kirsten St. George, director of the clinical virology program in the Wadsworth Center. “But it has become very clear with the analyses of the whole genomic sequence of hundreds of [viruses] that reassortment is constant and frequent in the population. It is a major, major component of the evolutionary path of influenza.”

In her office in Pitt’s Scaife Hall, Ghedin points to a colorful chart on the wall of her office (see p.18). “My favorite poster,” she says. Each color represents a different amino acid, a key component of the structure of the flu virus. The chart shows 207 flu viruses sampled in New York from 1996 through 2004. She points to a narrow column in November 2003, representing just three viruses out of dozens sampled that season. The colors match all of the other viruses in circulation at the time—but only at the very top of the chart, on the gene for the surface protein. At the lower part of the chart, which shows the other seven genes, the colors are wildly different.

“The take-home message of this one is that you can see reassortment occurring,” she explains. “And we knew that was occurring, but in this case it was really important, because it involved the surface protein.” In this narrow band representing three viruses, a surface protein appears to have been transplanted from one set of viruses to another. The human immune system only recognizes the flu virus by its surface proteins, so swapping one for another can be like donning a disguise. The results can be dramatic.

Reassortment may be the event that triggers the next pandemic. Imagine a farmer in China who is sick with a typical human flu and a deadly avian flu that he picked up from his chickens. He is dying, and his family gathers round him as he lies coughing, gasping, and shedding a new virus that is a combination of a deadly avian flu and a highly transmissible human flu.

In 2005, scientists modeled a theoretical avian flu outbreak. They predicted that the World Health Organization would have, at most, three weeks to trace the contacts of all those exposed and distribute antiviral medications in a protective ring around the outbreak. But in Sumatra, the first WHO official reached the site of the outbreak approximately 19 days after the first woman became sick. Others arrived a week later. Villagers were suspicious of health officials and did not always cooperate. Some of those infected apparently fled the hospital while still shedding virus.

Meanwhile, people moved about the country as people always do. They squeezed aboard crowded buses, visited distant relatives, cared for the sick, and sent their kids off to school. They boarded flights bound for the capital cities of Asia and beyond. Fortunately, the virus did not completely adapt to humans this time, and the chain of infection ended.

In North America, teams of scientists quietly went about the work of translating the peculiar alphabet that is RNA, learning to spell influenza 1,500 different ways. “Genomics has to really be looked at as a discovery science,” says Ghedin. “You may go in with a preconceived idea, but then you have to be really open to learning something completely different.”

In other words, she and her colleagues have every intention of learning practical things about influenza, such as which genes confer drug resistance and which virus is likely to be dominant next year. But the work is not all hypothesis driven. They are simply sequencing all of the random viruses they can get from one region—creating a mountain of data for scientists to mine. The questions they ask and the answers they find may warn us of the next pandemic, or they may ultimately teach us about other RNA viruses like H1N1, about the evolution of parasites, or about the properties of our own RNA and DNA.

“Increasingly, we see in biomedical research the interconnectedness of life,” says Lipman, “and discoveries in one area can all of a sudden inform searches in another area.”
Some say tuberculosis infected the first hominids. It was found in Egyptian mummies. Humans have lived and died with the bug for a long time, and it can be an ugly companion. TB has been known to destroy the lungs to the point where its victims cough blood. Its gruesomeness has been matched only by its success: TB is thought to have killed one-quarter of the adult population of Britain in the 19th century.

Fear of TB drove major reforms in social and medical policy at the turn of the 20th century, and today the disease is at record lows in the United States and other parts of the Western world. But it remains rampant elsewhere—and now it is changing in ways we don't understand.
In light of its age, it makes sense that Mycobacterium tuberculosis, the bug that causes TB, has a strong instinct for self-preservation. It is encased in a protective structure known as a granuloma. Treatments take six months, and TB has been learning how to shrug off those treatments. From 2003 to 2004, the percentage of drug-resistant TB cases in this country jumped up 13.3 percent. That was the highest such increase since 1993; experts wonder if a TB scourge might rise again in the West.

This ancient, and perhaps prehistoric, pathogen still infects almost 2 billion people today, a third of the world’s population. We’re not sure why it only kills about 2 million a year, one-tenth of 1 percent of those infected. Then again, we’re not sure why it can occupy its host for 50 years—hanging out at granuloma beach, sipping mai tai (or whatever it is) dormant pathogens do with themselves—then let something else kill its host. But Mycobacterium tuberculosis has always had a sense of the dramatic. In 1967, Vivien Leigh suffered a recurrence of TB that would kill her. This was dramatic. In 1967, Vivien Leigh suffered a recurrence of TB that would kill her. This was and well muscled—she’s a former triathlete and marathoner who still runs or cycles every single day—Flynn has an athlete’s easy self-confidence. She also possesses an athlete’s fondness for trash talk, and talks up her bug, TB, over the others being tackled by the new Pitt Center for Modeling Pulmonary Immunity.

“You know that TB is not the only thing being studied—even though we think it’s the most important,” she says, flashing a wide smile over her shoulder as she strides off to her office for a meeting.

Later, in her office, she busily arranges meetings with center researchers working on other formidable diseases. (Despite the trash talk about their chosen pathogens, she’s determined that this writer meet with every single one of her center colleagues and is setting up the appointments herself.)

When she’s comfortable hanging up the phone for a bit, she delves into her work using mathematical modeling to gain insight into how TB works. She started modeling more than seven years ago; that makes her one of her center colleagues and is setting up the appointments herself.

When she’s comfortable hanging up the phone for a bit, she delves into her work using mathematical modeling to gain insight into how TB works. She started modeling more than seven years ago; that makes her one of her center colleagues and is setting up the appointments herself.

She’ll explain how models do things that can’t be replicated in a lab. A model can simulate what might happen over several decades of infection, whereas a lab experiment that lasts more than a year requires tremendous effort to execute. A model can let researchers see what might happen if they knock out a specific disease protein—very difficult to do in a lab, says Flynn. A model can make it more effective to study multiple functions of cells.

They have met with early confidence-boosting successes.

They’ve also met with culture shock and the occasional crisis of faith.

Just after she was in Anton Chekhov’s Ivanov, playing the role of a woman dying of TB.

There are troves of TB data, from petri dish studies, from animal studies, from human patients, and it’s next to impossible to pull all this information together.

JoAnne Flynn, however, fully intends to do so. It’s her plan to develop faster treatments for TB and, by the way, a new vaccine. How? For starters, she’s learning some math.

She and her colleagues are adopting a new way of thinking and talking about a handful of the world’s most menacing diseases. They have met with early confidence-boosting successes. They’ve also met with culture shock and the occasional crisis of faith. Flynn is betting, however, that the new math will be worth all the trouble.

Flynn is a coil of energy, and in her working life, she unleashes it all on understanding TB. She holds associate professor appointments in three departments at the University of Pittsburgh School of Medicine: medicine, immunology, and also molecular genetics and biochemistry. Trim lab a model of sorts for the other researchers involved in the new center, which is led by Penelope Morel, an MD and associate professor of immunology and medicine.

Mathematical modeling is not second nature to Flynn. She turned to it to see if it could help her pull together the legions of data on TB. But she tends to master things fast. When she was in graduate school, Flynn decided to take up basketball and developed into a solid low-post player. She says she continues to develop her cooking skills even though she’s already a gourmet, and that she both ran and cycled every day until three kids and a good-sized lab forced her to cut back.

Flynn trained as a microbiologist, but her interest in TB vaccines led her to pursue a second postdoc in 1990, in Barry Bloom’s immunology lab at Albert Einstein College of Medicine in Bronx, N.Y. Not an easy shift.

“Immunologists don’t like microbiologists,” she says. “[Microbiologists] make life messy.” Immunology also uses a different language and these are the kind of points she herself heard through the years from Morel—friend and fellow foodie—has been modeling aspects of the immune system for more than a decade. Flynn would get an earful about modeling during their nights at the Pittsburgh Opera; the two have shared a subscription for years.

Flynn notes that convincing her colleagues of the merits of modeling has been a slow process, but she says, “Hey, I convinced my lab—or half of ‘em, anyway.”

That’s a start. But what they really need, she thinks, is the chance to play with her model and her data. If they could do that, they’d get it instantly, she says.

The National Institutes of Health believes the same thing. The agency’s National Institute of Allergy and Infectious Diseases (NIAID) is giving Pitt $9.1 million over five years so it can develop software modeling tools that will be freely available to immunologists. Pitt researchers, along with faculty members at Carnegie Mellon University and the University of Michigan, are building models of how the
The NIH is also funding Immune Modeling Centers at Duke University, the University of Rochester, and Mount Sinai School of Medicine.

Pitt might not have been on the list, if not for a dinner party back in the early 1990s, organized by Morel, the Center’s principal investigator. Morel’s husband, Benoit Morel, is professor of engineering and public policy at Carnegie Mellon, but he began his career as a high-energy physicist. At the time, he was teaching a course called Chaos and Complex Systems. One of Penelope Morel’s colleagues and dinner-party guests asked Benoit about chaos theory and the human immune system.

Benoit Morel talks with the force of a spring torrent, and when the immunologist asked about chaos theory, the words came gushing out. The immunologist asked him to give a lecture to his class about chaos theory, and he agreed gladly.

The lecture was a dud.

“You should’ve seen the glazed eyes of the biologists when exposed to math,” he recalls.

The Morels held fast to their belief that modeling could yield important results for immunology. Along with two colleagues, they proposed building a model to examine the behavior of Th1 and Th2 cells, immune responses that seem to antagonize each other instead of working together.

Penelope Morel, a soft-spoken Brit, says, “I didn’t think it would get funded.”

But the NIH gave them funding. Their initial work led to a paper, published in 1994, demonstrating that a model was able to effectively predict how the cells would work together in the body based on amounts of interleukin-2 and 4.

The NIH renewed its grant twice, so the Morels have spent nearly 11 years modeling elements of the immune system, while gradually bringing others into the fold, like Ted Ross.

Ross is an assistant professor of medicine who also holds an appointment in infectious diseases and microbiology in the Graduate School of Public Health. He concentrates on influenza and thinks modeling could shift the flu vaccine process from reactive to proactive.

“We know that every season, flu changes. A big question is, can we develop a model to show how a virus is going to move, and can we find ways that we can build [an accurately targeted] vaccine beforehand?” Ross asks.

But mathematical models are incredibly complex things to build. Flynn and University of Michigan mathematician Denise Kirschner needed two-and-a-half years just to populate a model they could use to test ideas and find new directions for experiments. And that’s in addition to time Kirschner had already spent building a model for TB. (Her earlier model predicted that shutting down IL-10, an immune system regulator best known for its anti-inflammatory properties, would prompt TB to become active. “That’s a change you’d miss in a wet lab,” says Kirschner. The conclusions were published in The Journal of Immunology in 2001.)

Modeling the human immune system is difficult because of its remarkable complexity. Ask anyone who has tried to parse just the medical literature on TB, which is vast, despite a significant slowdown in papers published between the 1960s and 1990s.

But, ultimately, the biggest challenge in modeling comes back to Benoit Morel’s initial eye-glazing lecture. Immunologists don’t tend to speak the language of mathematicians and vice versa.

Penelope Morel says that often means expectations are different as well. “Mathematicians always want to know everything about everything at every single time point,” she says.

“A lot of immunologists are either not willing to do those experiments, or the experi-
ments are just not possible to do.”

As part of the NIH grant, the various researchers gather for biweekly conference sessions, where mathematicians, computer scientists, and immunologists take turns presenting papers. The diversity of the group forces them to try to break things down—biologists don’t know the differential equations, and mathematicians have never worked in labs. Vacant stares still happen on both sides of the table.

Yet growing enthusiasm for the endeavor and camaraderie hold together the group in these still-early days. For instance, Michigan’s Kirschner and Pitt’s Flynn have developed a deep friendship.

Their first call went for two hours. Not only do they share research interests, they might be alter egos: They have the same cheery cadence of speech, they’re both quick to laugh, and they’re equally direct. They’ve both recently had babies, both are unrelentingly active (Kirschner is an aerobics fanatic), and both love food.

Their early bond has been reinforced by years of meals (sushi is the top pick) and late-night editing sessions fueled either by chocolate or bubble gum. (Both women love to crack bubble gum and are banned from doing so by their families.)

They’ve developed models for TB that Flynn is applying more broadly to her research. The models were key to a paper published earlier this year in *The Journal of Immunology*. That paper showed that a cell known as CD8 (cluster of differentiation 8) has a far greater role in containing TB than was previously thought. The work they’ve done so far will help them in the next five years, as they develop software tools that other researchers can use.

Penelope Morel is looking forward to that day: “We’ve got to have software to deliver so that others can use it. It’s no good for us if it’s just a few doctors here who are modeling.”

Flynn says once other immunologists get their hands on such software, they’ll discover that modeling is “really very, very fun.” She says models “allow you to put all the things you know and a lot of things you don’t know into one place.”

You don’t just stroll into a lab to glimpse *Mycobacterium tuberculosis* under a microscope. The bug is a biohazard, and the CDC requires that bench TB research take place in a Biosafety Level 3 lab. (Level 1 labs are used for nonhazardous activities, like testing water supplies. Level 2 labs are for risky diseases like Hepatitis B. Level 3 labs are for work on life-threatening diseases that spread through the air and through communities. Level 4 classification—that’s for “dangerous and exotic” aerosol agents for which there is no treatment available.)

Getting into a level 3 lab requires a skin test, a quick shot of a precursor protein to TB, followed by two days of waiting to see whether the skin swells, the telltale sign of exposure to TB.

Because TB spreads primarily through the air, working in a TB lab also requires being fitted for a mask. An industrial hygienist brings forms—there are always forms in hospitals. These probe for signs of potential breathing issues or claustrophobia. Then he pulls out an orange Kimberly-Clark N-95 Respirator Face Mask, designed to filter out aerosol particles. You strap it onto your head, tuck it under your chin, and pinch the nose plate. He puts a hood over you and sprays a saccharin-based aerosol into the hood. You nod your head, then shake it gently. If you can’t taste the saccharin, the mask works. If you can, he has a bevy of other masks. And if you count among the 5 percent of people whose faces can’t be fitted, he has something that looks like a World War II–style gas mask.

Entering a level 3 lab requires more than just a mask. It means a whole new wardrobe on top of what you’re already wearing: a hair bonnet, a pair of thick hospital scrubs, a set of rubber gloves taped over the wrists of the scrub shirt to seal it, a second set over that, and then two pairs of footies to cover your shoes.

You are then permitted to walk through a door with “BioHazard” warnings slapped on it. There are plenty more of those inside. Other than sporting warning labels, level 3 labs look pretty ordinary. The one Flynn uses has four rooms with hoods, flow cytometers, and notebooks. A novel sits on a computer keyboard in one of the rooms, for whiling
Gerard Nau, assistant professor of molecular genetics and biochemistry at Pitt, is a tall, slender man. He says that as an M.D./Ph.D. he was trained to bridge the gulf between the clinic and basic science. "As great as that divide is, there's a 10-fold gap between the molecular understanding of the bacteria that causes tularemia. If tuberculosis is a little-studied infectious bacterium, tularemia is the rabbit from *Monty Python and the Holy Grail*, savaging a human host in practically no time and often killing it. We can treat tularemia, if we diagnose it correctly. But it is also a Class A pathogen, on the fed's short list of the most-feared potential bioweapons along with anthrax, botulism, plague, smallpox, and viral hemorrhagic fevers.

Nau is no ready-made fan of modeling. He initially believed models tended to predict the obvious, like drug-resistant TB would have a global impact. But participating in the center's biweekly conference has slowly changed his mind—thanks, in large part, to Shlomo Ta'asan, a 50-year-old professor of mathematical sciences at Carnegie Mellon who is coprincipal investigator of the modeling center.

"His approach will help me build new experiments, come up with new insights—that was an epiphany for me" about modeling, Nau says.

Ta'asan is another accidental modeler of biological systems. He's a neighbor of the Morels and says he probably first heard about modeling the immune system at one of their Christmas parties. Further conversations with his friend Benoit Morel eventually led him to start developing models. Talking to researchers refined both his understanding of the science and his models.

Even so, the words don't always tell him what he needs to know. After spending months developing a model for data from microarrays, tiny chips that can process hundreds of thousands of biological samples at a time, he found that the immunologists hadn't explained a step in the experiment. "I think it was obvious, like drug-resistant TB would have a global impact. But participating in the center's biweekly conference has slowly changed his mind—thanks, in large part, to Shlomo Ta'asan, a 50-year-old professor of mathematical sciences at Carnegie Mellon who is coprincipal investigator of the modeling center."

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Donna Burke has seen a lot. He studied epidemic disease while serving as a doctor in places like Cameroon and Thailand. He founded the U.S. military's HIV/AIDS laboratory and was the associate director of emerging threats and biotechnology at Walter Reed Army Institute of Research. He ran the Center for Immunization Research at Johns Hopkins University. He is an expert on avian flu, AIDS, and tropical diseases. Yet, increasingly, no matter where his work takes him, he comes back to the power of computation.

Burke is the new dean of the University of Pittsburgh Graduate School of Public Health. He also directs Pitt's new Center for Vaccine Research and holds an appointment in the Department of Medicine.

A longtime believer in mathematical models, Burke uses them to help predict the course of disease outbreaks in the general population. As an MD who came to modeling to help cure people, he thinks it is a commonsense approach:

"All decisions are based on models. Every time you think about a problem, you put together a mental construct."

"His two main goals at the Graduate School of Public Health are to increase research on infectious diseases and boost the use of computation in public health."

"Computational modeling takes mental models, makes them explicit, and then helps make them more rigorous," Burke says.

Burke by no means thinks computer modeling holds all the answers for public health. But he does think that modeling reveals "what is unknown, and unmeasurable."

His models work on the level of entire populations. They are macromodels, as opposed to the models created in labs like Penelope Morel's or JoAnne Flynn's (see p. 23 story), where the focus, so far, is on modeling molecular-level interactions. But in time, Burke intends to develop groups of modelers and medical researchers who can work together to develop a model of "the whole enchilada: the evolution of the microorganism, the immune response of the host, the behavior change of the overall population, as well as underlying social dynamics," he says. —MF
Although he never focused on practical applications of the basic science he pursued, Ernst Knobil laid the groundwork for revolutionary treatments for dwarfism, infertility, and prostate cancer. He’s shown here with his wife, scientist Julane Hotchkiss, during their years in Pittsburgh. (c. 1981)
Ernst Knobil adored fast cars, and he drove them enthusiastically, if not well. Over the years, newer models replaced their mangled predecessors in the family garage—Karmann Ghias, Fiats, and finally, in the late '90s, a black BMW. Paternal goading earned son Nick his first speeding ticket while driving an Alfa Romeo through West Virginia. When a state trooper finally nabbed the pair, the teenage driver nearly burst into tears. Knobil leaned across the front seat to explain. “It’s all right,” he said. “I’m the boy’s father.” “He took my dad out of the car, and they sat in his cruiser for a long time,” says Nick, now in his mid-40s. “My dad came back, got in the driver’s seat, and we drove quietly for a while. Then he said, ‘Let’s not tell your mother about this.’”

Julane Hotchkiss would hardly have been surprised. “He got tickets all the time,” she says, recalling a stop in upstate New York when the officer informed her husband he’d been clocked at 92 miles per hour. “He almost said, ‘Hell no, I was going 120,’ but he clapped his hand over his mouth.”
Such episodes of reckless abandon form a stark contrast to the reputation for meticulous research of the reproductive endocrinologist. Armed with the knowledge of the human, he laid the groundwork for revolutionary treatments for dwarfism, infertility, and prostate cancer.

If not for his April 2000 death at age 73, and the medical establishment’s late 20th-century preoccupation with molecular—rather than organismal—biology, says colleague Knobil (pronounced no-bed) might have warranted a Nobel.


Knobil began his academic career in 1952, in Harvard Medical School, as a postdoctoral fellow in endocrinologist Roy Greep’s lab studying the adrenal gland and growth hormone in primates. And while the research yielded impressive results, Knobil became increasingly frustrated with a personal failing—he couldn’t understand the human menstrual cycle well enough to give a lecture on the topic as part of his duties.

“I could never understand it because it was completely based on beautiful work that had been done on rats and guinea pigs,” the scientist recalled in a 1995 interview.

“I had all these monkeys hanging around, left over from the growth hormone stuff, and I said, ‘Dammit, I’m going to find out how it works, starting from scratch.’ And that’s exactly what I did.”

As chair of physiology at Pitt from 1961 through 1981, he required his entire faculty to attend every first lecture medical students heard from a department newcomer.

“To this day, the most horrifying, terrifying day of my life was the day I gave my first lecture,” says Jimmy Nell, who completed a postdoctoral fellowship with Knobil in 1967, spent four years as a physiology instructor at Pitt, and eventually retired as a Distinguished Professor from the University of Alabama at Birmingham.

Tony Plant’s first lecture was on the endocrine basis of human sexual behavior.

“I spent several weeks getting the lecture ready, to impress Ernie and everyone else,” says Plant, a postdoctoral fellow in “Knobilab” in the ’70s and now a professor of cell biology and physiology and of obstetrics, gynecology, and reproductive sciences at Pitt.

“There was a student in the front row with his feet up on my desk, reading the paper. He raised his hand and asked if the lecture had a lab.”

Plant froze, mortified by the student’s insubordination. Like all who had preceded him, Plant later got a call from Knobil’s secretary, inviting him to come by and discuss the lecture.

“Ernie told me I should have answered that student with, ‘Yes, but only with wax models’.”

Knobil always began his own lectures by giving the history of the topic, says Nell, who later collaborated with Knobil on two editions of the textbook, The Physiology of Reproduction.

“The medical students hated it. But he felt that you must always know where the ideas you are currently studying came from.” Knobil’s tough exams and tougher grading didn’t boost his popularity, and his pass rates frequently lagged the rest of the school. “Some years we flunked more than were acceptable to the dean,” says Plant, “and that caused major friction.”

Even after decades in the classroom, Knobil never managed to avoid intense prelecture jitters himself. Clouds of blue smoke outside his office were a dead giveaway, says Nell.

“He was pacing up and down the hallway, smoking one cigarette after another, terrified that he had to give a lecture.”

Knobil was born in Berlin in September 1926 to Jewish parents. His family fled Hitler’s Germany for Paris when he was 6. In 1940, they boarded a boat to New York from Genoa, Italy. Fluent in German and French, Knobil began his study of English at 13. As an adult, he took great pride in his accent-free pronunciation.

Nell—raised on a hardscrabble, West Texas ranch—remembers being so intimidated by his mentor’s extensive vocabulary, he bought a notebook in which to record unfamiliar utterances. “As soon as he left the room, I’d look up the words,” says Nell, “then memorize them.”

In the Knobil household, only one book was allowed at the table—the dictionary.

A few weeks shy of his 16th birthday, Knobil entered Cornell University, and in December 1944, at 18, married classmate Nancy Berckmans. He took a two-year hiatus from his studies to join the army, and son Erich was born in 1947. The trio remained in Ithaca, N.Y., while Knobil earned his PhD with zoologist Sam Leonard. Leonard recalls his tall, blond protégé: “Smooth to talk to, smart as hell—never smart acting.” In fact, says Leonard, Knobil could be paralyzed with self-doubt—when anticipating the oral exam for his 1951 doctoral degree, for example. “I told him, ‘You don’t have to be nervous, D. Don’t forget you know more than anyone on your committee.’”

In 1951, the family moved to Cambridge, Mass., for Knobil’s postdoctoral fellowship where son Mark, now a cinematographer in Pittsburgh, was born. When the marriage dissolved, Nancy and the boys moved to New Hampshire, their father remained in Cambridge.

In Greep’s laboratory, Knobil examined why growth hormone isolated from the pituitary glands of cattle failed to affect human physiology. The problem was not, he speculated, lingering impurities in the hormone collected from slaughterhouses—as conventional wisdom then maintained. He instead hypothesized, and demonstrated, that the way the hormone evolved was different for each species, rendering, for example, a cow’s hormone useless to you or me. He presented his findings—uninvited—at an international symposium in Detroit in October 1954.

Greeted with hostility by senior academics whose own reputations were on the line, Knobil’s data ultimately led to the founding of the National Pituitary Agency, the development of synthetic human growth hormone, and the treatment of thousands of children afflicted with what’s known as hypopituitary dwarfism.

“Ernie’s original idea of species specificity not only produced a new and effective therapy but also had a unique role ushering in the new era of recombinant biology and the birth of the biotechnology industry,” says retired chair of physiology at the University of Massachusetts H. Maurice Goodman, who enrolled at Harvard in 1956 as Knobil’s first graduate student.

Goodman also served as a chaperone of sorts, as Knobil nurtured a budding romance with Julane Hotchkiss, another protégé of Sam Leonard. When afternoon turned to evening, Knobil would frequently visit the grad students’ lab to check on their data. “He’d say, ‘If I’d like to go out and have a drink,’” says Goodman, “‘By the way, ask Miss Hotchkiss if she’d like to join us.’” Hotchkiss soon found a new adviser for her PhD, and the couple married in 1959. Eugene Yates, who headed the lab across the hall, served as best man. Nick and Kate Knobil were born in the next few years.

In 1961, Knobil was appointed the Richard Beatty Mellon Professor of Physiology and founding chair of Pitt’s Department of Physiology. Benjamin Spock was in child psychiatry, Niel's
Jerne in immunology. "Pitt was a powerhouse," says Neill. "The one big hole they had was in physiology, and Dr. Knobil was the one they brought in to fill it."

It was at Pitt that Knobil’s investigations of the primate menstrual cycle really took off. But first, his lab needed monkeys—so Knobil founded Pitt’s Center for Research in Primate Reproduction, a venture he headed from 1974 until 1981, and built the Pittsburgh Primate Center. He also began developing radioimmunoassays (radioactive techniques) to measure the composition of minute hormone samples. He wanted to be able to detect the hormones released by the pituitary that stimulate the ovaries and testes.

On Knobil’s wish list: Understanding how the ovaries work; cleaning how the pea-sized pituitary, (the endocrine system’s master) and the brain (specifically, a region known as the hypothalamus) interact with the reproductive cycle; unraveling what causes the various organs to switch on and off during the menstrual cycle and throughout the life course (at puberty, during lactation, and at menopause).

He coined the phrase “pelvic clock” to describe the role the ovaries play in the menstrual cycle. In primates, Knobil’s team found, a pulsing secretion of hormone from the hypothalamus, directly above the pituitary, permits the stage to be set with pituitary hormones for ovulation. However, the ovaries are the menstrual cycle’s timer—its zeitgeber, as Knobil put it. (In the rat, the brain, not the ovary, is the timer.)

Knobil delved further into the pituitary’s effect on the ovaries, investigating the concentration of the various reproductive hormones in the bloodstream. The data seemed to be all over the place. The group began increasing the frequency with which they collected blood samples. Eventually, they measured the hormone levels at 5-minute intervals, a strategy that revealed the oscillation of the gonadotropins (hormones released by the pituitary that target the gonads) on a schedule of just 60 minutes.

“It’s something I wish I’d discovered,” says Yates, now a science adviser to the John Douglas French Alzheimer’s Foundation.

What mattered, Knobil learned, was not the average levels of the pituitary hormones in the bloodstream, but the fact that their presence was intermittent or discontinuous. The pulsatile secretion of gonadotropins is caused by a pulsatile secretion of hormones from the hypothalamus. That secretion, in turn, is set off by sporadic electrical activity—which can itself be affected by other hormones, stress, sleep, food, light, and other biological inputs. In fact, the normal functioning of the overall reproductive system relies on the timing and intermittency of such electrical activity in the hypothalamus. These findings led to new strategies for correcting the inability to enter puberty, for stalling precocious puberty, and for female contraception and assisted reproduction. They also pointed to a way to treat prostate cancer. Clinicians already knew that halting testosterone production slowed the growth of the disease—but surgical castration wasn’t exactly a popular treatment.

"Using Ernie’s research, they realized they could do chemical castration," says Yates.

Crafting a manuscript for publication in Knobilab was an art, and for myriad postdocs, pure agony.

Neill recalls the process: "I was really quite proud of my first manuscript. Dr. Knobil said, ‘Let's go in my office.’ He read through it quickly, said, ‘This is pretty good,’ and set it aside. He lit a cigarette and got another cup of coffee, pulls his pen and pad out, and starts right from the beginning, including a new title. He completely rewrote the thing.

'He really couldn't tolerate irrationality or sloppy thinking," says Plant. "If you wrote something stupid," says Plant, "he would tell you it was stupid, and why.”

It was a side of their father the four Knobil children rarely saw; they were more likely to recall how he could be reduced to tears of laughter when reading aloud James Thurber. But Nick Knobil does remember volunteering at Presbyterian University Hospital as a teenager. That's when he ran into one of his father's former students in an elevator while wearing an "E. Knobil" nametag:

"He was this doctor in his 40s, in a white coat, and he says, ‘Are you related to Ernst Knobil?’ I said, ‘Yeah, he’s my father.’ He looked at me with venom, and he said, ‘He failed me. I didn’t deserve it.’ I think I grumbled under my breath something about, ‘I get him every semester.’”

Knobil left Pitt in 1981 for the deanship of the University of Texas Medical School at Houston. The gig lasted only a few years, but it was long enough to impose administrative changes felt to this day. He recruited a host of new department chairs in his first year and then overhauled the tenure system.

He soon sparked conflict with the health science center’s president, and in 1984 Knobil returned to his laboratory, delving into the electrical mechanisms by which the brain releases hormones into the bloodstream.

Later, he led a panel convened by the National Research Council to investigate the effects on the environment of such endocrine disrupters as dioxins and PCBs. Knobil took heat for the panel’s cautious 1999 conclusion that the extent of harm caused by exposure to such compounds was debatable. But Knobil, always a stickler for adequate data, wouldn't back down. "This field is rife with uncertainty," he told The New York Times, pointing to questions of how DDT triggered fragility in an eagle’s egg. "What is the endocrinologic basis of eggshell thinning?" he asked. "No one has come up with one yet. If you don't know the mechanism, you can't ascribe the effect to endocrine disruption."

Without data, Knobil wouldn't be convinced. But given time, he would devote decades to understanding a whole system, creating the tools to collect the data he craved. Ultimately, says Hotchkiss, her husband had a clarity of thought, and a basic intuition about how systems worked, that she’s not seen rivaled in her five decades in the field. In the late 1970s, she recalls, Knobil had a hunch about a hormonal mechanism that launched puberty. Fellows in the lab disagreed, and soon the debate had escalated to a challenge, with Knobil crafting an experiment and his fellows waging bets—a bottle of wine here, a case of beer there.

"He said, ‘If I’m right, my name will be first on that paper,” recalls Hotchkiss, noting that ordinarily, the fellows’ names appeared first on a paper. Science published the resulting Knobil et al. paper in 1980.
A SUDDEN RUSH

A KISS BRINGS ON PUBERTY

BY ROBIN MEJIA

After surviving adolescence, you know the symptoms of that, er, exciting time: the body changes, the voice changes, the mood changes. Blame it on the hormones, people say. Well, although we all know that phrase—the hormones—even scientists are stumped by the changes that set the body on a course toward sexual maturity.

"It's really a fascinating mystery," says Tony Plant, who directs Pitt's Center for Research in Reproductive Physiology.

"Puberty is very important, not only to the individual going through it, but to the family and to society. Precious little is known about what starts this all," he adds.

Human sexual development is governed by a complex series of starts and stops that is pretty unusual in the animal kingdom. As a kid turns into a teen, the hypothalamus, a small region of the brain located just above the pituitary gland, starts to secrete gonadotropin-releasing hormone (GnRH), which begins a cascade of hormonal signals that lead to the maturation of both the ovaries and testes—it also leads to voice changes, new body hair, and moodiness.

The same system that launches puberty is unusual in the animal kingdom. As a kid turns into a teen, the hypothalamus, a small region of the brain located just above the pituitary gland, starts to secrete gonadotropin-releasing hormone (GnRH), which begins a cascade of hormonal signals that lead to the maturation of both the ovaries and testes—it also leads to voice changes, new body hair, and moodiness.

The combination of results hints at an answer to a question that has puzzled endocrinologists. In children, is the activity of the hypothalamus being suppressed? Or should we think of it as lying dormant, waiting for a signal to wake it up?

"Tony Plant showed that you can give kisspeptin to the brain and it's almost as if the reproductive system says, 'We've been waiting for you, where have you been?'" says Robert Steiner, a professor at the University of Washington, who studies kisspeptin in rodents.

"I think it gets us closer, much closer, to understanding the cellular changes that are associated with puberty," Steiner adds.

Plant cautions that he's not clear whether KiSS-1 activation alone is enough to start puberty. The hypothalamus of other primates plays the same start-and-stop game. So Plant's team, which included postdoctoral fellow Muhammad Shahab, as well as Crowley and researchers from the Oregon National Primate Research Center, decided to find out what was going on in the hypothalamus of monkeys.

If KiSS-1 activation really does set off puberty, they figured they should be able to start the process artificially by administering kisspeptin. And they did.

When four prepubertal castrated monkeys were given kisspeptin, their bodies immediately started producing the hormones that stimulate the maturation of ovaries and testes.

Then the team showed that the KiSS-1 system appears to turn on during a monkey's natural puberty. They also found that monkeys that had been through puberty had much higher levels of KiSS-1 genetic material (mRNA) in the hypothalamus than juveniles.

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HAMBURGERS cost only 15 cents at the White Tower restaurant on Craig Street when Sylvester Sutton Hamilton III (MD '61) was in medical school at the University of Pittsburgh. The bargain burgers were flimsy and greasy, but Hamilton scarfed down the low-cost belly bombs habitually to keep his expenses down.

Burgers have become a little more expensive—as has med school. But because of Hamilton’s generosity, Pitt med’s Brian Shirts (Class of ’08) gets the last two years of med school on the house, something not offered on the White Tower menu.

Shirts’ recently completed PhD research examined the interaction between genes and environment in relation to the development of schizophrenia. If a firm link is found, he contends, it may be possible to manipulate genetic pathways and modulate exposure to pathogens as a way to reduce risk.

As Shirts enters into his surgical rotation, the scholarship positions him well for the future by freeing resources for further training, he notes.

Students in the MSTP program are eligible for the scholarship if they have completed the PhD and are two years away from the MD degree. The award covers the last two years of tuition and includes a $2,000 stipend for the duration of the scholarship.

Years ago, when Hamilton joined the faculty at Penn, he was impressed by how his Pitt medical education stood up to those of his colleagues, and he grew to appreciate great teaching.

“As a youngster,” he says, “I thought that if I ever had a little bit of money, I would like to make the very best teachers available to students.”

Gathering in honor of the new scholarship, from left: Medical Scientist Training Program organizers Clayton Wiley & Manjit Singh, with Carol Hamilton, student Brian Shirts, S. Sutton Hamilton IV, S. Sutton Hamilton III

BOOSTER SHOTS

Vaughan Stagg was the clinical director of the Matilda H. Theiss Child Development Center in Pittsburgh’s Hill District from 1988 until he died in June 2004. Affiliated with Pitt’s Western Psychiatric Institute and Clinic, the center is a place where children and low-income families receive the sort of help that changes lives, including parenting programs, dental care, a preschool, and nursery programs for at-risk children. Stagg was a PhD and assistant professor of psychiatry in the School of Medicine. His memory will live on at the Theiss center, which has dedicated a children’s library and a memorial garden in his name.

When Henry Posner Jr., a prominent Pittsburgh businessman, ran into difficulty with his spine, he found himself in the right place—under the care of James Kang (Res ’91), a Pitt associate professor of both orthopaedic and neurological surgery. The quality of care motivated Posner and his wife, Helen Posner, to create a new faculty chair in orthopaedic surgery. Their $1 million gift, matched by UPMC, will support research on degenerative disc disease in Pitt’s Ferguson Laboratory for Orthopaedic Research.

The lab is directed by Kang, who is expected to be the first holder of the Posner family chair.

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FOR MORE INFORMATION ON GIVING TO THE SCHOOL: Mike LaFrankie, 412-647-9071 lmichael@pmhsf.org
NO FREE LUNCH

COUNTRY DOCS SAY “THANKS, BUT NO THANKS” TO PHARMA GIFTS

BY ELAINE VITONE
Last January in the 5,000-person high desert town of Madras, Ore., Dave Evans (MD '93), his wife, Suzanne El-Attar (MD '93), and their three partners at Madras Medical Group gathered around a trash can and pitched several hundred dollars worth of perfectly good medical and office supplies.

What did a bunch of tablets, cotton-swab holders, and pens ever do to them? Well, they couldn't be sure—and that's exactly why all of this stuff had to go. Out of concern for how pharmaceutical corporations' promotional gifts might be influencing their prescribing practices even at an unconscious level, this small office cleaned house of all pharma freebies for good. In July, Madras Medical and several other groups now engaged in a growing national movement were featured on the front page of The New York Times.

Evans and El-Attar believe that as much as doctors like to think they're not being influenced, drug companies wouldn't spend $5.5 billion on marketing each year—more than what all U.S. medical schools combined spend educating their students, according to a report in The New England Journal of Medicine—if the strategies didn't work.

Madras Medical's decision to go pharma-free didn't happen overnight.

A boom in the population of neighboring Bend, Ore., had made their office a popular stop for drug reps traveling between Bend and Portland in the past couple of years. With the boom, Madras staff began to experience the kind of visits that many doctors' offices throughout the country have come to expect: Complimentary lunches for the entire staff during which reps gave presentations on their products. On their way out, the reps left drug samples, marketing literature, pens, and other promotional items.

Once a rarity, drug-rep visits had increased to as many as three a day, and the chats were making the doctors late to see their patients. This concerned the group, and they questioned the reliability of the information representatives were distributing, given the conflict of interests inherent in the doctor/drug-rep relationship. The drugs they were promoting were often so new that independent, peer-reviewed studies were not yet available for comparison.

Then Evans and El-Attar read an alarming study that polled general practitioners. The poll asked if they had prescribed a certain free drug sample to an uninsured hypertension patient who later became insured, would they continue prescribing the same medication, even if prescription costs were later covered in full? Sixty-nine percent said yes. Eighty-eight percent said that if the patient had been insured in the first place, they would have prescribed a different medication.

The last straw for Evans was in 2005, when he learned of the extent of a cover-up linked to a marquee drug. Madras sits in a basin in the Cascade Mountains. Locals might farm alfalfa, wheat, or flower seeds. They might work in a nearby wood-product manufacturing plant or a lumber mill 14 miles up Route 26. Nearly 20 percent of the population lives below the poverty line.

"This is not a wealthy community by any stretch of the imagination," says Evans. He and his partners are the only general practitioners in town. They believed that free drug samples, courtesy of pharmaceutical companies, were highly valued by their uninsured patients.

So the group explained the reasons behind the new policy to their patients before making it official on "Pharm Free Friday," an event the Madras Pioneer covered. To Evans' pleasant surprise, since the big spring cleaning, complaints have been "very, very few," even among those who had been maintained by the samples. In fact, most feedback has been of the what-took-you-so-long variety.

"I got a note from one of my patients that said, 'Thank you for taking a stand,'" Evans says.

Many physicians meet with drug reps in AM SA—a national, multi-issue, multi-specialty, progressive activist organization. Two years ago at an annual meeting for AM SA alumni and current members, they made their dream a reality, founding the National Physicians Alliance (N PA). N PA advocates for such issues as affordable and equitable health care, safety-driven malpractice reform, and protecting Medicaid, in addition to resisting the influence of drug industry marketing.

Nowalk marvels at the promise of what began at that first gathering.

"There were probably only about 30 or 40 people in the room," says Evans, noting that a lot of them wrote checks to support the new organization.

Mitu (Suresh) Agarwal (MD '95) and Colleen Bush (MD '93) were among those who helped get N PA off the ground.

"Pitt was very encouraging of me developing some leadership skills," says Evans, "and I chose to do that through AM SA. ... Now that we're 10, 15 years out of medical school and more established in our practices and our lives, we decided that now's the time to do this."

Once a rarity, drug-rep visits had increased to as many as three a day, and the chats were making the doctors late to see their patients.
CLASS NOTES

‘40s As a resident at Pitt’s Western Psychiatric Institute and Clinic, Chapman Isham (Psychiatry Resident ’42) remembers walking by an art therapy class and stopping when he saw patients using watercolors. He asked the occupational therapist about painting, and she gave him a book on watercolors that directed him to a lifelong avocation. Now a Distinguished Fellow of the American Psychiatric Association, Isham has retired and is a practicing artist. He teaches watercolor at several Texas community centers. Isham shows his artwork regularly and has the honors to prove it, including a regional “artist of the year” award, several “best of show” awards, and a raft of first-place juried show awards.

His kids always said, “Dad, you’ll never be rich,” but David Flom (MD ’42) didn’t go into medicine for the money. Flom has been practicing out of the same office in Pittsburgh’s Oakland neighborhood for 60 years. At 88, he cannot envision retiring. “Retiring is for old people. I’ll be practicing till I get it right,” he says. Flom never received his bachelor’s degree because at the time, he didn’t have the $10 required to process the degree. With the help of his family physician, he was accepted into Pitt’s med school and graduated near the top of his class. Since then, he has treated five generations of patients. Flom says he will not charge patients for visits he knows they cannot afford. That may not be the best business practice, but with three children, 25 grandchildren, and 31 great-grandchildren, Flom says his life is tremendously rich.

‘70s Forty-six million people in the United States are without health insurance, and Scott Tyson (MD ’79) would like to give them a safety net. As an advisory board member of Pennsylvania HealthCare Solutions Coalition, Tyson advocates for Pennsylvania Senate Bill 1085, the “Balanced and Comprehensive Health Reform Act,” which aims to essentially eliminate private health insurance companies in favor of a common healthcare trust managed by appointed experts. Tyson expects opposition from insurance agencies and, for pleasure, paints his surroundings in Sutton Bay, Mich.

‘80s In 1957, before going into medicine, Fred Lamb (Pediatric Critical Care Fellow ’82) began working as a commercial artist. He says he never could have anticipated that 20 years later he would be saving children’s lives as a pediatric critical care physician. Lamb sometimes refers to Detroit as “Murder City.” In one year there, he says, he saw 47 gunshot-wound victims under the age of 17. He remembers another young patient: A girl in junior high had overdosed on a prescribed psychotropic drug. She went into cardiac arrest and was put on life support. Lamb’s team administered a charcoal-filter stomach wash for two-and-a-half days. Three days later, she woke up. After her recovery, Lamb attended her bat mitzvah and later saw her become a pediatric psychologist. These days, Lamb has retired from medicine and is working occasionally as a freelance artist again. He creates medical illustrations for malpractice lawsuits and, for pleasure, paints his surroundings.

Swarna Varma (Endocrinology Fellow ’83) sees patients suffering heart attacks, strokes, leg amputations, and impaired vision as complications of diabetes. Varma, a private practice endocrinologist in Bridgeville, Pa., believes that half of these complications can be eliminated simply by focusing on prevention. She notes that 20 years later he would be saving children’s lives as a pediatric critical care physician.

RAMESH RAMANATHAN
THE HERITAGE OF HELPING

As a child in Colombo, Sri Lanka, Ramesh K. Ramanathan (Hematology/Oncology Fellow ’95) accompanied his physician grandfather on house calls. Ramanathan remembers his grandfather’s attentive bedside manner: “He used to sit and just listen, which was a rarity in those days.”

After the tsunami in 2004, Ramanathan, who is an associate professor of medicine and director of the gastrointestinal cancer program at the University of Pittsburgh Cancer Institute, returned to Sri Lanka to assist in disaster relief. He found himself adopting his grandfather’s mannerisms and spending time listening to stories of tsunami victims. Ramanathan and others at Pitt then partnered with the Batticaloa Teaching Hospital in Sri Lanka to establish a program for doctors to train in Pittsburgh.

Located on the east coast of the island, Batticaloa is the only teaching hospital in Sri Lanka, a region of more than 1 million people. However, it lacks much modern medical equipment. So UPMC and its employees raised money for relief and donated equipment. This summer, Batticaloa physicians Peetharam Jeepara, a laparoscopic surgeon, and Sivalingam Naveenakumar, a dialysis specialist, came to Pittsburgh for three weeks. Both doctors hope to improve the standard of care at their hospital. Currently,
developed a “team of four” approach to diabetes, incorporating a physician, support staff, the patient, and the patient’s family. She is collaborating with the University of Pittsburgh Diabetes Institute to demonstrate and publish her results from following 395 diabetic patients for five years. Her patients are given homework: They call once a week to check in with a nurse. They take Varma’s grocery list to the supermarket, not their own. She envisions her paper as a road map for primary care offices to provide observant, participatory care, instead of writing a prescription, dispensing advice, and hoping for the best. “We’re already spending the money on treating the complications,” she says. “We’ve got to invest in controlling... the ABCs [A1C (blood glucose levels), blood pressure, and cholesterol]. It’s all in the mindset.”

‘00s

A toddler ingests cleaning solution.

A middle-age heroin addict overdoses. A depressed teenager takes too many sleeping pills. Any of these people could be Daniel Brooks’ Emergency Medicine Resident ‘00 next case. As chief of medical toxicology at UPMC, Brooks, who originally considered a career in psychiatry, appreciates the deductive challenges of his field. His patients don’t always tell the truth, and when they deny consuming harmful substances, he tries to approach them with empathy and pragmatism.

Currently a Pitt assistant professor of emergency medicine, Brooks is investigating how patients tolerate Acetadote, an acetaminophen antidote.

Richard and Kristen Kuk (both MD ‘03) shared the same group of friends during their first year of medical school. Their friendship grew into a romance during their second year and the couple matched at Hershey, Pa.—Richard in internal medicine and Kristen in obstetrics and gynecology. After a year of residency, Kristen decided the obstetrics’ lifestyle was “too crazy.” However, a look at the couple’s peregrinations tells us they haven’t exactly settled down. After they married in 2004, Richard switched to internal medicine at Virginia Commonwealth University. Kristen (née Cobb) took a year to do research in surgical oncology there while she investigated which specialty to pursue. She settled on an ophthalmology residency at Louisiana State University and moved into a first-floor apartment in downtown New Orleans one month before Katrina hit. (Somehow, it did not flood.) Kristen now travels to hospitals across the state. (The hurricane shut down Charity Hospital, the main source of LSU rotations. See related story on p. 39.) And Richard is currently doing a hospitalist year in internal medicine in Covington, La. But don’t expect to see the Kuks shopping for a house or furniture anytime soon—Richard begins a cardiology fellowship at the University of Maryland in July 2007.

At Pitt, Ali Radfar (MD ‘03) worked on fat cell metabolism research with William Futrell, Pitt clinical professor of surgery, the summer after his first year of medical school. On that project, he was intrigued by the synergistic intersection of technology, medicine, and business—so much so that he didn’t even apply for residency after med school. Instead, Radfar went to work for the venture capital company iNetworks in Pittsburgh. He’s now with Cowen and Company Healthcare Investment Banking in New York City. One hot topic he works on is how to use stem cells from fat for therapy and cosmetic procedures.

—Katie Hammer & Alicia Kopar

patients in need of specialized care must drive seven hours to a hospital in Colombo, the capital.

The doctors learned diagnostic techniques they can put to use in Batticaloa. Jeppara says he was impressed by the minimally invasive surgical and diagnostic techniques he observed at Pitt. In Sri Lanka, for comparison, bariatric surgery and hernia repairs require a sternum-to-pubic-bone incision and a stay of two or three days. Naveenakumar found the efficient system of communications between specialists at UPMC “astonishing.”

The next step for this grassroots project: Ramanathan and his Sri Lankan colleagues hope to give Pitt med students the opportunity to study tropical diseases and tertiary hospital care in Batticaloa. —AK
James Zehner (MD ’77, Family Practice Resident ’80) just celebrated 25 years in private practice near Titusville, Pa. “In the rural community, I end up wearing an awful lot of hats,” Zehner says. In the mornings, he rounds at Titusville Area Hospital, visiting referred patients and checking on newborns. Then he’ll see 25 to 30 patients at his office, where he provides a lot of geriatric care. Janet Waller (MD ’77, Radiology Resident ’81) met Zehner in anatomy class. They were seated alphabetically, so Mike Wusylko (MD ’77), now a primary care physician in private practice in Cranberry, Pa., and a few other classmates separated them, but not for long. Waller and Zehner married immediately after their first year of med school. She considered a specialty in primary care, then switched to radiology. It made it easier for her to work part-time when her three children were young. Nine years ago, she joined Northwest Medical Center (now UPMC Northwest), in Seneca, Pa.

Freddie Fu (MD ’77, Orthopaedics Resident ’82) is the standard-bearer for his class. Chair of Pitt’s Department of Orthopaedics, Fu is the guru of anterior cruciate ligament (ACL) repair. His department is doing pioneering work exploring anatomical reconstruction of the ACL as a “double bundle” of fibers, rather than the standard single bundle. As president of Pitt’s Medical Alumni Association a few years ago, Fu once remarked that admission to the med school has become so competitive that he would not have been accepted by today’s criteria. Dean Arthur S. Levine immediately offered to give Fu’s application a second look.

— Katie Hammer & Chuck Staresinic

James Mclaughlin
SEPT. 18, 1918–JULY 13, 2006

Shortly before his death at age 87 on July 13, James Mclaughlin (MD ’41) made his way from Pittsburgh to Washington, D.C., to talk about his new book, The Healer’s Bent: Solitude and Dialogue in the Clinical Encounter, at a psychoanalysts conference.

Those in attendance, including some who had known him for decades and considered him a mentor and inspiration, were pleased that Mclaughlin completed a work they see as the culmination of his career as an analyst and his life as a learner and teacher.

Mclaughlin’s colleague Mervin Stewart (MD ’53) says, “If you want to know what he was like, you ought to get a copy of this book. It’s a marvelous insight into him as a human being.”

Mclaughlin was the first director of the Staunton Clinic, originally part of the Falk Clinic, and directed the Pittsburgh Psychoanalytic Institute.

His 1981 paper, “Transference, Psychic Reality, and Countertransference,” has become a classic in the field. It posits that in the realm of psychoanalysis, as Mclaughlin put it, “transference is a matter of equal rights, both on and behind the couch.” — Joe Miksch

William Cooper
JAN. 12, 1919–SEPT. 12, 2006

It’s unusual for physicians to solicit charitable donations from their patients, but William Cooper had known Henry and Elsie Hillman for decades. He was their friend, their physician, and the chair of the Shadyside Hospital Foundation, which was planning a home for the University of Pittsburgh Cancer Institute (UPCI) adjoining the hospital. Cooper approached the Hillmans for their support, which resulted in a $10 million gift and the completion of UPCI’s Hillman Cancer Center in 2002. Cooper was instrumental in raising an additional $35 million for the center; its clinical wing was named the Cooper Pavilion in his honor. He died in September after a long illness.

Cooper (Internal Medicine Resident ’48) was the first medical director of the Central Blood Bank of Pittsburgh, which he helped create in 1951. He joined the Pitt faculty in 1954 and became chair of medicine at Shadyside Hospital in 1980. Ten years ago, he was named a Distinguished Clinical Professor of Medicine.

At age 69, Cooper graduated from Pitt’s law school. “There were days that he went to law school, saw patients, chaired the department of medicine, and drove his granddaughters to school,” said Louise Brown, director of the Shadyside Hospital Foundation. “He was an extraordinary man.” — Chuck Staresinic
It has been more than one year since the storm called Katrina raked and swamped the Gulf Coast of Louisiana and Mississippi, but Barry Riemer has emphatically not moved on. The storm raised too many questions for him, few of which have been resolved. The storm's enduring turmoil is a part of who he is now. This is clear from the way he introduces himself as someone who works in a hospital that no longer exists.

“I’m the chairman of orthopaedics at LSU in New Orleans,” says Riemer (MD ’75, Orthopaedic Surgery Resident ’80). “I’m also the chief of surgery at Charity Hospital.”

Charity was a linchpin for health care in southern Louisiana and the primary teaching hospital for Louisiana State University. With more than 3,000 beds, it was the only public hospital in a city where tens of thousands lacked health insurance. Eighty-five percent of its patients earned less than $20,000 annually. By chance, Riemer was not on the schedule as Katrina approached, so he evacuated to Lafayette, La.

Conditions at Charity became nightmarish. No electricity or water. No functioning toilets. Humidity became nearly unbearable. Sealed windows were shattered to provide ventilation. The mercury rose above 120 degrees in some rooms, Riemer says. Patients previously on mechanical ventilators needed someone to squeeze a bag, breathing for them 24/7, without pause. Riemer’s orthopaedic residents and others carried patients up and down more than 10 flights through pitch-black stairwells in sweltering heat.

Other stairwells were filled with the bodies of the dead, because the morgue had flooded. Charity was evacuated five days after Katrina. Some escaped by boat as snipers fired from windows and desperate, armed people demanded food and water.

“Some of the residents still have difficulty talking about that trip,” Riemer says. “There were bodies floating in the water. There was one body with seven bullet holes that they tied to a telephone pole.”

Why?

“Just to get it out of the way,” he says. “I wonder, after all this time, what else is there to do? How do you make decisions in those kinds of times?”

The big issues Katrina blew open run the gamut: civil rights, crime, poverty, martial law, ethics, ecology, racism, and the millions of uninsured in this society. In addition, Riemer was moved to rethink his relationship to the residents in his department and their role in a disaster. He climbed into a car with his wife and four residents to retrieve personal items and check for damage at each of their homes.

“I have a picture of me and one of my residents looking very nervous while I hold his M 16,” Riemer says. “I’d say that the number one rule of orthopaedics is, ‘Never arm your chair.’ It’s a dumb thing to do. The guy dates my daughter.”

But Riemer agonized over the unequal power balance between a resident and a department chair in such an environment. He voiced his insistence that they were equals that day and no one should feel coerced to go anywhere or do anything he or she felt was unsafe. He still wonders whether residents should be staffing a hospital as a city is evacuated, because they essentially have no freedom to say yes or no to those who supervise them. These are important questions, he says, when hospitals must plan for natural disasters, pandemic flu, and radioactive “dirty bombs.” His personal experience indicates that residents are selfless and heroic in a disaster, he says, but that doesn’t mean they should be required to stay in a worst-case scenario.

One thing is clear to Riemer: Charity Hospital will never reopen.

“We are running a trauma center with only two operating rooms and 34 total beds, and that’s the best that we can do,” Riemer says. “If you had ever asked me, ‘Would that be a reasonable thing to do?’ I’d have said, ‘No.’ But here, it’s a godsend. It’s the only trauma team in the metropolitan area.”
Gathering for quinine and whiskey rations, as these soldiers are, may have saved the Union, according to Michael Flannery of the University of Alabama at Birmingham. Flannery visited Pitt this fall as a C.F. Reynolds Medical History Society lecturer. He notes that the average foot soldier, for both the North and the South, would have been twice as likely to die of a camp disease than a war injury. For instance, malaria afflicted its share of Union soldiers (522 in 1,000), yet it may have been the Union’s secret weapon. The North’s blockade of Southern ports that received Peruvian cinchona bark (the raw material for the malaria antidote quinine), its ability to keep the high and dry ground on the battlefield, and its ready supply of reinforcements for sickened men all made an “appreciable impact,” notes Flannery. “The longer the war continued, the longer disease became an ally of the North,” he says.
FISHER LECTURE  
FEBRUARY 28, 2007  
3:30 p.m.  
Scaife Hall, Lecture Room 6  
Robert A. Weinberg, MD, Speaker  
For information:  
www.surgery.upmc.edu

WINTER ACADEMY  
SCHOOLS OF THE HEALTH SCIENCES  
FEBRUARY 2, 2007  
Naples, Fla.  
To request an invitation:  
Pat Carver  
412-647-5307  
cpat@pitt.edu

STARZL LECTURE  
APRIL 21, 2007  
10 a.m.  
Scaife Hall, Lecture Room 5  
Christian P. Larsen, MD, PhD, Speaker  
For information:  
www.surgery.upmc.edu

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SIMMONS LECTURE  
MAY 23, 2007  
8 a.m.  
Starzl Biomedical Science Tower  
Room S100  
John C. Alverdy, MD, FACS, Speaker  
For information:  
www.surgery.upmc.edu

UPCOMING HEALTH SCIENCES ALUMNI RECEPTIONS  
MARCH 20, 2007: Raleigh-Durham, N.C.  
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May 18–20, 2007

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