DARK ARTS
THE WORLD BEYOND VISIBLE LIGHT
EAST COAST TREMORS
Not only is Pitt Med a very attractive publication, but the articles are excellent. I find them a wonderful resource for information about science, health, and the people responsible for such important work.

I remember the “triumph of the Salk vaccine” well and, in particular, how reticent the East Coast MDs were to accept solutions that did not originate with them.

The Massachusetts Crippled Children’s Program was set up to care for the victims of the 1938 polio epidemic that devastated the area. We really had no treatment other than the warm wraps of the Sister Kenny Method, the respirator for severe pulmonary cases, and orthopaedic surgery. (My job from 1940 to 1946 was to arrange for surgery, then braces, shoes, etc.) How relieved we were when we were able to have the vaccine available for our own children in 1955. It's wonderful that Pitt Med records the history so well. I do so enjoy reading all issues.

Catherine Petrou
Pittsburgh

ALMOST READY FOR PRIME TIME
I enjoy reading Pitt Med and found the enclosed picture [from the Class Notes reply card, shown right] in the last several issues. The individuals were not identified, but I assume they are on the editorial staff. The reason for this note is to point out the remarkable resemblance of the circled gentleman to one Jerry Seinfeld.

Edwin S. Kremer (MD '55)
Erie, Pa.

The resemblance is more than skin-deep: Seinfeld look-alike Josh Englert (MD ‘05) was a head writer of Lasix Unloaded, the Scope and Scalpel Society’s 50th production. He appears with fellow Lasix head writers Brad Sobolewski (MD ‘04, top) and Neil Badlani (MD ‘05, bottom). Producers Jonathan Bickel (MD ‘04) and Rachel Norris (MD ‘04) are shown wearing glasses. The photo originally appeared in our May 2004 issue. Although we’d enjoy their contributions, none of these creative docs is on the magazine staff.

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

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

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

CLARIFICATIONS / CORRECTIONS
In our November issue, we mistakenly listed the 2004/05 slate of Medical Alumni Association officers. In this issue, we list the current officers (p. 39).

RECENT MAGAZINE HONORS
IABC Best of Show (Magazine Design, Elena Gialamas Cerri)
IABC Golden Triangle Award of Excellence, Magazine Design
IABC Golden Triangle Award of Honor, Magazines
CASE District II Accolades
Silver, Visual Design in Print, Covers
CASE District II Accolades
Bronze, Best Article (Jessica Mesman’s “So You Want to Change the World?”)

STRONG DRIVE
The Annual Pitt Med Golf Outing, created and run by students, benefits them as well. Proceeds go to two graduating Pitt med students who stand out for their community service efforts. So play 18 for them. It’s the least you can do.

ANNUAL PITT MED GOLF OUTING
APRIL 29
Quicksilver Golf Club
Midway, Pa.

For information:
Rob Klune or Matt Kaufman
klune.john@medstudent.pitt.edu
kaufman.matthew@medstudent.pitt.edu
412-648-9090
www.pittmedgolfouting.org
PITTMED

DEPARTMENTS

OF NOTE
Carnegie Museum star faculty will teach at the med school. Alzheimer’s and daydreams. Whose liver is it, anyway?

CLOSER
Now showing: one defibrillator, one parrot, a bucket of fried chicken, and Chuck Norris.

INVESTIGATIONS
Gene therapy trials for muscular dystrophy. This microvesicle influences the immune system in ways no one imagined. A new course focuses on day-to-day practice dilemmas.

98.6 DEGREES
Faculty honoraria benefit students.

ATTENDING
The evangelical pathologist.

ALUMNI NEWS
Fellowship alum George Mazariegos cures MSUD with transplants.

LAST CALL
George Washington with all of his teeth.

FEATURES

Dark Arts
Plying the world beyond visible light.

What Matters Most
How to treat people. Perspective-changing moments from members of the new Charles G. Watson Chapter of the Humanism in Medicine Society.

FORGET IT?
Guo-Qiang Bi tells us how we remember and forget.

Eye on Glaucoma
Joel Schuman can see into your future.

CONTRIBUTORS
Art director Elena Gialamas Cerr| says keeping this magazine visually "fresh" is the sine qua non of her design philosophy. Cerri has designed all 26 issues of Pitt Med. Her approach blends classical typography and unconventional images, among other artistic secrets.

Dark Arts

What Matters Most

Forget It?

Eye on Glaucoma

With their dark arts, structural biologists explore the world beyond visible light, becoming privy to evolutionary lineages of viruses, how to make machines out of molecules, and then some.

IMAGE ESSAY
IMAGES BY JAMES CONWAY, ANGELA GRONEBORN, AND JOANNE YEH; TEXT BY CHUCK STARESINIC

COVER STORY / IMAGE ESSAY
IMAGES BY JAMES CONWAY, ANGELA GRONEBORN, AND JOANNE YEH; TEXT BY CHUCK STARESINIC

What Matters Most
How to treat people. Perspective-changing moments from members of the new Charles G. Watson Chapter of the Humanism in Medicine Society.

ANONYMOUS SUBMISSIONS
FOLLOW-UP BY CRAIG CAHALL

Susan Dunmire (MD ’85, Res ’88) and her predecessor, Ross Musgrave (MD ’43).

COVER R
With their dark arts, structural biologists explore the world beyond visible light, becoming privy to evolutionary lineages of viruses, how to make machines out of molecules, and then some.

IMAGE COURTESY JOANNE YEH.

What Matters Most
How to treat people. Perspective-changing moments from members of the new Charles G. Watson Chapter of the Humanism in Medicine Society.

ANONYMOUS SUBMISSIONS
FOLLOW-UP BY CRAIG CAHALL

Susan Dunmire (MD ’85, Res ’88) and her predecessor, Ross Musgrave (MD ’43).

COVER R
With their dark arts, structural biologists explore the world beyond visible light, becoming privy to evolutionary lineages of viruses, how to make machines out of molecules, and then some.

IMAGE COURTESY JOANNE YEH.

What Matters Most
How to treat people. Perspective-changing moments from members of the new Charles G. Watson Chapter of the Humanism in Medicine Society.

ANONYMOUS SUBMISSIONS
FOLLOW-UP BY CRAIG CAHALL

Susan Dunmire (MD ’85, Res ’88) and her predecessor, Ross Musgrave (MD ’43).

COVER R
With their dark arts, structural biologists explore the world beyond visible light, becoming privy to evolutionary lineages of viruses, how to make machines out of molecules, and then some.

IMAGE COURTESY JOANNE YEH.

What Matters Most
How to treat people. Perspective-changing moments from members of the new Charles G. Watson Chapter of the Humanism in Medicine Society.

ANONYMOUS SUBMISSIONS
FOLLOW-UP BY CRAIG CAHALL

Susan Dunmire (MD ’85, Res ’88) and her predecessor, Ross Musgrave (MD ’43).

COVER R
With their dark arts, structural biologists explore the world beyond visible light, becoming privy to evolutionary lineages of viruses, how to make machines out of molecules, and then some.

IMAGE COURTESY JOANNE YEH.

What Matters Most
How to treat people. Perspective-changing moments from members of the new Charles G. Watson Chapter of the Humanism in Medicine Society.

ANONYMOUS SUBMISSIONS
FOLLOW-UP BY CRAIG CAHALL

Susan Dunmire (MD ’85, Res ’88) and her predecessor, Ross Musgrave (MD ’43).

COVER R
With their dark arts, structural biologists explore the world beyond visible light, becoming privy to evolutionary lineages of viruses, how to make machines out of molecules, and then some.

IMAGE COURTESY JOANNE YEH.
Life levels all men: death reveals the eminent. — George Bernard Shaw

The world has lost two great women in the span of a week. No person is ignorant of the life of Coretta Scott King—a force for peaceful social change and an icon of grace and courage. Fewer know the circumstances of the life of our own Katherine Detre, for many years one of our university’s most distinguished faculty members, who came to Pitt in 1974. As a young, Jewish woman in Budapest, Katherine survived the German occupation by cloaking her religion and ancestry as she worked as a streetcar conductor and lived in a Catholic convent. While in medical school, she learned that her father and brother had perished in concentration camps, and she immersed herself in her medical studies as an antidote to despair. Later, to escape the Communists, she managed to slip across the border to Austria.

Katherine completed her medical studies in Canada—no small feat after landing on North American soil without speaking English. A friend from Budapest, Thomas Detre (who would become her husband and my predecessor as senior vice chancellor for the health sciences at this university), encouraged her to join him at Yale. There she studied biometry. She blossomed into an important and singularly creative scientist.

At Yale in 1970, Katherine served as the principal epidemiologist and biostatistician for the first clinical trial to compare the effectiveness of surgery to that of medical treatment for coronary artery disease. Not everyone welcomed the results, which demonstrated a survival benefit for surgery for left main-stem coronary artery disease but not for other manifestations of coronary artery disease. Despite making many “experts” unhappy, the trial results became highly influential and remain widely respected. This would become a recurring theme in Katherine’s life. As she built the Epidemiology Data Center in Pitt’s Graduate School of Public Health, she was steadfast in her assertion that therapies could be proven safe and effective only through rigorous science. The center, which celebrated its 25th anniversary last year, has coordinated the design, data management, and analysis for more than 60 major medical research projects. Katherine’s work persuaded a generation of physicians and epidemiologists at Pitt and elsewhere of the importance of careful statistical analysis and well-managed clinical trials. Her work has had major implications for patient care—notably in determining the most effective approaches for treating coronary artery disease in diabetic patients.

Katherine had many of the traits that we associate with this city. This Distinguished Professor of Epidemiology was resilient, diligent, civil, generous of spirit, and creative. I think of her now while Pittsburghers wave their Terrible Towels and pray for touchdowns. By the time you read this, the Super Bowl will have been played. But as I write, an entire city is inspired to perform at its finest. Dr. Katherine Detre was another kind of champion. The millions who suffer from diseases ranging from cardiovascular disease to depression will profit from her labors to identify the very best available treatments for them.

Katherine was the kind of scientist and person we all aspire to be.
Starzl Wins National Medal of Science

In November, Thomas Starzl, who is credited with establishing the field of transplantation medicine, was named one of eight recipients of the 2004 President's National Medal of Science, the nation's highest scientific honor. He says he was pleased to be one of 425 scientists so honored since 1962 and praised the colleagues and institution he says made his work possible. The fertile intellectual climate at Pitt, he reports, is unique and served to nurture his career.

Starzl, 79, is a Distinguished Service Professor of Surgery in the University of Pittsburgh School of Medicine and director emeritus of the Thomas E. Starzl Transplantation Institute. He is the first President's Medal recipient with a primary appointment at Pitt. —Joe Miksch
Do not expect to see rats lounging on beanbag chairs and eating Doritos in Michael Chancellor’s lab. Chancellor’s team injected a THC derivative (THC is the primary active component in marijuana) into these rodents. The derivative was first modified so that it wouldn’t cross the blood/brain barrier and cause the rats to, well, get high. Nevertheless, what good can come of introducing modified pot to rats?

Chancellor, an MD and University of Pittsburgh professor of urology and director of neurourology and female urology, is investigating the efficacy of a THC-derived drug called IP 751 to reduce bladder pain. In the case of Chancellor’s rats, bladder pain is induced via a diluted acid. The rats, much like people suffering from hypersensitive bladder disorders, urinate frequently to relieve the discomfort.

IP 751 works on receptors that block pain. Chancellor’s study shows the rats’ pain was relieved, and they returned to a normal urination schedule when administered the drug. If all goes well in clinical trials scheduled for later this year, Chancellor says, it’s possible that some form of the drug will be on the market by 2009.

Changing the way doctors treat the deadliest of skin cancers ought to get a fellow an award.

John Kirkwood, professor of medicine and dermatology and director of the University of Pittsburgh Cancer Institute’s melanoma program, was recently recognized with two. Both the European Society of Cytokine Research and the Melanoma Research Foundation honored the MD for uncovering the ability of interferon alpha to prevent relapse in and prolong survival of melanoma patients. The drug is now used by cancer centers around the country; with surgery, it can reduce relapse incidence by one-third, he says.

“The whole melanoma and skin cancer center should share in the pride of this recognition,” says Kirkwood.

The brain of an anorexic patient responds curiously to the chemicals it produces. Walter Kaye—an MD, director of research in Pitt’s eating disorders program, and professor of psychiatry—correlated increased serotonin levels in the brains of anorexic patients with increased harm avoidance and anxiety (factors that trigger anorexia). Anorexic patients, Kaye has found, are also likely to have higher than usual dopamine receptor activity. A greater sensitivity to dopamine, which is associated with food, may account for why many of these patients feel full after having very little to eat, Kaye contends. —JM

Go to http://pittmed.health.pitt.edu for more interview excerpts.
As Minds Wander

Back in school, did you ever gaze out the window, waiting for the minutes to pass, not thinking about much in particular? The areas of the brain active as young adults daydream the minutes away—a process called the “default state” of cognition—are also the first to succumb to Alzheimer’s disease, according to a recent study published in the Journal of Neuroscience.

This default state is defined as any time the brain is not engaged in a specific task—when we daydream, muse, or recall pleasant times, for example. Researchers hypothesize that somehow early default patterns contribute to metabolic changes over time that lead to Alzheimer’s. They speculate that memory networks are also modulated as young adults let their minds wander.

The study relied on an experimental dye developed at Pitt. The dye, known as Pittsburgh Compound B (PIB), is the brainchild of Pitt coauthors William Klunk, an MD/PhD, director of psychiatry in the Alzheimer Disease Research Center, and associate professor of psychiatry, and Chester Mathis, a PhD professor of radiology and pharmaceutical sciences as well as director of the PET facility. It was one of five techniques used in the study. PIB PET scans helped reveal sites of the characteristic amyloid plaque associated with Alzheimer’s. The dye can be used in living research subjects. Until the advent of the dye, the plaque could not be identified without an autopsy.

The paper’s lead author, Randy Buckner of Washington University in St. Louis, says that PIB not only contributed to this recent study, it’s likely to change the Alzheimer’s research landscape.

“The development of Pittsburgh Compound B was really a watershed event for Alzheimer’s research and human imaging,” Buckner says. “We were waiting for it. We didn’t know where it would come from, and Klunk and Mathis’ team did it.” — Sharon Tregaskis

WHOSE LIVER IS IT, ANYWAY?

Linda Boig, not in nurse’s clothing, but rather in a black dress and a short jacket, still can’t help but ask her former patient a nurse’s question: “You haven’t gone back to smoking, have you?”

“Never!” says Joan Brown, turning to her daughter, Tonya Moore, and patting her on the knee. “I wouldn’t do that to your liver.” The three laugh—Boig, a Pitt nursing grad, coordinated last year’s surgery in which Moore donated 60 percent of her liver to her mother.

The trio is surrounded by 300 others, brought together by UPMC’s first Living Donor Appreciation Dinner for liver and kidney donations. After a three-hour drive from Clearfield, Pa., to the Westin Convention Center Pittsburgh, Brown and Moore begin many introductions with, “Are you the donor or the recipient?”

In 2004, Brown’s internal bleeding necessitated emergency air transport to UPMC C’s first Living Donor Appreciation Dinner for liver and kidney donations. After a three-hour drive from Clearfield, Pa., to the Westin Convention Center Pittsburgh, Brown and Moore begin many introductions with, “Are you the donor or the recipient?”

In 2004, Brown’s internal bleeding necessitated emergency air transport to UPMC C. Diagnosed with primary biliary cirrhosis, she needed a liver transplant to survive. Brown looked toward her only daughter—a perfect match. Like the others at the autumn dinner, Moore and Brown had their surgeries at the Thomas E. Starzl Transplantation Institute, which performs more living donor liver transplants than any other center in the country. — Sarah Z. Wexler

FLASHBACK

Eben Byers, Pittsburgh industrialist, ladies’ man, socialite, 1907 U.S. Amateur Golf Champion, and expert trapshooter, injured himself on a party train returning from a 1928 Harvard-Yale football game. Pittsburgh physician C.C. Moyar prescribed Radithor, a supposedly therapeutic radium-infused drink. Byers liked it. Felt great. So much so that he drank three bottles a day for two years. He quit his Radithor habit after his bones began to disintegrate. Byers died in 1932. (Note: Moyar was not a Pitt med grad.)
Appointments

Mary Phillips wants to know what’s happening in the brains of patients who have difficulty regulating their emotions. Using functional magnetic resonance imaging, Phillips explores abnormalities in brain systems of people with conditions such as bipolar disorder, obsessive-compulsive disorder, and depression. She hopes to improve prevention, diagnosis, and treatment. Phillips, an MD, joined the University of Pittsburgh School of Medicine in July as a professor of psychiatry. She directs the Western Psychiatric Institute and Clinic’s functional neuroimaging program. Phillips comes to Pitt from the Institute of Psychiatry in London.

After two decades at the University of Alabama at Birmingham, where he most recently served as a professor of anesthesiology and biochemistry, Bruce Freeman signs on at Pitt as professor and chair of the Department of Pharmacology. Freeman, a PhD, is noted for his research on nitric oxide, which, among other things, accelerates tissue inflammation in diseases such as arthritis, hypertension, and atherosclerosis through contact with oxidants and free radicals. His team is studying nitrated fatty acids, signaling molecules created through a reaction between fatty acids and nitric oxide derivatives, which appear to weaken inflammatory processes. Freeman hopes to create synthetic versions to treat conditions such as cardiovascular disease, diabetes, and metabolic syndrome.

James Luketich, professor of surgery, is the new chief of the Heart, Lung, and Esophageal Surgery Institute, which combines all cardiothoracic surgery departments at UPMC. Luketich says the integration will allow for better education, training, research, and clinical care. Luketich, an MD known for his advances in minimally invasive surgical as well as nonsurgical treatments of esophageal and lung cancer, has been a faculty member at Pitt for 10 years, most recently serving as head of thoracic surgery. He has also been named the Sampson Family Endowed Professor in Thoracic Surgical Oncology (see p. 33).

—Erin N. Lawley

UNWOUND

DNA molecules wrap tightly around a histone core, creating a nucleosome. So how do other proteins squeeze in there and interact with the DNA? We asked Pitt assistant professor of cell biology and physiology Sanford Leuba. He discovered that, on occasion, DNA briefly unravels from the core and stays unfurled in durations long enough for RNA transcription and DNA repair to take place. Leuba and his team were the first to provide direct evidence of these alterations in nucleosome structure. TOP: A DNA molecule, unwrapped. BOTTOM: Frontal and side views of a nucleosome. —JM
INTRO TO PATIENT CARE

The patient's heart stops. The medical types act quickly: Charge the defibrillator. Apply paddles to the chest. Deliver shock.

Sounds about right. Well, it would have been had the patient not been a cardboard parrot and the defibrillator not caused said parrot to explode and transform into a bucket of fried chicken.

These are the sorts of things that happen when Pitt med students take over an auditorium in Scaife Hall for the annual talent show. (The parrot incident was part of the Class of '09's skit, which also involved, naturally, a pirate and, maybe not so naturally, a man with a spear through his chest and a weeping med student. The skit's title? "Intro to Patient Care.")

On a winter night, Scaife's hallways were crowded with students doing vocal exercises, tuning instruments, stretching, and, in the case of first-year Kevin Carl, explaining how he secured onto his torso the aluminum foil spear that appeared to pierce his chest: "Wire coat hanger."

The man who gave the world TV's Walker, Texas Ranger—Chuck Norris—also made an appearance, in the form of an image projected above students heaping praise on the master of the roundhouse kick.

"Factual," first-year student Chetan Irwin deadpanned from the stage. "Chuck Norris doesn't read books. He stares them down until he gets the information he wants." —Joe Miksch

ILLUSTRATION BRIDGET LASCH
The first U.S. gene therapy trial for Duchenne muscular dystrophy gets off the ground. The therapy uses a miniature gene engineered by a Pitt researcher.
A boy is born. Much like any other little one, he gurgles and cries. Eventually, he grins and rolls around. Then, sometime before he turns 3, the boy's legs weaken. He begins to lose control of his muscles.

The worried parents take their son to the doctor. A muscle biopsy confirms what the physician feared—the little boy has Duchenne muscular dystrophy (DMD), a genetic disease marked by continual disintegration of muscle tissue. There's no cure for the disease, which affects one in every 3,500 boys born, and there is no effective treatment. The boy will almost certainly die before he sees 30.

University of Pittsburgh investigator Xiao knows such stories and is intent on changing their endings. This year his work will result in the first gene therapy trial for Duchenne muscular dystrophy in the United States.

His collaborators include gene-vector production expert R. Jude Samulski of the University of North Carolina-Chapel Hill and clinical scientist Jerry Mendell of Ohio State University.

Xiao, associate professor of orthopaedic surgery, has, for almost two decades, been exploring the efficacy of a once-ignored virus, adeno-associated virus (AAV), as a delivery system for gene therapy. AAV, the easy-going and avuncular Xiao jokes, should stand for "almost a virus," because it doesn't cause disease—potentially hurdles come up, Xiao explains.

"With people, everything is different."
A

s far as minuscule fragments of biologic material go, the exosome is a bit like the late Rodney Dangerfield. Historically, it has gotten precious little respect.

The tiny vesicle, emitted from all manner of cells, was first noticed in 1978. The most significant purpose anyone could divine for the exosome was to get rid of cellular junk. Few scientists’ curiosity was piqued by a cellular garbage man.

Today, the exosome, about the size of a virus, is still not fully understood. However, it is gaining prestige. Pitt scientists are examining its role in cancer, immunosuppression, and as a treatment for autoimmune disease.

The exosome—a former afterthought—is now on a few Most Wanted lists.

Theresa Whiteside, professor of pathology and of otolaryngology at the University of Pittsburgh and director of the Immunologic Monitoring and Cellular Products Laboratory at the University of Pittsburgh Cancer Institute, is one of the investigators pushing exosomes to the forefront. In the case of cancer, the exosome is a nasty little devil; Whiteside explains that it helps tumor cells thwart the immune system’s protective instincts.

Emitted from tumor cells, exosomes travel far and wide. Their surfaces are dotted with FAS ligand, a molecule that induces cell death when it meets its receptor. When a FAS ligand-laden exosome meets an anti-tumor cell (CD8+ T-lymphocyte), the ligand finds its receptor on that cell’s surface, rendering the cell shriveled and lifeless. With these anticancer cells out of the way, the immune system is impotent against the tumor.

Whiteside says there may be a couple of ways to stop this wholesale slaughter of anti-tumor cells. Find a method to remove these particular exosomes or develop protections for the immune cells affected by these marauding microvesicles. But such an antitumor vaccine is far from a reality today, she says.

Exosomes can manipulate the immune system in other ways as well.

Paul Robbins, Pitt professor of molecular genetics and biochemistry, got interested in exosomes by accident. He had been looking at modes of gene therapy for autoimmune diseases. After injecting a therapeutic dose into the paw of a mouse afflicted with rheumatoid arthritis, Robbins noticed a couple of things. As he had hoped, the condition at the site of the injection improved. But something else befuddled him. The paw opposite the injection site got better, too.

The injected gene did what was expected. It helped suppress the immune response that was causing rheumatoid arthritis. (You may have read about this breakthrough in our August 2005 issue.) Then the affected dendritic cells emitted exosomes that traveled through the bloodstream. The exosomes seemed to carry news through the circulatory system to the other joint that the immune cells shouldn’t call for the destruction of the mouse’s joints.

Robbins is now working on generating exosomes from immune cells in vitro and injecting the resultant immunosuppressive exosomes into mice. He considers this method a potentially viable treatment for all manner of autoimmune disease. But why use exosomes rather than cells?

Exosomes, Robbins says, don’t change. An exosome is an exosome is an exosome. Whereas the immunosuppressive attributes of a cell can be reversed in the body, those of exosomes cannot, it seems. They’re a more stable and, he believes, safer method of achieving immunosuppression.

Immunosuppression is also the province of Adrian Morelli’s research. The assistant professor of surgery and member of the Thomas E. Starzl Transplantation Institute hopes to use exosomes to eliminate the need for immunosuppressive drugs, which often have serious side effects, after organ transplantation.

Exosomes, he says, carry MHC (major histocompatibility complex) molecules, which allow the immune system to differentiate between self and nonself. Imagining a transplantation scenario, Morelli sees taking exosomes from the organ donor and injecting them into the transplant recipient. The exosomes would be internalized by the recipient’s dendritic cells, which would process them with the cell’s MHC molecules, creating a hybrid molecule that recognizes both the donor tissue and recipient tissue as self. Morelli plans to graft donor tissue to a hybridized mouse later this year. Clinical trials, though, are a long way off. “This is a futuristic view,” Morelli says. “But two years ago, I didn’t know much about exosomes at all. We’re making a lot of progress.”
Uncover a disease mechanism.
Identify a compound that targets it just so.
Develop a drug.
Get it past clinical trials, and voilà—the hard part is done, right? Next stop is the reward for all that persistence and intellectual sweat: effective treatments and cures. Maybe. From here on out is not necessarily a free and clear road to dispensing good health. Many obstacles can stand in the way of getting the right pill into the right patient’s mouth. Here’s a short list: How big is the market for the drug? Will anyone manufacture it? What if a hospital staff member misreads the doctor’s handwriting on an order for it?

Yet if medical schools offer discussions of ways to address such implementation issues, or examine how the profession is systemically changing, they tend to do so only informally or in electives.

Pitt med’s class of 2008, however, will have a head start on understanding the science behind implementing good modern care. That’s because it’s the first class to take a required course, “The Basic Science of Care,” developed by a team from the medical school as well as from Pitt’s nursing, public health, health and rehabilitation, dental, and pharmacy schools.

The course focuses on subjects that threaten to compromise the quality of care and patient safety, even seemingly simple things like illegible handwriting. These are also the kinds of subjects that can enhance care and safety if given proper attention, says Loren Roth, one of the course designers. Roth is chief medical officer and senior vice president of quality care at UPMC as well as Pitt’s associate senior vice chancellor, health sciences.

In fall 2003, Vladimir Manuel (Class of ’06) and several of his classmates began organizing dinner lectures on malpractice insurance and other aspects of the healthcare system not addressed in depth in the curriculum.

Roth was a guest lecturer at some of those meetings. For some time, he and other faculty members (including the chairs of medicine and anesthesiology and head of the medical center’s electronic records system) had wondered whether there was a curricular way to cover some of the topics Manuel had identified.

While planning, Roth and others were joined by Allison DeKosky (Class of ’08). DeKosky had worked in U.S. Senator Arlen Specter’s office as a health policy adviser and in the private sector as a consultant. In her experience, many doctors knew the medical issues involved in policy but didn’t always have a clear understanding of the bigger picture—of how the system worked. When DeKosky started at Pitt, she learned that planning was under way for a required course and worked closely with the course directors, sharing her policy perspective.

The resulting course has generated a buzz of interest from other medical schools.

It’s been an ambitious project. A session late in the fall, for example, began with an overview of the history of patient care and doctor-patient communication, followed by a demonstration of an experimental program that lets patients communicate with some UPMC doctors via e-mail and access records online. Linda Tashbook, a patient whose physician, Gary Fischer, helped develop the program, talked about her experiences using the system, assuring students that e-mailing the doctor was far more convenient in many situations than navigating the phone system, a conclusion Fischer readily seconded.

In a discussion that followed, students raised a host of questions for a panel that included Fischer and Tashbook.

“Should patients be charged for e-mail interactions with doctors?”

“Does this kind of system alienate anyone?”

“Should medical records and test results be available online to patients?”

“Should patients be charged for e-mail interactions with doctors?”

“If so, should they be sent to patients straight from the lab?”

“What if the doctor won’t be in until Monday, and at 7:30 p.m. on a Friday a chest x-ray shows a 5-centimeter mass on the lung?”

“I think that if patients want access to their data, they should be responsible for accepting the data, whether or not they have to wait two days to talk to their physician,” said a nursing student working on a master’s degree.

Others in the class weren’t so sure.

“Maybe you can release normal results and not send abnormal results right away,” suggested a med student across the lecture hall.

“But if we’re just sending out results, then does that reduce our role as doctors?” asked another concerned student.

All too quickly the class was over, and students trickled out of the lecture hall in twos and threes, weighing the pros and cons of learning about a possible lung cancer by e-mail on a Friday afternoon.

“Everyone agreed that [class] was a good one,” says DeKosky, who is now taking the course.

“These are real things to think about when you go into your practice.”
PROTEINS DO VITAL WORK THAT KEEPS US ALIVE, not to mention the work that allows us to philosophize, explore the universe, and manipulate molecules. Yet there is no telling how many proteins a human being harbors. And each is a mystery: Out of a near-infinite number of ways to fold, a protein "chooses" one particular pathway and arrives at one particular "destination." Using nuclear magnetic resonance technology, Angela Gronenborn has studied this dynamic process in a streptococcal protein called GB1, which sometimes folds into mutant or amyloid forms. Her folding landscapes illustrate the energy state of the protein as it folds. A smooth landscape shows a protein that efficiently reaches a low energy state. A rough landscape shows an unstable process with myriad opportunities to fold into an alternate form. Understanding this process can provide a window into diseases like Alzheimer's, in which fibroid amyloid proteins entangle in the brain as plaque.
visible light streams outward from the Sun in endless undulating waves clocking 300,000 kilometers per second through the vacuum of space. Eight minutes into that journey, the earth gets in the way. At the University of Pittsburgh's Biomedical Science Tower 3 (BST3), sunlight filters through the great glass windows facing Fifth Avenue. It refracts, reflects, and otherwise rattles around the open stairwells, hallways, labs, and offices. By virtue of a long, open well on the ground floor, a surprising amount of natural light finds its way 25 feet below street level, where it warms the hearts of structural biologists like Angela Gronenborn.

Down here, computer workstations overlook a concrete slab holding six enormous superconducting magnets. These magnets are the ponderous tools of Gronenborn's trade—they have relegated her to basements at the National Institute for Medical Research in London, the National Institutes of Health (NIH), and now Pitt. When architects asked Gronenborn, who heads Pitt's new Department of Structural Biology, if she wanted anything special in her BST3 workspace, she answered, a bit wistfully, "Sunlight." They delivered.

Gronenborn is trim and affable with fine blond hair that goes straight to her jawline and stops. Her pronunciation of consonants reveals her German birth, and her vowels disclose her years spent in the UK. She is an expert in nuclear magnetic resonance spectroscopy (NMR), meaning she uses magnetic fields to create images of important biological molecules, right down to the atoms. As cellular proteins fold (or misfold, as they do in many diseases), Gronenborn can actually watch and understand the process. Each of the magnets she uses is essentially an upright MRI machine in a vat big enough for treading water.

A wavelength of natural light that finds its way to Gronenborn's workstation measures anywhere from 3,000 to 8,000 Angstroms (300 to 800 nanometers)—small enough that it repeats 100 times or more as it travels the width of a human hair. With modern microscopes, you can see objects and living things that approach this size. However, anything smaller than the wavelength of visible light—viruses, DNA, certain proteins, and organelles—is in a world of darkness. This is the world plied by structural biologists.
Walk down the corridor away from Gronenborn’s magnets, and you’ll cross onto another concrete slab. The microscopes here are so sensitive that vibrations originating elsewhere in the building can ruin attempts to capture images of samples. This is where associate professor James Conway practices what he calls (in a New Zealand accent) a “black art.”

The art, in a nutshell: Place your sample—a solution containing viruses, for example—onto a copper grid. Use blotter paper to soak up the excess. (Herein lies some alchemy—the proper length of time to apply the paper is a guess, but timing is critical to image quality because it determines the thickness of the ice surrounding the sample.) Plunge the grid into a bath of liquid ethane, which rapidly freezes the sample. Now it’s ready for the cryoelectron microscope, which fires a beam of electrons with a wavelength measuring a fraction of an Angstrom.

Conway uses cryoelectron microscopy to produce detailed structural images of viruses and other large protein complexes. With colleagues at Pitt, the NIH, and Scripps Research Institute, he has unraveled some of the secrets of virus life cycles. And he’s advancing this black art. In 1997, he succeeded in improving resolution from 17 Angstroms down to 9—the difference between seeing a red line on a baseball as it whizzes past and noticing individual stitches in the leather as you hold it in your hand. At Pitt, he aims to break the 5-Angstrom barrier.

SEPARATED AT BIRTH? Scientists have long assumed that viruses plaguing humans don’t have much in common with those that affect bacteria. Now they’re rethinking that premise. The background image here shows bacteriophages (SPOs) viewed with electron microscopy. Pitt’s James Conway, working with Roger Hendrix and Robert Duda of the Department of Biological Sciences, used cryoelectron microscopy to compare the bacteriophage’s outer protein shell (left) with that of a human herpes virus (right). Shell proteins are color coded, showing a shared structural pattern, which had previously been associated exclusively with herpes. This lends support to the theory that these viruses share a common ancestor.
Upstairs, Pitt associate professor Joanne Yeh grows microscopic crystals that glimmer and shine as light refracts from their surfaces. Although the recent recruit from Brown University admires the crystalline beauty of these formations, they are only an intermediate step in figuring out the structure of the protein molecules within.

In 1952, working in a cellar at King’s College in London, Rosalind Franklin used x-ray crystallography to produce an extraordinary DNA image that she labeled “Photo 51,” which, without her knowledge, was shown to James Watson and Francis Crick, giving them clues they needed to decipher the double helix structure. Yeh’s work is in Franklin’s tradition (in fact, her department head, Gronenborn, holds the Rosalind Franklin endowed chair in structural biology), though x-ray crystallography has come a long way from those days. Yeh can reveal the structure of molecules to atomic resolution detail. And analyses that might have taken Franklin a year, Yeh can do in an afternoon with computational advances and 3-D modeling programs. Once her lab prepares a pure sample of protein to crystallize (this form ensures the molecules are stacked in an orderly fashion, like rows of identical parts packed into a warehouse), she fires an x-ray beam at it. By solving the diffraction pattern, Yeh can generate a 3-D model, showing the location and orientation of each and every atom. With this information, pharmacologists can design drugs and bioengineers can make nanomachines that work at the molecular level.

**HOW DO YOU BUILD A MACHINE OUT OF A MOLECULE?** First learn its exact structure. Joanne Yeh crystallized a pure solution of an enzyme that metabolizes hydrogen peroxide (a marker of inflammation); analyzing patterns of x-rays diffracting off the crystals allowed her to then solve the enzyme’s structure. **INSET:** With physicists and engineers, Yeh linked the molecule to a gold nanoparticle (large sphere) using a peptide (green ribbon) bound with cobalt (small yellow spheres). When the team immobilized the enzyme assembly onto gold nanoelectrodes, the tiny machine conducted electrical signals in the presence of hydrogen peroxide. This technology may one day be used to create biosensors to diagnose disease states like inflammation long before symptoms become detrimental.
Gronenborn admits that she could have happily remained at the NIH, where she led a vigorous and successful program. But she says she was thrilled by the opportunity to bring NMR together with x-ray crystallography and cryoelectron microscopy. Each is such an expensive enterprise that most institutions have added them piecemeal in scattered departments and buildings. At Pitt, structural biologists are next-door neighbors, each practicing his or her obscure art with the latest generation of equipment. These investigators can interact daily with Pitt’s computational biologists, pharmacologists, and clinicians (and, of course, with each other) to bring the finest bits of life out of the darkness and into the light.

**STRUCTURAL WORKHORSE:** When proteins mutate to amyloid forms, bad things happen like type 2 diabetes. To understand the basics of this process, Angela Gronenborn probes a protein called GB1—the “workhorse” of her lab. GB1 sometimes mutates and forms long amyloid fibers, as seen in the gray cryoelectron microscopy images. Using NMR, Angela Gronenborn creates cartoons to decipher the arrangement of the thousands of atoms involved. Red and teal ribbons represent two presentations of the backbone atoms and show how they arrange themselves into a long helical strand; many strands together form an amyloid fiber. Such representations help scientists design drugs to interfere with the amyloid formation process, like the protease inhibitors that are the current standard of care for HIV/AIDS.
David Steed (M.D. ’73, Res ’76, Fel ’77, Res ’79) remembers joining the University of Pittsburgh Department of Surgery in 1979—an office wasn’t available for the new junior faculty member, and it wasn’t clear when space would open up.

“Share my office,” said Charles Watson, the senior and celebrated surgeon.

It was an offer no one had to make—certainly not the chief of general surgery—but the kind Watson was likely to.

When the tall, slight-framed Watson walked the halls of Pittsburgh hospitals, students stood a little straighter. His very presence, in its mild manneredness, reminded those who worked with him that rapport and empathy count. In Chuck Watson’s world, there was always enough time in the day to visit with every
He had just been poked, prodded, and questioned by multiple teams.

The last thing he needed or wanted was another medical student collecting information that she could just as easily find in his voluminous charts.

I met 11-year-old Joseph during my pediatric rotation. He was in Pittsburgh, far from home, awaiting a liver and small bowel transplant. I was assigned to conduct his history and physical. As I started to collect his history, he averted his eyes and changed his tone of voice. It quickly became apparent that I could not connect with him through medical questioning. He had just been poked, prodded, and questioned by multiple teams of specialists and their entourages of fellows, residents, and med students. The last thing he needed or wanted was another medical student collecting information that she could just as easily find in his voluminous charts.

So we stepped out of our assigned roles that night and played video games. This started our ritual of play, through which I learned about his pressing medical conditions, his fears, his hopes, and his dreams. This boy had been both irreparably damaged and sustained for the past several months by TPN (total parenteral nutrition, an intravenous feeding process for patients whose intestines can’t absorb nutrients). He had been unable to eat or drink, yet he articulated a dream of becoming a chef. He was one of those kids who could simultaneously break your heart and make you fall in love.

Two days after our meeting, Joseph was transferred to the pediatric intensive care unit (PICU) for treatment of a near-fatal condition. This strange environment with its lack of privacy and incessant beeping would become his home for the following months. Despite all this, we continued our play. We found ourselves playing Simpsons Operation as he waited for his own operation. Eventually, the interminable waiting, the multiple failures of his organs, and the lack of normalcy in his life chipped away at his hope. He became more withdrawn as the months passed. One day, I came to visit and did not find him in the PICU. I quickly checked the board; his name was listed next to bed 9. I went over to that bed but didn’t see Joseph. A different child was lying in his place. My heart began to quicken. Did something horrible happen? When I asked the nurses where he was, they pointed once again to bed 9. I walked back to the bedside and looked at the stranger in Joseph’s bed. Then it hit me. This stranger had Joseph’s blanket and toys. In fact, this stranger was Joseph. His facial features were imperceptible, swallowed by his bloated flesh. He floated in and out of consciousness. His breathing was shallow and rapid. He was drowning in a sea of tubes and wires. Most notably, he was alone. Without thought or awareness, I ran out of the PICU and found myself halfway home.

I am still haunted by guilt and regret from that day. At that precise moment in his life, Joseph needed someone to hold his hand. He did not need a playmate. Out of my own fear and rage at death, I abandoned him. Partially because of my guilt over this, when he needed...
team, regardless of how long he'd been at the hospital or the duration of the surgery. During surgeries, he went out of his way to involve me in the procedure, despite the fact that it would take longer. My first “solo” experience was amputating a small toe while he stood next to me, calmly explaining each step and even joking how well I normally hid my “shakes.” (When I’m nervous my hands shake—not a helpful trait during surgery.)

During morning rounds, this same resident would stop and talk with patients, sitting on the edge of the bed, really listening. When he saw a patient smoking outside after multiple promises to quit, the resident still treated him with respect and continued to challenge him to break the habit. His example rubbed off.
She softened and smiled slightly, saying, “Honey, I know you are trying to make me feel better, but don’t ever assume you know how I feel. Ask me. Don’t tell me.”

to be free of the emotional weight he’d been carrying for so long. I was surprised he’d taken this step but thankful that despite a disappointing diagnosis, he was at least able to help himself during his hospital stay.

It began as a typical emergency room shift. A man in his late 30s was brought into the ER with multiple stab wounds to his leg. As a third year, it was my task to attend to him. He was a big man who groaned and mumbled. He seemed agitated and angry—not so much by his cuts, but by being there. As I prepared to sew up his wounds, he huffed and puffed. I was nervous about what his reaction would be if I hurt him.

Rather deliberately, I asked him if he was okay, and I couldn’t have predicted his response.

He began telling me the story of how he’d ended up there. He confessed that he couldn’t tell anyone how much pain he was feeling and how scared he actually was, because he was “the strong one” in his family. As he repeated his story again and again, I became less concerned with the procedure I was performing and turned my attention to what he was saying. The hardened shell of this robust, distressed man was crumbling, revealing someone who had gone through trauma and felt unable to express himself—until we talked. His eyes welled with tears as he spoke, not because the suture was painful.

When I was done, he was serene and thanked me for listening. For a split second, I thought, He didn’t even thank me for sewing up his leg.

But then it dawned on me—that wasn’t what mattered to him most.

During my internal medicine rotation, our team visited a middle-age woman with inoperable cancer. We entered into a discussion with the family about how much time she had left to live and whether a hospice might meet her needs. It was a big group of us, maybe eight, including the patient, her brothers, the attending, resident, myself, and another medical student. I had just met the patient; it was awkward being part of the discussion. She seemed distrustful of me being there, and I felt like a stranger eavesdropping on a private conversation.

So I tried to make her feel more comfortable, saying, “I know this must be a difficult time for you.”

She looked me in the eye and snapped back in anger, “You have no idea what this time is like for me. I doubt you’ve ever been in this situation, have you?”

I was shocked and taken aback, yet I immediately realized that I had made an assumption that I did not know what her pain was like. I had not the slightest idea, really. I was quiet for a moment; then I said, “You were right. I’ve never been through this before. I was just trying to make you feel more comfortable.” I looked down at the floor, embarrassed.

She softened and smiled slightly, saying, “Honey, I know you are trying to make me feel better, but don’t ever assume you know how I feel. Ask me. Don’t tell me.” I’ll never forget her words.

Ralph was my patient for more than a decade, through his 60s and into his 70s. He suffered from hypertension, anxiety, and chronic pain. He had adult children and two grandchildren he adored.
BIG SHOES TO FILL

OR, FINDING WARMTH IN THE COLD

BY CRAIG CAHALL

I was smitten with the practice. My brief visit had rekindled the idealism that had led me to abandon a career in investment banking to go into medicine.

Jackson’s retirement party made front-page news in the local papers. Because of space limitations, only 350 people were able to attend. Former patients came from all over the country. Their stories were filled with love, admiration, and humor: tales of house calls at 3 a.m., textbooks bought anonymously for needy students, lives inspired or saved. At the end of the evening, Jackson’s speech evoked a seven-minute standing ovation. Like the rest of the audience, I found myself in tears.

The reality of Jackson’s commitment to his calling became apparent as I began to see his patients in the following months. (I still didn’t have the audacity to call them my patients.) Repeatedly, they revealed details about my life that made me wonder how they could have known. They asked after my children or inquired about the renovations going on at our newly acquired 100-year-old home.

At first I wrote those personal comments off as just part of life in a small town where there are no secrets. But I later learned that Jackson had called every one of his patients to apologize for retiring and to thank them for giving him so many years of happiness. He’d also reassured them about their future care. He’d told them he had wanted to retire for a long time but had waited till he found the right person to take his place. He’d told them of his children’s names, about his passion for music, and my ability to listen. These people didn’t care about my education or my achievements. They only wanted to know if I was like him. By telling them I was, he paid me the greatest compliment I’ve ever received.

His daily visits to his old office dwindled only after a year of my taking over. He’s run out of excuses to visit, but they’re no longer necessary. He has found another life full of family, friends, and travel—a life he had too long ignored for the sake of his patients.

I’ll always remember how he warned me never to neglect my family for the sake of my patients. He told me not to miss my children’s growing up, to take time to indulge in my hobbies, and not to give my entire life to medicine, as he had done. But he spoke without regret.

Today, Jackson’s patients continue to teach me what it means to be a good doctor and a good person. At first they warned me that I had some pretty big shoes to fill. They were nervous about the fact that the man they could tell anything about was gone. But slowly they began to reveal themselves to me as I listened to their complaints. They taught me that to be a good doctor is to be a good listener. While they care little about the beneficial effects of ACE inhibitors, they care very much about being heard.

Several weeks ago, one of my patients told me that I reminded him of a doctor he’d once known. Frazzled after a very busy day in the office, I absentmindedly asked who he meant. He put his hand on my shoulder and said, “I think you know.”

J. Fraser Jackson handed over his practice at the age of 82 in 2002. He’s finally content in his retirement. To learn more, see p. 36.
Guo-Qiang Bi's work shows us that forgetting helps us remember.
You catch a whiff of something sweet. You taste bitter coffee. Your eyes take in a towering oak. Your ears hear the teacher tell you “A squared plus B squared equals C squared.” You feel the softness of a velvet Elvis.

Moments later, the input is gone. Yet after the stimulation stops you can conjure up the scent of honeysuckle, the bitter Folgers, the lush tree, the Pythagorean theorem, and the smooth visage of Elvis. You can do this seconds later, hours later, years later. You’ve learned and remembered. So, how the heck did that happen? Well, clearly, your senses gathered information, nerves pumped that stuff into your brain, and it hung around up there in your noodle, available for recall. Simple. Next question.

What? You want to know how that happens? You want to understand how you learned that cloying scent, inhaled for a period of time, was honeysuckle in the first place, and you’d like to know how that odor went from being a bunch of molecules in your snoot to some kind of neuro-something or other rattling around inside your head—what we call a memory? Boy, you’re demanding, but here goes.
In the mid-1920s, aspiring novelist Donald Olding Hebb was swayed by practical concerns to assume another vocation. A native of Nova Scotia, Hebb graduated from college and became a school principal in Quebec. Seemingly settled in for a nice, comfortable life, Hebb kept his mind sharp by taking graduate classes in psychology at McGill University in Montreal. By 1936, Hebb had not only quit the life of a secondary school administrator, he had earned his PhD in psychology from Harvard University, having taken a particular interest in how brain injury affected intelligence and behavior.

Then came the book. In 1949, Hebb published *The Organization of Behavior: A Neuropsychological Theory*. He intended to posit a “general theory of behavior that attempts to bridge the gap between neuropsychology and behavior.” In doing so, the psychologist paved a path that neurologists still tread today, a path that leads from chemical and electrical interactions between neurons to learning and memory.

Hebb proposed that an external stimulus causes a signal to be fired across a synapse, and that when this action is repeated, the synapse is strengthened, making it more likely to stimulate the next neuron to fire. Neurons firing in a series—“cell assemblies,” Hebb called them—form a circuit. The brain has then established a pathway in response to a unique stimulus. This is learning. And it is in such circuits where extremely short-term—“working” or immediate and instantly accessible—memory exists, in reverberating cell assemblies, before being transferred to long-term memory.

Hebb laid down the theory, and investigators today are still laboring to reveal the underlying mechanisms that guide what Hebb intuited, notably the University of Pittsburgh's Guo-Qiang Bi.

Bi has figured out quite a bit about how we're able to remember or forget.

He is an assistant professor of neurobiology and member of the Center for the Neural Basis of Cognition. Other scientists describe Bi as self-effacing, humble, and quiet. A visit to his office reveals these adjectives to be apt. It also suggests Bi may be the owner of the most jumbled dry-erase board—red slashes here, blue words there, black scribbles on top of it all—in the land.

As he eagerly explains his work, Bi pops up from his chair, erases a portion of the board with his balled-up-hand, draws a pair of neurons, sits down again, jumps up and, poking at the board with a marker, draws neurotransmitters crossing the synapse pointillist-style. Then he sits down again. Sort of a neurology aerobics routine.

From his seat (for a few moments at least), Bi explains that scientists have been exploring Hebb's postulate since it was first published. It is generally accepted, Bi says, that learning and memory take place on the synaptic level.

"Guo-Qiang identified some very new and interesting temporal relationships that people hadn't known before," Simons says. "Well, they sort of did, but Guo-Qiang came up with a very careful characterization of these timing relations."

The resulting paper, says one of Bi's former UCSD colleagues, physics professor David Kleinfeld, has become a classic. It led to a more precise understanding of the time factor involved in making memories. The data have been used in more than 300 subsequent papers related to the topic.

"It's very likely that [this] paper will become textbook material," says Kleinfeld.

Two years after that seminal paper was published, Bi found himself recruited to join the faculty at Pitt. He knew he had farther to go with his work and at Pitt held have access to what he recognized as one of the largest and most diverse—in terms of disciplines—neurobiology departments in the country. (Since coming to Pitt, Bi has advanced his research by tapping into experts throughout Pitt and at Carnegie Mellon University. "There are quite a lot of resources within walking distance," Bi says.)
“The crucial thing with this kind of description is that it’s not complete” and is far from representative of how things actually work, Bi says of his 1998 paper.

Simple pairs of neurons and the synapses between them don’t account for how we learn and remember. Instead, we use discrete and ever-changing networks of multiple neurons.

Bi had figured out the precise timing of inputs required to strengthen or weaken the synaptic connection between one pair of neurons. Now it was time to find out how the simple rules he put forth applied to more realistic neuronal networks. He cultured small networks of rat hippocampus neurons in a dish and set about stimulating the network.

With adequate stimulation, one cell fired the next and the next and the next. An interesting thing happened when Bi removed the external stimulation. The neurons continued to fire.

There is a reverberation, as Hebb had postulated.

“It won’t last forever, but for a few seconds or fractions of seconds, the activity is actually preserved,” Bi says. He compares it to your computer’s working memory—it’s only briefly active.

To translate this residual firing to learning as it is commonly understood, Bi talks about the process involved in remembering a phone number.

We hear the digits once—the input—and a neuron fires. We attempt to cement the number into our memory, so we repeat the number. As we do, the continued input creates a network, a cell assembly, in which this information is stored. The synapses in the network become stronger from the repeated firing, and it is in these synapses where the number—our memory of it at least—dwells. This is long-term memory. Once a strong neural network is established, even a very weak input can trigger the reverberation pattern.

“You remember the phone number, then eventually the person’s name will be linked to the phone number. And if you hear the person’s name, you can retrieve this phone number by activating this reverberation,” Bi says.

After enough repeating, Bi notes, the synaptic network becomes stronger and can be activated.

But quickly after explaining this, Bi throws in a caveat. The above is a mere analogy. To be candid, Bi says, he and others in the field are still, more or less, at the beginning of a long journey toward understanding learning and memory. What transpires in the Petri dish with a limited network of rat neurons may extrapolate to what happens inside our heads. But to really know what’s going on in the working human brain, you have to study the working human brain. A tough thing to do.

“What’s the mechanism underlying this persistent activity? We don’t know,” Bi says. “It’s really hard to study this in vivo. There are too many neurons, and we don’t know which is activated.”

His colleague, Simons, agrees but points out that, well, you’ve got to start somewhere when it comes to painting a complete picture of learning and memory. And where better than on the most fundamental level?

Bi, Simons says, has started from the bottom and continues to build increasingly complicated physiological systems in the lab. With the basic rules in place, Simons says, Bi’s work has great promise.

Here at Pitt, Bi says he’s gotten as far as he has thanks to former postdoc Huaixing Wang, graduate students Rick Gerkin and David Naen, and postdoc Pakming Lau.

Next on the Bi lab agenda is the identification and investigation of the chemical processes that mediate what happens in these circuits. Of course, this is no small task either: A legion of molecules is involved in cellular processes. Bi thinks that these chemical interactions are modular, that the perhaps 100 molecules that play a role in detecting and converting neuronal activity into changes in synaptic strength can be grouped together into two or three cohorts. Each cohort, Bi believes, is triggered by a specific type of activity and controls the strengthening and weakening of synapses. In the long term, a precise understanding of how these modules work will help craft what Bi calls “a complete set of rules” regarding the behavior of neural networks.

But what happens when something goes wrong with these networks? Here we can go to cinema for the answer, or at least one plausible possibility.

The 2000 film Memento features a character, Leonard Shelby, who seeks vengeance after being assaulted during the murder of his wife. His problem, as the character repeats throughout the movie—"I can’t make any new memories," Shelby carries a stack of photos to jog the old ones and tattoos new things he learns onto his skin. The character, Bi says, has a lesion in his hippocampus, a part of the brain rich in neurons, full of connections, and vital for learning and converting short-term memory into long-term memory.

Simons sees potential in Bi’s research to assist someone like the fictional Shelby.

“We know that the brain does have capacity for reorganization after brain damage, and we know it has a mechanism to do that,” he says. “If we knew the mechanism better—perhaps it relates to something like learning—then maybe we could enhance it either by pharmacological intervention or by physical therapy. This work has very important implications for that.”

Likewise epilepsy, in which neurons become too strongly excitatory and fire at the same time. Bi’s lab, Simons says, might be able to eventually explain how these abnormal neural patterns end up creating cell assemblies that become highly synchronized and release toxins into the brain.

What else can be gained by establishing the “complete set of rules” that Bi seeks? Simons sees endless possibilities: tracking how the infant brain is formed by sensory experience, determining why one person perceives a stimulus as threatening and another sees it as benign. All sorts of questions related to the normal development and activity of the brain could be probed with such rules.

Of course, it’s not going to be Bi’s lab alone that takes neurobiology to this golden moment. If anything is clear after spending time with Bi, it’s this: No one, Bi included, is anywhere near unraveling the Gordian knot first presented by Hebb.

But if there ever is a complete set of rules for the operation of learning and memory, neuroscientists will doubtless remember what they learned from Bi.
Joel Schuman has given physicians new tools for diagnosing and understanding glaucoma. These images were made by a prototype high-speed and ultrahigh resolution optical coherence tomography instrument, at a resolution of 3.5 microns—less than half the size of a red blood cell.

The indented structures in the images here are cross sections of optic nerves. The small inset images are the same optic nerves shown from another angle. In the healthy eye (above), you can see the bottom of the nerve “cup.” In the eye with glaucoma (below), the pit is so deep, you can’t see the bottom in the scan—too much tissue has been lost to glaucoma. The same deterioration is evident in the bottom left image. Blue indicates thin tissue.
Am I going blind?
Joel Schuman will tell me.
Let me back up—you see, I can't see.
Well, this isn't entirely true. I wear glasses or contacts.
Without the advances of ultrathin lenses, I'd be the woman who wears the proverbial Coke-bottle glasses. Each time I go to my eye doctor, I'm told my eyes have worsened.
If I'm not wearing corrective lenses, I fumble around my house, unable to distinguish the difference between my cat and an end table. Everything looks like the same blurry blob.
I often wonder what life would be like if I couldn't see.
Maybe I'm melodramatic. I could just have poor eyesight, but if there's something more to my hazy vision, I want to know about it. And it's not every day that I'm offered insight into my future.
To be clear, I’m not a patient of Joel Schuman’s. I’m getting to know him on an article assignment about important advances in glaucoma detection and how he helped make them happen. Schuman is chair of the University of Pittsburgh Department of Ophthalmology; he has offered me a tour of his lab full of tools for diagnosing eye disease. How could I refuse?

Almost immediately after my arrival at Schuman’s lab, Bill Dilworth, the department’s ophthalmologic imaging technician, shows up and asks if I want a test. Dilworth wears blue scrubs over his broad chest and has big hands; his hair is cut closely.

“Yes,” I say without thought.

Dilworth wants to give me an exam on a machine that uses optical coherence tomography (OCT). The machine detects abnormalities years before traditional tests can find evidence of glaucoma. It is the most powerful tool available to clinicians, and Schuman was instrumental in its development.

I don’t think anyone in my family ever had glaucoma; I’m younger than 40, and it isn’t something my parents or siblings would suffer from. Yet the “what-ifs” are anxiety inducing. What if there really is something wrong? What if I think about what’s actually happening.

Light beams are plunging through my eye tissue, examining the layers within. Red light vibrates and shoots across the screen; what is reminiscent of a video game is how Schuman has figured out how to scan for deep-set damage in my optic nerve.

As I hold my breath and watch lights, I hear Schuman talking to some grad students about their work, patiently listening to their concerns, giving them tips.

“Okay, you’re going to see a dot in the right-hand corner. Keep looking at that,” Dilworth says.

The black field looks like the background for Atari’s Space Invaders, especially when red beams shoot across it. Red light flashes and dances as I struggle to keep my eye focused on a green target. I’m holding my breath because I want to focus so I can “pass” the test.

Now it looks like the red lines are vibrating. Where’s that dot I should be looking at? It’s hard to concentrate with red beams shooting all over the place.

Harder still if I think about what’s actually happening.

If anyone can render an accurate verdict on questions concerning glaucoma, it is Joel Schuman. Throughout his career, he has been at the forefront of diagnostic testing for glaucoma. He also discovered the first molecular marker for the disease. The man has devoted his life to treating and curing glaucoma, and he is not satisfied with the current state of diagnostics and markers. Even though he is responsible for the development of the most powerful tool available for detecting glaucoma, he’s determined to make it better.

Dilworth cleans off the eyepiece of a rectangular white machine. I place my forehead on the headrest to begin the exam. As he works, Schuman stands back, allowing Dilworth to run the show.

The machine detects abnormalities years before traditional tests find evidence of glaucoma. It is the most powerful tool available to clinicians, and Schuman was instrumental in its development.

As I hold my breath and watch lights, I hear Schuman talking to some grad students about their work, patiently listening to their concerns, giving them tips.

Shortly after he finished his own training in the early 1990s, Schuman, at Harvard University and then at Tufts University, partnered with James Fujimoto—a professor of engineering at Massachusetts Institute of Technology interested in the use of lasers in medicine. Schuman approached Fujimoto because he wanted to find a diagnostic technique that would identify glaucoma before the onset of often-debilitating symptoms. That’s when they developed this OCT technology, which is about to reveal my visual future.

According to the Glaucoma Research Foundation, probably 3 million Americans suffer from glaucoma, yet only half of them know it. The disease is the leading cause of preventable blindness, but in its earliest stages people experience virtually no symptoms.

Glaucoma is characterized by damage to the optic nerve, usually because of high intraocular pressure. The disease causes blindness when nerve damage is so great that the brain and eye can no longer communicate. It is most commonly found in people older than 40, yet it does occur in children and young adults.

Gradual progression disguises the disease. Glaucoma’s quarry may notice that she can’t see out of the corners of her eye—she turns her head to observe something. Even on hazy days, she wears sunglasses because the light causes discomfort. You would think night would bring relief, yet it makes driving stressful. The halogen lights burn brightly, and she struggles to see the road and other cars. Fluorescent lights in the mall, her office, and the grocery store affect her ability to see.

This could easily be me. I don’t keep my office lights on—they give me headaches and don’t help me see better. And at 26, I have a hard time seeing at night.

As I continue to keep my eyes wide open, I ask whether the results will be different because I am wearing contact lenses. “Naw,” Dilworth says.

OCT emits beams of infrared light (more specifically, low coherence waves; one of this year’s winners of the Nobel Prize in Physics studied this phenomenon). By bouncing light off both the object of interest, in this case ocular tissue, and a reference point (usually a mirror), the machine creates a profile detailing the exact location of structures within the tissue. The OCT then makes a few other scanning maneuvers and in the end produces a scan of what’s at the back of the eye, including retinal or nerve damage. Because there’s very little wave interference, the technology produces high-resolution images.

The technology uses light waves much like an ultrasound uses sound waves—the reflecting light waves create a picture of an internal structure. And as with ultrasound, OCT is safe for probing live organisms (like yours truly), without taking invasive measures.

What Schuman and Fujimoto accomplished with OCT allows clinicians to examine eye tissue without the subjectivity of what has been the gold standard in glaucoma detection technology—the visual field test. (In visual field tests, patients are asked to push a button when they see a light. Both the exam and the doctor’s interpretation of the results are subjective, notes Schuman.)

If a doctor can detect damage with a visual field test, a patient has already lost 30 percent to 50 percent of her ocular nerve tissue. By that point, she may still not have a lot of trouble seeing.
Alternatively, the OCT creates a cross-section of the eye, so that physicians can actually see damage done to the nerve fiber—the telltale sign of glaucoma. Commercially available OCTs can measure tissue at 10-micron resolution and detect nerve damage years before a visual field test can.

When Schuman first used OCT in Boston, physicians grumbled, This thing only works in Boston. Only expensive eye centers could use such sophisticated diagnostic equipment, many thought.

Schuman used the first commercial OCT in 1995; a decade later, 5,000 are in use in clinical and research settings, and he believes most of those machines were bought in the past few years. He dreams that one day, ophthalmologists worldwide will have OCTs in their offices. It has become the new gold standard for retinal disease and is now more widely sought out for glaucoma.

Why have some clinicians been slow to adopt OCT for glaucoma diagnostics? Some worry “abnormalities” that OCT users are seeing deep within patients’ eyes aren’t related to glaucoma. They suggest there isn’t enough information about what a normal eye looks like compared to an eye with glaucoma at such an early stage.

Who’s to say abnormalities detected by OCT are glaucoma related and not a result of normal wear and tear?

Schuman, that’s who.

He is confident that this machine is detecting glaucoma, and he has the data to back that claim.

Further, he knows that treatments for early glaucoma are both easier for the patient and more effective at preserving undamaged retinal nerves.

“The worse the disease, the harder it is to treat,” Schuman says.

“I would want to treat [patients] sooner rather than treating them too late.”

If Joel Schuman asks questions, he genuinely listens to the answers. He puts people at ease. In his few hours off, you might see the ophthalmologist with his children in the Apple Store or at a Black Eyed Peas concert. He keeps a guitar in his office. His other big hobby isn’t surprising for a man of vision: photography. There’s something about him that’s, well, kind of cool.

As an undergraduate at Columbia University, Schuman pursued a psychology degree. That’s when he became interested in how people perceive objects. Soon questions of optical illusions captured his attention. Questions like, Why does the moon look bigger when it rests on the horizon than when it’s overhead? He started wondering why the retina itself seemingly played tricks on the mind. Inspired by his older brother, he attended medical school at Mount Sinai School of Medicine. He went on to cofound Tufts-New England Eye Center. (In addition to becoming vice chair and a professor of ophthalmology there, he served as an electrical engineering and computer science professor.)

When I am done with my OCT test, Dilworth waits while the computer processes the results of my scan. I blink and blink, now offered the freedom to do so. Dilworth waves me back to the computer screen behind the OCT, so I can look at some charts and graphs.

“You’re normal,” he declares, “you can go back to work and tell everyone you’re normal.”

“Well, you can tell them that your eyes are normal,” Schuman deadpans.

The tour continues. I take another eye test. This one resembles a firefight Luke Skywalker might have in mid-space. The tests become a jumble of alphabet soup—GDX, HRT, UBM. These are all machines Schuman brought to Pitt. Few hospitals or labs in the country have such sophisticated screening devices. There’s something that looks like a gauge to check air pressure in tires. Another contraption resembles headgear unlucky children with braces might have worn. And though the machines look clunky and the tests remind me of sci-fi, they give Pitt docs the ability to diagnose eye disease more accurately and give Schuman other standards to test OCT results against.

Dilworth and Schuman grin each time they demonstrate a new machine. This feels like an engineer’s playground, yet Schuman does not think of himself as an engineer. He declares that he is a physician-scientist. He’s not interested in technology that doesn’t benefit patients.

And Schuman isn’t just known for his work on diagnostic technologies. Ten years ago, while still at Tufts, Schuman was treating a patient who suffered from leukemia. The man—we’ll call him John Rudd— was in his 60s but not a prime candidate for glaucoma. Schuman wondered what
it was about leukemia that caused Rudd to have glaucoma.

And, more urgently, he asked himself, What causes glaucoma? Schuman saw patient after patient with the haze of glaucoma settling in, but he had no answers for why they had the disease. That simply wouldn’t do for Schuman—who is always looking to fill in the blanks. (Schuman is the kind of guy who needs to know how the DVD player works, his wife, Carole Schuman, reports.) So for years, he saved samples of eye tissue. He screened the tissue samples from his surgery patients (with their permission, of course) and compared them to eye samples from normal cadavers to see whether he could find a difference.

In most cases of glaucoma, the fluid in the eye does not drain into the body like it does in a healthy eye. By examining the trabecular meshwork—a network of channels that drain fluid from the eyes—Schuman learned there were basic differences between the meshwork in an eye with glaucoma and an eye without the disease.

Schuman wondered what it was about leukemia that caused Rudd to have glaucoma.

Schuman started screening cells involved in the aqueous outflow of the eye. In every eye with glaucoma, a particular marker showed up—ELAM 1, or endothelial leukocyte adhesion molecule 1. It was never in eyes without the disease.

And he eventually figured out why Rudd had the disease: Leukemia cells cause basic changes in the trabecular meshwork that may be related to inflammation and healing.

Schuman’s lab was the first to identify the marker that could indicate glaucoma at an early stage. He was able to decipher this with the help of a few students and a research associate. He knew they’d discovered something big but didn’t have the time with his patient load to organize his data in a way that would be appropriate for publication.

Besides, he was more at ease in an OR than a lab. It was time that someone who knew her way around data came at the problem.

Enter molecular biologist Elizabeth Fini.

In 1995, Fini arrived at Tufts’ medical school. The PhD always thought of herself as a student of wound-healing mechanisms, not someone particularly interested in ophthalmology. Although she came to the school to research wound healing and the cornea, she often thought it funny she was examining such a small entity when she could be studying a large organ like skin.

But Schuman talked her into sticking with the eye for a bit longer. Fini joined his project, and the amount of data astonished her. Hundreds of samples of the trabecular meshwork lined his freezer shelves. Schuman had harvested and collected the specimens for nearly a decade.

Fini watched Schuman in the OR, where the PhD took to heart the human component of their pursuit. She was inspired to dig deeper. Soon she was encouraging Schuman to think about the data in a different way, to try to understand the disease mechanism behind glaucoma. They eventually figured it out.

In the early stages of glaucoma, damaged cells lining the outflow encourage production of a molecule (NF-kappa B) that stimulates inflammatory cytokines such as IL-1 and ELAM-1. A damaged trabecular meshwork results in high intraocular pressure and optic nerve damage characteristic of the disease.

If a paper about a biological marker for glaucoma in itself is exciting, a paper reporting on a marker and a disease mechanism is outstanding.

Schuman and Fini’s work landed the cover of the March 2001 issue of Nature Medicine. The abstract also appeared in Nature. Reviewers and reporters called to find out more.

After knowing about ELAM-1 for years, Schuman finally was able to reveal to the world a biological culprit behind glaucoma. “Joel should be pretty proud of this,” says Fini.

When asked how it felt to make that contribution, Schuman looks down and says, simply, “Great.” Understanding the disease mechanism is a big step toward developing a better treatment. It means that maybe someday doctors like Schuman won’t have to tell patients with glaucoma, You can’t drive anymore. Or, You’re going to find it hard to continue your work as a painter.

In 2001, Fini left Tufts for the University of Miami to become the scientific director of the Evelyn F. and William L. McKnight Vision Research Center and the Walter G. Ross Chair in Ophthalmic Research. Schuman came to the University of Pittsburgh in 2003 to be the Eye and Ear Foundation Professor and chair of ophthalmology.

After I complete my tests, Schuman opens a door to what looks like a closet. Inside, the guts of a computer are splayed over a desktop. This is the future of OCT. Schuman says there are only two other machines of this caliber in the world: one in Fujimoto’s lab at MIT and another at Tufts.

Massachusetts General Hospital, Duke University, the University of Miami, and the University of California, Davis, are each trying to develop an OCT prototype on this scale—which is 75 times faster and has three times clearer resolution than the instrument Dilworth used on me.

This prototype is designed to allow docs to see minute details of a living patient’s eye, like how much oxygen and blood flow are present, in a way not possible using any other imaging technology. Schuman credits the 15 members of his lab for doing “yeomen’s work” to move this technology forward. He notes that colleague Gadi Wollstein, assistant professor of ophthalmology and director of Pitt’s Ophthalmic Imaging Laboratories, has been the lead author and study designer on a number of “the most significant OCT studies over the past three years.” Assistant professor of ophthalmology and bioengineering Hiroshi Ishikawa developed new algorithms for the OCT prototype. (Both men came to Pittsburgh from Boston with Schuman.) Larry Kagemann, research instuctor of ophthalmology, joined the group recently after several years at Indiana University in the world’s top ocular blood flow laboratory.

Schuman expects to detect a number of diseases with this new OCT.

But we’ll have to watch for his lab’s next big thing. At this point, Schuman is concentrating on getting the OCT prototype up and running smoothly.

“The cool thing is that we can provide cutting-edge diagnostics for patients as well as study the tools,” Schuman says.

The cool thing is that Schuman is not done with being the first.
STRAIGHT TO THE STUDENTS

FACULTY HONORARIA FUND SERVICE ABROAD
BY ERIN N. LAWLEY

Without the technological fittings of American hospitals, second-year University of Pittsburgh med students Nicole Christian and Janet Leath were in unfamiliar territory. A patient couldn’t get an x-ray, MRI, or CT scan—the Ghanaian clinic had no such equipment. So instead, the two emulated the diagnostic techniques of the clinic’s doctors: careful, extensive patient interviews and physical exams.

Christian spoke of how humbling the experience was: “In America, we are privileged to have such advanced medical technology but are also much more dependent on it.”

Through a mission coordinated by the Student National Medical Association, Christian and Leath spent two eye-opening weeks in Ghana last summer. They participated in the Save a Million Lives project, which coordinates public health education and testing for HIV and AIDS in that African nation.

The young women were beneficiaries of the School of Medicine’s Summer Enrichment Fund.

This new faculty- and alumni-sponsored program allocates from $1,000 to $2,000 each to medical students who want to learn about medical practice abroad.

Several years ago Beth Piraino (Res ’80, Fel ’82), Pitt associate dean of admissions, professor of medicine, and director of peritoneal dialysis at UPMC Presbyterian, began putting some of her honoraria from speaking and consulting engagements into an expense-reimbursement account in the renal division.

The account quickly fattened beyond those needs. Piraino then decided she’d like the money to go to students. The summer stipend evolved from there.

In her conversations with alumni office staff, Piraino discovered that many students want to spend the summer between their first and second years overseas, enriching their practical experience and helping communities. Yet few students can afford such ventures. So Piraino—along with Susan Dunmire (MD ’85, Res ’88), executive director of the Medical Alumni Association, and Lisa Wick, assistant director of admissions and financial aid—thought it would be a good idea to channel some of the honoraria donated by Piraino and others to that cause.

Five thousand dollars is a lot of money—until it’s stacked up against $120,000. The latter is the mean debt Pitt med students face upon graduation. The former is how much UPMC Presbyterian’s medical staff organization donated to the student scholarship fund before Andrew Peltzman (MD ’76), former medical staff president, current professor of surgery, and vice chair of Pitt’s surgery department, perused his budget. “Five thousand dollars seemed kind of silly,” he says. Peltzman proposed fully funding one Pitt med student for four years, using funds from staff dues. The newly created scholarship is need based. —ENL

FOR INFORMATION ON GIVING: 1-800-MED-ALUM or mhsf@ia.pitt.edu.
A FINE SPECIMEN

THE EVANGELICAL PATHOLOGIST

BY HATTIE FLETCHER
A slide pops up on the screen in a dimmed study room. To the untrained eye, it looks like modern art, a blobby arrangement in ketchup red, mustard yellow, and rusty brown. Students sitting around a table squint up at the image.

"Jane?" the instructor, Bernard Klionsky, prompts. He sits near the computer—a small man in baggy short sleeves and a bow tie. His thick beard and full head of black hair belie his age; he turned 80 in October.

"Well..." a young woman in a T-shirt begins, stalling for time. "It's cardiac related—because you just said the whole disk is hearts." She giggles. This course is a summer elective, filled mostly with medical students who have just finished their first year. A couple of undergraduate students sit in as well. Even if they can't quite keep up with the medical students, they're welcome. Klionsky gives no tests and no final grade. Still, there is pressure to come up with an answer.

"Yes, it's a heart," Klionsky agrees with a smile. "But what is the slide showing?"

"It appears to be a thrombus," Jane [not her real name] says hesitantly.

"Yes," Klionsky says. "But that's opinion. First, describe it. Give me a description a blind man could understand."

On one level, this is a lesson about cardiac pathology, about recognizing abnormalities in hearts. Klionsky, who has been a professor of pathology at the University of Pittsburgh School of Medicine for 44 years, is fond of saying, "To most students, 'heart attack' is just a word. And it's not enough just to know the word." To become effective doctors, he believes, students need to be able not just to diagnose a heart attack (or any other medical condition), but to recognize where each particular patient falls along the spectrum of a disease's possible outcomes.

Ultimately, though, this lesson—like all of Klionsky's—is really about how to approach problems. He is teaching his students pathology; but more importantly, he, like any good teacher, is showing them how to think, how to become, as he puts it, "highly trained problem solvers."

"What else could it be?" he pushes each student in turn. "Answers have to come at least in threes."

Through the years, Klionsky has pursued more than a few problems in depth. He identified the structure of Fabry's disease. He figured out how to end an epidemic of yellow hyaline membrane disease and low bilirubin kernicterus, a disease that was once a major cause of death among premature infants. He became an expert in the pathology of the cervix and chaired the U.S. Public Health Service Committee on Reproducibility of Diagnosis. Once, he did an autopsy on a lactating dolphin. He made a synthetic formula of dolphin milk, but failed to keep the calf alive.

Sometimes, Klionsky says, he regrets not having become one of the country's leaders in a particular area of pathology, as many of his colleagues and some of his former students have. The trouble was, his definition of "problem" was always too broad: Developing computer programs, finessing budgets, figuring out how to make residencies more productive and satisfying—to Klionsky, these issues were almost as interesting as lab work. Besides, he doesn't like to do the same thing even two years in a row.

A stint in the navy during World War II convinced him that he was capable of repairing almost anything mechanical. (He trained as an electronic technician and shipped out for the South Pacific on August 1, 1945, landing in Okinawa just after the signing of the terms of Japan's surrender.) That skill came in handy. Early in his career, Klionsky invented the open-top cryostat for collecting samples in the O.R. It forever changed surgical pathology. The horizontal door on earlier models let cold air spill out, and the cryostat could not be used until it re-equilibrated—which usually meant an unacceptable delay for the patient. (Klionsky never profited from this invention, as he wanted it to be widely available.)

In the '70s, residents at Magee-Womens Hospital taught him how to program on the Apple II, and he built systems to track and share test results across the hospitals more effectively. Later, he collaborated on a program with Howard Seltman, faculty in Pitt's central chemistry lab, that would allow even technologically illiterate professors to put together lessons on the computer. At one time, it was the best teaching tool in the field. (Ironically, Klionsky, the former technophile, fears that the dusty computer in his cluttered office might be in its final resting place—the computer worked last year but now seems to be dead.)

He stepped down as vice chair of pathology in 1995. Although technically retired, Klionsky works almost five months a year. He's trying to cut back; his wife would like him to spend more time at home. He teaches the summer course (part of the Klionsky Summer Fellowship Program, which he supervises) and interviews med school applicants. His interviews are famous for running twice as long as others. He follows up with pages of meticulous, single-spaced notes, including quotes from the conversations and exquisitely detailed descriptions.

"Students come out of it, and they say, 'That was long, but it was really cool,'" says Linda Berardi-Demo, former director of admissions. She says the candidates are inspired by Klionsky's dedication, especially if they learn his work for Pitt nowadays is free.

Yes, free. Klionsky would rather the department put what it would be paying him to use elsewhere—like offering more financial support to students. (There's a Bernard L. Klionsky fund, which supports students who take on pathology-related projects.)

Part of the reason his admissions interviews take so long is his tendency to extol the virtues of a career in pathology to anyone who will listen: the luxury to pursue interesting problems, the freedom that comes from not billing patients directly, the flexibility to spend time with family, the ability to combine teaching with research and practice. Klionsky makes his case with the enthusiasm of a recent convert, though it has been nearly 50 years since a compulsory rotation at a crucial point in his own medical school experience "saved" him from following a favorite uncle into pediatrics.

He warns students who show up for his classes that they have just increased their odds of going into pathology by a factor of 10. Certain that he himself has had the most satisfying career in the world, Klionsky is letting others in on the secret. It's hard not to think that, if students who take his courses end up as pathologists—and over the years, many have—it's not just because he's a passionate advocate. He's also exhibit A.
J. Fraser Jackson (MD ‘44) learned there is life after medicine—but not until he hit the age of 82. Now, he and his wife travel extensively (they recently returned from the Cook Islands)—a very different life than when he was running his family medicine practice in East Liverpool, Ohio. He reports he devoted 18 hours a day, seven days a week for more than 50 years to his patients. (On p. 23 of this issue, Craig Cahall writes about how intimidating it was to take over Jackson’s practice.)

Jackson was inspired by his own family doctor, Pitt grad Albert Michels (MD ‘19), to attend medical school at Pitt. That’s where he met his close friend and classmate David Pugh (MD ‘44), who later set up a practice in Chester, W. Va., across the Ohio River from East Liverpool. When Pugh died a few years ago, the town dedicated a park along the river in his name. Likewise, Jackson was honored with a river park in his hometown on his retirement in 2002. “If I stand in my park,” says Jackson, “I can see Dave’s right across the river.”

‘60s Stewart Sell (MD ‘60) is a busy man. In October of 2001, Pitt Med featured Sell in “The Oval Wave,” an article about the discovery of liver stem cells, called oval cells, as a source of liver cancer. Since then, Sell, senior research physician at the Wadsworth Center, senior research scientist at Ordway Research Institute, and professor of biomedical sciences at SUNY Albany, has continued to push his stem cell research forward. He is currently investigating the risk factors for liver cancer, the role of bone marrow stem cells in aging and as a possible origin of liver cancer, and the function of adult tissue stem cells in repairing injuries to organs and the spinal cord. In 2005, Sell was named a Pitt Legacy Laureate and received Leadership Medica’s Virchow Award and the American Association for Cancer Research’s Gary Miller Memorial Award. Adding it all up—research, awards, lecture invitations abroad, and the regional success of the Swing Docs Big Band (in which he plays saxophone and clarinet)—Sell says of 2005, “It’s been a great year.”

Jack Myers, renowned physician and chair of the Department of Medicine at Pitt med from 1955 to 1970, was David Morris (MD ‘61) idol and role model. “He showed me how important it was to have knowledge,” Morris says. “He made medicine so fascinating.” However, Morris didn’t listen to his mentor when Myers told him to buy a lifetime subscription to the New England Journal of Medicine for $75 in 1959. Today Morris, who says he’s read every major journal cover to cover for the past 40 years, regrets this lapse in judgment; he pays $150 per year for NEJM. Morris, 80, works three days a week at the New York Neurological Rehabilitation Center in Manhattan.

Since his 2000 retirement from internal medicine in Melbourne, Fla., Richard Baney (MD ‘63) has been stretching his sea legs. Baney is the ship’s doctor aboard a 110-passenger cruise ship, the National Geographic Endeavour. While afloat, Baney sees patients for about an hour per day and then explores terra firma in places like Western Europe, Antarctica, and the South Pacific islands as if he were a regular passenger. “It’s hardly work,” he says. On dry land,

Fred Brancati

THE PIMPING LIFE

Before Fred Brancati (Res ’88) took over in 1987 as chief resident at UPMC Presbyterian and the VA hospital, his predecessor led him to a back office to show him the secret to his success: a file cabinet full of articles on such obscurities as genetic conditions associated with extra fingers and rare conditions of the Old Order Amish. The chief resident suggested that if Brancati used this material when training others, he would really impress people.

After reading up on polydactylism, Brancati was inspired to put those who practice “pimping”—the tradition of humbling students and interns with a barrage of virtually unanswerable questions—in their place. Two years later, he submitted a satirical essay, “The Art of Pimping,” to the Journal of the American Medical Association. The editors published it within weeks (JAMA, July 7, 1989). Brancati’s tongue-in-cheek essay demonstrates how pimping “rids the intern of needless self-esteem.” And it notes, “Furthermore, after being pimped, he is drained of the desire to ask new questions—questions that his attending may be unable to answer.”

The essay prompted laudatory letters from across the country and requests for autographs in the halls of Johns Hopkins Hospital, whose staff Brancati joined as the article went to print. Now director of the Division of General Internal Medicine
Baney spends much of his time with his nine grandchildren and his wife, whom he met while attending Pitt med.

**’70s** Rheumatology was Neal Birnbaum’s (Intern ’70 –’71, Internal Medicine Resident ’73 –’75, Rheumatology Fellow ’75 –’77) first residency rotation. To this day, Birnbaum isn’t sure if it was the charismatic division chief, Gerald Rodnan, or the excitement of returning to his training in 1973 after serving two years in the air force that prompted him to make rheumatology his specialty. Birnbaum, who is the director of the division of rheumatology at California Pacific Medical Center, a clinical professor of medicine at the University of California, San Francisco, and president-elect of the American College of Rheumatology, was only 25 years old when he had the responsibility of running a large emergency room in Vietnam. He describes the experience as, simply, “a maturing process.”

Some of the patients that Johanna M. Seddon (MD ’74) sees can’t see her. In the advanced stages of age-related macular degeneration (AMD), some people’s vision is so poor that reading, driving, and even distinguishing faces right in front of them become impossible. Working with those people can be heart wrenching, Seddon says, but it’s one of the things that motivates her to research the disease. Seddon is an ophthalmologic retina surgeon, the founder and director of the epidemiology unit at the Massachusetts Eye and Ear Infirmary, and an associate professor of ophthalmology at Harvard Medical School and Harvard School of Public Health. She recently received the first Dr. Maurice F. Rabb, Jr. Award presented by Prevent Blindness America for her research and prevention work. Seddon’s team is currently pursuing a study to find specific genes related to the development of AMD.

Mark Vatavuk (MD ’77) loves baseball. He became a member of the Society for American Baseball Research in 1984. He was the associate physician for Erie’s minor league baseball team, the SeaWolves, in 1995. And in May, a book Vatavuk coauthored, Baseball in Erie, a pictorial history of the region’s long love affair with minor league ball, was published. Vatavuk is a family practice physician at Saint Vincent Health Center in Erie. He describes his role there—where he works in occupational health, precepts residents, and sporadically fills in for vacationing doctors—as that of a “utility infielder.”

**’80s** In any given week, Grace Alfonsi (MD ’83) might prescribe medication to a homeless woman, treat the chief of police, diagnose a man with an STD, and teach a group of residents to deliver a baby. Alfonsi is a family practice doctor in the community health division of Denver Health. She works in both the HMO clinic for city, county, and hospital employees and the public health clinic for low-income patients, where she also is a preceptor for residents. In addition, Alfonsi is on the attending staff at Denver Health’s STD clinic. In her scholarly work, she is investigating the causes for discrepancies between the results of a DNA-based test and culture results for gonorrhea detection. Alfonsi suspects that DNA tests sometimes produce false positives because of variant lab procedures.

**’90s** According to William Li (MD ’92), president and medical director of the Angiogenesis Foundation in Cambridge, Mass., today’s medicine will be unrecognizable in 20 years. Angiogenesis, the growth of new blood vessels in the body, is a process that underlies diseases ranging from cancer to diabetic blindness. Li oversees numerous research projects that he hopes will lead to treatments that can induce angiogenesis to restore circulation, as well as ones that stop it to halt disease progression. Because of the breakthroughs he sees on the horizon, Li believes researchers will soon find ways to make Alzheimer’s preventable, blindness reversible, obesity controllable, nerves regenerable, and cancer a chronic condition.

**’00s** Maureen Busher (MD ’02) is on a mission. The American College of Obstetricians and Gynecologists, in which Busher is a district officer, is trying to recruit more students to the discipline. So Busher, an ob/gyn resident at the MetroHealth Medical Center in Cleveland, started an ob/gyn student interest group at affiliated Case Western Reserve University School of Medicine. She wants to increase medical student interest in the field that stole her heart while she was at Pitt. “Halfway through my third-year clerkship, I realized this is what I love. There’s just such a great variety in the field.”

Robert Sobehart (MD ’03) was strapped into a helmet and 40-pound flack jacket. Rocket-propelled grenades and mortar rounds exploded only meters away. He worked as quickly as he could. During the initial eight-day invasion of Fallujah in November 2004, more than 300 wounded marines were brought to Sobehart’s makeshift trauma bay in a train station just outside the city. Sobehart and his team rushed to treat and stabilize the wounded for emergency medical evacuation to an outpatient surgical center. Although the experience was sometimes frightening, he says it was invaluable to his training. Sobehart is currently an emergency medicine resident at Naval Medical Center in San Diego.

—Erin N. Lawley & Erica Lloyd

at Hopkins, Brancati notes the meaning of the term “pimping” is lost on many new doctors. “A lot of pimping has gone out of the business,” he says. “That’s a good thing.”

“The Art of” is Brancati’s most widely read article, though he is doing more serious work today as a top diabetes and obesity researcher. He is a principal investigator for the Look AHEAD study, an 11-year clinical trial of 5,000 obese people with type 2 diabetes. He hopes his work will ultimately influence policy to reflect the importance of weight management in preventing problems further “downstream.” Brancati credits his Pittsburgh training for inspiring him to follow a clinical research path, especially the guidance of Pitt professors of medicine Wishwa Kapoor, interim chair of the Department of Medicine at Pitt, and Victor Yu, chief of the Infectious Disease Section for the VA Pittsburgh Healthcare System. They believe, Brancati notes, in an art much higher than pimping—teaching. —Elaine Vitone
Imagine a premature baby just moments out of the womb, weighing 2.7 pounds and incapable of inflating her own lungs. Eileen Tyrala had been working in neonatology for more than 10 years when this typical preemie came along. It was 1989, and Tyrala (M.D. ‘71) was the director of the neonatal intensive care unit (NICU) at Temple University Hospital, which was participating in a clinical trial of one of the first surfactants—a treatment that would forever change neonatology. Tyrala supervised the team as they rushed the baby to the NICU and inserted an endotracheal tube and a catheter. Along with a puff of air from a bag, the surfactant entered the baby’s lungs through the catheter, broke the surface tension within, and made it possible for the baby to breathe. “It was one of the most dramatic things I’ve ever seen,” says Tyrala. “This baby would have been horribly, horribly sick and on a ventilator.” The nurses in the NICU burst into applause when the baby’s lungs started working. The newborn was breathing room air within a half hour.

Tyrala credits Pitt for sparking her passion for the adventure of academic medicine. But after 20-some years of long shifts at Temple, she joined a pediatrics practice in 2003 outside of Philadelphia. Today, she’s active with SIDS of Pennsylvania, which promotes safe infant sleep education, and is the medical advisor to the Cribs for Kids program.

Michael Johnston (M.D. ’71) came to med school at Pitt so that he could one day join his dad’s family practice in Lancaster County, Pa. Eugene Johnston (M.D. ’47) had a jeep on hand so he could make house calls in any weather—that included delivering babies in the homes of his Amish neighbors. After a pediatrics residency at Johns Hopkins University, the younger Johnston and colleagues did head-turning work in the role of glutamate in pediatric brain injury. They found that the immature brain relied on glutamate for plasticity, but injury often resulted in high levels that were extremely toxic. Johnston’s lab discovered that a drug that blocked the glutamate receptor reduced this toxic effect. His pursuit of academic medicine never did lead him back to the Lancaster practice of his now-deceased father. Currently, Johnston is professor of neurology and of pediatrics at Hopkins and medical director at Kennedy Krieger Institute, which focuses on brain disorders. He sees patients with cerebral palsy, movement disorders, and genetic diseases.

In 1930 William Carter started a plastic surgery practice from scratch in Edina, Minn., just outside of Minneapolis. Back then, the field was primarily dedicated to reconstructive surgery, and Carter (M.D. ’71) set out to help patients who had suffered serious burns, massive cancers, and disfiguring injuries. “There’s a joy you get from this,” Carter says, asserting that it’s the sort of work that all young doctors and med students want to do: “They want to lay hands on and help.” Carter built his practice by visiting every hospital in the region and getting to know the doctors there. Today, he has three other surgeons as partners. “I brought Beverly Hills to Minneapolis,” Carter says, noting that 98 percent of their work is now cosmetic. To continue to lay hands on and help, Carter travels regularly, primarily to Central and South America, to donate his services to people with cleft palates, burns, and other disfiguring problems. — CS

IN MEMORIAM

'40s
GILBERT B. MEYERS JR.
MD '47
OCT. 6, 2005

DAVID L. ROSECRANS
MD '47
DEC. 4, 2005

CARL H. EISENBEIS JR.
MD '49
OCT. 7, 2005

DOROTHY J. POLLACK
MD '49
OCT. 22, 2005

'50s
JOHN F. OSTERRITTER
MD '50
OCT. 13, 2005

JOSEPH S. MAGILL
MD '52
AUG. 3, 2005

OREST J. TOMMASINO
MD '52
AUG. 22, 2005

'60s
WILLIAM J. HARVEY
MD '53
OCT. 11, 2005

RUTH KANE-COYNE
MD '53
DEC. 18, 2005

'70s
WILLIAM F. PEKRUHN III
MD '75
JUNE 23, 2005

MICHAEL MCCHESEY
COYLE
MD '77
OCT. 1, 2005

'80s
GEORGE KARCHONG MOY
MD '83
DEC. 19, 2005

HERBERT TAUBERG
MAY 13, 1924–OCT. 9, 2005

H erbert Tauberg chose orthopaedic surgery at an auspicious moment in Pitt’s history. Albert Ferguson had just been chosen to head the new orthopaedics department, and Tauberg (M.D. ’33, Res. ’34) was the legendary Fergie’s first resident here. Tauberg had married 21-year-old Madeline Bowling during his second year of med school, and the two struggled through his early years of training until he became a successful private practitioner and, eventually, a Pitt clinical instructor. Tauberg was known for his great appreciation and knowledge of wines (his private cellar still includes hundreds of bottles). Through the National Council for Jewish Women, the couple created the Madelain and Herbert Tauberg Fund, which has awarded annual scholarships to Pitt med students for more than 10 years and has been enriched by numerous donations in his memory. — CS

JAMES J. LEONARD II
JUNE 17, 1924—DEC. 16, 2005

J ames J. Leonard was a cardiologist known for his own heart, says his colleague Robert E. Lee (M.D. ’51). “He just showed great kindness and joy. He was easy to work with.” Leonard came to Pitt in 1968 as an associate professor and chief of cardiology. From 1970 to 1976 he was professor and chair of the Department of Medicine. He moved from Pittsburgh to Bethesda, Md., to become chair of medicine at the new medical school of the Uniformed Services University of the Health Sciences. Leonard coauthored a classic chapter on the physiological origins of heart sounds and murmurs. — CS
In 1989, George Mazariegos survived a monthlong immersion in Pittsburgh’s relentlessly intense transplant program. He told his family about the brutal pace and the dramatic manner in which patients would present. Their response: “You’re not actually thinking about going back there, are you?” Actually, he was. And he did.

Mazariegos returned for Pitt fellowships in critical care medicine and transplantation (1991–93). He’s now a Pitt associate professor of surgery and director of pediatric transplantation at Children’s Hospital of Pittsburgh. The intensity of his training, however, doesn’t seem to have affected his demeanor.

“I think he’s the most soft-spoken man I know,” says Susan Jasin, whose son, Jakob, had a liver transplant at Children’s at age 4 in 2004. Mazariegos was among a handful of Pitt transplant surgeons who met with the Jasins when they were searching for a program that would give Jakob a new liver. The boy was born with a genetic disease that left him unable to process three important amino acids found in dietary protein. They accumulated in his bloodstream, sometimes rising to toxic levels that threatened to cause permanent neurological damage.

His condition, named maple syrup urine disease (M SUD) for the distinctive smell of afflicted children’s urine, was not a disease of the liver. However, a transplanted liver generates enough metabolic activity to control an M SUD patient’s amino acids. This had been discovered by accident a few years earlier, when a girl with M SUD had a liver transplant for vitamin A toxicity.

Jasin says that the transplant team in Pittsburgh regarded her and her husband as the experts on M SUD. The parents spoke of life on a tightrope. An imbalance in protein consumption, or an unexpected event like a cold or flu virus, and Jakob could slip into a metabolic crisis from which he might not recover.

“I’ve seen kids [with M SUD],” says Jasin, “who are normal one day and changed forever the next.” She describes how difficult it was to enjoy watching her child play without praying silently, Please, not today. Don’t let it happen today.

Jakob became the first child at Children’s—and the sixth in the world—to undergo a liver transplant to cure M SUD. Children’s is the only hospital to develop a protocol for the procedure; it involves extensive pre- and post-transplant evaluation and care that differs from more typical transplant procedures. To date, 11 M SUD patients have received new livers at the hospital. Eight more are on the waiting list. All of the recipients have been cured of M SUD and are on a normal diet. Complications have been manageable.

Mazariegos and his colleagues will report on their success in an upcoming edition of the American Journal of Transplantation.

At Children’s Hospital recently, Mazariegos met with the family of Mihir, a chubby-cheeked fireplug of a boy who received a new liver a few months earlier. Mazariegos, in blue scrubs, leaned on the exam table next to the boy and chatted with the parents, who moved from India to find help for Mihir. As they spoke, the boy happily drove a toy motorcycle across the charts in Mazariegos’ hand.

(“I feel like they’re all my children,” Mazariegos sometimes says of his patients.)

Later, the surgeon meets with the family of Arturo, who came from Brazil for a transplant, and there is an impromptu reunion in the hallway. Arturo’s father excitedly shows everyone a photograph of Mihir and his mother with Arturo’s mother.

“This is the day we met at the M SUD conference,” he says to Mazariegos in broken English. “On this day, we promised we would find a solution for our children’s M SUD.”
George Washington did not age well. He was pockmarked and lost all but one of his teeth, along with bone in his jaw, before his first inauguration at 57. But there was a time when he was quite a looker, apparently. One Mount Vernon representative noted in The Washington Post that we should think of him as an “action hero” rather than the sleepy-lidded patriarch we recognize on our dollar bills. Pitt professor of anthropology Jeffrey Schwartz is doing anatomical detective work to reimagine a youthful Washington in three dimensions. No sculptures of the man exist from those days. Forensic scientists may be used to the challenge of constructing aging composites of people, but it is unusual to de-age someone, notes Schwartz. The anthropologist is working with 3-D computer simulation experts to provide the Mount Vernon estate with reconstructions of Washington at ages 19, 45, and 57 that will be on display there later this year. Here is the father of our country reimagined at 19.
CALENDAR
OF SPECIAL INTEREST TO ALUMNI AND FRIENDS

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

WINTER ACADEMY
SCHOOLS OF THE
HEALTH SCIENCES
FEBRUARY 17
Naples, Fla.
To request an invitation:
Pat Carver
412-647-5307
cpat@pitt.edu

BLACK BAG BALL
FEBRUARY 17
LeMont
Pittsburgh

NEW JERSEY & NEW YORK METRO ALUMNI RECEPTION
SCHOOLS OF THE HEALTH SCIENCES
MARCH
Tenafly, N.J.
Hosted by Mary Ann Michelis (MD ’75)
For information:
Pat Carver
412-647-5307
cpat@pitt.edu

STARZL PRIZE & SYMPOSIUM
MARCH 10 & 11
Alumni Hall
Nancy L. Ascher, MD
Starzl Prize Speaker
For information:
412-647-8232

BAHNSON LECTURE
MARCH 15
7 a.m.
Lecture Room 5, Scaife Hall
W. Randolph Chitwood Jr., MD, Speaker
For information:
www.surgery.upmc.edu

MINORITY ALUMNI WEEKEND
APRIL 8–9
Pittsburgh
For information:
412-648-8987
diversityaffairs@medschool.pitt.edu

CALIFORNIA ALUMNI RECEPTION
APRIL 28
San Francisco
Hosted by David Mendelson (MD ’64)
For information:
Pat Carver
412-647-5307
cpat@pitt.edu

PITT MED GOLF OUTING
APRIL 29
8:30 a.m.
Quicksilver Golf Club
Midway, Pa.
For information:
Rob Klune
klune.john@medstudent.pitt.edu
www.pittmedgolfouting.org
412-648-9090

SIMMONS LECTURE
MAY 3
8 p.m.
Biomedical Science Tower
Room 5100
Michael Longaker, MD, Speaker
For information:
www.surgery.upmc.edu

MEDICAL ALUMNI WEEKEND 2006
MAY 19–22
Classes Celebrating:
1941 1976
1946 1981
1951 1986
1956 1991
1961 1996
1966 2001
1971

SENIOR CLASS LUNCHEON
MAY 19
11:30 a.m.
Twentieth Century Club
Pittsburgh

SCHOLARSHIP APPRECIATION TEA
MAY 19
3:30 p.m.
Bigelow Room, Pittsburgh Athletic Assoc.
Pittsburgh

SCOPE AND SCALPEL
MAY 19 & 20
7 p.m.
The Antonian Theatre, Carlow University
Pittsburgh
For information:
www.scopeandscalpel.org

ALUMNI BREAKFAST & REUNION GALA
MAY 20
8:30 a.m. & 6 p.m.
Omni William Penn Hotel
Pittsburgh

GRADUATION CEREMONY
MAY 22
10 a.m.
Carnegie Music Hall
Pittsburgh
For information:
412-648-9040
student_affairs@medschool.pitt.edu

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

It’s nice to have someone to lean on when you’re just starting out. Someone who’s been at this medicine thing for a while. Someone to ask all those questions: How do I make the most of my med school experience? How do I choose a specialty? What does it mean to be a successful physician? A successful scientist? How do I get there from here?

The Pitt Career Network is a new resource that helps students tap into the experience and expertise of Pitt alumni. To learn more and to join the network, visit [www.alumni.pitt.edu/networking](http://www.alumni.pitt.edu/networking).