WHAT IS A GOOD DEATH?
ASK A COMPUTER.
A DAY’S WORK
Your article in the August 2005 issue about Richard L. Day filled me with joy, because he made pediatrics so attractive to me that I spent more than three decades of my life in it and am very pleased by that choice. Dr. Day and his fellow faculty showed me, as a med student, that pediatrics had large challenges and really nice people with whom to work. So I interned under his guidance and he challenged me and embarrassed me many times in the most positive of ways. He called upon me to speak at the first grand rounds that I ever attended as an intern, when I was trying to hide, listen, sleep, etc.

The great picture on p. 12 shows Dr. Day with, I believe, “Briney,” his seafaring dog. Why is the great man carrying Briney? (And why is the picture cropped in such a way that it is impossible to see if the beautiful moored sailboat is a sloop, a yawl, or a ketch?) I believe that Briney was named for a saturated solution of salt in water, which would mean that he was both pickled and preserved at the same time.

Richard D. Day gave me faith in myself when I had very little of that. He opened me to the world of pediatrics where the emphasis was on children and scientific help for them. He deserves all the good things said about him in your article.

Richard W. Dodds (MD ‘64, Intern ‘65)
Boston, Mass.

Richard L. Day’s daughter Betsy (Day) Darlington writes that the sailboat in the photo she lent us (already cropped) was a yawl. The dog was Susie, old and unable to take “real” walks. Briney came later.

I was fortunate to have been a pediatric resident from 1960 to 1963 at Children’s Hospital of Pittsburgh in Richard L. Day’s program. He was certainly an expert clinician, tireless researcher, and exemplary teacher. Personally, I found him to be, first and foremost, the quintessential Gentleman, and that’s with a capital “G.”

Charles P. Ashe (MD ‘59, Res ‘63)
Lower Burrell, Pa.

YOU CAN GO BACK
The following letter is in response to our February 2005 “A&Q,” in which former Peace Corps volunteers who are now Pitt med students asked the question, “For others who’ve had this type of experience in the developing world, did they ever do it again?”

I am a Pitt med graduate (graduated in the terrific class of 1970) who enrolled in 1966 as a returned Peace Corps volunteer. I think I may have been the first Peace Corps volunteer to become a Pitt med student; I was, at least, an early one. And, yes (in response to the question), such persons do pursue international work again!

I served in Malawi as a secondary teacher and TB control volunteer, had a wonderful experience (mostly), and then was fortunate enough to be chosen by Pitt med. My training is in internal medicine and infectious disease. I worked with the CDC Epidemic Intelligence Service and in international health. During that time, I was involved with a number of international tasks, including smallpox eradication.

So yes, the combination of Peace Corps experience and primary care medicine is extremely powerful, and one can do all kinds of international development work with it.

Do continue to think of working overseas. The current tasks include remarkable new opportunities to begin controlling HIV/AIDS, be in on the eradication of polio, and control TB. Who would want to miss these things? I’ll be glad to talk with any interested Pitt med students.

James Jerry Gibson (MD ’70)
State Epidemiologist
Director, Bureau of Disease Control
State of South Carolina

SOUTHBOUND
Pitt wants to reconnect with far-flung alumni and friends, so we’re on the road again—this time to sunny Florida in February. We’ve lined up programs to show you the best in science and medicine at Pitt.

WINTER ACADEMY, SCHOOLS OF THE HEALTH SCIENCES
Feb. 17, in Naples, Fla.

For an invitation: Contact Pat Carver
412-624-5307 or cpat@pitt.edu
DEPARTMENTS

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What’s a good death? How much stock does a patient put in luck when making decisions? Computer models answer questions clinical trials can’t.

COVER STORY BY MICHAEL FITZGERALD

CONTRIBUTORS

It’s been a year of big changes for JOE MIKSCH (“Smoking Out Cancer” and “Hidden Connections”). Pitt Med’s new associate editor recently returned to the ‘Burgh from Connecticut, where he’d most recently been a reporter for the New Haven Register and the Fairfield County Weekly. But for Joe and his wife, it seems everything new is old again, including their house in the Mexican War Streets (fin de siècle), their brick patio (Joe’s handiwork, reclaimed brick), and their new dog (“a sweetheart,” he says, rescued, with a slight limp, from less natty digs). As a young grad of Allegheny College, Joe’s first writing job was with Oil City’s daily. More than a decade later, he’d moved up to profiling the attorney general of Connecticut for Greenwich magazine. (His current editor was not aware he has yet to kick the tobacco habit when she assigned him “Smoking Out Cancer.”)

Photographer CAMI MESA (“Smoking Out Cancer” and “Dreams and Good Care”) enjoys the part of her job that requires her to make strangers feel at ease while she snaps away. Apparently, at times, these strangers make her feel comfortable, too. After photographing the doings at Salud Para Niños mobile clinic, the Colombia-born Mesa felt so welcome that she volunteered to help with Spanish-English translations. Mesa, whose work has also been published in Latina and Los Angeles Times Magazine, lives in Pittsburgh with her husband, son, and cat.

COVER

Recalling the tragedies, we might not look to the ancient Greeks to describe a good death. But what can a computer model tell us? (Detail from Attic red-figure pottery showing women at the shrine of Apollo. Attributed to Apulian artist, c.380 B.C.E. © Bridgeman Art Library.)
First, a love story.

Long ago, a wealthy Pittsburgher, William Croghan Jr., built a mansion, and in it, a ballroom for his daughter, Mary. But it is said that she never danced there. Mary eloped at age 15 with Captain Edward Schenley, a British officer. They sailed off to adventures in England and what is now Suriname. Through the years, the Croghan mansion fell into disrepair. But you can still see elements of the ballroom; they were restored and placed in the Cathedral of Learning in 1955.

We have just added a ballroom of a different kind to this university's campus, and this one will indeed be used for dancing—but not the waltzes Mr. Croghan envisioned. Just a few blocks down Fifth Avenue from Pitt's great Cathedral, in a building envisioned as its modern architectural bookend, now stands a great campanile. In its vast halls, diverse researchers are already choosing their partners and choreographing their scientific steps. In October, we opened the Biomedical Science Tower 3 (BST3). Its very design bows to the collaborative nature of some of today's most exciting science. The laboratories are open and flexible, modeled after Thomas Edison's lab bench prototype. Each floor has common space—coffee and dining areas and nooks with places to schmooze scientifically or just to meditate while taking in grand views of Pittsburgh.

It is one of the finest research buildings in the world. Even before we opened its doors, the BST3 served as a magnet for scientific talent, enabling us to recruit top scientists from the critical disciplines in which our most challenging research questions demand inquiry. These men and women join a core of Pitt faculty members, many of whom have built their careers at Pitt and, in doing so, have also built the University's reputation for excellence.

We've allocated the space not to traditional departments but to interdisciplinary programs like structural biology, computational biology, and the neurosciences. The building also houses programs in developmental biology, bioengineering, drug discovery, and infectious diseases, including vaccine development—fields critical to the next era of biomedical progress. The work that goes on here will lead to greater insight into how our cells and tissues function and to new medicines that will sustain and prolong that function. We can expect advances in our understanding of heartbreaking conditions as well as a transformed regional economy, spurred on by University-derived intellectual property.

Nearly 70 years ago, around the time he drove the last rivet into the Cathedral of Learning, Chancellor John Bowman wrote of that tower, "They shall find wisdom here, and faith. In steel and stone, in character and thought, they shall find beauty, adventure, and moments of high victory." I have the same confident aspirations for those who inhabit the BST3. If only Mary could join us—let the dance begin!
PITT RANKS SEVENTH IN NIH FUNDING

The latest data from the National Institutes of Health show that the University of Pittsburgh and its affiliates were awarded $396 million in NIH grants for the 2004 fiscal year, making Pitt the seventh-highest-ranked university in the United States for the agency’s funding. (Pitt was ranked eighth the year before.) The funding is largely driven by the work of medical school faculty.

That’s good news for the whole Pitt med body—not just its research arm—says Arthur S. Levine, senior vice chancellor for the Health Sciences and dean of the School of Medicine.

“There are no objective, nationally competitive, peer-reviewed benchmarks that measure the strength of the faculty or the quality of patient care,” says Levine. “But no institution ranked this highly in research support does not also have a strong faculty, a strong student body, and an excellent track record of providing quality patient care.”

—Elaine Vitone

CHILL, REPAIR,REWARM, REVIVE

Years ago, Peter Safar, the late University of Pittsburgh Distinguished Service Professor, decided that the only way to save the lives of some trauma victims would be to “preserve” them until surgeons could repair their wounds. By flushing the circulatory system with cold saline solution, he found lab animals could go as long as two hours without breath or pulse, then be revived, astonishingly, with no neurological damage. Now, Safar’s protégés Samuel Tisherman (MD ’85, Res ’93, Fel ’94), associate professor of surgery and critical care medicine, and Patrick Kochanek, professor of critical care medicine and director of the Safar Center for Resuscitation Research, have extended this time to three hours by adding glucose and oxygen to the saline solution. Tisherman is working toward a clinical trial to test the approach and hopes the therapy will soon be applied to save the life of a patient. That person is likely to be a gunshot victim who loses too much blood and slips into cardiac arrest around the time of arrival to the emergency department. If all goes as planned, the patient will be chilled, surgically repaired in one to three hours, then slowly rewarmed to recover from a traumatic insult that otherwise would have been fatal.

—Chuck Staresinic

FLASHBACK

“People in the Graduate School still talk about the time in 1953 when such a heavy snow fell that the city was virtually at a standstill; classes were cancelled and driving was impossible. [Vice Chancellor for the Schools of the Health Professions] Dr. [Francis Sargent] Cheever snowshoed himself from his home in Point Breeze to the animal labs ... and fed the animals.”

—Pitt Physician, spring 1971 issue
Learning how NSAIDs work against colorectal cancer.

How do anti-inflammatories like Suldinac work against colorectal cancer? Non-steroidal anti-inflammatory drugs (NSAIDs) are effective at warding off colorectal cancer. But they’re nothing without certain genes.

Lin Zhang, assistant professor of pharmacology, and his team of researchers have identified two genes, BAX, and, more recently, SMAC, which are integral to programmed cell death and play a significant role in the effectiveness of NSAIDs as chemopreventive agents.

Without these genes, the cell-death inducing properties of NSAIDs are thwarted.

There’s this enzyme that’s, well, a bit promiscuous.

Richard Wood, the Richard Cyert Chair of Molecular Oncology, and Mineaki Seki, research associate in the basic research division at the University of Pittsburgh Cancer Institute, recently discovered polymerase-Q. During DNA replication, this saucy little number will plant base A opposite wherever bases are missing. It does so to keep the process going and the cell alive. Which is nice. Yet the enzyme is indiscriminate. It’ll just plop that A wherever it sees the need, regardless of which base belongs in the chain. And it doesn’t stop there. Polymerase-Q goes back and adds a second base next to the first, creating the illusion that all is normal in the chain. Eventually, these stopgap errors are fixed by other DNA repair mechanisms. Sorting out how that happens is the next step of investigation for Wood and Seki and could have implications for cancer treatments.

Membership nominations are in for the School of Medicine’s new Academy of Master Educators.

A rigorous peer-review process continues this fall, after which the School of Medicine will announce the inaugural members. About 50 of the 800 faculty members who teach students in the School of Medicine will receive the honor.

The program recognizes those who have contributed to the medical program in innovative ways as teachers, mentors, researchers, and leaders. The names of those honored will be made available at http://pittmed.health.pitt.edu.

— Joe Miksch

With Gene-Therapy Point Man Joseph Glorioso

During the pretrial days of hype and promise in the early ‘90s, it seemed that gene therapy would quickly become the new cure for every genetic disorder imaginable. A decade of lackluster clinical trials then quieted enthusiasm, and the death of a participant in a study at the University of Pennsylvania in 1999 raised concerns that the risks of gene therapy might outweigh its potential benefits. Two years ago, two Severe Combined Immunodeficiency (SCID) patients in France developed leukemia as a result of a study, overshadowing the study’s treatment successes. Yet, to date, 17 SCID patients—who otherwise would’ve likely died young—are now cured, living normal lives, attending school.

It’s a familiar tale of public opinion on a pendulum. But Joseph Glorioso (above), director of Pitt’s Molecular Medicine Institute and chair of the Department of Molecular Genetics and Biochemistry, remains optimistic, quick to tell you that new treatments have always taken a slow, uphill climb. The PhD researcher says that, historically, new treatments have been made possible by key breakthroughs in technology. For transplantation, it was immunosuppressants. In the case of gene therapy, he says the next step will likely be an advancement in engineering vectors: “Genes already know what to do, but the problem is how to get them there.”

On media scrutiny of gene therapy
Why would the press be so eager to emphasize two or three cases of leukemia and ignore all the [SCID patients] who are back in school?

On the future of gene therapy
Most new medical treatments that require new technology generally take 20 to 30 years to develop. We’re kind of midway now. ... Gene therapy will become, I think, standard practice. We’re just in the process of seeing the first successes, and I think we have a long way to go to make it generally available.

His question for the world
What are people’s expectations? If they expect gene therapy to be a treatment for a broad spectrum of problems in the near term, that’s not gonna happen. But I think that if they ask the question, “What diseases will be treatable by gene therapy in the next 10 years?” I can give them some reasonable guesses: arthritis, diseases that result from nerve degeneration, certain problems related to heart disease, and some forms of cancer.

—Interview by Elaine Vitone
Dreams and Good Care

The stethoscope around Diego Chaves-Gnecco's collar waggles as he weaves among 13 people crowded inside a mobile clinic on Pittsburgh's South Side. Some are physicians, nurses, and pharmacists volunteering their time at Salud Para Niños (Health for Children). Others are patients and their parents. Josue, 2, clings to his mother, Estela Mendoza. His wide eyes peer over her shoulder. He waves as he weaves among 13 people crowded inside a mobile clinic on Pittsburgh's South Side. Some are physicians, nurses, and pharmacists volunteering their time at Salud Para Niños (Health for Children). Others are patients and their parents. Josue, 2, clings to his mother, Estela Mendoza. His wide eyes peer over her shoulder. He waves as he weaves among 13 people crowded inside a mobile clinic on Pittsburgh's South Side. Some are physicians, nurses, and pharmacists volunteering their time at Salud Para Niños (Health for Children). Others are patients and their parents. Josue, 2, clings to his mother, Estela Mendoza. His wide eyes peer over her shoulder. He waves as he weaves among 13 people crowded inside a mobile clinic on Pittsburgh's South Side. Some are physicians, nurses, and pharmacists volunteering their time at Salud Para Niños (Health for Children). Others are patients and their parents. Josue, 2, clings to his mother, Estela Mendoza. His wide eyes peer over her shoulder. He waves as he weaves among 13 people crowded inside a mobile clinic on Pittsburgh's South Side. Some are physicians, nurses, and pharmacists volunteering their time at Salud Para Niños (Health for Children). Others are patients and their parents. Josue, 2, clings to his mother, Estela Mendoza. His wide eyes peer over her shoulder. He waves as he weaves among 13 people crowded inside a mobile clinic on Pittsburgh's South Side. Some are physicians, nurses, and pharmacists volunteering their time at Salud Para Niños (Health for Children). Others are patients and their parents. Josue, 2, clings to his mother, Estela Mendoza. His wide eyes peer over her shoulder. He waves as he weaves among 13 people crowded inside a mobile clinic on Pittsburgh's South Side. Some are physicians, nurses, and pharmacists volunteering their time at Salud Para Niños (Health for Children). Others are patients and their parents. Josue, 2, clings to his mother, Estela Mendoza. His wide eyes peer over her shoulder. He waves as he weaves among 13 people crowded inside a mobile clinic on Pittsburgh's South Side. Some are physicians, nurses, and pharmacists volunteering their time at Salud Para Niños (Health for Children). Others are patients and their parents. Josue, 2, clings to his mother, Estela Mendoza. His wide eyes peer over her shoulder. He waves as
HEAR THEM ROAR

By 1912, it had been three years since women were admitted to the Western Pennsylvania Medical College (what is now Pitt’s School of Medicine). Women and men studying the healing arts together? How embarrassing, the administration thought. That year, organizer of the local Women’s Medical Society, Amelia Dranga (MD ’10) weighed in on the issue, telling the Pittsburgh Press, “Bosh!” The administration subsequently saw things Dranga’s way.

Evidence of such was seen at the Falk Library Aug. 24 through Oct. 14. Falk was the first of 61 stops for “Changing the Face of Medicine,” an exhibition presented by the National Library of Medicine and others that recognizes the accomplishments of women who are physicians.

Ten of the 350 women featured have a lineage that includes Pitt: Katherine Detre of Pitt’s Graduate School of Public Health is internationally recognized for her research on coronary artery disease and diabetes. Jeannette South-Paul (MD ’79) chairs Pitt’s Department of Family Medicine. A former army physician, she is probably the first African American woman to permanently run a department in an American medical school. Marjorie Price Wilson (MD ’49) served as senior associate dean at the University of Maryland School of Medicine in Baltimore before her death in 1997. She was one of the first women to achieve such a high academic post. Elizabeth Theresa Lee-Rey (MD ’90), of the Albert Einstein College of Medicine, co-directs New York’s Hispanic Center of Excellence. Roz Diane Lasker (MD ’76) founded the Center for the Advancement of Collaborative Strategies in Health at the New York Academy of Medicine. Catherine DeAngelis (MD ’69) is the first woman to edit the Journal of the American Medical Association. Surgeon Nancy Snyderman (Res ’83) was a health correspondent for ABC for 15 years. Diane Gail Snustad, former Pitt med faculty member, is medical director of the University of Virginia Geriatric Clinic. June Osborn, former Pitt postdoc, was dean of the University of Michigan School of Public Health. And Nunzia Bettinsoli Giuse served as a medical informatics consultant at Pitt from 1985–1994; that work made her an authority in her field.

—Nita Chowla and Joe Miksch

Appointments

Ignorance is more than bliss. Fadi Lakkis, the new scientific director of Pitt’s Thomas E. Starzl Transplantation Institute, believes that it may also be a key player in the future of organ transplantation.

Immune ignorance is what happens when a given microbe fails to reach the lymphocytes. In this context, the immune system fails to “see” the microbe so it doesn’t “know” that it might respond. Lakkis has studied the complementary role that natural occurrences of immune ignorance and transplant tolerance—the body’s acceptance of transplanted organs in the absence of immunosuppressants—have played in successful transplantations. He imagines that in the future, scientists will be able to encourage tolerance and ignorance for the benefit of transplant patients. Lakkis, former director of transplant medicine and associate professor of medicine and immunology at Yale University, was drawn to Pitt because of his interest in conducting both fundamental and clinical research to discover more about what triggers rejection. (Most other transplantation research institutions focus on one or the other, he says, not both.)

Jonas Johnson, a faculty member in Pitt’s otolaryngology department since 1979 and vice chair of otolaryngology since 1982, has been named the department’s new chair. He is the editor of The Laryngoscope—the most prestigious ear, nose, and throat journal in the country—as well as the principal investigator for a study supported by a federal Specialized Program of Research Excellence grant that seeks to develop a vaccine for cancer of the head and neck. Johnson succeeds Eugene Myers, who led the department to its stature as one of the best in the country. Myers will remain at Pitt as a clinician, faculty member, and adviser to mentees like Johnson.

George Gittes, formerly of the University of Missouri–Kansas City School of Medicine, joins the pediatric surgery division as its new chief. The Society of University Surgeons has elected him its next president (that makes Gittes the fourth Pitt surgeon in recent history to hold this prestigious post). With the help of a new real-time imaging technology (ultrasound backscatter microscope), Gittes hopes to engineer mature pancreatic cells to one day free patients with diabetes of their dependence on insulin, “because insulin is not a cure.”

He sees Children’s Hospital of Pittsburgh as “poised to go to the next level, which is to be the premier surgical program in pediatrics.” —EV
TOMORROW IS ANOTHER DAY

In late August, in anticipation of Katrina’s wrath, thousands of Pitt healthcare professionals stood at the ready, waiting to be called to respond by FEMA or a state emergency management agency. No one called. Some went anyway.

By mid-September, Louisiana was trying to pull itself together. Andrea Fox, an associate professor in Pitt’s School of Medicine and a geriatrician, was sweltering in Hammond, La., along with fourth-year medical students Young-Sin Kim and Jonathan Landry. All three had volunteered through the Veterans Administration.

The thermometer hit 115 degrees. Downed trees were everywhere, as were bugs. A curfew was in effect, and the National Guard patrolled. Fox, Kim, and Landry tended to the needs of military veterans, evacuees, and aid workers.

During 12-hour days, they saw patients with common conditions made more serious by the world Katrina had left for them. With other volunteers, they heard sorrowful tales and witnessed resiliency to the tune of 250 patients a day.

“A dentist from the New Orleans VA dropped by,” Fox says of a woman whose home had been destroyed. “She always seemed to me, even though she was extremely helpful and worked extremely hard, on the verge of tears the whole time.” — Joe Miksch

PHOTO | C.E. MITCHELL
INVESTIGATIONS

Explorations and revelations taking place at the medical school

Kids with serious illnesses bounce back emotionally.
Robert Noll had been interested—on an intellectual level—in coping and stress since he took a class as an undergrad at the University of California, Berkeley, with the famed psychologist Richard Lazarus. That was in the ’70s—when both Berkeley and Lazarus did a lot of boat rocking. (Lazarus made waves by demonstrating that denial can actually help patients fare better.) As a young PhD clinical psychologist transplanted to Cincinnati in the ’80s, Noll wanted to help kids cope with serious illness. So he designed a study with colleagues at the University of Cincinnati, Ohio, to measure how kids with cancer (excluding those with brain tumors) were getting along. From that, he figured, he’d build a case for developing intervention strategies. He had no idea he’d end up rocking some boats himself.

The Cincinnati group assumed they would find that the kids, all of whom were undergoing chemotherapy, were seen by their peers as being more sensitive and isolated and having fewer friends. The researchers’ next step would be to find out why: If it was because of the way the children looked from the treatments, they’d design school interventions; if they were depressed, cognitive behavioral therapy might be appropriate. So they conducted evaluations in the children’s homes. Then they went into the schools and talked to the kids’ peers. Without revealing that the study’s purpose was to determine how a sick child in a class was faring, they asked all of the children questions like, “Who are your three best friends?” In another exercise, kids cast their classmates in a mock play whose characters demonstrated traits such as disruptiveness, bossiness, politeness, or leadership ability.

The researchers asked the teachers to evaluate their pupils, as well.

The results came in, but Noll didn’t find what he’d expected. The kids with cancer weren’t perceived as being any more withdrawn, depressed, or isolated than their peers. No one could have slipped through the cracks. This was a comprehensive study—nearly every child in that region of Ohio ages 8 to 15 with cancer (94 total) had participated.

“It was,” says Noll, “a grand, noble experiment that yielded not much.”

So they tried again with another disease. “We thought, Sickle cell—that’s an excruciatingly painful disease. Well find something there,” Noll says. But the results were the same. When it came to social and emotional adjustment, the kids were all right.

Noll, who is now Pitt’s chief of developmental and behavioral pediatrics, reapplied methodology to study kids with juvenile rheumatoid arthritis and kids with hemophilia. He got the same results. He has studied thousands of children, and except in cases where a disease affects central nervous system functioning, like neurofibromatosis or brain tumors, he has found that children with serious illness adjust well. (A colleague in Buffalo, N.Y., used Noll’s methodology to study very short children and found they, likewise, aren’t any less well-adjusted than their taller peers.)

“Kids are inherently hardy,” Noll says, adding that adults are more prone to experience depression as a result of an illness than children are. How can this be? Noll has a theory.

Referring to teenagers, he asks, “Why do these kids get pregnant? Why do these boys drive 100 miles an hour? What they were thinking about is the pleasure of the moment.

“When 15-year-olds are diagnosed with cancer, they don’t say, ‘Will I be able to have children or go to college?’ They say, ‘When will I be able to go to class again?’” And this behavior, Noll says, is “inherently protective” in the sense that it helps kids bounce back.

“As we start to get older, into our 20s, we start to think long-term. Adults with chronic illnesses don’t stay in the moment. Kids do.”

Although it makes perfect sense to him today, Noll was surprised by the results of his initial classroom study. So was everybody else. The Cincinnati group had assumed that the children with cancer would have ongoing adjustment problems—that’s what the literature had predicted.

But Noll takes issue with how other studies of children with chronic illness have been carried out. For one, he avoids questioning kids in the hospital—a place associated with dismal memories such as lumbar punctures and chemotherapy treatments. Other contextual cues are key as well, he says, like the order in which one asks the questions. He points out, for example, that a researcher might ask a sick girl whether or not she is able to get out as much as she used to. Imagine she says, “No.” If the next question is “Are you sad?” she is more likely to say “yes” than if the researcher had first asked whether she was sad.

(Noll has observed, however, that mothers of children with chronic illnesses are a vulnerable group. Mothers, more than fathers, are at risk of internalizing children’s experiences and suffering from depression.)

Noll doesn’t pretend that kids with serious illnesses don’t face emotional and social issues. But if a normally pleasant kid is acting out or pulling back, perhaps there’s a good reason. Perhaps the prednisone has made him irritable. Perhaps she’s scared of another difficult procedure. Helping kids and parents address specific issues can make both feel better.

One recent day at Children’s Hospital of Pittsburgh, Noll mentions that he has been asked to consult on a case of a boy with a chronic illness who seems depressed. The boy’s doctor wants to know: “Should I prescribe an antidepressant?” Noll’s response: Wait to find out if the boy’s mood has something to do with his hospitalization or illness that can be remedied or if it’s a real, long-term condition.
WRECKING BALL

THE HEAVY EQUIPMENT BEHIND GLIOMA INFILTRATION  |  BY JOE MIKSCH

It's got to be tough for a physician to tell a patient that the cause for the headaches, blurred vision, and failing coordination is a glioma, an extraordinarily aggressive form of brain cancer. It's hard to give anyone bad news. What's harder still is when the patient discovers that of the 20,000 Americans who get that diagnosis each year, fewer than half live another 18 months.

Glioma cells worm their way into tissue throughout the brain. They seem to end up everywhere at once, rendering the cancer incurable, immune to the art of the surgeon, the radiologist, the immunologist, and the chemotherapist. Tame a Hydralike tumor in one region, and another grows back in its stead.

Cheng imagines the day when "glioma" needn't be read as "poor prognosis." He envisions new treatments, perhaps in the form of small Ang2-suppressing molecules circulating through the bloodstream to afflicted areas of the brain. Ideally, a treatment that inhibited Ang2 and its effects, including the wrecking crew, would keep the tumor from bulldozing forward.

In the mid-1990s, Cheng was a postdoctoral fellow working with Webster Cavenee, a professor in the University of California, San Diego's cancer genetics program and director of the Ludwig Institute for Cancer Research. With Cavenee, Cheng determined that a certain growth factor (VEGF) is a critical stimulator of blood vessel growth in brain tumors and that its overabundance could lead to robust growth of tumor vessels.

"We were one of the first in the world to demonstrate that VEGF was the molecule for angiogenesis, or blood vessel growth," Cheng recalls. He says this with a little self-deprecation, because scientists now know that VEGF isn't the only player in blood vessel growth in gliomas.

The entire process by which tumors grow is complex, Cheng says, referring to what he later learned about Ang2.

"One molecule cannot do it all. Many molecules act in concert. They're coordinated very, very, very well," he says.

Cavenee has followed Cheng's career—the last six years of which have been spent at the University of Pittsburgh. He praises Cheng for uncovering the fact that angiopoietins influence where cells go and how tumors overtake healthy tissue.

Cheng's work, he says, is likely to have important therapeutic value down the road. Perhaps it will one day give doctors the wherewithal to call off Ang2's deadly demolition crew.
When everything known about a protein is bad, scientists might start to wonder why nature—evolution, that is—hasn’t gotten rid of it. It’s a question that was asked a few years ago in a review article about one cellular receptor. After describing its role in complications of diabetes, its tendency to propagate inflammatory responses, and its role in tumor growth, the authors noted that “it seems difficult to fathom how one receptor could be involved in an adverse manner…in so many and such diverse situations.”

The receptor—named RAGE, for receptor for advanced glycation endproducts—had been widely studied, but no one had looked at what it did in the lung. Tim Oury didn’t intend to either. The associate professor of pathology’s work on an enzyme that protects against pulmonary fibrosis was keeping him busy. Consults on asbestos damage were stacking up. (Literally. A small mountain of Fed Ex boxes with slides waiting to be reviewed greeted him on return from his family vacation last summer.) And there was the new test for PSA (prostate-specific antigen) levels that he’d patented and needed to move forward. RAGE wasn’t even on his radar screen until the receptor started turning up in his experiments.

In fact, when he figured out what it was, the name seemed appropriate. RAGE had interfered with his experiments, and he’d already decided it was a “very aggravating protein.” It also turned out to be an interesting lead.

Oury quickly discovered in the literature that RAGE helps cause renal fibrosis. Fibrosis—be it of the lung or the kidney—is a disease in which normal healthy tissue is replaced with scar tissue. The scarring can interfere with the normal functions of the tissue, such as transferring nutrients and waste. (Imagine what it would feel like if your lungs were full of scar tissue, and you can see why Oury studies pulmonary fibrosis.) RAGE is present on epithelial cells, where it binds a variety of other proteins and ligands. In cases of renal fibrosis, if you stop RAGE from doing this, you can stop the disease. For example, if you give mice a soluble form of RAGE—which apparently binds ligands, keeping them away from the epithelial cells—it stops renal fibrosis in its tracks.

It was natural for Oury to hope that the same would hold true in the lung. Could he treat pulmonary fibrosis by targeting RAGE activity? He started experimenting with mice. “We gave them soluble RAGE and, lo and behold, it made the mice really bad. The exact opposite of the kidney.” Similarly, mice bred so that they didn’t produce RAGE in the lung promptly developed the disease.

The results were initially disheartening, but they’ve opened up a new avenue of research. Oury has gone on to show that RAGE is heavily expressed in healthy lung tissue, just as it is expressed in diseased kidney tissue. He now jokes that he has become remarkably accurate in his prediction of how RAGE will behave in the lung. He simply reads the existing literature on what the receptor does in other organs and hypothesizes that in the lung, it will do the opposite.

He’s a long way from translating his increased understanding of the protein into a treatment, but he’s aware of the implications of his findings. “If we can figure out why RAGE is high in the lung and not other tissues and can exploit it, I don’t think we can reverse the fibrosis, but maybe we can stop the progression.”

And his results are shedding light on an old question—that is, why a receptor that can do so much harm is still around. As the otherwise aggravating receptor’s role in lung health becomes clearer, Oury’s starting to think that perhaps we do need a little RAGE after all.
Pitt med grads at some of the nation's most prominent residency programs talk about how things are going.
(From left: Adam Frymoyer, Jin Hui Joo, Ryan Madder, Josh Lovelock)
Lying in a hospital bed, Ralph Aaron rasped and wheezed. His nerves were rattled. He struggled to breathe.

What if he stopped breathing? he wondered. Perhaps more oxygen would help.

His wife sat beside him. She listened to his labored inhalations, fearing they would end. Ralph Aaron (not his real name) was in his late 40s. It was only six months ago that doctors had discovered metastasized cancer in his lung.

The Aarons called for the doctor.

Ryan Madder (M.D. '04) was on call as an internal medicine resident in the intensive care unit. It was his first week at Washington University in St. Louis.

When he arrived at the bedside, Madder couldn't give the patient more oxygen—Aaron was already at the limit.
“We don’t have a lot of options,” Madder explained. “I could intubate and put in a breathing tube for the ventilator. I could give you more morphine so you’d be more comfortable.”

Madder knew Aaron was dying and would be more comfortable in a hospice. The intern spoke with a senior resident to see what he thought. The resident assured Madder that he was treating the patient correctly and told him to call if he had more problems.

Returning to his patient’s bedside, the young intern explained that though Arthur hadn’t been sick for long, the illness was serious, and he might want to consider palliative care.

This was the first time Madder told a patient that he wasn’t going to get better. He felt drained and tired. The news shocked the couple. Ralph Aaron, after all, was not yet 50.

Aaron asked for morphine.

Medical schools anticipate many of the challenges their graduates will face in the world of medicine, yet educators can’t prepare students for every situation, no matter how stellar the faculty or the curriculum. No professor truly prepared Madder to peer into a middle-aged patient’s face and tell him that his options were limited. Sure, classes gave Madder a chance to practice, but it wasn’t the real thing. Once Madder worked with patients directly, he says, he “learned a lot about people.”

“I guess you learn how to deal with people at their best and worst extremes of emotion,” he says, reflecting on cases like Aaron’s. “The worst comes a lot more frequently than the best,” he admits.

There are many ways to mark a passing year. Students might divide it by terms and midterms, final papers and final exams. First-year residents might mark the time by rotations completed or the number of times they are on call. Or maybe not. Perhaps they are more likely to remember the first night, the first time they have to run a code alone, the first time they realize a patient is completely their responsibility. Perhaps they recall how it felt to diagnose a rare condition themselves. Or to come face-to-face with the reality that sometimes a doctor is helpless, that she has done all she can. These are the impressions that echoed as I talked with several Pitt med graduates about their experiences during the first year of residency at some of the nation’s most prestigious residency programs. (You’ll read some of their stories here.) We talked about how prepared they felt, about venturing into the world after med school. They spoke of a life of great reward, frustration, meaning, and consequence. In other words, they told me how it feels to be a doctor at last.

T he pager on Josh Lovelock’s (MD ’04) belt squawked. He was in the hospital on call. A 30-year-old man with leukemia was crashing on the floor. As Lovelock entered the room, he saw the young man lying on a bed. The patient gasped and choked. His blood didn’t have enough oxygen.

It was Lovelock’s first month as an internal medicine intern at the University of Chicago. Everything was new. The resident with whom Lovelock had been working was somewhere else, treating another patient. Lovelock had no choice; he had to stabilize the man. This was his patient.

Okay, he told himself. Give him fluids. Give him oxygen. Give him an EKG. Call for a transfer to the ICU. If fear crept into his thoughts, Lovelock quickly dismissed it. The only thing he allowed himself to think about was that he had to control the situation.

As he worked, in the back of his mind, he recalled his experiences from his Pitt med classes. He had learned how to run codes by working with Pitt’s patient simulator SimMan, which, of course, isn’t a real person, but no student wants SimMan to die. The dummy was real enough for Lovelock to gain some experience handling the unexpected under pressure. One of the other grads interviewed for this article brought up Pitt’s simulator training as well, saying it “gives me an advantage. It seems like a fairly unique thing at Pitt.” (Though many schools have simulators, the size and scope of Pitt’s Peter M. Winter Institute for Simulation Education and Research is such that students get to know SimMan well. And about 4,000 people visit Pitt annually for tours of the center.)

After half an hour, Lovelock stabilized the patient and transferred him to the ICU. Lovelock’s take on the situation was mixed. Sure, he’d helped the patient, but there was still so much to learn.

Lovelock and other grads noted that they knew being an intern would mean more responsibility. Yet, they still found themselves surprised by how accountable they were. Lovelock expected that he would have to order tests, but he didn’t expect he would have to make sure that the patient actually went to get blood drawn or a CAT scan. During medical school, he’d spent a year as a Samoff Fellow conducting cardiology research. The experience gave him an advantage, he says, because the lab work he conducted required answerability—he became accustomed to developing internal check systems, which helps him treat patients today.

A fter about three months of being on call, Adam Frymoyer (MD ’04) was exhausted.

One morning, Frymoyer dragged himself into one of the community clinics at the University of California, San Francisco, dreading the on-call night awaiting him after his day shift.

He walked into the exam room where a young couple and their 8-month-old son sat. Frymoyer had seen the boy several times before.

“Here’s your doctor,” the baby’s mom cooed to her son.

That’s when it hit Frymoyer—he was the only doctor this boy had ever known. At that moment, with the utterance of three simple words, he finally felt like a doctor. The parents trusted and respected Dr. Frymoyer.

He went into his normal routine, trying to make the baby smile and laugh while examining him. Frymoyer, who is upbeat and thoughtful when he speaks, loves playing games with children and connecting with them and their families. He has long days when he tires of being on call—and it’s always tough to deal with sick kids—but he feels like he is part of a team with the parents, looking out for the children’s best interests.

When Frymoyer talks about his days at Pitt, he thinks about the art of the interview. He says that from the moment he stepped into Scaife Hall, professors stressed the importance of the human connections in medicine. He took the basics on interviewing from Pitt and added his own flair—smiling or placing a hand on a patient’s arm. Frymoyer and other graduates say they mastered the basics in Pittsburgh, but they agree that to really excel at interviews and physicals, they have to
Yet just when an intern seems to get a handle on things, there’s a disease that presents abnormally or patient who isn’t forthcoming—like the middle-aged man who’d entered the psychiatry emergency department at the Hospital of the University of Pennsylvania.

He was hearing voices. He was afraid he would hurt himself.

It was already months into Jin Hui Joo’s (MD ’04) intern year when this man walked into the ED. She interviewed him, probing for reasons why he might be hearing voices. He hesitated before he spoke; he was holding something back. His answers didn’t make sense to Joo.

Joo admitted the man overnight, even though she was wary of his motivations. Could he just be describing symptoms to get a meal and a place to sleep?

She interviewed him again. This time, she asked more questions, digging deeper. She learned he usually used heroin, but for his last fix, he mixed heroin with cocaine. The mix seemed to be causing the hallucinations.

After Joo’s first rotation in the hospital’s psychiatric ED, she had seen enough to recognize that the man had been hiding something in his first exam. Pitt gave her a foundation for figuring out such mysteries, too: She thinks the problem-based learning sessions at Pitt, where professors presented students with a problem or condition they were instructed to work through on their own, helps her as she probes real cases today.

As a psychiatry resident, Joo treats many patients like this man, who suffers from a variety of problems. Joo must make diagnoses without literally being able to get inside someone’s head. The tools she relies on are not lab tests or x-rays.

One day, Madder headed to a Washington University clinic. As an internal medicine intern in St. Louis, Madder worked in mostly urban settings, treating poor and uninsured patients.

Walking into the exam room, he saw a 20-something woman sitting on the table. She was losing feeling in her legs. She complained of weakness and lethargy. She’d lost vision in one eye. She also showed the intern her elbow, which was swollen.

Bunched together, these symptoms were atypical. Madder started searching journals online for similar cases. He kept digging, pushing himself to find what was wrong.

After many tests and a lot of research, Madder found the patient had Ewing’s sarcoma, a rare bone cancer that generally affects children and young adults. The lump on her elbow, which she’d had for a year, was where the cancer had started. By the time Madder treated her, the cancer had spread to her spine and brain.

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She would undergo chemotherapy and radiation, yet the oncologist estimated she would live less than five more years. This was one of many times throughout the past several months when Madder felt overwhelmed with frustration and sadness. If only she’d come in a year earlier when she first noticed the lump, then her prognosis would have been much better. While at Pitt, Madder encountered many patients like this young woman, people who were poor with insufficient or no insurance, who were a little fearful of the hospital and only entered it when the cancer had started. By the time Madder treated her, the cancer had spread to her spine and brain.

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After the Class of 2004 walked out of Scaife Hall and into new, freshly pressed, long white coats emblazoned with the names of their residency programs, how did it go? Were they prepared? Yes, they told us resoundingly.

For our feature “One Year into Residency,” writer Meghan Holohan spoke at length to several graduates of the Class of 2004. We wanted to find out how their classmates were doing as well, so we cast a wider net, sending a survey to the entire class. Here are their most informative responses.

All respondents said Pitt provided the necessary tools for residency.

We’ve seen a substantial increase in the number of Pitt med graduates entering the country’s most competitive residencies. Still, the majority of respondents said they felt better prepared than their peers in their programs.

What has the Class of 2004 wielding tongue depressors with such confidence? It seems Paul Rogers, professor of both critical care medicine and medicine, has something to do with it. Slightly more than half of the respondents listed his Critical Care Medicine course as the most helpful one they took; and again and again they referred to their simulator training with Rogers and associate professor of emergency medicine Susan Dunmire (MD ’85, Res ’88) as among their most salient Pitt memories. What other classes did they deem most helpful? Anatomy, Emergency Medicine, and Third-Year Medicine were among the many favorites.

On respondents’ wish lists? When we wrote, “If only the School of Medicine had a course in ______,” one grad suggested “Hawaii.” (Not a bad idea.) Some said they would have benefited from more exposure to pharmacology and clinical procedures. Where is their crystal ball? Pitt has intensified the first-year pharmacology block, and the second-year organ courses now integrate pharmacology. Likewise, students have even more opportunities for simulator training and working with “standardized patients” (trained actors with whom they practice examinations and history taking). The class also said more on the business, economics, and law of medicine would have been helpful. This is, indeed, a pre-scient group. The school has put more focus on these areas in the first and second years.

What was most striking to the Class of 2004 about residency experiences?

Some grads talked about the amount of work and knowledge needed—others said the program was easier than they had anticipated. Some noted the regional differences in healthcare needs and practices; others the autonomy of residents. Grads were also moved to mention the fatigue, paperwork, and the number of patients without adequate healthcare coverage.

What memories of learning at Pitt remain?

A mixed bag of responses. “The awesome experience of observing the heart, lungs, and small bowel in vivo during surgery/anaesthesia.” “Dr. Jamie Johnston’s grace dealing with the announcement of 9/11 during renal lab.” “Dr. Shaver rapping/humming/singing heart murmurs.” (We’d like to hear that, too.) Grads also recognized those who may be their finest lifelong teachers—“interesting patients.”

—Erin Lawley & Erica Lloyd
Baseball causes cancer.
Yep, heading out to the old ball yard and watching nine innings: nothing but trouble for the lungs. Such was the conclusion of a decades-ago epidemiological study regarding the causes of lung cancer. Oh, smoking seemed to play a role, too. That nasty little habit came in number two in the cause-and-effect game.
“Cigarette smoking was the second-most-highly correlated factor that they asked about,” says Bernard Goldstein, dean...
of the University of Pittsburgh Graduate School of Public Health (GSPH). “Going to baseball games was the first. You're describing a phenomenon that has a lot to do with the old days. Going to a baseball game, you were just assailed by smoke. And lots of sports fans were smokers.”

That's the value of one particular study without the work of investigators toiling away in labs—an incomplete glimpse of the big picture. You realize something is up pathologically speaking, but you're still, more or less, swinging at curveballs in the dark.

Regardless, smoking is bad for you. Check. Not as bad as baseball, perhaps, but still. …

It has long been known that carcinogens in cigarette smoke mutate DNA, leading to cancer. But recently, a team of Pitt researchers got further inside smoking and cancer. They found that not only is the smoker's DNA sequence scrambled—kind of like letters being rearranged in a word—cell division is thrown into disarray. That's more like the chapters of a book being mixed up, with the first half of Chapter 1 followed by the second third of Chapter 5. And whereas mutations affect the functioning of one gene, chromosomal instability affects a whole host of genes.

When damaged by cigarette smoke, DNA strands are broken, chromosomes are either torn apart or elongated, and the resulting imbalanced cells don't die like they should. They keep on reproducing.

So smoking's reach is more profound than we knew, affecting us on the most fundamental level as it sends cells spiraling out of control.

A couple of Pitt researchers have stepped into this vortex, hoping to learn how such knowledge might one day change cancer prognoses.

In the early 1970s, Harvey Gollin, a non-smoker in the grip of a lymphoma that would prove fatal, was abed in suburban Chicago. At that time, his daughter, Susanne, was pursuing a bachelor’s degree in biological sciences at nearby Northwestern University.

The two often talked about how the world worked, and Susanne learned from these conversations. As a young girl interested in biology, she'd immersed herself in books on tropical fish to understand what was going on in her father's aquarium. (An attempt to rear angel fish hatched in the tank didn't work out so well. “I think we overfed them and contaminated the water with bacteria,” she says, looking back.) In high school, she cultured plant tissue in media she made. (The commercial stuff wasn't available.)

Harvey, an obstetrician, and his wife, Pearl, a pediatrician, encouraged their daughter's inquisitive nature. They'd do things like arrange visits north to the University of Wisconsin, Madison, so that Susanne could learn about plant tissue culture from professors there.

But shortly before Harvey Gollin's death in 1974, his daughter had become the teacher. “I was taking genetics classes, and this was when amniocentesis was beginning,” Susanne Gollin recalls. She is now a professor of human genetics (in GSPH), of otolaryngology and pathology (in the School of Medicine), and director of the University of Pittsburgh Cancer Institute (UPCI) Cytogenetics Facility.

“My father the obstetrician very much wanted to learn everything I knew about genetics,” she says. So as the doctor lay in bed, his daughter taught him.
"I really believe that, subconsciously, I went into cancer genetics as a result of my father enjoying genetics so much and my father dying from cancer," she says today.

"My goal is to help somebody else’s mother or father so other young people don’t have to go through what I went through in college."

Gollin joined the faculty of the University of Pittsburgh 18 years ago. As a PhD researcher, she focuses on head, neck, and oral cancers. If diagnosed early, these cancers can be treated, but if discovered in later stages, the five-year survival rate ranges from 15 to 30 percent. Gollin is determined to make these cancers into chronic rather than acute illnesses.

On a beastly hot August morning, a bespectacled Gollin, wearing a loosely constructed orange blazer, sits in her cool office at the GSPH building. Her bookshelves are stuffed with cytogenetics texts, and her walls are dappled with photographs of former students, lab cohorts, colleagues, and sundry candid shots of family and friends (including President Bill Clinton). The composed Gollin chooses her words carefully, asking on occasion to restate an answer. Yet she readily talks about her family, and is even more forthcoming when it comes to her work.

In her early days at the University, she encountered data that showed certain tumor cells seemed unaware that they should have 46 chromosomes—no more, no less. In cells she studied, harvested from head and neck cancers, the chromosomes numbered as high as 100.

So there’s a correlation between a cell having too many chromosomes and that cell becoming cancerous, she noted. Gollin was witnessing evidence of a correlation Bavarian biologist Theodor Boveri had suggested in 1914. If she could only figure out why this happened.

Here began Gollin’s search for the root cause of chromosomal instability, a phenomenon that allows cells to grow like kudzu, without regard for cellular convention and likely to bypass the DNA repair process. DNA’s repair system either fixes problems that arise during cell division or kills the mutated cells, cleaning out the cellular garbage and voiding misfit cells. If these types of cells are allowed to live and divide again and again they become cancerous tumors.

Boveri glimpsed this phenomenon while Woodrow Wilson was president. In the early part of the last century, the biologist studied sea urchin eggs and worms. Under his microscope, he noticed that cancer developed when abnormal numbers of chromosomes were present in a cell. Chromosomal imbalance in one cell, he predicted, would be enough to engender a cancerous tumor. As the muddled cell divided, it would produce similarly flawed daughter cells. Thus the process would continue, evolving into cancer.

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"This was driven by her enthusiasm to learn about how these things work, to bring in outside expertise, someone with a slightly different orientation, a slightly different focus, into her sphere to help her figure out what was going on," Saunders says.

As the two explored the possible glitches in cell division in Saunders’ lab, they hit upon a discovery that Boveri would have relished making himself. In 2004, Gollin and Saunders pinpointed the manner in which cigarette smoke damages chromosomes. It was the first study to connect cigarette smoke directly with chromosomal instability.

"In addition to knowing that cigarettes cause cancer, we need to know how," Saunders says. "That may lead us to ways of preventing the damage other than just telling people to stop, which has limited effectiveness." Finding the link between cigarette smoke and a known cancer mechanism—cell division defects—Saunders says, is akin to the point in a mystery novel where the detective links the butler with the bloody axe.

By studying the fundamentals, Saunders and Gollin have made an invaluable contribution to understanding the overall biology of cancer, says Graham Hatfull, chair of the Department of Biological Sciences. He adds that such an understanding is key to controlling the disease.

Referring to the collaboration, UPCI Director Ronald Herberman says that’s the way things are supposed to happen in research.

"It’s a great example of the type of synergies that occur when you do this type of match-
making or interaction amongst faculty doing things within very different areas of expertise," he says. Herberman was instrumental in recruiting Gollin to come to Pitt from the University of Arkansas for Medical Sciences. Her charge upon arriving in Pittsburgh was to head a facility created to provide cytogenetics expertise, to apply her deep understanding of the chromosome, to a variety of clinical programs and cancer researchers. She did that well, Herberman says. Then she went on to do much more by pursuing the most elemental causes of cancer as her research mission.

"As often happens with the faculty I bring in, we have one particular need in mind, but once they're here, and they become part of the environment and see the opportunities, they evolve in directions that none of us had the wisdom to foresee initially," Herberman says.

In other studies, Gollin has gone on to pinpoint a specific chromosome band that she believes plays a primary role in the proliferation of head, neck, and oral cancers. In nearly half of these cancers that Gollin has studied, she found that chromosomal band 11q13 appears 10 to 40 times as often as it should. Extra copies of 11q13 are also seen in breast, lung, and bladder cancers and in all cases are indicative of a poor prognosis. In head and neck cancer in particular, the overall survival rate has hovered around 50 percent for decades; the unlucky 50 percent have a particularly high concentration of 11q13.

In 2002, Gollin's lab mapped 11q13 and, in the course of that effort, discovered a new gene that is found in abundance in oral cancer cells.

Gollin recently discovered and subsequently mapped the breakpoint regions on 11q13, places where the chromosome snaps, leading to extra copies of the band. These breakpoints, called fragile sites, are susceptible to all manner of abuse—including alcoholic beverages, the human papilloma virus (long associated with cervical cancer), and tobacco smoke.

You might say that Gollin and Saunders' team is swinging for the fences; it's one to watch. When Saunders' lab explored the role of cigarette smoke in chromosomal breakage, grad student Li Luo found that one or two puffs of a cigarette was enough to cause irreversible changes. Cultured cells were exposed to an R.J. Reynolds-cigarette-smoke condensate equal to that produced by about 4 percent of a cigarette. That miniscule amount—with its thousands of carcinogenic compounds—was enough to cause breaks in both DNA strands, a situation that can lead to chromosomal imbalance.

It happens like this: When a cell prepares to divide, its DNA is copied and crammed into identical copies of each chromosome. Under normal circumstances, each of two "daughter" cells created during this process possesses a full copy of the parent cell's genetic material. When smoke is introduced into the mix, this elegant little display of cellular reproduction is thrown into disarray. Chromosomes are torn apart, creating what are called anaphase bridges and leaving incomplete, broken chunks of genetic information—either that or they don't divide at all and remain stretched and misshapen. Anaphase bridges have been correlated with chromosomal instability in cancer cells.
Before Saunders' lab reported its findings, it wasn't clear that cigarette smoke caused these defects.

Before Saunders' lab reported its findings, it wasn't clear that cigarette smoke caused these defects.

But now, says Saunders, they've established a concrete, observable link between smoking and anaphase bridges, a well-known source of mutations and, subsequently, cancer.

The good news is that antioxidants have been shown to halt this process. The bad news or, rather, the incomplete news is that so far this recourse has been successful only in the lab.

"Chemically, there are certain ways of resisting or preventing DNA damage," Saunders says of antioxidants. "I can show you quite readily in the laboratory things that are common in food (vitamin C, beta-carotene, vitamin E) that actually prevent DNA damage. But that doesn't necessarily mean those treatments are going to prevent cancer."

He explains that when people take a lot of vitamin E—or other vitamins—in supplement form over long periods of time, their bodies make less of other antioxidants.

"It's a two-edged sword: If you take too much of one type of antioxidant, you might suppress your own synthesis of other types," he says.

Gollin tempers her optimism about potential treatments that will turn infamously aggressive cancers from mortal illnesses into manageable conditions:

"The rate of progress of research has exploded with genome sequencing; but, again, I believe that just the cell, let alone the human body, is so complex that it will be quite a while before we fully understand all of what's going on in cancer cells."

Her hope is that a new understanding of chromosomal instability will one day lead to screenings to find out who would respond best to a particular therapy. The work may help doctors tell whether a specific treatment is suitable for a person with certain genetic characteristics. Conversely, it could also be used to find out if the treatment a doctor is considering giving a patient would be too dangerous to administer, in light of the patient's genetic makeup.

What's the biology of quitting smoking? "Never a bad idea," says Saunders, noting that quitting is not, of course, a foolproof safeguard against cancer. Kicking the habit may allow cell division to return to normal, yet the damage done earlier remains. There is hope. As Saunders explains, our bodies have a mechanism for destroying cells with DNA damage.

"The more damage that is allowed to happen, the more likely a cell will escape this repair, either by mutational loss of sensitivity or by chance," he says.

Quitting, Gollin would say, is the best thing the 26 percent of Americans who smoke can do to protect themselves from cancer.

For 12 years, Gollin served on the Allegheny County Board of Health; she has also been involved with Tobacco Free Allegheny, an antitobacco agency funded with proceeds from the settlement of the federal government's suit against tobacco companies.

"I'm very much in favor of smoke-free restaurants and bars," she says. "It worked in California; it certainly could work here. Not just for the patrons, but also for the employees, because secondhand is almost as dangerous as firsthand smoke. When somebody is exposed to it possibly for an eight-hour shift, it's really dangerous."

The Graduate School of Public Health's Goldstein appreciates her mind-set and efforts.

"She, personally, is someone who not only talks the talk, she walks the walk. Dr. Gollin took [the board of health position] as a challenge. She is someone I tremendously respect."

Acting on her concern for others, Gollin says, is a natural extension of her upbringing. She remembers dinnertime conversation with her pediatrician mother and her obstetrician father. She heard a lot of discussions like this: "I saw Mrs. So-and-so today; she brought her kids into my office.

"Oh, I delivered those children. How are they doing? How is she doing?"

"It was a very warm, caring environment," Gollin says.

She gets to Miami as much as she can these days to see her mother. Thirty years after Harvey Gollin's death, Pearl Gollin is grappling with inoperable lung cancer.

"This brings it home every day," says Gollin. "This is why I have my own personal crusade against smoking. In terms of public health, smoking is one of the very few preventable causes of cancer deaths."

**SECONDHAND MUTATIONS**

**Identify the nonsmoker.**

Is she someone who's never puffed herself or is she the person who doesn't smoke and also very rarely spends time in the company of others as they puff away?

Stephen Grant takes the latter view. Labels aside, he believes that passive smoke is just as dangerous to a fetus as a smoking mother.

Grant is a Pitt associate professor of environmental and occupational health and director of the toxicology facility at the University of Pittsburgh Cancer Institute. He reanalyzed data from three studies—one of which he coauthored—regarding the effect of cigarette exposure on fetuses. The initial analysis from these studies found little difference in the likelihood of umbilical cord mutation in mothers who smoked versus those who didn't. But a premise behind the work didn't sit well with Grant. Those studies lumped passive smokers together with mothers who had almost no exposure to cigarette smoke. Believing that a nonsmoker often exposed to secondhand smoke is, in essence, a smoker, he took another look at those studies. He determined that the pregnant women who actively smoked and the pregnant women who inhaled smoke passively were equally as likely to have genetically mutated umbilical cord samples. His study was published in the online journal *BMC Pediatrics.*

To Grant, his reanalysis not only confirms the obvious—pregnant women should snuff out their cigarettes—but also suggests that women who may become pregnant should avoid exposure to secondhand smoke.

Because of the relatively small size of these studies, which involved 150 subjects overall, it's not clear that Grant can generalize his reanalysis directly to the larger population. He recently completed a follow-up study of 300 newborns at Magee-Womens Hospital and is preparing it for publication with his collaborators. —JM
Some scientists call it the Principle of Limited Sloppiness. Sounds better than, “Holy cats! Never thought that’d happen. Oh, um, I meant that’s exactly what I intended. Really. Think they’ll publish this in Science?”

Examples:
Louis Pasteur tried to kill a bunch of chickens with cholera as he studied the disease, hoping to find a way to prevent it—they merely got sick. When he tried again with a more virulent strain, the chickens clucked and pecked like nothing at all was amiss. And thus the path to vaccination was paved.
Wilhelm Roentgen was experimenting with electrical discharge. A nearby screen coated with a barium compound fluoresced when an electrical tube he was watching discharged. While he was trying to figure that out, he found a photographic plate in his desk drawer. On the plate, he could see the image of a key that had been sitting on his desk. Not much later, he could see a medal bearing the image of Alfred Nobel hanging around his neck. He had observed evidence of what he called x rays.

One day, Alexander Fleming noted that the bacteria in a culture dish he was studying was contaminated by mold. The bacteria nearest the mold—which had apparently arrived from another lab—was dying and failing to regenerate. Why? You got it, penicillin.

Of course, pure serendipity would not have propelled the work of any of these men forward. It's hard not to notice, however, that sometimes the best-equipped, best-prepared scientist can benefit from a confounded expectation.

In December 2004, the University of Pittsburgh School of Medicine's Russel Salter, associate professor of immunology, and Simon Watkins, professor of cell biology, physiology, and immunology and director of the Center for Biologic Imaging (CBI), were investigating dendritic cells. Dendritic cells, members of the immune system, gobble up various and sundry pathogenic trespassers that would otherwise make us ill, take news of these interlopers to lymph nodes, and get the immune response rolling. The scientists wanted to learn exactly how the cells captured bacteria.

Well, they ended up figuring that out, thanks in no small part to a unique imaging system. But what they discovered in the midst of this effort—that's the stuff of limited soppiness. In the end, an Oops! amounted to the discovery of how a little-seen method of cellular communication works.

In a paper published in February 2004, a team at the University of Heidelberg, in Germany, announced it had observed something bizarre while looking at rat adrenal cells: thin, long physical connections. They were like strings floating in the media. The researchers called them "tunneling nanotubes."

In August of that year, a London team made a similar observation regarding human immune cells.

Before this, physical connections between cells were, if not unheard of, at least given little credence. Sure, cells communicate via gap junctions or chemical signaling, but physical connections?

Daniel Davis of the London research group says that since the publication of his team's paper, "A lot of people said they saw [the nanotubes], even when they were students in the '70s, but they ignored them." These tubes were thought to be just cellular junk, he adds, and were relegated to obscurity.

Hans-Hermann Gerdes, the University of Heidelberg team's senior author, believes nanotubes connect all manner of cells. The London team suggested that finding out what these little tubes do would be an intriguing new goal for cellular immunologists.

Yet Russ Salter and Simon Watkins had never heard of these nanotubes when they were in the thick of a collaboration last winter, months after the Heidelberg and London teams reported their findings. The two were busy watching dendritic cells consume bacteria like the Hungry, Hungry Hippos of the 1970s children's game gobbled marbles. Much as the plastic hippo head would thrust forward and drag a marble to its belly, dendritic cells flattened out and issued forth diaphanous, veil-like folds that enveloped bacteria, drawing them into the heart of the cell.

"It was a much more active process than we had been led to believe based on the literature," Salter says. "That's what the Pitt researchers were looking at, and, really, that's all they were looking for: How dendritic cells internalize bacteria. But they found more.

Wanting to learn the specifics of what makes dendritic cells change shape and actively hunt down bacteria, Salter (an expert in the uptake and processing of antigens, who bears a slight resemblance to Rob Reiner) and Watkins decided to introduce a calcium-sensitive dye into the system. One of the signs that a cell has been activated is a change in its concentration of calcium. The dye would allow the investigators to watch when and how and, perhaps, why the cells reacted to the bacteria.

As the two examined the images generated by Watkins's microscopy masterpiece, they saw the bacteria turning on dendritic cells, fluxing calcium, as expected. Flash, flash, flash.

Yet this is when the scientists' examination of the dining habits of dendritic cells began to take a detour.

The location of the flashes was off. Cells nowhere near the bacteria fluxed and flashed...
away. They flashed and fluxed before bacteria introduced to the dish even came into view. Cells whose purpose in life is to capture pathogens and take antigens to lymph nodes to prompt immune response seemed to be getting excited and sharing news of a bacterial assault without actually touching bacteria.

“That started to make us think something else was going on,” Salter says.

Did the cells know something was coming? Did they have a sort of cellular ESP?

Salter and Watkins devised an experiment they hoped would shed light on why these cells seemed to be jumping the bacterial gun. They placed cells in a sterile base medium. They loaded bacterial solution into an extraordinarily small microinjection tip (about 400 nanometers across and invisible through a 10-times magnification lens), intending to squirt the stuff onto the dish. If the locally delivered bacterial solution started a flux eruption on the other end of the dish, they’d know something was up. Because it’s easy to clog an opening that’s considerably narrower than a cross section of a human hair, Watkins and Salter also placed dye in the bacterial broth, so they could see if anything was coming out of the tiny tip.

Squirt. Wait and watch. Squirt. The researchers injected the bacterial solution onto the dish medium at specific sites. The field of cells responded like paparazzi at a red-carpet premiere.

The flash and flux, however, did not radiate out as each cell in the bacteria’s path was activated. The investigators had assumed that one cell would fire, then the one next to it, then the one next to that. ... They assumed wrong. Cells blinked, but not just those juxtaposed. Not all of the bursts of light were even in the same bacterial field (denoted by the haze of the dye). And not all of them lit up.

It looked like the cells might be linked in a network. But linked with what?

Here’s where the Principle of Limited Sloppiness, with a good dose of doggedness, came into play.

Later that day, Watkins, at work in his microscopy playground, was manipulating the microinjection tip. He pressed the injection button and looked for dye to come out. It emitted nothing. The tip was clogged.

Then Watkins happened to touch one of the cells in the dish with the tip and saw calcium flux flying across the dish. Not one, but several cells got excited by the little poke—without the tip even releasing bacteria.

Immune cells have been scraped from the area outlined. A calcium flux, one of the early signs of cellular activity, moves through nanotubules and spreads around the corner to remaining cells in the course of 25 seconds. The red star indicates the cell that was prodded with a microinjection tip, prompting the calcium response.
Watkins thought, “Well, that’s very strange. It was a surprising finding because I didn’t expect to see anything,” says Watkins.

This had to be explored, explained. Watkins called Salter. Salter came to CBI, and the pair, in Watkins’ words, spent the rest of the morning running around poking cells with a clean microinjection tip.

“Every time we did it, there was flux flying across the dish. It was incredibly dramatic and exciting,” he says.

On their cell-prodding spree, Watkins and Salter again noticed what seemed to be networks of cells firing.

If chemical communication were at work—that is, if the poked cell were releasing something to alert the others—that substance would radiate out like a disturbance in water when a pebble is dropped into a pond. All the cells in the field would eventually react. That’s not what Watkins and Salter saw.

They would touch one cell, and one group of cells would respond. When they touched another cell, another group of cells would respond.

The lab was abuzz. This didn’t appear to be a chemical secretion response. It seemed likely that some sort of physical connection existed.

At the end of the day, Watkins, Salter, and research specialist Jenny Karlsson headed home, sat down at their computers, scoured the literature, and came across the exact same paper: the Heidelberg group’s description of nanotubules.

So nanotubule-hunting they went. Isaac Newton saw farther because he stood on the shoulders of giants. Salter and Watkins delved more deeply into the world of nanotubules because they could peer through remarkable imaging equipment. They saw wispy tubules 200 to 300 nanometers in diameter that were about 2,000 times longer than they were wide. They saw that nanotubules are capable of carrying small molecules. They saw calcium flux transmitted through the tubes, which confirmed for them that communication was taking place between networked cells. And they saw evidence, by inhibiting gap junctions as well as chemical signaling functions, that no other known mechanism could be responsible for that communication.

At a January meeting in Vancouver, Salter delivered a presentation on what they’d learned.

“At the beginning, there were people saying, ‘It’s all secretion. It’s this, that, and the other,’” Watkins says. “But they all, by the
end of the meeting, were saying, 'It's probably these darn tubes,' which was kind of cool for Russ.”

Salter and Watkins published their findings in the September issue of Immunity, that caused a bigger stir. The paper quickly became one of most downloaded items from the journal's Web site. A recent Google search for “Watkins, Salter, and nanotubules” yielded about 100 hits, including one site that argues nanotubules are evidence of intelligent design. “It’s bizarre,” Watkins says.

The discovery is compelling to the scientific community and laypeople alike, Watkins thinks, because, “It's not incremental; it's something completely new.” Watkins and Salter actually saw the nanotubules in action.

“Had we five years ago had some hint of this, the microscope probably wouldn't have allowed us to see the tubules,” Salter says. “Live-cell imaging capabilities are just now advanced enough to see [nanotubules] at this stage.”

Before this technology, cells had to be fixed in formaldehyde to be observed, a deadly proposition for the cell.

“If (nanotubules) survived fixation pretty well, they would have been described in 1970,” Salter says.

The German and British teams had seen the stringlike connections. What Salter and Watkins did, with the aid of a stunningly precise imaging system, allowed the pair to tell the scientific community exactly what the connections were and what they did.

“We really just showed that these connections exist,” Davis says. “We didn't show any specific signaling event from one cell to another. The recent work from Pittsburgh has identified why (nanotubules) are important.”

Put it this way: The earlier work is comparable to looking at a single aerial photograph of Oakland. One can see the roads (nanotubules) and the cars (information) and can subsequently assume that the cars travel along the roads. What Salter and Watkins did was equivalent to installing a video camera on a blimp overhead to record images throughout the day. Such images would show you a massive influx of traffic during morning rush hour and an equally large clearing out of traffic at the end of the business day. This would help you figure out, with some certainty, what the roads were for. And if you kept watching, you could understand all manner of things about Oakland: How commuting works, how many people work there, etc.

Metaphors aside, the upshot of Watkins and Salter’s work is an explanation of how the immune system responds so quickly to challenges.

Watkins discusses this one day recently, hands clasped behind his head, his feet resting on his desk: He explains that if just one dendritic cell were aware that an invader had entered the system, the chances of it surviving the epic journey, by cellular standards, from, say, the fingertip to a lymph node in the armpit, are minimal at best. With nanotubules spreading the news to a wider network, some insight into things that haven’t been seen before.”

The two will attempt to answer new nanotubule questions that have arisen, including how big something can be and still move through the tunnels.

In terms of potential applications, Salter wonders if these tunnels might play a role in vaccination; he's particularly interested in tumor immunology. If the tunnels were somehow prompted to relay tumor antigens to the lymph nodes, they might be able to help instigate a quicker and better immune response.

It’s also possible, Salter says, that nanotubules play a role in HIV transmission; HIV affects dendritic cells.

The scientists would like to observe nanotubules in action in a living human body, if

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“Were so excited about this. I haven't had this much fun since I was working on dystrophin [which is critical to muscle function] in the late ’80s when I was at Harvard.”

Salter, who is also 47, shares his enthusiasm.

“We did these experiments together and really didn’t have involvement from other people in our groups. We have just treated it like our pet project that’s fun to do,” he says. “We’re two relatively old— or at least established—investigators that might have for no other reason than to prove that they’re not simply a lab-dish phenomenon.

“The obstacles to that are optical,” Salter says, laughing at the wordplay mouthful he just uttered. He’s pretty confident that if anyone will be able to refine the technology to make that happen, it’s Watkins and his Center for Biologic Imaging.

“H’s a tremendous asset to this place [Pitt],” Salter says of Watkins, who describes himself as “a biophysicist cum wannabe immunologist.”

“I’m pretty sure this is the biggest user-friendly microscopy center in the country,” says Salter.

In some circles, Watkins’ reputation now precedes him. During a recent trip to Moscow for a conference, a large Russian man approached him and said, in heavily accented English, “You are the Steven Spielberg of Immunology.”

When pressed, Salter identified himself as the set designer. Together, both plan to craft a more complete depiction of how the immune system works, one frame and many little tubes at a time. Two immune cells connected by nanotubules.
Among the questions Pitt researchers are turning to computer models to help answer: What is a good death?
A patient is telling his doctor about episodes of shortness of breath and chest pain, telltale signs of angina. “So, you said you’re having chest pain five times a week,” the doctor notes. “I have a couple of options for medications for you. One will cure you, but I have to tell you that there are side effects, including, very rarely, death. The other won’t cure you, but it will reduce your pain.”

The patient doesn’t pause even a moment before responding. “Does the second one cause death?”

“No,” says the doctor.

“That’s the one for me, then,” says the patient.
The doctor is curious. “Why, when there’s less than a 1 percent chance of dying?”

“Doctor, bad things always happen to me. If someone is going to die from this, it’ll be me.”

Most people don’t think much about luck when it comes to health care. But for some people, whether or not they feel lucky matters, says Carol Stockman, who heard this story from a physician she interviewed. Stockman is an experimental economist and a research assistant professor in health policy and management in the University of Pittsburgh’s Graduate School of Public Health.

“The role of luck was not really anything I had ever thought about before,” she says, speaking with an economist’s mind-set. “I believed people behaved rationally—you did your calculations and made your highest utility choice.” But in talking to doctors, she found otherwise.

Stockman is studying what you might call the Eeyore effect: what people choose when they believe they’re not lucky.

They believe they’re not lucky.

The answer may help explain some disparities in treatment preferences.

For instance, African Americans with heart problems choose life-saving procedures like bypass operations less often than whites, even when researchers control for type of insurance, income levels, location, physician bias, and levels of pain. Stockman wonders, do African Americans feel especially lucky or unlucky, and how might that influence their healthcare decisions? Might such perceptions contribute to the disparities?

These are the kind of questions Mark Roberts encourages people to ask. Roberts, associate professor of medicine, health policy and management, and industrial engineering, is chief of the School of Medicine’s Decision Sciences and Clinical Systems Modeling Section.

Stockman’s questions can’t be answered with clinical trials. It’s a complicated issue. There may be multiple right answers—or none. This may be true anytime you ask the question, How do patients make decisions? Likewise, resource and cost questions often can’t be studied in randomized clinical trials. But many such questions can be modeled using computers, and researchers at Pitt, notably those associated with or collaborating with Roberts’ group (like Stockman), keep expanding their use of mathematics to try to capture the nuances of medicine and health care.

Some of the questions Roberts and his colleagues are asking:

- Can predictive models show the best combination of drugs to give HIV-positive patients when antiretrovirals stop working?
- How do you get the best results for patients undergoing in vitro fertilization, ensuring that a patient with enough money for only one such procedure has the best chance of conceiving—or that couples can lower their odds of twins or triplets?
- Is it more cost-effective to invest in quickly identifying an outbreak of bioterrorism or in the preparation required to respond to it?

Roberts would tell you that in the end this effort has little to do with computers. It’s about helping people—doctors, patients, policy makers—make better decisions about health care.

“I believed people behaved rationally—you did your calculations and made your highest utility choice.” But in talking to doctors, she found otherwise.

Two doctors have coffee after rounds. Some of the patients they’ve just seen won’t be leaving the ICU until they leave this world.

“You know, we talk a lot about quality of life for our patients. What do you think they might trade to have a better death?”

“What do you mean?”

“Well, instead of lying around in a hospital bed for months, getting worse and worse, what if people could guarantee an excellent experience at the end of their lives? Would they trade some part of their healthy lives?”

The question wasn’t just a sign the doctors—Derek Angus, professor with appointments in the Departments of Critical Care Medicine, Medicine, and Health Policy Management, and Robert Arnold, the Leo H. Crip Cancer Professor of Patient Care—needed to cut back on their caffeine. After more discussion, they approached Cindy Bryce, a policy analyst and assistant professor of medicine and of health policy and management, to see if she would be interested in looking at the economics involved.

Bryce thought the questions they were raising were pretty good. Worthy of study, in fact.

From that caffeine-stimulated encounter has come a significant, National Institutes of Health-funded examination of the calculus of cost-effectiveness, which has traditionally boiled down to measuring cost of care versus lives saved. Hospice care may actually shorten a life, which makes it look very expensive relative to other kinds of care. But hospice care may be less painful and make for an overall easier, more peaceful death for some patients. With other researchers at Pitt, Carnegie Mellon University, and the University of Toronto, Bryce crafted a study that may ultimately shift how some healthcare dollars get spent.

First the researchers had to find out how patients would define excellent end-of-life care. Essentially, they wanted to know: What is a good death? To get at this fuzzy question, they asked people about four facets of end-of-life care: level of pain and symptoms, control over conditions in the hospital, control over treatment choices, and emotional and financial family support received.

They found, among other things, that almost three out of four people would give up time, as much as two years, for less suffering at the end of their lives. If people knew they would die at about 80 and could have a one-month period of exceptional care before dying, they would, on average, surrender more than eight months of their lives in exchange.

Bryce is aware such questions raise other questions. “Whose values do we care about?” she asks. “Society is the big gold standard. But a lot of research shows that what patients value and what society values is different.”

She acknowledges that some people question whether quality can be measured but believes that using models to help analyze decisions is valid and useful for doctors helping patients with hard decisions. How does this work translate to the clinic? A doctor may never punch patient-decision parameters into a software program (though that could happen as well), but the efforts of decision scientists can help a doctor understand how her patients make choices and what’s important to them as they do.

Bryce is also involved in the best known and most advanced research on decision making under way at Pitt. Led by Roberts, she and others have since 1997 published a series of papers that ask challenging questions about
liver transplantation. Among them: Should the sickest patients receive new livers, or the patients most likely to benefit? Should we maintain the current regional system, where transplant candidates in one of 11 regions typically get access only to livers donated in their region, or should we distribute livers nationally? And when is the best time to give a patient a transplant?

Their research has fueled national debate on these and other questions related to liver transplantation.

"It's truly groundbreaking," says Stephen Pauker, associate physician-in-chief at Tufts-New England Medical Center, founder of Tufts' Center for Clinical Decision Making, and one of Roberts' early mentors. (Pauker published several seminal papers in the decision-making field.)

Groundbreaking is exactly what Wishwa Kapoor, Falk Professor of Medicine and chief of the Division of General Internal Medicine, wanted when he began encouraging Roberts to pursue research into decision making. Roberts came to Pittsburgh in 1992 to run the internal medicine residency program at UPMC Shadyside. Prior to that, he had been an instructor of medicine and a research fellow at Harvard Medical School with a research focus on how doctors make decisions.

Kapoor knew that Roberts was one of the best decision-science researchers in the nation—Pauker calls him "a mainstay of the field, and one of the best modelers we have." Kapoor also knew that questions involving resource allocation were becoming more and more important in health care.

"It comes up in everything we do," Kapoor says. "If we have some new treatment that is really, really expensive, is it cost-effective to use it? Or if we have something that is cheap but doesn't improve quality of life or quality of care, should we keep using it? Decision sciences is one way of objectively looking at it."

Kapoor saw an opportunity for Pitt to become a leader in national policy discussions, and he's been right. Since Roberts established his section in 2000, the group has produced more than 40 published papers, with another 20 submitted or in process—and those are just the ones Roberts is coauthoring.

Not long after he came to Pitt, a cautious Andrew Schaefer walked into a doctor's cluttered, book-filled office.

He sat down and immediately announced, "I see I've come to the right place."

Schaefer, now an assistant professor in both industrial engineering and medicine, was hoping to find a doctor willing to apply industrial engineering techniques to health care. In graduate school, Schaefer says, "the conventional wisdom was that there are great problems in medicine, but you can never find an M.D. to work with you."

In that office, he knew he'd found the M.D., because he was sitting eye level with Martin Puterman's *Markov Decision Processes*, a mathematics text engineers use to help resolve questions whose answers vary depending on circumstances. He knew that if a doctor had a copy of Puterman, there had to be work they could do together.

That doctor was, of course, Mark Roberts, and he and Schaefer have found plenty of uses for mathematical techniques from the world of industry to look at supply-chain questions like donor organ allocation. They've also used the predictive math of finance to determine when patients might need certain treatments.

Schaefer has taken to calling such research "therapeutic optimization." By next August,
Viagra might seem like a frivolous drug, a “lifestyle enhancer.” But does that mean it isn’t cost-effective?

That’s what Kenneth J. Smith, assistant professor of medicine, decided to find out five years ago. Smith, at the time a clinician at Mercy Hospital, was frustrated that he had to fill out extra forms to get insurers to consider covering Viagra prescriptions, not something he had to go through for, say, migraine treatments. Yet insurers didn’t seem to have any trouble paying for penile implant surgery, which Smith thought was a costlier way to treat erectile dysfunction than the typical lifetime payout for Viagra.

“So Smith contacted Mark Roberts, associate professor of medicine, health policy and management, and industrial engineering, who is chief of the School of Medicine’s Decision Sciences and Clinical Systems Modeling Section. Smith and Roberts, who had collaborated on research since 1993, decided to examine the cost-effectiveness argument. They knew that Viagra was less expensive than surgery, but it also has potential side effects, including heart problems and death. An insurer could argue that the potential for such side effects would make no treatment better than using the drug. To model potential changes in health over time, Smith and Roberts drew on decision models used by industrial engineers.

They examined data from a number of studies on erectile dysfunction. Even adjusting the data so that death occurred much earlier and much more often than what happened in the actual studies, Smith and Roberts found that Viagra was clearly cost-effective when compared to other standard treatments for non-life-threatening conditions that insurance companies routinely cover.

“It skewed popular wisdom,” Smith says, and gained national attention. Insurers could find other reasons not to pay for Viagra, but no longer could they say it wasn’t cost-effective. —MF
PLANTING THE SEEDS

PROGRAM GROWS PROMISING NEW CANCER RESEARCH

BY ELAINE VITONE

How do you get the money you need for your research if you have to do the research to get the money? How do you get funding if you don’t have the chance to prove that your idea is worth the investment? This seeming catch-22 can be frustrating for new researchers, but it’s not stopping Vera Donnenberg, University of Pittsburgh assistant professor of surgery and pharmaceutical sciences. Thanks to a pilot seed-fund program sponsored by the Henry L. Hillman Foundation, she’s grown her hypothesis into promising new research on cancer recurrence. And thanks to a more recent Hillman gift of historic proportions, the seed-fund program is growing, too.

A couple of years ago, UPMC President Jeffrey Romoff e-mailed Donnenberg, who’d just received her PhD from Pitt’s School of Pharmacy, an article about a cancer-cell study at the University of Michigan. The Michigan team showed that only a small percentage of breast cancer cells could actually make a new tumor. They were surprised to find that the cells that caused tumors were not rapidly dividing. Reading the article, Donnenberg noticed that the tumor-causing cells contained a population of small, “meek looking” cells that reminded her of normal adult stem cells. She recalled a hypothesis of cancer stem cells, originally proposed in the 1960s, and wondered: Were these small cells actually stem cells that can “wake up” and give rise to tumors?

Testing her hypothesis would be costly. She’d need to isolate the cells and implant them in immunocompromised mice. Just one experiment would cost $16,000, and Donnenberg knew that major funding agencies needed solid, preliminary data before they’d back her. So there she was, caught in a common dilemma of a researcher trying to make her way early in her career.

Ronald Herberman, associate vice chancellor for cancer research and director of UPMC Cancer Centers and the University of Pittsburgh Cancer Institute, has been explaining the difficulties of funding such early stage research for a long time. To attract the best young cancer researchers, he says, the University needs seed funds to support their work. In March 2004, the Henry L. Hillman Foundation took Herberman’s concern to heart and initiated a pilot seed-fund program that got Donnenberg’s study, as well as 12 other new projects, off the ground. Since then, Donnenberg has been awarded $3.7 million from the Department of Defense, and her two pending National Institutes of Health applications look promising. “I am very grateful,” she gushes, clearly in love with her work, not appearing the least bit anxious to leave her lab on a Friday night.

The majority of the other studies funded by the pilot program have since garnered major funding as well. The effort was so successful that in June, the Henry L. Hillman Foundation and the Hillman Foundation decided to establish the new Hillman Fellows Program for Innovative Cancer Research with a $20 million gift—the largest contribution ever made to UPMC and Pitt.

Not only has Donnenberg found what she believes to be cancer stem cells in every one of the 42 primary and metastatic tumors her team has tested so far (including tumors of the breast, lung, esophagus, prostate, colon, and kidney), but she has also discovered that these cells are resistant to chemotherapy. Like other stem cells, they may lie dormant for decades.

This research, which, Herberman says, “has the potential to be revolutionary,” may not have happened without the initial Hillman gift. Donnenberg is grateful; at the same time, she maintains belief in the system: “I think struggle is good for you.” In her male-dominated field, she says, jokingly, “That’s what separates the boys from the men.”
W.P. Andrew Lee tried to visit everyone on the planet who was using a hand that once belonged to someone else.
A new Zealander lost both hands when a bomb exploded—giving him just one hand, and his thumb to the pinky finger. The man in the picture has become an insulin-dependent diabetic—a side effect of his anti-rejection medication. One of his hips has been replaced (because of avascular necrosis) and the other may be next.

Lee pauses at a photo of a grinning, ruddy-faced man with an arm around his wife. The fingers of the hand cup her shoulder, almost. The thumb sticks up a little stiffly, not fully participating in the embrace. Lee notes that only two patients showed true intrinsic muscle function, which is best demonstrated by touching the thumb to the pinky finger. The man in the picture has become an insulin-dependent diabetic—a side effect of his anti-rejection medication. One of his hips has been replaced (because of avascular necrosis) and the other may be next.

Lee lingers over a photo of two transplant recipients. One proudly shakes hands with Lee. Another—a policeman who lost both hands when a bomb exploded—gestures animatedly. “He was in a hurry to leave after the interview,” says Lee. “He was going on a long-distance motorcycle trip.”

Those who received one hand talked of improved body image, of being able to eat and go to the toilet without the help of a spouse or caretaker. A Chinese man said that he could play mahjong and eat with chopsticks. “No small feat,” notes Lee, who was born in Taiwan. One man stated simply that without his hands, he could not have had the relationship with his wife that led to the birth of their daughter.

Lee notes that it was experimental, and the doctors readily admitted so. His answer, finally: “No.”

Still, Lee expects to offer an amputee a hand transplant one day here in Pittsburgh. He is reticent about when this will happen, but he says, “I will be disappointed if we don’t make meaningful progress on tolerance induction in five years.” When I can offer this surgery to a patient and be comfortable in telling the patient that I would do the surgery for my family members or myself if we had the same condition—I think that’s when I’ll offer it to a patient.”
When Thomas Medsger (Rheumatology Fellow ’65–’66, Internal Medicine Resident ’66–’68) started his rheumatology fellowship at the University of Pittsburgh, Professor Gerald Rodnan introduced him to scleroderma, the rheumatic disease. That pointed Medsger toward a research subject and career path. When Rodnan, also known as the “Father of Scleroderma Research” died unexpectedly in 1983, Medsger assumed his position as chief of the Division of Rheumatology and Clinical Immunology. Medsger also directs the Scleroderma Research Program.

Since he assumed that position, he has treated nearly 3,000 patients with systemic scleroderma (which can cause the skin and internal organs to harden) and 500 patients with localized scleroderma (which affects only the skin); his patients are referred to him from physicians all over the world. Medsger created the first National Registry for Childhood Scleroderma, which keeps a blood sample from every child known to have the disease; the antinuclear antibodies found in the blood could yield interesting answers in researching this autoimmune disease, he explains. Recently, the Scleroderma Foundation named him Doctor of the Year.

In 1988, the Chinese Medical Association invited Constance Keefer (MD ’69) and other pediatricians to China. As Keefer toured Chinese maternity wards, she noticed that mothers and babies were kept separate, except during feeding time. She told her host, Zhang Peiying, the now retired director of Taiyuan Children’s Hospital, that in the United States, babies stay in their mothers’ rooms, fostering healthy bonds. In 2000, Peiying invited Keefer back. As she toured the hospitals, she saw mothers and babies together in rooms. When Keefer mentioned it, Peiying said, “Oh yeah, we listened.” Keefer studied with Harvard University’s famed pediatrician T. Berry Brazelton and works at Brazelton Touchpoints Center, affiliated with Children’s Hospital of Boston, where she trains people how to interpret a child’s behavior and nurture a child. In addition, Keefer directs the newborn nursery at the hospital.

Since 2004, the Sentara Norfolk General Hospital, in Norfolk, Va., has experienced an 84 percent decrease in ventilator-related pneumonias and a 63 percent drop in overall ICU infections. Who’s the mover and shaker behind these changes?

In the mid-1970s, Gerald Sonnenfeld (PhD ’75) arrived at Stanford University’s infectious disease lab, only to be sent away—well, sort of. It seemed the lab had an opportunity to send a postdoc down the highway a few miles to the NASA Ames Research Center. Sonnenfeld, the new guy in the lab, put aside his initial disappointment at being singled out. Being part of the space program could have exciting outcomes, he thought. This was the age of the moon walk, when some hoped space travel would become as common as air travel.

Sonnenfeld fell in love with the research. He wanted to spend as much time in the NASA lab as possible. He studied what is now called interferon gamma, which is a protein secreted by immune cells in response to inflammation and viruses. The topic became a career-long pursuit. Sonnenfeld has conducted nine experiments in space (oftentimes, animals were sent for experimentation). He went on to discover that outside the earth’s atmosphere, people experience lowered production...
of interferon gamma. The impact of this immune response isn't fully understood, but Sonnenfeld suspects it makes astronauts more likely to contract infections on long flights.

In 2004, the American Society for Gravitational and Space Biology awarded Sonnenfeld its Orr E. Reynolds Distinguished Service Award.

Sonnenfeld holds three patents, but not every development has borne fruit: "Some are carried forward into clinical trials, but others just sit there. There's no way to know whether something will work or not."

When President George W. Bush suggested that intelligent design be taught in school, Eric Lenze (Geriatric Psychiatry Fellow ’98–’99, Late Life Mood Disorders Fellow ’99–’00) felt overwhelming frustration. You may have seen his letter to the editor of The New York Times expressing his annoyance. It ran in August. Lenze is an assistant professor of psychiatry in Pitt’s School of Medicine.

The pager beeped. Tara Williams (MD ’99) returned the call. She learned that one of her patients just died in an accident—the patient was an infant. What do I say to the parents, she wondered. Williams, mother of four girls herself, found it hard to think of something comforting to say to the baby’s mom. As associate director of the pediatric residency program at Case Western Reserve University and MetroHealth Medical Center in Cleveland, Williams thinks a lot about training the residents she mentors to be empathetic. —Nita Chawla, Meghan Holohan, Erin Lawley, Erica Lloyd

William Brock (MD ’80, Internal Medicine Resident ’80–’83). Brock is medical director of critical care quality for Sentara Healthcare; with his colleagues, he standardizes healthcare practices at Sentara’s six hospitals in Virginia. The American Hospital Association Quest for Quality rated Sentara Norfolk General the best-performing hospital in the nation.

Elizabeth Jaffee (Internal Medicine Intern ’86, Internal Medicine Resident ’86–’88, Research Fellow ’88–’89) remembers being on rounds one March night in 1986 when she waspaged. It was her father. Her 51-year-old uncle had pancreatic cancer, he told her. She started crying. "Why are you still crying?" her father asked—he thought that chemotherapy and radiation would cure Jaffee’s uncle. Jaffee knew that these treatments were considered largely ineffective for pancreatic cancer. Two months later, her uncle died. The incident led Jaffee, now at Johns Hopkins University, to develop vaccines for cancer of the pancreas and breast. Her pancreatic cancer vaccine (it serves as both a treatment and a preventative) is now in Phase 2 of clinical testing. She plans to test another vaccine on patients within the next two years.

'S90s

Susan Dorr Gold (Internal Medicine Resident ’87–’90) is associate professor of internal medicine at the University of Michigan, Ann Arbor. She has created computer games and other activities to educate patients about HMOs and the importance of making smart choices about health care. Gold has been researching and writing about medical ethics since 1990, covering issues such as financial incentives for physicians and how they affect patient care.

In medicine, the “golden hour” refers to the first 60 minutes after a critical injury—it’s when surgical intervention is most likely to save lives. Kevin Ralph Ward (Emergency Medicine Resident ’89–’92) says there is no golden hour for wounded soldiers on the battlefield. Ward is associate director of the Virginia Commonwealth University Reanimation Engineering Shock Center, a critical illness research center. As director of a special program there, Ward develops new therapies for severely wounded soldiers. Among the weapons his program is hoping to add to the army medic’s arsenal: new blood substitutes, tourniquets, bandages, monitors to measure intracranial pressure, and ways to control abdominal pain without surgery.

Inspired by the work of Pitt psychiatric epidemiologists Nancy Day (an expert on alcohol and drug abuse) and Mary Amanda Dew (known for her heart-transplant research), Andrea DiMartini (Psychiatry Resident ’87–’91) created her own research niche. Since 1998, DiMartini has served on the liver transplant team at Pitt’s Starzl Transplantation Institute. She’s interested in the behaviors of liver transplant patients before and after their transplants and getting them other help they need, which may include rehab. She has two National Institutes of Health grants to investigate outcomes in these patients.
When Sheldon Weinstein was a medical student, he joined Henry Bahnson in the operating room for the first time. The seasoned surgeon turned to Weinstein, saying, “Shelly, if there is any way you can improve my surgical skills, tell me. If there is anything that I can do for you, I’ll tell you.” Bahnson’s modesty impressed Weinstein (MD ’63, Res ’67), whose experiences with both Bahnson, then chair of surgery, and Bernard Fisher (MD ’43), who is now a Distinguished Service Professor of Surgery, influenced him to go into obstetrics and gynecology.

Bahnson and Fisher’s student has an inventive streak. While at Pitt, Weinstein developed an early model fetal EKG. While in private practice in Dallas, he helped develop a technique (an electrosurgical excision procedure) that replaced vaginal cold-knife biopsies, which were often risky for women. This year, he won the Distinguished Surgeon Award from the Society of Gynecologic Surgeons; it is unusual for a private practice physician to win the award.

When Philip Raskin (MD ’66) was a medical student at Pitt, an intern at Magee Womens Hospital by the name of Sheldon Weinstein taught him how to treat gonorrhea. Later, Raskin, too, migrated to Texas. He says if he hadn’t been traveling that weekend, he would have joined in on the fun at a Sept. 30 reunion for Pitt med alumni that Weinstein hosted in Dallas, which went off despite Texas’ uninvited guest, Hurricane Rita. (Weinstein’s wasn’t the only gathering for Southwest alumni this fall: Bruce Coull, MD ’72, hosted a Sept. 16 event in Tucson, Ariz.)

Even though Raskin enjoyed working with Weinstein, he pursued a career in endocrinology. In 1993, Raskin, the Clifton and Betsy Robinson Chair in Biomedical Research at the University of Texas Southwestern Medical Center in Dallas, participated in a study showing that if patients manage diabetes early on, they do not suffer from serious vision and foot problems. Raskin is now the principal investigator at UT Southwestern for a follow-up study, in which researchers at several centers are determining what drugs best treat type 1 diabetes.

Bert O’Malley (MD ’63), also based in Texas, says he is still doing research on female hormones. O’Malley, one of Pitt med’s most eminent alumni, talks about how much he enjoys the scientific method, even though “Mother Nature gives up her secrets grudgingly.” He reports that little has changed since we last talked to him in 2000, when he was this magazine’s cover model; he has moved closer to the infamously Dimple Rock rapids. It takes composition to navigate that gnarly pass. Phillips has it down. In his 35 years at the med school, the recently retired associate professor of molecular genetics and biochemistry and associate dean for graduate studies has been known for his enthusiasm but also as the calm in the storm.

“I have heard people say that he must have been a pastor in a former life,” says Mike Turner (PhD ’96). “No matter how serious or urgent the situation, one would always leave his office feeling comforted.” Phillips knew how to connect with students and did it often. Once, he hunted Turner down in the lab to ask his opinion on some changes to a course he’d done it often. Once, he hunted Turner down in the lab to ask his opinion on some changes to a course he’d

WE KNEW YOU WHEN STEVE PHILLIPS

Every summer, Steve Phillips took graduate students from Pitt’s School of Medicine whitewater rafting on the Youghiogheny River. Students loved it when he’d steer his raft through the infamous Dimple Rock rapids. It takes composition to navigate that gnarly pass. Phillips has it down. In his 35 years at the med school, the recently retired associate professor of molecular genetics and biochemistry and associate dean for graduate studies has been known for his enthusiasm but also as the calm in the storm.

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IN MEMORIAM

**’40s**

MARTIN R. SCHLESINGER
MD ’44
JULY 20, 2005

J. ALBERT JACKSON
MD ’48
NOVEMBER 20, 2004

**’50s**

THOMAS Q. SPITZER
MD ’52
JULY 1, 2005

RAYMOND J. BOYLAN SR.
MD ’53
AUGUST 21, 2005

RICHARD ALAN PETERS
MD ’54
MAY 23, 2005

MARWIN A.K. LOMMEN
MD ’55
JULY 1, 2005

**’60s**

ROGER K. JONES
MD ’63
NOVEMBER 4, 2004

FRANK B. KERN
MD ’66
JULY 13, 2005

**’70s**

SARA JAYNE MILLER-LEWIS
(SNYDER)
MD ’79
AUGUST 20, 2005

**FACULTY**

RAY MCKENZIE
SEPTEMBER 27, 2005

WALTER JOSEPH REIS
JULY 24, 2005

**’80s**

WALTER JOSEPH REIS
JULY 13, 2005

RICHARD ALAN PETERS
MD ’54
MAY 23, 2005

MARWIN A.K. LOMMEN
MD ’55
JULY 1, 2005

**’90s**

ERIC RICHARD KOHR
MD ’90
NOVEMBER 24, 2004

**2000s**

RAY MCKENZIE
SEPTEMBER 27, 2005

WALTER JOSEPH REIS
JULY 24, 2005

**’10s**

STEVE PHILLIPS
NOVEMBER 1, 2004

WALTER JOSEPH REIS
JULY 13, 2005

RICHARD ALAN PETERS
MD ’54
MAY 23, 2005

MARWIN A.K. LOMMEN
MD ’55
JULY 1, 2005

Want to host a reunion in your town?
Contact Pat Carver at:
cpat@pitt.edu or 412-647-5307.
Early in his career, Robert Wells (PhD ’64) worked under a level of surveillance the biochemist had never experienced before. In 1965, after finishing his PhD at the University of Pittsburgh School of Medicine, Wells had secured a postdoctoral fellowship at the University of Wisconsin with Gobind Khorana, bypassing a faculty offer from Princeton University because he thought Khorana’s work was where the action was. Though the term “genetic code” hadn’t been coined at the time he joined Khorana’s team, Wells knew that the molecules Khorana studied—DNA—would shape the future of his field, biochemistry. Apparently the press agreed. Reporters were camped out monitoring the lab’s progress.

History has shown that both Wells and the reporters were right. Within two years of Wells’ arrival in Wisconsin, the group had cracked the genetic code. Khorana was awarded a Nobel prize, and Wells launched his own career fresh from having participated in one of the fundamental advances in biochemistry. It’s a fact that still manages to amaze new colleagues, especially younger ones.

“Most people I talk with assume ... that anyone who was part of that must be very old and very gray and probably dead by now,” says Wells. They’re very wrong. Khorana himself, now at MIT, is still active. And the same mentality that helped Wells recognize the importance of what was happening in Khorana’s lab in the 1960s has kept his work extremely relevant.

Today, Wells studies what he calls “nonorthodox” DNA structures. Sometimes strands of DNA forgo the traditional double helix shape we’ve all become familiar with and form other, “sticky” shapes like hair pins, cruciforms, or tetrplexes—not so orthodox.

One way this happens is when certain sections of DNA decide to expand. These sections are likely to form nonorthodox structures, often causing trouble, including changing the level at which a gene is expressed. These structures are also, Wells discovered, hot spots for mutations.

“There are at least 50 human diseases that are caused by these conformations,” he explains, including numerous neurological conditions and leukemias.

“Bob Wells is really a pioneer in the study of nontraditional DNA structures. He has been studying this for years and years. He knew this was important. But the rest of the scientific community didn’t appreciate it until the last 10 years,” says Joel Gottesfeld, a professor of molecular biology in the Scripps Research Institute, in La Jolla, Calif.

The two scientists are collaborating on a disease called Friedreich’s ataxia. People with Friedreich’s slowly lose their ability to make voluntary movements. Wells identified a region of sticky DNA important to the disease.

Wells is now the director of the Center for Genome Research in the Institute of Biosciences and Technology at Texas A&M University Health Sciences Center in Houston. There, he and his current crop of up-and-coming researchers are studying the effects of nonorthodox DNA structures on early onset Parkinson’s, myotonic dystrophy (a rare condition that causes muscles to waste away), and chronic myeloid leukemia.

“In the next 20 years, we hope to model these diseases and develop therapies for their treatment,” he says.

There was a time when such statements were met with skepticism. No longer. This coming March, more than 125 researchers who focus on nonorthodox DNA structures will descend on Houston, Texas. Wells is organizing the first-ever conference dedicated to the topic.

When he recalls his time with Khorana, Wells likes to say, “I was in exactly the right place at exactly the right time.”

It’s not hard to imagine that someday his students will say the same thing.

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NONORTHODOXY:
ROBERT WELLS

BY ROBIN MEJIA

Wells also has taken a lead role in voicing concerns of the scientific community to government officials. Here he’s shown (center, gesticulating) during a meeting with Vice President Dick Cheney (seated directly across from Wells).
Care to guess the origin of this curious and macabre image? (We found it on the office door of pulmonary expert Tim Oury. His story is on p. 11.)

a. Painted by Vincent van Gogh, probably in the winter of 1885–86, when he was enrolled at an art academy in Antwerp.

b. Propaganda art from the 1956 U.S. government-issued comic book *Death by Tobacco!*


See the credit line (below left) to learn the correct answer.
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OF SPECIAL INTEREST TO ALUMNI AND FRIENDS

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Roland W. Moskowitz, MD, Speaker
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Lawrence Norton, MD, Speaker
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