SHOWTIME

LIFTING THE VEIL ON THE MOLECULAR MASTERPIECE THAT IS LIFE
COSTS AND CARE

Arthur S. Levine’s “Dean’s Message” from our Winter 2007/08 issue was published simultaneously as a November 2007 op-ed piece in the Pittsburgh Post-Gazette. In it, the dean suggested issues to be addressed to bring health care costs down before a national system is put into place. The letter below was sent in response to that op-ed.

An excellent column. There is a great need for changing the health care financing and delivery system, or we will continue to have health outcomes that are below most other peer nations. I strongly agree with Arthur Levine that a national solution must attend to quality and prevention to make a dent in cost outcomes.

I have been asked to cochair the Pennsylvania initiative of the Governor’s Office of Health Care Reform related to changing the way chronic disease is managed and prevented. We are drafting a set of recommendations to implement an approach to the management of chronic disease, which includes strong emphasis on providing appropriate early intervention, prevention, and health coordination, as well as patient self-management, education, and support.

Of course, the plan assumes that there will be a growing and robust system of primary care providers, which, as Dr. Levine’s article points out, is a real question.

Thank you, Dr. Levine, for your ongoing efforts to lead medicine and policy in the right direction.

Diane Holder
Executive Vice President, UPMC
President, UPMC Health Insurance Division & UPMC Health Plan

LET THEM EAT LUNCH

Hold the lunch?

There is no doubt that the pharmaceutical industry has influenced physician-prescribing behavior through its sales efforts and gifts. I applaud UPMC and the University of Pittsburgh for their aggressive stance in protecting their integrity by eliminating gifts and free lunches from industry sales reps (“A New Diet for Docs,” Spring 2008). Many academic health centers around the country are adopting similar policies. The unfortunate result of these policies, of course, is who gets stuck paying for the food. Cash-strapped departments have curtailed much of their dining budgets. At the same time, ever-increasing educational requirements and duty-hour rules make early morning and noon conferences more essential.

When I give a noon lecture to residents that includes food, I can expect to have significantly better attendance than I would otherwise. The typical department response is to require resident/student attendance with a penalty for noncompliance. Young people, already in debt, spend their lunch hours racing through a cafeteria line, arriving late to the conference, and learning less. It is difficult to see the benefit of this teaching method.

Compare a typical academic health center with a software company. Both employ highly motivated and smart people working long hours. The cafeteria at Google provides free food for its workers, including treats for birthdays and special occasions. Surely a profit-driven organization would not waste its resources frivolously. Google realizes that employees dining together—learning and discussing—nurtures its business interests.

I urge UPMC and other academic health centers to supply food for residents and students who attend conferences during mealtimes. That would eliminate the pervasive presence of drug reps at conferences at the same time it nourishes both mind and body.

James Berman (MD ’81)
Loyola University, Stritch School of Medicine
Chicago, Ill.

I agree with most of Sharon Tregaskis’ excellent article, “A New Diet for Docs.” However, there is a way to engage with the pharmaceutical industry that is productive for physicians, patients, and the industry while protecting the integrity of all.

When I was in practice, I was approached by Pfizer’s Roerig Pharmaceutical Division representatives to organize and moderate a series of yearly infectious diseases symposia. For 13 years, an average of 125 physicians, nurses, and physician assistants attended each of these one-day meetings, which included lunch, without charge. The program content and speakers (academicians and private practitioners) were organized by a committee entirely independent of Roerig.

Roerig provided a stipend of $10,000 per meeting, which was used for mailings, honoraria, and food. Roerig maintained a drug booth in the hallway outside the meeting room.

When I confronted the Roerig representatives about the apparent absence of a quid pro quo for this arrangement, their response was, “What is good for medicine is good for us.” Such arrangements are not unique. Let’s not throw out the baby with the bathwater.

U.G. Hodgkin Jr. (MD ’59)
Albuquerque, N.M.

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

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CONTRIBUTORS

Swedish photographer LENNART NILSSON (Cover, “Showtime”) used an endoscope with a wide-angle lens and an electronic flash to do the live fetal photography in his 1965 book, A Child is Born. Nilsson received Emmy awards for his documentaries on reproduction, fetal development, and childbirth in 1982 and 1996. He also received the Hilis Quorum, the highest honor given to a Swedish citizen by the government of Sweden.

MICHAEL FITZGERALD (“Liquid Gold”) is a Boston-based writer who aims to bring out the personalities behind innovations. Revision is essential to his craft. “The key thing is making sure you’ve got something on paper so you can go back and change it.” Fitzgerald writes a column for The New York Times and has lent his talents to publications such as The Economist, Boston Globe Magazine, Inc., and Wired News.

JULIETTE BORDA (“Liquid Gold”) says she brings “the endless possibilities within the form of the human body” to her illustrations, which have been featured in Bon Appetit, The New Yorker, and The New York Times. Pittsbughers have likely seen her designs dashing past them on the sides of Carnegie Library vans. No matter what Borda is illustrating, “it’s all about the clarity of the message and the simplicity of the design,” she says. Borda lives in New York City.

COVER

In the beginning … The mysterious start of a healthy human life. (Cover: A fetus at four months, weighing about 7 ounces. © Lennart Nilsson/Albert Bonniers Forlag AB, A Child Is Born, Dell Publishing Company.)
Life is no brief candle to me. It is a sort of splendid torch which I have got a hold of for the moment, and I want to make it burn as brightly as possible before handing it on to future generations.

—George Bernard Shaw

Although I have written before about the dearth of physicians now undertaking a career in clinical investigation, much of my evidence was anecdotal. Recently, however, the Association of American Medical Colleges surveyed 837 clinical department chairs to determine the number of junior physician–clinical investigators (i.e., assistant professors) in their departments, the number of vacancies, and the rate of success in filling them. More than 70 percent had vacancies (2,100 total), and a third went unfilled.

This is happening just as the opportunities for clinical research have grown to unprecedented proportions. We have new insight into human biology and the root causes of disease in the wake of the Human Genome and Human Proteome Projects and as a consequence of imaging techniques and computational methods that border on science fiction.

For many reasons (e.g., insurance, access, and cost), too few of these awesome advances are reaching patients. But one of the most striking reasons is the growing paucity of clinical scientists charged with developing evidence, in direct interactions with patients, for the safety and efficacy of clinical advances. Why is this unique breed of researcher disappearing at a time when the need is so pronounced?

First, we live in a harsh time: With federal support so constrained, funding for research of any sort has become sparse and unpredictable; the regulatory environment for patient research has become overbearing; and most graduates will confront a debt for tuition and living expenses of almost $250,000 by the time they complete their residencies. Even when graduates do embark on a career in research, unless they have abundant support and protected time, they will not be competitive for grants, and the pipeline will ultimately leak.

There also have been dramatic changes in medical student demographics, e.g., half of all students are now women. Both young female and male physicians are now more focused than ever on the balance of work and life, notably the demands of starting families (all good, in and of itself). And even those graduates whose innate curiosity about the human condition provokes their interest in research must be rigorously trained in research methods and have superior role models and mentors. All too few institutions offer such a structured environment.

Our own institution is among the very few that are relatively privileged with respect to financial resources and commitment to clinical research training. We are taking full advantage of that largesse, but it’s far from enough. As with so many other daunting and durable challenges that our country faces, it is the young who will be most affected. At the same time, that generation has the creativity, commitment, and intellectual energy to address these challenges. My hope is that our nation’s future leadership will deeply engage and inspire our young to rise to the occasion; for us, at the least, that occasion must be a life in clinical investigation.

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

Ordinarily, ER patients aren’t eligible to be organ donors, mostly because of logistical, but also ethical, concerns pertaining to withdrawal of care. But the University of Pittsburgh’s Michael DeVita says, “We have a moral obligation to allow those who want to donate to do so.” The MD professor of critical care medicine and internal medicine is leading a Health Resources and Services Administration-funded project called Condition T (the “T” stands for “transplant”). It’s intended to develop protocols to harvest much-needed transplantable organs, particularly livers and kidneys, after cardiac death in the ER.

DeVita emphasizes that Condition T in no way compromises patient care and involves only patients who’ve indicated an intention to be an organ donor.

Emergency rooms aren’t typically equipped for organ donation procedures, so DeVita has his work cut out for him. “We’re going to need the same level of attention to detail that we use for our living patients,” he says.

DeVita expects to implement a pilot version of Condition T at UPMC Presbyterian this summer. That may serve as a national model.

—Joe Miksch

FOOTNOTE

More than 60 University of Pittsburgh students gyrated, shook their respective tail feathers, and/or got down for 24 consecutive hours in December. Their long-term limbo raised $60,000 for the University of Pittsburgh Cancer Institute. The marathon was part of a five-year Office of Fraternity and Sorority Life effort to raise $500,000 for cancer research.

Participants were proud of the sum raised; turns out though, boogying for 24 can be more demanding than you might think. Pitt student Jeffrey Bergman summed it up for the Pittsburgh Tribune-Review: “Not pleasant.”

CLUE TO SUDDEN CARDIAC ARREST

In 1996, a man was having lunch at his workplace in Erie. Then he fainted. After a series of tests, doctors diagnosed the man with Brugada syndrome, a recently discovered and rare inherited arrhythmia. More than a decade later, after studying the man’s family genetics, the University of Pittsburgh’s Barry London led a team that found the mutation that causes the disease.

London, an MD/PhD who is Pitt’s chief of cardiology and director of the UPMC Cardiovascular Institute, says that the identification of the mutated gene GPD1-L may provide clues to treating all kinds of arrhythmias, which lead to more than 250,000 sudden cardiac deaths per year. He believes the gene plays a role in stabilizing heart rhythm by regulating sodium channel traffic to the cell membrane. Finding other genes that affect rhythm, London says, will lead to a deeper understanding of how the heart keeps ticking in time. —JM
The cause of autism isn't known, but the disorder affects one in 150 children worldwide. For more than two decades, Nancy Minshew (shown above) has sought to untangle autism's complexities. She is an MD professor of psychiatry and neurology at the University of Pittsburgh and directs Pitt's center devoted to understanding the disorder. Her group recently received a $9.6 million National Institutes of Health grant to establish an Autism Center of excellence. We caught up with her this spring after she'd been energized by advances reported at international scientific meetings.

**On recent advances**

There is movement toward identifying a genetic link. Recent studies have found mutations in a number of genes coding for synapse formation and maintenance as well as the formation of neuronal connections. Also, promising progress has been made in possible treatment, with adult mouse models of the disease [in particular fragile-X-syndrome and Rett-syndrome-related autism] exhibiting pharmacologic rescue [the use of drugs to treat genetic problems] in response to emerging drugs. Treatments used in animals are far from a drug used in humans, though. That process can take a long time.

**What we know about how the disorder develops**

There's early overgrowth of the brain in most children with autism. Before you get gross changes in brain size, there are earlier changes that have to go on. If by six to nine months, you're already seeing the acceleration in brain size to the extent it's changing head circumference, the disorder started way before then. The majority of the evidence suggests that it's a disorder of connections of cortical neurons and abnormal development of synapses that starts in the last part of pregnancy and proceeds.

**On the future of autism research**

Just like those with Down's syndrome, each person with autism has a qualitative similarity to the next person but a wide range of severity of expression, and we have to begin to account for that. If you know the why, you can ask, "What can I do to change that?"

**Her question for us**

Why is this disorder not a high priority, an action item for those in positions of influence? It is a serious public health issue. It is a venue for learning about the genetic, neurobiologic, and cognitive bases of human social, communication, and reasoning competencies. — Interview by Joe Miksch

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**Next Generation**

David Chou, a Howard Hughes–Medical Institute–National Institutes of Health Cloister Scholar, is spending a second year in Bethesda, Md. The University of Pittsburgh med student’s research focuses on immune regulation related to infection caused by *Leishmania major*, an intracellular parasite. Chou says his mentor, Yasmine Belkaid, chief investigator of the Mucosal Immunology Unit at the National Institute of Allergy and Infectious Diseases, has inspired him. And Chou plans to maintain contact with other students from the HHMI-NIH program. “You meet 41 other medical students from across the country, and you form a tight bond with that group,” Chou says. “They may very well be future colleagues.”

MD/PhD student Cyrus Raji spoke at a recent Radiological Society of North America meeting on his findings linking hypertension to Alzheimer’s. Raji is in his second year in Pitt’s Cellular and Molecular Pathology graduate program. “I think the main point of the findings is that good heart health equals good brain health,” says Raji, who hopes to identify other preventable and treatable Alzheimer’s risk factors like high blood pressure. Raji loves the puzzle-solving element of research. “It’s like the ultimate Rubik’s Cube,” he says, adding that research also offers “the ability to create knowledge that could impact more people than I could ever see individually as a clinician.”

Kate Dickman wasn’t quite ready to head back to the States at the end of her Fogarty Research Fellowship in Uganda last year. Instead, the Pitt med student accepted a Howard Hughes Fellowship to stay on and continue her tuberculosis research. This year’s project: exploring the prevalence of multiple or mixed infections of TB. For Dickman, research is more than just fulfilling—it has its thrilling moments, too. She recalls the euphoria of first identifying multiple strands in one sample. “I shouted, ‘It’s multiple infections!’ and went running around the lab,” she says. “When things are going right, I get excited and think that maybe I’ll do something worthwhile that might help out a lot of people.”

— Meaghan Dorff
Knocking Down Silos

The five students taking the University of Pittsburgh’s Interprofessional (IP) Health Care Teams Elective looked on, some open-mouthed, as associate professor of surgery Henkie Tan extracted a living donor’s kidney at UPMC Montefiore. IP team member and med student Marc Larochelle helped prepare the kidney before the team, guided by a transplant fellow, rushed the organ to its recipient in Children’s Hospital of Pittsburgh of UPMC.

“We needed to get that organ to the recipient as quickly as possible,” recalls Larochelle’s IP classmate Kristen Shimko, Pitt pharmacy student. “It was educational in a different way than anything else I’ve experienced.”

During the implant procedure at Children’s, Pitt professor of surgery Ron Shapiro tossed questions at the team: “What’s this artery? What’s this structure?” The students—from Pitt Schools of Social Work, Pharmacy, Nursing, and Medicine—conferred with one another as they huddled close to the action, careful not to breach the sterile field.

A few of Larochelle’s classmates had never seen an operation before—watching gave them insight that their specialized educations wouldn’t normally have provided. Larochelle, in turn, reeled at the problem a nutritionist posed on another day: If a hospital’s liberalized diet policy lets a diabetic patient order cake with lunch, his doctor might be the last to know. “I’m definitely more likely to follow up on that issue,” Larochelle says.

A group of faculty representing Pitt’s medical, pharmacy, social work, and nursing schools designed the elective two years ago to promote interprofessional understanding. The professors also structured the course to help students gain a deeper sense of what it’s like to live with chronic illness. This year’s students focused on patients with end-stage renal disease. Course organizers will add a cardiology component next year, as well as another student team.

“Often, you imagine somebody siloed in one role, and it helps to understand the breadth of what they do,” Larochelle says. —MD

Holland Gives Fisher Tribute

James Holland proposes that some breast cancers are related to a virus carried by common household mice. The Distinguished Professor of Neoplastic Diseases at Mount Sinai School of Medicine visited Pittsburgh in February to give the annual Bernard Fisher Lecture, named for the Distinguished Service Professor of Surgery at the University of Pittsburgh.

The incidence of human breast cancer in regions with the mouse species *Mus domesticus* lends support to his suggestion that the human mammary tumor virus (a variant of what’s carried by *Mus domesticus*) should be added to the growing list of known cancer-causing viruses. (See related story on Pitt researcher discoveries on p. 10.)

Fisher himself (MD ’43) overturned the prevailing view that breast cancer was a sequential and orderly disease. Much of that work was done with his brother, recently deceased pathologist Edwin Fisher (MD ’47, see story on p. 38). The Fishers also were at the forefront of popularizing lumpectomy, as an alternative to radical mastectomy, and tamoxifen as effective treatments for breast cancer.

“He’s done more than any other man on the planet to change the outlook on breast cancer,” Holland says of Bernard Fisher, who, he adds, has been a friend for more than 40 years. —JM
After unraveling the mouse genome, scientists made the data widely available. Now you can even find it on Pitt’s Oakland campus. Outside the new Biomedical Science Tower 3 stands a sculpture consisting of 14 perforated stainless steel tubes. Each tube represents a mouse chromosome. Water glides down the tubes, creating a waterfall within each. At night, multicolored lights shine through the perforations. The John C. and Darlene D. Mascaro Water Wall was made possible with a donation from the Mascaro Construction Company. Jack Mascaro, a Pitt engineering grad, is chairman of the company, which was the construction manager for the tower. —MD

Appointments

Paula Davis assumes the newly created post of assistant vice chancellor for diversity for the schools of the health sciences at the University of Pittsburgh.

She is responsible for ensuring that the University’s Schools of Medicine, Dental Medicine, Health and Rehabilitation Sciences, Nursing, Pharmacy, and Public Health attract and retain students and faculty from underrepresented groups.

Davis has worked at the School of Medicine since 1994. In 2005 she became the school’s assistant dean of admissions, financial aid, and diversity.

Derek Angus considers Pitt’s School of Medicine to be at the vanguard in the field of critical care. So when he was offered the position of department chair, he was elated. “This is one of the most important positions in the field,” he says. “Anyone who loves critical care would love to have this job.”

Angus, an MD, has been at Pitt since 1991, when he was appointed assistant professor of anesthesiology and critical care medicine. He has authored or co-authored 137 papers, mostly focusing on the consequences of severe infection, particularly the epidemiology of sepsis and septic shock. He intends to guide research toward deepening the understanding of how the body’s immune system reacts to insults and how the essentially internally inflicted damage of sepsis might be treated or prevented.

Angus also hopes to lead the way in the use of information management systems to help standardize patient care in the fast-paced world of intensive care units.

Minh-Hong Nguyen and Cornelius Clancy have joined the School of Medicine’s Division of Infectious Diseases from the University of Florida. Nguyen, an MD professor of medicine, also serves as director of the Transplant Infectious Diseases and Antimicrobial Management Programs at UPMC. She and Clancy, an MD associate professor of medicine and director of the Mycology Research Unit at Pitt, research the ways in which fungal infections prey on immunosuppressed patients.

The pair is particularly interested in understanding the pathogenesis of, and developing diagnostic tests, vaccines, and drugs for, the common fungi Candida and Aspergillus. These fungi frequently attack, and kill, those with AIDS, as well as patients recovering from bone marrow or solid organ transplants.

Nguyen and Clancy’s work is funded by the National Institutes of Health, the U.S. Department of Veterans Affairs, and the American Lung Association. —JM
NOT SO EASY RIDERS

This is a story of bikes, beer, broken bones, and a satisfying dip in the ocean.

A couple of years ago, Jason Dragavon Dahl, now a third-year University of Pittsburgh med student, left his home in Duluth, Minn., for an impromptu bike ride ... to Girdwood, Alaska. In rural Alberta, a rapid 30-degree temperature increase caused his body to rebel and the resulting crash left him bleeding by the side of the road. Things took a turn for the better when, on another day, a passing motorist left him an iced can of brew at the top of a long, hard climb.

In 2007, Brack Hattler, MD/PhD professor of surgery and executive director of the Medical Devices Laboratory at Pitt, was part of a 40-person ride to raise money for the American Lung Association.

He garnered $35,000 in donations but didn’t see the end of the road; instead he wiped out near Huron, S.D. His fractured skull and pelvis healed, Hattler hopes to try again but says, “I’ll have to negotiate with my wife.”

Second-year student Anita Chang also rode for a cause — Bike & Build, which raises money for affordable housing projects. In May 2007, her group left North Carolina. Two months and 3,400 miles later, she safely dipped her wheels, and her toes, in the Pacific.

— Joe Miksch

To read Hattler’s and Chang’s blogs:
anitasbikeadventure.blogspot.com/
INVESTIGATIONS

Explorations and revelations taking place in the medical school
CONFRONTING
OUR OWN WORST ENEMY

TINY BEADS DESIGNED TO TAKE ON SEPSIS,
THE OFTEN FATAL IMMUNE RESPONSE

BY REID R. FRAZIER

One afternoon, a patient comes into John Kellum's cardiothoracic ICU at UPMC Presbyterian shaking with chills. Lisa Davis, 33, is usually a healthy math teacher. But today she feels like a bus hit her. Davis (a fictional but typical case) developed a cough and fever two days ago. Now she has pneumonia.

By evening, Davis is in a hospital bed with infusion pumps delivering intravenous antibiotics and an oxygen mask pressed over her mouth and nose. Despite the antibiotics she is taking, her husband thinks she looks even worse than she did in the morning.

Inside her lungs, bacteria have been multiplying for the last few days, kicking off a full-blown battle with the immune system. Macrophages, special white blood cells that seek out pathogens, first discovered the bacteria. They sent out signals that attracted chemicals called cytokines (“cell-movers”), which in turn draw other white blood cells to the lungs. But the cytokines inflict a kind of collateral damage on Davis' body. Her brain senses the cytokines and cranks the thermostat in her body to a sweltering 103 degrees— hence her shaking chills. The cytokines also make her capillaries leak. This allows more white blood cells to enter the lung tissue in search of bacteria, but it also causes her blood pressure to drop, as fluids leak out of her blood vessels into skin and soft tissues. If her blood pressure falls too low, her organs could become deprived of oxygen. Davis is in the throes of sepsis, the systemic inflammatory response to infection. In sepsis, the immune system causes most of the damage. It can trigger organ failure and is a rapacious killer of ICU patients. Sepsis is far from a household term, yet every surgeon and intensive care staff member is all too aware of its threat. Sepsis affects more than three-quarters of a million Americans each year and takes the lives of hundreds of thousands of them.

“No one who works in an ICU doesn't want something to treat sepsis better than what we have now, which is supportive care— basically treating the symptoms, and waiting,” says Kellum.

Kellum, a University of Pittsburgh professor of critical care medicine, thinks we can do more for these patients. He'd worked with dialysis patients during his training in internal medicine and began wondering whether some form of blood filtration could remove cytokines before they initiate sepsis. Three years ago, he assembled a team of Pitt docs and bioengineers, received a $5 million National Institutes of Health grant, and got to work.

The early result of their efforts sits on a shelf in Kellum's office in Scaife Hall and looks like something you might get if you used the pneumatic tube at a bank teller's drive-through window. It's a foot-long, clear plastic cylinder. Each end has a screw-on lid with a plug in the middle. Inside the cylinder is a whitish substance—a collection of beads—that, at first glance, resembles grated Parmesan cheese.

It's a souped-up version of a hemodialysis filter, designed to extract toxins from the blood of kidney patients.

Kellum is excited about the beads. He hopes to modify them to absorb the out-of-control cytokines that cause sepsis. “Under a scanning electron microscope, one of the beads looks like a giant sponge. In every gram of the beads, there are 850 square meters of surface area for binding,” he says.

Designing the beads is the difficult part. You don't want to filter out all cytokines—they help white blood cells know where to go to fight an infection, and you certainly want white blood cells to pass through. “Think of the cytokines like trucks in a distribution system,” says William Federspiel, Pitt professor of chemical engineering, surgery, and bioengineering, whom Kellum tapped to help design the device. “We've got to design a system that will regulate which trucks we keep on the road and which we keep off.”

To do that, the team will first have to conduct a traffic study of sorts. Gilles Clermont, associate professor of critical care medicine, is calculating the body's immune response in blood. Clermont wants to measure the amount and type of cytokines the blood normally carries, compared with cytokine levels in the blood of a sepsis patient. Call it "normal" versus “rush hour” traffic. When Clermont's calculations are complete, Federspiel and scientists at MedaSorb, the medical device company creating the beads, will modify the beads' structure to regulate cytokines. Take out a couple of 18-wheelers here, a dump truck there, and, hopefully, the roads will clear. Early results in animals are promising.

“Coming up with a therapy for sepsis would be a huge deal, obviously. This is a process that literally kills a quarter-million people every year, and if you could reduce that by even 10 percent, that would have a substantial impact,” Kellum says.

“Do I think it'll work? I wouldn't have devoted my entire academic career to it if I didn't think it had promise.”

Bacteria like Streptococcus pyogenes, shown left, can kick off sepsis, the overactive immune response. The condition kills hundreds of thousands of ICU patients each year in the United States. A team of Pitt bioengineers and physicians hopes to dampen cases of sepsis with tiny absorbent beads.
Fifteen percent of human cancers owe their existence to the molecular debris field created in the wake of a viral infection. Sometimes, as in the liver cancer that emerges in response to hepatitis-induced inflammation, it’s hit-and-run—no trace remains of the nucleic acids that first derailed cellular function. But sometimes, the virus leaves its tag on every tumor cell it generates. Cervical cancer carries the ghost of the human papillomavirus. Burkitt’s and Hodgkin’s lymphomas give a nod to the wake of a viral infection. Sometimes, as in the case of Merkel cell carcinoma (MCC), the virus that got it started.

The concept isn’t new. Scientists identified the first cancer viral precursor—murine polyomavirus (MuPyV)—in lab mice with leukemia in 1953. Finding such links could provide a critical boost to human health, refining screening, treatment, and public health initiatives. But in the half-century since MuPyV was isolated, and despite massive efforts since the first human tumor-inducing viruses were identified in the early ’70s, just seven viral precursors have been definitively tied to cancer in people.

University of Pittsburgh neuropathologist and professor of pathology Yuan Chang and husband Patrick Moore, an epidemiologist who is a professor of microbiology and molecular genetics, have contributed two to the list. The scientists have devoted their careers to stalking the biomolecular cues that link a tumor to the virus that got it started.

In 1994, they bagged their first: KSHV, a herpes virus that causes Kaposi’s sarcoma, the most common cancer in sub-Saharan Africa and the leading malignancy in AIDS patients. This winter, they did it again, revealing Merkel cell polyomavirus, a double-stranded ring of DNA responsible for an aggressive form of skin cancer known as Merkel cell carcinoma (MCC). Science printed their findings in February. In the past 15 years, no other research group has identified a novel viral precursor to cancer.

Moore credits the couple’s success to the breadth of their collaboration, joking that they have to work together every day just to feed their son breakfast.

Moore sparked the pair’s focus on cancers with a link to the immune system. A healthy immune response generally fends off infections before viral DNA can rewire human cellular biochemistry to fuel tumor growth. Epidemiological analysis reveals the cancer link: Those who develop cancers sparked by viral infection have suppressed immune function, such as the elderly, people with AIDS, and transplant and cancer patients undergoing immune-suppressing treatments.

Now codirector with her husband of the Hillman Cancer Institute’s KSHV lab, Chang saw MCC for the first time as a pathology resident at the University of California, San Francisco, working up a biopsy taken from an elderly man whose cancer had already metastasized. At the time, there were fewer than 500 cases of MCC diagnosed each year. In the past two decades, its incidence has tripled.

“It was a diagnostic problem, because this particular tumor has so many look-alikes ranging from small-cell lung cancer to malignant lymphoma,” says Chang. “The workup to find the right diagnosis was intensive.” Years later, the disease struck a medical student in a class Chang taught. Those two cases made a sharp impression. In 2002, the scientist read a report linking MCC with immunosuppression, a common clue to a viral precursor. She was hooked.

Chang and Moore discovered a virus (MCPyV) that causes an aggressive form of skin cancer. This image shows a similar virus (SV40) as the T antigen binds to the viral DNA. Binding allows the virus to replicate.

Chang and Moore spent the next five years collecting MCC tumor samples with extensive strings of genetic material and sequencing all of it—with an eye to identifying the protein transcripts left behind by viral nucleic acids. To find them, they relied on a technique they developed called Digital Transcript Subtraction (DTS). Using a Macintosh computer and data available from the Human Genome Project, the pair cross-checked tumor DNA with sequences in the database, eliminating anything other researchers had already identified as human.

“That leaves us with a small group of sequences that are errors, previously unidentified, or—if we get lucky—a viral transcript,” says Moore. (The strategy emerged during their inquiry into the epidemiology of squamous cell conjunctival carcinoma—a previously rare cancer now common in Uganda and long suspected of having a viral precursor because of its association with AIDS.) With DTS, Moore and Chang logged two hits: The novel technique disproved the viral precursor theory in the conjunctival carcinoma; it also revealed the nucleic acids at the root of MCC.

The next step, says Moore, is to decipher the protein structure of tumor cells. “Viruses have a vested interest in not letting their proteins degrade,” he says. “If we could look at the proteins and differentiate viral from human proteins, that would be huge.”

Chang and Moore discovered a virus (MCPyV) that causes an aggressive form of skin cancer. This image shows a similar virus (SV40) as the T antigen binds to the viral DNA. Binding allows the virus to replicate.
A TEST FOR TOLERANCE

THE SEARCH FOR A GENETIC CLUE FOR SUCCESSFUL TRANSPLANTATION

BY JOE MIKSCH

Rakesh Sindhi has a proposition: Give him the resources, and he’ll give you a genetic test that can predict a transplant patient’s odds of rejecting a new organ.

Such a tool, the University of Pittsburgh MD associate professor of surgery suggests, will reduce the incidence of rejection from 50 to 20 percent—cutting down the amount of time patients spend in the hospital and saving the health system significant expense. It will also give doctors better guidelines for prescribing antirejection drugs.

Sindhi codirects the Hillman Center for Pediatric Transplantation at Children’s Hospital of Pittsburgh of UPMC. The center believes that Sindhi’s optimism is well-founded, having recently given him a three-year, $300,000 grant to pursue this research. The Hillman Strategic Award funding is in addition to a 2006 $1.1 million National Institutes of Health grant Sindhi received for the genetic fingerprinting project.

Sindhi says current methods of predicting the likelihood of rejection are not bad but imprecise. A doctor might be able to predict that a prospective recipient is likely to reject, but not the degree of the immune response. It’s all but impossible, then, to do anything but guess the level of antirejection drug needed to stave off an immune attack on the new organ.

Too much antirejection drug can be toxic to patients. Too little means the graft won’t survive.

“The question remains then, how do you predict a rejector or a nonrejecter right off the bat?” Sindhi says. If this question can be answered, he says, antirejection medication could be tailored to individual patients. Doctors would immediately put likely rejecters on high doses of antirejection medicine and those less likely to reject on lower doses.

One way to measure the likelihood of rejection is to measure genetic predisposition. Is there a genetic mutation, or combination of mutations, that makes a transplant recipient’s immune system more or less likely to recognize a new organ as a threat and go on the attack?

As genetic information is passed down from generation to generation, it’s common for small mistakes to be made. Let’s say a genetic message is supposed to read, “I love my mom,” and ends up being transcribed as “I love mi mom.” It’s still pretty clear what the message is, despite the error.

“These single alphabet flaws don’t alter the meaning of the code,” Sindhi says. “The majority are flaws that don’t really matter in [terms of] disease origin.”

However, Sindhi says, these inconsequential errors sometimes point to larger sections of garbled genetic code. Perhaps the path to finding genetic variants responsible for rejection lies in these mutations.

Sindhi conducted a study of 150 children who’d undergone liver transplants, as well as their parents. He took 500,000 “snips” (shorthand for single nucleotide polymorphisms; these are essentially revealing snippets of genetic code), looking for mutations common to those who had rejected organs and those who tolerated transplanted organs well. He also recently began genotyping another 250 patients—all of whom had transplants after suffering from biliary atresia, a blockage in the tubes that carry bile from the liver to the intestines—and their parents and plans to replicate the process outlined above. Sindhi chose this group to examine mutations within a stable genetic population suffering from the same disease.

He is looking for variations common among those who reacted well to their new organs and those who struggled to assimilate new organs. The challenges here, Sindhi says, are significant.

“Of 50,000 genes, let’s say 600 turn out to be candidates,” he says.

“There are still a lot of so-called false candidates. If it’s a real variation in the gene, we also need to look for associated changes in the expression of the gene.”

His next step will be to look for genes whose functions are tied specifically to different types of white blood cells (which are key to rejection and tolerance). If he finds a correlation between a mutation in one of these cells and the degree of tolerance, that could mean he has identified a genetic marker.

Sindhi relates this story with the zeal of a true believer. He says he’s sure it can be done. Then he pauses and says a bit wistfully, “If somebody invested $3 million today, I could deliver a first-generation product.

“We have the patients, the technology, and the understanding. It’s purely a matter of investment.”
SHOWTIME

The ovaries of a fertile woman release an egg roughly once every 28 days. Among the billions of cells in her body, this one is an oddball. The largest cell in the body, it is actually visible with the naked eye. With only 23 chromosomes, it’s also a halfling. It will begin to degenerate in about 24 hours unless it melds with a sperm cell—a much smaller and highly mobile chromosome-delivery mechanism—containing a complementary set of 23 chromosomes.

After fertilization, there is a short period of time when this speck of nascent human life is completely unmoored from the mother who will harbor it for the next nine months. The fertilized egg traverses the fallopian tube like a rudderless skiff on a lazy river. The journey can take a week, during which the cell divides repeatedly until it is a mass of a few hundred cells called a blastocyst. It arrives in the uterus untethered—in the womb but not yet of the womb. What happens next is critical. If it does not implant in the lining of the uterus, then there is no pregnancy; the little ball of cells will wither and fade, and nobody will ever know it existed.
Sadovsky's almost seems too big for the unexceptional, temporary office he occupies on the seventh and penultimate floor of the Magee-Womens Research Institute (MWRI) in Pittsburgh. He is moderately tall, with a boyish face and demeanor and wisps of brown curls. He reacts to others with a gentle sort of wonder and interest. He sits at a desk in a brown snowflake-patterned sweater. A round table and two thin chairs are tucked between him and the door with little room to spare. There is one window. With a bit of neck craning, it’s possible to see the two narrow lanes of Craft Avenue below and, beyond, the red brick walls of Magee-Womens Hospital of UPMC. For a recent presentation, Sadovsky says he took a street map and drew a bridge linking the research institute and the hospital.

“1 call it the ‘Bridge over Craft Avenue,’” he says with a smile, liking the dramatic sound of his metaphorical creation. “That's what captures my job here. A virtual bridge of knowledge, education, and translation of discoveries to the bedside.”

Since 2007, Sadovsky has been the scientific director of this institute and the Elsie Hilliard Hillman Professor of Women's and Infant's Health Research in Pitt’s Department of Obstetrics, Gynecology and Reproductive Sciences. For the first time in his career, he does not provide direct care for patients. Instead, he devotes all of his time to laboratory research and the leadership of a cadre of scientists studying the health of women and infants at MWRI.

To the lay reader, Sadovsky's scientific papers—more than 80 since 1992—may as well be written in Sanskrit. He does not publish papers with titles like “Folic acid is associated with fewer birth defects.” His papers bear titles such as, “Microarray-based identification...
of differentially expressed genes in hypoxic term human trophoblasts and in placental villi of pregnancies with growth-restricted fetuses” (Placenta, 2005). Got that?

“What are the mechanisms that the placenta utilizes to respond to these types of injuries?” Sadovsky asks rhetorically. “Some proteins and some pathways we are pursuing actually enhance the ability of the placenta to withstand injury. Or some of them may actually potentiate injury. So, using samples from pregnant women and also using mouse systems, we are trying to understand the effect of the environment on placental gene expression. How do proteins within the placenta either accentuate the injury or mitigate the injury? The goal of this line of research is to identify pathways that we can potentially regulate to improve pregnancy outcomes. Some of these proteins that we are after can be regulated by drugs, so pharmacology is one way to do it. Another is molecular biology—regulation of gene expression by gene therapy, which is not yet here in pregnancy. But I think that a lot of the research we are pursuing right now may lay the groundwork for gene therapy in 10 or 20 years.”

Sadovsky’s scientific peers and colleagues say that they admire his implacable drive to take the most cutting edge-science available and look for ways to move it to real-world applications.

For example, with colleagues at Washington University in St. Louis—his professional home from 1993 to 2007—Sadovsky became interested in a gene that was suspected to be involved in the release of the labor-inducing hormone prostaglandin at the onset of labor. He wrote a grant to study an animal model with this gene knocked out.

“He took the results of those animal studies and applied [them] specifically to humans,” says Michael Nelson, one of Sadovsky’s longtime scientific collaborators at Washington University. “He collected specimens from human pregnancies, including [placental tissues] and studied gene expression and prostaglandin production and came to the conclusion that this gene was a key component of prostaglandin production in both premature and full-term labor. “Then he took it one step further,” continues Nelson, explaining that this was when the drug celecoxib, which inhibits the expression of this same gene, had just gone on the market for arthritis treatment.

“The question was, could [celecoxib] be used safely in pregnancy for preterm labor? So he spearheaded the development of a protocol … It was going to go to a randomized trial to show it was as safe as the other medications that were being used for preterm labor,” says Nelson. Then the Vioxx scandal hit. Both drugs act on the same target, and it suddenly became a nonstarter, despite the fact that they are drastically different drugs.

“Celecoxib is still on the market and doing well,” says Nelson. “It’s just not yet been tested for preterm labor. There are some studies—one of the first ones was the one that Yoel spearheaded—but it’s difficult to do clinical studies in pregnancy because of the concern for the mom and the fetus. The possibilities of adverse effects are untoward.”

Nelson expects studies like Sadovsky’s, plus the slow accumulation of a preponderance of anecdotal evidence that the drug could be safe and effective in preterm labor, will eventually make another trial possible.

In the very first week of his residency, in 1986, Sadovsky was one of several new interns in a gaggle of doctors making rounds in the obstetrics and gynecology department at Washington University. He was 29 years old, with a crown of unruly curls and, in his own words, “a funny accent.” (Born, raised, and educated from childhood through medical school in Jerusalem, Sadovsky had arrived in the United States less than a month earlier.)

The group was to cover each patient on the floor, with the interns presenting some patients and Nelson, a serious and meticulous man who had just recently been made attending physician, going over the management plans with the chief resident and the fellow. In front of one patient, Nelson made a comment about the success rate for women attempting to deliver a child vaginally after having previously birthed a child by caesarean section. But he got it wrong, and the curly-haired new guy with the funny accent knew it.

“He challenged that statement,” says Nelson, who later checked the literature and found that his new intern was correct. “And it was in a very academic way; it wasn’t like he was putting me down. But it was clear that he knew what he was talking about and that he had read the literature—even as an intern, which is pretty amazing, because there is so much to learn.”

“In the first week that I worked with him, I knew he was one of the smartest people I’d ever seen in a residency,” Nelson continues. “I said at that time, ‘I want to work with this guy.’”

Today, Sadovsky seems slightly embarrassed that Nelson persists in telling this story after the 20 years that they have been close friends.
and colleagues. Trying to duck the compliment, Sadovsky shrugs and says, “For him, it was unusual because he is a very knowledgeable person. He also has a very good memory.”

After the four-year residency, Sadovsky undertook a fellowship in maternal-fetal medicine at the University of California, San Francisco, considered the place to train in women’s reproductive health. There, he came under the tutelage of James Roberts, a well-known expert in high-risk pregnancies who ran the fellowship program.

For Sadovsky, who had just completed his clinical training, Roberts was a role model of what it meant to be a physician scientist. When Sadovsky stayed on at UCSF for an extra year to do research, Roberts made an interesting career move: He left UCSF for the University of Pittsburgh. It was 1992, and Pitt had taken the unusual step of creating a research institute dedicated to women’s health. Roberts would become the first director of the Magee-Womens Research Institute.

Within a year of leaving UCSF for Pittsburgh, Roberts tried to recruit Sadovsky to his fledgling institute. At the same time, Nelson was recruiting him back to St. Louis. Sadovsky chose the latter, unknowingly delaying his arrival in Pittsburgh by 15 years.

Nelson recalls meeting up with Roberts at a grant review session that year.

“You won,” said Roberts.

People in Pittsburgh, even within the University of Pittsburgh, may not be aware of what they have in MWRI. It’s now a research powerhouse with a scientific focus that makes it unique in the nation. Established in 1992, it was the first independent research institute dedicated solely to the health of women and infants. Starting from almost nothing, it is now the largest such institute by far. Since 1992, it has brought more than $185 million in project funding to Pittsburgh from the National Institutes of Health and other sources.

The scores of investigators who do the scientific work at Magee have one thing in common, says Sadovsky: a scientific interest in the health of women and infants. Yet their academic homes in Pitt’s schools of the health sciences are all over the departmental map: epidemiology, surgery, oncology, infectious diseases, psychiatry, pediatrics, pharmacology, and microbiology and molecular genetics, to name just a few. Their scientific tools, perspectives, and approaches are equally diverse. Having a group of scientists this large and diverse under one roof with one overarching purpose is unheard of in women’s health.

As an independent research institute affiliated with the University of Pittsburgh, the institute alone is something special. In combination with its partner hospital across Craft Avenue, it presents opportunities for scientists that are otherwise hard to come by.

“It’s the combination of strong research and strong clinical volumes side-by-side,” that is particularly valuable, says W. Allen Hogge, professor and chair of Pitt’s Department of Obstetrics, Gynecology and Reproductive Sciences. Magee is one of the highest-ranked and busiest women’s hospitals in the nation, allowing investigators to easily plan joint projects that include both a basic science and clinical component. “There’s also a huge database of biological samples [such as placental tissue], so it’s one of the few places that all of the barriers that normally get in the way of research that involves clinical and basic science are taken away,” Hogge adds. “The barrier is the width of Craft Avenue, and that’s fairly unique. I don’t know of another place in which the clinicians and investigators are as closely aligned geographically and scientifically.”

Hogge’s department, which includes many of the approximately 90 MWRI investigators, can be considered a boon to the institute, as well. “The department is far and away the most funded ob/gyn department in the country,” he says, “with over $30 million of federal funding. There’s nobody that comes close to that.”

Of the position Sadovsky accepted at Magee, Nelson says, there’s no job like it: “Magee-Womens Research Institute is a unique setup. There’s no question in my mind.”

Sadovsky is motivated by the opportunity he sees in Pittsburgh to change how scientists view the field of women’s health, which he says has long been undervalued. “Many issues that occur in women were perceived as normal physiology,” he says. “Like osteoporosis was considered normal physiology. Women after menopause are a little bit slower, have more fractures, and so forth, and this was considered normal. And a lot of disorders of pregnancy were just accepted as inevitable.”

The field does not have the same prestige as, for example, neurobiology, immunology, or pathology. Young physicians considering the field may be told it’s all about “catching babies” or doing hysterectomies. At a place like MWRI, Sadovsky says, it’s an exciting opportunity to use the best tools that science has to offer in a historically neglected area.

Roberts has left a significant legacy for Sadovsky to build upon. He guided MWRI for 15 years, giving up the directorship in 2007 to concentrate on his own research on preeclampsia, a leading cause of preterm labor. A $31 million expansion in 2007 doubled the institute’s research space. The 70,000-square-foot addition offers stunning views of Pittsburgh’s hills and the Monongahela River, plus open rows of laboratory benches that run the full length of the building—independent scientists can literally take down the walls that separate them and expand or join their labs if they choose to do so.

Sadovsky is pursing a commensurate expansion of core scientific capabilities at the institute. These include a histology core facility staffed with experts able to do detailed analysis of tissue structures, physiology, function, and hormone levels. This is how an incidental finding in something like a mouse with a gene knocked out can quickly turn into a meaningful discovery.

Sadovsky wants to recruit a cadre of mouse experts to populate the institute, too, because the mouse is such a fundamental tool for understanding physiology and the function of proteins. He envisions involving teams of researchers in computational biology from Pitt and neighboring Carnegie Mellon University.

The energy is attracting some existing Pitt labs to set up shop at Magee, as well. A proteomics core from the University of Pittsburgh Cancer Institute moved to MWRI in 2007.

“Proteomics is a cutting-edge, complex technology that deals with understanding protein structure as a means to make predictions of protein function in physiological conditions and diseases,” Sadovsky says. “As you can imagine, both our institute and the cancer institute would focus on gynecological cancers. I think, together, building on technology such as proteomics, we can quickly go a long way.”

Roberts, who once had qualms about leaving the leadership of MWRI to another scientist, admits that he has none now. In 2007, nearly 15 years after he ran into Michael Nelson and congratulated him on his recruitment of Sadovsky to Washington University with the words, “You won,” Roberts bumped into Nelson at yet another professional meeting.

Nelson looked at him for a moment and said, “No. You won.”
James Roberts actually didn’t like doing research. His heart was in the clinic. This may be surprising news for anyone who knows him as the founding scientific director of the Magee-Womens Research Institute (MWRI) and a University of Pittsburgh professor of obstetrics, gynecology, and reproductive sciences and of epidemiology. But that was in the late 1960s, during his residency in obstetrics and gynecology at the University of Michigan, and he felt that he didn’t need any distractions from a job that was demanding enough—caring for the health of his patients.

That all changed during his maternal-fetal medicine fellowship at the University of California, San Francisco. He was given a research project and protected lab time.

“It was thrilling,” he says now. For the first time, he was involved in uncovering mechanisms underlying physiology. In this case, they were looking at the myometrium—the muscle tissue that makes up most of the uterus—of rabbits and identifying the receptors on these muscle cells that were responsible for initiating contractions of the muscle. It led to publication in *Nature*, and the experience of discovery changed Roberts’ direction.

He has now published more than 230 peer-reviewed papers, and his lab is the leading group in the country looking at mechanisms responsible for preeclampsia, a common pregnancy disorder that can cause preterm labor and lead to complications for the mother and child. This spring, a federally funded trial, led by Roberts and aimed at reducing the number of women who suffer from preeclampsia, reached its recruiting goal of 10,000 women.

The scientific work that makes this trial possible began more than 20 years ago, when Roberts and colleagues, including Pitt assistant professor Carl Hubel, submitted a grant proposal based on the hypothesis that a major mechanism for preeclampsia, which is marked by high blood pressure in the mother, could be found in the endothelium, the layer of specialized cells lining our blood vessels.

“Nobody had ever, to our knowledge, made this connection before,” says Roberts. “But it was the kind of thing where, if you gave a talk on it, everybody left thinking it was obvious, as if we’d known it all along.”

The group was funded with what the National Institutes of Health calls a program project grant—several interrelated grants rolled into one—which it had for 20 years now. In that time, the investigators have identified cellular mechanisms and risk factors for preeclampsia, as well as potential interventions. Perhaps most notably, Roberts’ group determined that although preeclampsia is a complex disorder linked to many factors, antioxidants might be able to prevent some women from developing it.

The clinical trial will help determine whether massive doses of nutrients like Vitamin A and E (exponentially higher doses than those found in prenatal vitamins) can stop preeclampsia in some women.

Roberts’ energy has inspired the likes of Yoel Sadovsky, the institute’s new scientific director. Roberts himself is at a loss to explain what he did for Sadovsky at UCSF in the early 1990s, back when he was in charge of the fellowship program. He mentored Sadovsky, but he says that mostly involved steering the promising fellow to labs where other investigators were doing things that interested him. But Sadovsky says that he was at his own moment of transition, and Roberts embodied the role of physician as scientist. It is fitting that Sadovsky took the reins of leadership at MWRI directly from Roberts in 2007. (See related story, p. 12.)

Last year, just as he handed over the directorship of MWRI, Roberts stepped aside so that Hubel could be the PI on the latest renewal of the program project grant. “It was a test for me: Could I stand not being the star?” says Roberts, who is still very much an active investigator in the project. “It felt great.”

“When I was invited to take the job, I came here and found there was no institute except in the minds of a few people,” Roberts says of the birth of MWRI. “I guess we had a little over a million dollars in grants when we started in 1992, and I think we had three basic scientists and maybe 20 or so clinical scientists. And by [2007], I think we were up over $100 million in committed grants and probably 30 or 40 basic scientists, with another 50 or 60 people doing other types of research—clinical, epidemiological, and so on. It’s been very gratifying.

“But now,” he adds with a laugh, “I’m enjoying the opportunity to actually read, and think, and teach.”
“TEST MY BLOOD. I’M NOT A DRINKER.”

When she couldn’t fall asleep at night, she’d take long, hot baths, or sit on the couch, hugging her knees and rocking, rocking, rocking. Her relationships suffered. She couldn’t keep a job. It went on like this, with debilitating pangs of pain surging through Rebecca Newman’s left side, for 10 years.

Worst of all, everyone kept telling her it was her fault.

They said she had a benign little nothing of a cyst in her pancreas, a side effect of chronic pancreatitis. They said the pancreatitis was caused by alcoholism. “Test my blood. I’m not a drinker,” she insisted. They called her a liar.

Other times, they told her she was exaggerating the pain or making it up completely—as a ploy for pain pills, or because she was crazy.
The truth was that Newman didn’t want shots of morphine in those desperate, late-night trips to the ER, or bottles of Percocet from the pain specialists who passed her around like a hot potato. She just wanted the pain to stop.

The pancreas, that tongue-shaped organ/gland below the stomach that neutralizes stomach acid and produces digestive enzymes, is arguably one of the least understood organs in the body. It’s difficult to diagnose and treat, and extremely easy to injure. (“Don’t mess with the pancreas” is one of the three cardinal rules for new surgeons, right behind “Eat when you can” and “Sleep when you can.”)

Historically, pancreatic-disease research has moved at a snail’s pace, ever short on funding and enthusiasm.

Eighty out of every 100 pancreatic-cancer patients will not respond to treatment. Their disease occurs in only about 1 percent of the population, and yet it’s so formidable that it ranks as the fourth-leading cause of all cancer deaths. Precious few survivors are around to advocate for the cause.

Chronic pancreatitis was long considered a disease of drunks. It was shrouded in shame and mystery, and those old misconceptions endure. It wasn’t until 1996 that we knew the real mechanisms behind chronic pancreatitis (a disease in which the pancreas slowly and gradually self-destructs, one painful episode of inflammation at a time) and acute pancreatitis (when the patient suffers a single attack of the inflammation so vicious that sometimes it’s even lethal). It all has to do with trypsin, one of more than 30 digestive enzymes produced by the pancreas.

In all of us, trypsin occasionally activates inadvertently inside the pancreas instead of the stomach, but a protective enzyme disables it. However, in pancreatitis patients, trypsin is mutated and therefore impervious to our defenses.

That breakthrough 1996 study, which was published in Nature Genetics, was led by David Whitcomb, the University of Pittsburgh’s chief of the Division of Gastroenterology, Hepatology and Nutrition; director of the Center for Genomic Studies; and professor of medicine, of cell biology and physiology, and of human genetics. By studying families with hereditary pancreatitis, who make up about 2 percent of all chronic pancreatitis cases, Whitcomb’s group identified the first of several individual genes that were found to cause trypsin to doom the pancreas. (This magazine ran a feature on Whitcomb’s discovery in the January 2002 issue. You can find it online at pittmed.health.pitt.edu.)

The trypsin insight set in motion a kind of domino effect, with subsequent research gradually shedding light on other inflammatory diseases of the pancreas. Whitcomb’s group found that mutations in other molecules that normally protect the pancreas from trypsin also lead to acute pancreatitis. They found that acute pancreatitis leads to chronic pancreatitis, and that any inflammation of the pancreas increases the risk of pancreatic cancer.

They’re hunting for patterns using comprehensive databases to chart UPMC pancreatic-disease patients’ progress on the molecular level, genetic level, diagnostic level, and treatment level. Gradually, they’re discovering how each factor interacts with the next, and how genetic variants change the behavior of the whole organ.

Whitcomb is tall—6’ 2”—which seems apropos. He and the division he leads approach diseases of the pancreas in a big-picture, lay-of-the-land sort of way. Although Whitcomb is known internationally as a geneticist, he’s a physiologist at heart, trained to see genomics more like a means to an end. He speaks in terms of concepts rather than results, much less interested in talking about the next wave of yet-unpublished studies in the pipeline than the extensive body of work his group has published so far in The Journal of the American Medical Association, Gastroenterology, among others.

In one new study, Whitcomb and his group are laying to rest for good the myth of the alcoholic patient. Twenty centers studying more than 1,000 chronic-pancreatitis patients recently found that these patients don’t drink any more than the rest of the population.

In another study, dubbed “SAPS” for Severe Acute Pancreatitis Study, they’re determining why 80 percent of people who come down with acute pancreatitis are in the clear after a couple of days in the hospital while the other 20 percent end up in the ICU fighting for their lives—and what can be done to improve outcomes for the latter.

In other studies, Whitcomb’s group is finding that pancreatic cancer and nonhereditary chronic pancreatitis each have many different kinds of causes, and that each cause is too complex to be sleuthed out by looking at a single genetic or environmental factor. Rather, these diseases result from perfect storms of several genes—many of which are fairly common in the population—combined with environmental factors. So far, they’ve identified four distinct, complex causes that trigger chronic pancreatitis.

Whitcomb believes that for each perfect storm, a specific condition will cause a specific set of abnormal reactions, each requiring its own therapeutic approach.

“Our suspicion is that the treatment that will help one actually makes the other one worse,” he says. “For example in some [pancreatitis patients] we want to reduce the stimulation of the pancreas because the cells that make the enzymes are so sensitive. But in other people we want to stimulate it.”

Pitt has come to be known as a leader in the fields of pancreatic-cancer genetics, early pancreatic-cancer diagnosis, and minimally invasive pancreatic surgery. Members of Whitcomb’s division frequently present at the American Gastroenterology Association meetings and literally wrote the book on pancreatic diseases. Advances in the Diagnosis and Treatment of Pancreatic Diseases, an issue of Gastroenterology Clinics, is due out in June.

Even though diseases of the pancreas are complex, the organ itself is relatively simple. Whitcomb says, “The environmental factors affecting it are simple, the disease process is simple. And, if you have an injury, the inflammation is so intense you know exactly the moment that it started and narrow your number of variables considerably.”

Consider the big-picture, Whitcombian view of what’s ahead: With fewer variables, our odds of cracking the complex codes for problems that affect the pancreas—like inflammatory disease, severe abdominal pain, and cancer—would be that much better. The lessons learned might then be applied to the same problems as they affect other parts of the body. One insight could lead to another, then another—the dominos tumble down.
Herbert Zeh (left and above left) and A. James Moser consult on Pancreas Day, which is every Wednesday.

Last year, a $3 million renovation doubled the size of the Digestive Disorders Center (DDC) in UPMC Presbyterian. Amid this period of tremendous growth, the gastroenterology division refined its approach to running the center.

In the traditional model, on any given day you’d find patients with different kinds of digestive disorders cycling through. A patient would start by seeing a gastroenterologist, who would then refer her to a chain of additional appointments with a dietitian, a surgeon, a pain specialist, a clinical psychologist, then an oncologist and back—and sometimes even to another gastroenterologist with specialized skills.

In contrast, the DDC is organized so that for each patient, a multidisciplinary team collaborates on a comprehensive plan of attack, following it through in the most time-efficient way possible. They do this by focusing on a different set of complex disorders each day of the week. Wednesday is Pancreas Day.

A. James Moser and Herbert Zeh, who codirect the Pancreatic Cancer Center, hold court here each Wednesday. Both are Pitt assistant professors of surgery. Zeh also codirects the University of Pittsburgh Cancer Institute’s GI Oncology Program.

Their temperaments seem to complement one another. Moser brims with optimism, rattling off success stories and beaming about the progress of recent years that UPMC’s exceptional, multidisciplinary approach has made possible. He talks about “an embarrassment of riches,” with all the talent on hand. “In the last year, we’ve been able to bring it together very nicely. It takes a team.”

Zeh, who’s known by his colleagues for his no-nonsense candor, stresses that the hard facts of pancreatic cancer are just as important as optimism. “This is a devastating disease,” he says. “One of my pet peeves is reading articles that overplay what I consider to be modest advances and give people false hope. All of that has to be balanced with a healthy dose of realism.”

On an overcast hump day in January, a computer-filled, Mission Control-type office at the DDC is abuzz with the comings and goings of people with patient folders in hand—blue folders for pancreatic cancer cases, manila for pancreatitis. The room is a hive of specialists, nurses, and patient ambassadors—staff members paired with patients to coordinate scheduling for every single test, procedure, and appointment.

Pausing to chat between patients, Adam Slivka, MD/PhD professor of medicine and associate chief for the division, says the DDC’s new approach is making everyone’s time here more efficient. “A lot of times we don’t need to see [patients] first. If we get their tests first, we can get a lot done more quickly. So by the time they come in here, I can say, ‘Okay, this is what you have. It’s been diagnosed and staged. We generate a game plan and an OR date—boom—all in one office visit. Many patients come from far away, and I think they appreciate that.”

Down the hall in Exam Room 5, patient Brice Kriebel—a wiry 37-year-old with a yellow Lance Armstrong Foundation LIVESTRONG wristband—and his wife, LeaAnn Kriebel, are staying late after their appointment to share their story. They’re glad to do it, they say, because they’ve found very little they could relate to in the eight months they’ve spent surfing the Web since they heard the words “pancreatic cancer,” uttered by Kriebel’s doctor, Moser.

Kriebel lifts his shirt, revealing a long, curved, purple scar across his abdomen. He talks about how active he was before—he had to be to keep up with his former professionturned-hobby: dirt-bike racing. “Endurance racing through the woods for like three hours,” he says, “in the rain and the mud or whatever, or when it’s like 90 degrees out, and you have all that stuff on. I was working out, running my elliptical 40 minutes a day, because I'd planned on racing a lot more this summer. Last time I raced was on Memorial Day [2007].”

The couple exchange a knowing, smiling look—a memory.

“No we’re passing that on to our son,” LeaAnn Kriebel says softly.

“He’s 5. Just took his training wheels off,” says Kriebel, a proud dad.

Kriebel has a lot going for him—the resilience of youth and fitness, the expertise of a vanguard treatment center, a supportive family. Still, he and his wife are aware that pancreatic cancer is notoriously difficult to contain. When it recurs—which it does in 80 percent of cases—it almost always hits the patient somewhere else in the body besides the pancreas. It’s a come-up-from-behind killer.

Hoping to improve his odds, Kriebel participated in a study led by Moser, which is testing a series of neoadjuvants—in this case, chemotherapy agents designed to be administered before surgery. The more urgent issue for Kriebel may not be the initial tumor in the pancreas, but another nascent cancer that isn’t yet big enough to show up on a CT scan.

Thus far, Kriebel and others have responded well. (Moser will present the study’s results to the American Society of Clinical Oncology in June.) Kriebel is down to just two microscopic patches of cancer cells. He’s eating almost normally now, putting on weight, and looking forward to heading back to work next week. He shifts in his seat, a restless athlete benched far too long. “I just can’t stand sitting and watching TV anymore,” he says with a laugh.

Another 37-year-old is waiting in the patient room on the other side of the wall—
Other times, they told her she was exaggerating the pain or making it up completely—as a ploy for pain pills, or because she was crazy.

Newman, whose life for the past 10 years has seemed every bit the classically tragic pancreatitis case. But there's nothing tragic about her demeanor today as she sits sock-footed on the edge of the exam table.

"I love to brag," she says, glowing.

In March 2007, an ER in Altoona, Pa., referred her here. Soon after, Newman had a novel test that originated at UPMC and that is only available at a handful of centers across the country. The test determined that the cyst on her pancreas was the reason Newman had been in pain all those years, not pancreatitis.

In time, her cyst developed into early-stage cancer, and incredibly, the doctors caught it when it was still curable.

"The day I got that test was the luckiest day of my life," says Newman.

In most hospitals, when a CT scan shows that a patient has a pancreatic cyst, the next step is a biopsy, to be analyzed under a microscope—a rather subjective method. A human being decides whether the cells on the slide are inflammatory cells or cancer cells, basing that call purely on looks. Up to 15 percent of the time, the tests are wrong, sending cancer-free patients into dangerous surgery needlessly or cancer patients home thinking they are in the clear.

Sydney Finkelstein, former Pitt professor, came up with a better way. He found that by running biopsies through genetic testing, doctors could spot mutations that allowed them to differentiate between a benign cyst, a precancerous cyst, and a malignant cyst. (Finkelstein left Pitt in 2004 to found RedPath, a company that specializes in molecular-level cancer diagnostics.) Asif Khalid, Pitt assistant professor of medicine, recently completed a seven-center study confirming that detailed DNA analysis significantly improved upon the yield of traditional tests.

Newman shows off the scars from the surgery that cured her.

Instead of one long incision, she has several that are small enough to be covered with Band-Aids. Because her tumor was not too entangled with any major blood vessels, and because it was located in the tail end of the pancreas, Moser was able to perform her surgery laparoscopically. (Such surgery on cysts at the head of the pancreas might be too risky because of its intricate plumbing.) UPMC has performed more than 100 minimally invasive pancreas surgeries. That's more than any other center in the world, more than surgeons have done on the entire continent of Europe.

Newman's story began with years of unimaginable pain and isolation—the hallmarks of everything wrong with pancreatic disease treatment. Yet it offers a glimpse of what the future may hold for pancreatic cancer. The crucial step is early detection.

Randall Brand directs the GI Malignancy Early Detection, Diagnosis and Prevention Program. In the coming months, he hopes to resume at Pitt an optical-analysis project he developed at Evanston Northwestern Healthcare with Vadim Backman of Northwestern University. It uses light-scattering spectroscopy.

His colleagues at Northwestern initially found that analyzing light signatures calculated from the reflection of white light on normal-appearing colonic tissue allowed them to predict whether a patient had an advanced polyp or cancer throughout the colon. Brand took the concept a step further and showed in a pilot study that the technology worked for diagnosing pancreatic cancer. It was able to discriminate between patients with and without cancer with 95 percent accuracy.

Zeh and Anna Lokshin, Pitt assistant professor of medicine, hope to launch another study this year in order to develop a blood test for early-stage pancreatic cancer. Using a technology called xMAP, they'll be able to simultaneously measure the quantity of multiple proteins in a given sample, then apply mathematical processes to hunt for patterns. Their pilot study found that by using combinations of proteins together, they could detect cancer with up to 98 percent sensitivity.

One of the big challenges in early-detection research is access to blood from patients with early-stage cancer. For years, Brand has worked hard to foster collaborations to create a large, common pool of samples. He'll be the principal investigator developing a Pancreatic Cancer Reference Set through the National Cancer Institute's Early Detection Research Network.

"We feel very strongly that we need to collaborate and support promising projects whether we're the ones that came up with the idea or not," says Brand. "Because we want to find the answer."

Wednesdays at 4 p.m., Pancreas Day wraps up with a mass exodus to a conference room in UPMC Montefiore for a meeting. It's a production—20-some people in a darkened room looking at CT scans on one screen, pathology slides on another, and on a third, streaming video of a conference table full of more specialists telecommuting from Hillman Cancer Center. Wednesday is Pancreas Day there, too.

Watching this giant brainstorming session, it's clear why Whitcomb and his colleagues tend to recite the words multidisciplinary team like a mantra and punctuate each statement with something to the effect of, "Yeah, but I'm just part of it—you've gotta talk to So-and-So." Chalk this modesty up to the experience of working through so many patients' stories together, from the start, and in real time.

Or, chalk it up to the humbling facts of the diseases they're facing.

"Most patients who have pancreatic cancer will not survive it," says Zeh.

"The toughest part of my job is balancing realism with hope. ... Each patient comes in at a different level, and each one needs something a little different."

For Newman, it's been a matter of sorting out the long-misunderstood conflict inside her, from crazy to cancer to what appears to be cured. What she needed was to redefine optimism completely.

Last October, she celebrated her one-year anniversary working as an administrative assistant for a trucking company whose name she wears on her sweatshirt. It's the longest she's ever held a job.

"With last week's check I started a 401K," she says. "That's something I never thought I'd have."

For Kriebel, it was a matter of gearing up for the hardest endurance race of his life.

What he needed most was to get rolling.

Kriebel and his wife recall the day they came back to the DDC after he'd finished his pre-op trial. They sat in silence, the tension mounting as they waited to find out where they stood.

"That was the longest half-hour of our lives," LeeAnn Kriebel says.

"But Dr. Moser was great," says Kriebel of that heart-pounding moment when the door finally opened, and Moser smiled and very succinctly told him that yes, the cancer had shrunk and was still quite operable. Kriebel was OR-bound.

"He didn't beat around the bush. He just came in the room and said, 'Are you ready?'"
A few words of advice for those who have urgent business to attend to at the Thomas E. Starzl Biomedical Science Tower when the Biomedical Graduate Student Association (BGSA) has its October research symposium and poster exhibition:

Rearrange your schedule.

Regardless of your intentions, if you walk through the Starzl Tower on that day, you are likely to be sucked into a vortex of more than 125 young PhD-seeking researchers eager to share the details of their budding careers. The enthusiasm of these earliest of early-career investigators is seductive.
So you really should just plan on setting aside some time to learn about the remarkable things these students are thinking about.

These budding basic scientists may not be the type of student that immediately pops to mind when one hears “University of Pittsburgh School of Medicine.” The white coat ceremony, anatomy lectures, rotations, and residencies: This is the path of the medical doctor, but it’s not the path of every student at the school. Wait—med schools produce stethoscope-wielding, tongue-depressor-brandishing doctors, don’t they? Of course, but as Pitt continues pursuing its mission to mold clinicians, the School of Medicine has also placed increasing emphasis on forming bench scientists—especially those looking to find answers in the lab that have significance for patient care in the not-too-distant future. About one-third of the 875 or so students in Pitt’s School of Medicine are pursuing PhDs—more than twice as many as a decade ago. To say that graduate training at the school is burgeoning is almost an understatement.

As this reporter enters the Starzl Tower lobby on a warm October day, students share news of their discoveries with one another amid a warren of posters. Angela Pardee—an enthusiastic third-year immunology student—notices my pause by her display. She pounces.

“I’m working on how costimulatory therapy can induce tumor rejection,” she says, before outlining the process by which the administration of two recombinant cytokines (a kind of signaling compound) caused antitumor T cells (vanguards of the immune system) in mice to be more effective, halting and, in some cases, reversing their sarcomas.

“It looks like we can break immune tolerance to tumors, and that’s the first thing we’re looking for,” she says, adding that the ultimate goal of her research is to develop a new cancer therapy.

“I’m really interested in translational research,” she says, using the jargon for investigations focused toward developing new treatments.

The lesson concluded, this reporter walks away. Then, a few steps later, second-year molecular virology and microbiology student Abigail Boster approaches. She is investigating the role of microRNA in human papillomavirus—caused head and neck cancer. The cycle of friendly, impromptu education repeats.

The school’s Interdisciplinary Biomedical Graduate Program, whose students are part of the BGSA, represents about two thirds of the School of Medicine’s 279 grad students. The rest are pursuing their PhDs in one of five other disciplines: biomedical informatics, neuroscience, integrative molecular biology, molecular biophysics and structural biology, and computational biology.

Two of these programs—molecular biophysics and structural biology, as well as integrative molecular biology—are in their infancy, having hatched in the past few years. A seventh program, in clinical and translational science (made possible by a five-year, $83.5 million National Institutes of Health grant received in the fall of 2006), is on its way to the birthing room.

The School of Medicine has been bestowing PhDs since the 1950s, says John Horn, associate dean for graduate studies and a PhD professor of neurobiology. But of the 500 or so PhDs Pitt has granted, more than 40 percent have been earned in the past seven years, he says. Horn adds that PhD programs have been growing nationwide, but Pitt has made a concerted effort to lead the pack.

“There are some things we’re doing thataren’t unique,” he says. “Having an umbrella program in the form of the integrated biomedical graduate program isn’t unique, but we’ve had it as long as anyone. We bought into it early.” On the other hand, Pitt’s Program in Integrative Molecular Biology—which pairs the School of Medicine with the School of Arts and Sciences—is a rare bird, taking students who’ve had enough investigative experience for them to jump feet first into the study of the most basic biology.

Also, Horn says, the new joint Pitt–Carnegie Mellon University PhD Program in Computational Biology is sort of a reward for paying attention to trends in science: the creation of a novel discipline.

“Students are what virologists might call a ‘vector.’ They take an idea from one part of our community and express it somewhere else.”
“This is a field that includes neurobiology, structural biology, pharmacology, biochemistry, and genetics,” Horn says. “People have taken this [inclusive, cross-disciplinary] approach before, but now it’s emerging as a new, freestanding discipline.” Codifying the field, Horn says, will help Pitt PhD graduates rank among the best equipped to solve biological problems through computational methods.

Wishwa Kapoor, an MD/MPH who is Pitt’s Falk Professor of Medicine and chief of the Division of General Internal Medicine, explains that Pitt’s graduate programs emphasize translational and cross-disciplinary education because the questions being asked by biomedical science are considerably more complicated than they ever have been.

The easy, within-a-discipline questions have been answered, says the man who will lead Pitt’s embryonic program in clinical and translational science. To study the genetic links to congestive heart failure, a researcher would need expertise in cardiac disease, genetics, the lab procedures necessary to analyze genes, and statistics. Although one researcher may not be able to have expertise in all these areas, Pitt’s graduate programs encourage discipline-hopping even as students develop specialties.

The demand for institutions to inculcate basic scientists with the skills necessary to translate their work to the clinic, Horn says, is another factor that’s driven the growth of Pitt’s graduate programs.

A handful of colleagues, Horn reports, have said that perhaps their labs could make quicker progress if they worked exclusively with postdocs or researchers at the beginning of their independent careers rather than students. He disagrees.

“First of all, our mission is that of an educational institution,” he says, “but it makes for a much more vibrant intellectual environment, a more productive one, to have people at different stages of development working together.”

“Students,” Horn says with a laugh, “are what virologists might call a ‘vector’. They take an idea from one part of our community and express it somewhere else.”

After Pardee and Boster explained the ins and outs of their research projects, it’s time to track down Christi Kolarcik, a member of the symposium planning committee. I want to learn who might attempt to corral all this intellectual energy while learning a bit about Kolarcik’s own.

As an undergraduate at Penn State University, Kolarcik was immersed in the world of chemistry. She wanted to go to grad school. Logic dictated that she consider chemistry programs. An undergrad professor suggested she look at Pitt. And she did, though something other than chemistry caught her eye.

“As I was researching programs I found out that I was interested in the translational [that bench-to-bedside] aspect of science,” she says. “I decided I didn’t just want to be in the lab and find out something about a protein and say, ‘That’s great!’ I wanted a program where I could find out what that protein means in the big picture.”

With its university-affiliated hospitals, broad and deep research programs, and expansive clinical network, Pitt’s Interdisciplinary Biomedical Graduate Program lured her.

Kolarcik enrolled in 2004 and hopes to complete her PhD in cellular and molecular pathology in May 2009. Her mentoring professor is Robert Bowser, a PhD in the department of Pathology and Neurobiology whose lab focuses on neurodegenerative diseases, especially amyotrophic lateral sclerosis (ALS). She’s done with classes and has passed her comprehensive exam but still participates in journal club, researching ALS, is learning to craft scientific papers and apply for grants, and, at this moment, shepherds her fellow poster-presenting students. She is busy. This becomes clear when, shortly after this reporter meets her, she seems to disappear into the ether—apparently there’s work to be done out among her peers.

Later on a less hectic day, in Bowser’s lab, where she spends more than 40 hours a week, Kolarcik is in the company of several glass slides containing thin cross-sections of spinal cord. Her omnipresent iPod is turned off in deference to her visitor. With speed and precision, she places the slides into a xylene bath, which erodes the paraffin coating on the sections; sets a timer; and changes her blue latex gloves.

She then grabs a set of slides that have been through the saline treatment, outlines them with a special pen that creates a kind of moat that will hold a solution containing an antibody she’s studying on the slide. She dips the slides into a bath that will block antibodies she’s not interested in from interacting with the sample.

She sets another timer. “Without these, I’d be lost,” she says. “My world revolves around timers.”

As the digital clocks wind down, Kolarcik...
explains her latest project. Some of her slides, taken from the ALS Tissue Bank—which her adviser, Bowser, directs—are from people who suffered from a familial form of ALS. Others are controls who died from non-ALS causes.

She's looking to sort out the difference between how a particular protein—retinoic acid receptor beta (RAR-beta)—interacts with the nucleus of motor neuron cells in each population. It turns out that RAR-beta is present in the nucleus of motor neuron cells in both ALS patients and the control group, but it's much more abundant in the former. Kolarcik and Bowser think that may contribute to cell death and the progression of ALS. Controlling RAR-beta, they suspect, may help ameliorate ALS.

What’s exciting about the work, says Kolarcik, is that there’s already an FDA-approved RAR-beta-related drug for cancer that could hold promise for ALS. Kolarcik is a bit coy about going into further detail.

“I want to be first,” she says, with a smile.

“ALS, I think, has a researcher in me for life,” she adds.

She found out that Colby would extend her stay if she were to find an internship. She called on the Pasteur Institute and was offered a two-month gig in a Nuclear Magnetic Resonance (NMR) lab.

“It was completely different from what I was doing on my organic chemistry track,” she says.

At Pasteur, Zorba was assigned to use NMR, which employs magnetic fields to divine the structure of molecules, to develop an image of a small peptide.

“It was a simple project,” Zorba says, “but I very much looked forward to going to work each day.” She was hooked on NMR. She asked her adviser at Pasteur for the names of a few prominent professors under whom she could learn more about structural biology and biophysics. One name was Angela Gronenborn.

In 2006, Zorba netted another NMR-related internship in Japan. There, she asked her adviser for the names of prospective mentors. Again, Angela Gronenborn’s name came up. Gronenborn is Pitt’s UPMC Rosalind Franklin Professor and inaugural chair of the Department of Structural Biology. Pitt recruited her from the National Institutes of Health in 2004 not only to lead the department, but also to play a major role in establishing the graduate program in molecular biophysics and structural biology.

“If you look at where medicine is going, biomedical science is less about describing phenomena than it is about looking at the more quantitative aspects of what’s happening on the subcellular level,” Gronenborn says. “We’re using the methods of chemistry, physics, and math to look at biomedical problems in that way.”

This approach, she says, means the next generation of treatments and potential cures can be tackled on the most fundamental level. While investigators may understand the “big picture” of many diseases, drilling down to the molecular level of illness and injury may provide new and better treatment targets, she says.

“When I came here for my interview, I found that she’s not only a great scientist,” Zorba says of Gronenborn, “but she has a great
personality and a desire to help students. I also saw that Pitt has the latest equipment available in terms of NMR.” (The 900 megahertz magnet that dwells in the basement of Biomedical Science Tower 3—known as BST3—is one of a handful of such devices in the United States.)

So the program director was great, as was the equipment, but why join a program in its first year?

“I was so impressed by the faculty who were recruited to this program,” Zorba says. “I did think [the program] is very new, and sometimes it’s risky to take that step, but I could see that [faculty] research was very exciting, that the faculty was very experienced and very approachable. And I loved the intimacy the department offered.”

By “intimacy,” Zorba says she means the deeply collaborative environment she found herself in from the moment she arrived on campus. She cites Thursday’s lunchtime lectures as an example. Students, faculty, and postdocs from Pitt’s structural and computational biology and chemistry departments, along with their counterparts at Carnegie Mellon University, assemble to hear a speaker over their midday meal.

“We can learn from the course of [the speaker’s] career,” Zorba says. “And [with the variety of investigators present], I think the lectures help all of us think about our problems on a larger scale.”

Then there are the weekly lab meetings—the record setter went from 2:30 to 8:30 p.m.

“Our lab meetings are not traditional,” Zorba says. “There are no PowerPoint presentations.” Participants take turns critiquing another’s work, Zorba says, and students are fully vested in the process.

In the lab, Zorba has veteran structural biology colleagues to tap for information. And elsewhere in BST3, she has computational biologists, neuroscientists, and others who, she says, are always willing to help.

“Being in this building is like being at a conference. Everything is here, and it’s up to you to take advantage of it, to exploit the opportunities,” she says.

Zorba is attempting to determine the structure of a protein kinase (the aurora-A kinase) involved in promoting the growth of various cancers.

She says that if she is able to figure out what makes the kinase active, it might be possible to develop a drug to deactivate it or to at least inhibit its function, slowing cancer’s spread.

As part of this process, she’s trying to figure out the structure of a terminus on the kinase that has yet to be mapped. Zorba thinks the terminus functions “like an arm waving very, very rapidly.” In doing so, she thinks, it blocks an anticancer drug from attaching to the kinase and doing its job.

She’d like to find a different protein that will bind to the end terminal, putting an end to its relentless waving and allowing the drug to connect with the kinase. Her approach is analogous to removing the goalie from a hockey game and allowing free shots at an open net.

NMR will help her map the domain of the terminus and conduct experiments with the other blocking proteins; the method captures proteins in action.

“It’s exciting. The applications are there, and I think that NMR offers the best picture of what proteins look like in our bodies,” Zorba says. “Right now it’s as close to the truth as I can get.”

Horn expects that Pitt’s menu of grad school options will keep expanding. New ones, he says, will spring from the emergence of new ideas in science that can’t be furthered by existing programs. This is one of those situations, he adds, in which progress is driven from the bottom up: One scientist with a novel way of doing things spreads the word to the greater community, others refine that idea, discoveries are made, and a discipline emerges.

Pitt, Horn says, will keep an eye on emerging fields of inquiry and, in the meantime, will strive to be a medical school that nurtures both ends of the bench-to-bedside path of medicine.
Inside the bright, spacious operating room lies a 40-year-old woman, anesthetized, with her arms spread wide. Her side is being pierced by an aspirating tube used in liposuction. The surgeon pumps the tube into the fat over her oblique muscles. Hard work. He breaks out in a sweat, and after a few minutes, the thin plastic visor attached to his surgical mask is clouded with steam, and he has to take a break to replace it with goggles. The procedure yields a stream of golden, aspirated fat mixed with blood, which flows out into a sterile container.
The atmosphere in the operating room is genial. Pop and alternative music streams from a computer at the back wall. J. Peter Rubin, the attending surgeon, talks casually with the surgical fellow assisting him, Jeffrey Gusenoff.

Later, Rubin will focus intently on the precision work needed during the operation. (This is a routine operation, but Rubin accepts the axiom that “you cannot operate without complications,” particularly in an operation where the surgeon is acting as a tailor, altering the human body.) But during the liposuction, things remain chatty until there are 800 milliliters of fat in the container. Then Rubin starts peppering the nurses with questions and instructions. “Is that stable?” he asks about the container. “We don’t want it to tip over. Is the lid sealed? We can’t lose that. I need to call Dan [his lab technician]—we’re earlier than I thought we’d be.”

If the fat gets contaminated, it can’t be used in research.

“We have to be careful with that—it’s mission critical!” he says, referring to the role the lipid plays in his experiments. “That’s liquid gold.”

(Rubin later notes that, of course, all fat tissue used for research work is done with consent from patients and approval from the University’s Institutional Review Board.)

After a few minutes in the container, the fat floats on top of saline solution in a thick golden layer. Uncontaminated human fat is incredibly valuable to Rubin, because it supplies his research. He believes it will one day be invaluable to many patients, as well. He and others have found that stem cells from fat can be coaxed to become different kinds of tissue. The first paper establishing that fat tissue, technically adipose tissue, held stem cells with such promise was published in 2001, by collaborators at Pitt and UCLA.

“To think about where the field is now is just mind-boggling to me,” says Adam Katz (Res ’01), an author on that 2001 paper who did his research while a resident at Pitt.

Katz, now an associate professor of plastic surgery at the University of Virginia, started his research in 1996. He remembers, “People scoffed at the concept and were incredulous that there would be stem cells in waste tissue like fat.”

Questions remain about the unique aspects of different types of stem cells, including fat stem cells. But researchers have shown that these cells, once called pre-adipocytes, can turn not just into new fat tissue, but bone, cartilage, nerves.

Generally, stem cells have generated more hype than hard facts, more questions than answers. For instance, under certain circumstances, some think adult stem cells (Rubin and Katz study such cells) could become a source of cancer—as suggested by experiments where a stem cell was used to build too many generations of cells. And when scientists recently touted the research community by manipulating normal skin cells to act like embryonic stem cells, concerns were raised regarding whether a certain retrovirus used to implant the cells could cause cancer. Research published in Science in February found otherwise regarding the retrovirus, but more work needs to be done on even this basic question.

On the other hand, researchers have used fat stem cells to kill cancer cells in mice. One thing is clear to Rubin: Fat stem cells, which lie between the cells that actually store fat in our bodies, have promise. While no clinical trials using these cells have yet been sanctioned in the United States, other countries with less stringent and less glacial requirements for approvals have seen exciting developments. In Japan, a group has started a clinical trial to use fat stem cells to engineer tissue for breast reconstruction. In Germany, researchers used fat stem cells to help regenerate the skull of an injured child. In Spain, fat stem cells were used to help repair bowel fistulas in patients with Crohn’s disease. In Finland, fat stem cells were grown into a human jawbone, trumping a German group that used bone marrow stem cells to grow a jawbone, but could not prove that the stem cells had actually done anything.

In this country, investigators have suggested that fat stem cells can create bone and cartilage. Because fat stem cells are adult stem cells (found in adults, not a developing embryo), they skirt the ethical minefield of embryonic stem cells. They appear to have some advantages over other types of adult stem cells, as well. For one thing, they’re easy to get (one Texas doctor demonstrated this by doing a liposuction on himself in front of journalists), so they can be taken from any potential patient, eliminating the risk of the body rejecting them. They also are hardy cells, and plentiful.

Very plentiful. America, a nation used to throwing its weight around, now has problems getting out of its chair. More than two-thirds of Americans are overweight, and one-third are officially obese. Gastric bypass operations, which shrink the stomach and let food move more quickly into the small intestine, have become more common: In 2004, American doctors performed 140,000 such procedures. But what does a morbidly obese person do once he’s lost two-thirds of his body weight?

Extreme weight loss can leave people with enough excess flesh to make an elephant look taut. Rubin, who has become known for re-sculpting such patients, might remove more than 10 pounds of skin and fat from just one person. (His record is 136 pounds; that was from a patient with a giant apron of skin. Such cases are unusual.) Each pound might have 200 million stem cells in it.

Rubin takes some of that extra fat and invests it in what he hopes will become a gold mine of research breakthroughs. Investigators

Katz started his research in 1996. He remembers, “People scoffed at the
can grow into nerves and repair injuries.

Katz says that Rubin's work helped establish that fat stem cells derived from different parts of the body behave differently, and in particular, that stem cells from the abdominal area seem to be the most effective.

His work targeted toward breast reconstruction is one reason why Rubin won the Presidential Early Career Award for Science and Engineering (PECASE) for 2006, one of fewer than a dozen National Institutes of Health–funded researchers so honored. The awards are given to scientists beginning their independent careers and are based on criteria like the quality of research, academic and clinical records, potential to make significant scientific contributions, and community service. Federal agencies such as the National Science Foundation and NIH forward names to President Bush for the honor. The National Cancer Institute recommended Rubin.

"Rubin method, but Rubin himself will have none of that.

On a recent Wednesday—after a two-day stint as a visiting professor at a medical school in Georgia—Rubin starts at 8 a.m. with a PhD student's two-hour preliminary thesis examination. Then he's off to the clinic, where he has 16 patient appointments scheduled. He wears a pinstriped blue suit, a red tie with a red paisley pattern, and a white shirt with red pinstripes and his initials on one of the French cuffs.

He checks his Blackberry at a stoplight. He has an e-mail from a collaborator, Vera Donnenberg, discussing plans for an experiment. She needs, to be blunt, some fresh fat. Rubin thinks he can help—he has an operation scheduled for the next day.

Even in clinic, Rubin thinks research. A patient asks him about having a fat injection, a technique plastic surgeons use to do things like fill in facial wrinkles. He tells her that as much as 40 to 50 percent of the fat could be resorbed—but research he's doing into how to recreate tissue might change that. (On a day this writer tagged along, he talked patients working with other scientists.

"I need to collaborate with people who have a skill set I don't have," he says. "Collaboration is incredibly important. If you bring the right people together, really cool things happen."

One of the nurses comes up to him and reminds him, gently, of the patient. He waits a few moments after she enters the room then follows her in.

By 10 o'clock Thursday morning, the liposuction is done, and the tummy tuck is under way. For tummy tucks, Rubin favors a Number 22 scalpel, a blade that looks like it was designed by Hollywood, tapered like a shark ready to bite flesh.

When Rubin gets ready to sew his patient's belly back together, he stops and says, "Now I'm going to show you something really innovative." He holds up a bit of suture thread. The thread has odd little bumps on it but looks otherwise unremarkable.

The bumps, it turns out, are small barbs. "It will hold in place when you put it in. That's much better than tying knots." He starts sewing the thread into one of the triangles of belly cut off the patient, to demonstrate how it won't budge if pulled in one direction, because of the barbs, but pulls easily out the other way. The technology had been around a while, he says, but it hadn't been applied in plastic surgery broadly until a surgeon at Duke University used it to suspend the skin in a minimally invasive face-lift.

The technique seemed to work well, initially, and got a lot of attention. Rubin remembers attending a session at a conference that was standing room only. Senior-level plastic surgeons there were skeptical.

"They were right. The procedure didn't have the longevity people hoped for," he says, speaking from experience. He tried the technique himself.

That does not diminish his enthusiasm for the thread for other plastic surgery procedures. "It's perfect for wound closure."

The surgeon is a student of innovation. On a shelf in his office sits a book on Robert Oppenheimer.

"They picked him to run the Manhattan Project because he was still young enough to be open-minded about what approach to take," says Rubin. "There were better-
Rubin has tried some of the techniques he has read about. He’s attempted to create a specific place or time to let the creative juices flow, for instance, but that didn’t work so well for him. What does seem to work is talking to scientists with different perspectives, he says.

In weeks when Rubin is in town, he typically blocks out five hours each Tuesday for lab meetings and related activities. Thursday is operating day. But because he only had one operation today, and he was in Georgia on Tuesday, a somewhat impromptu lab meeting is scheduled for this Thursday afternoon.

When Rubin breezes in, still dressed in his operating scrubs, he says, “Where is Han Solo?” a reference to Han Li, who is both to Li, who is investigating whether fat stem cells could more easily yield the kind of pluripotency that scientists recently derived from normal skin cells.

This work, they hope, will build on the jaw-dropping breakthroughs made in 2006 and 2007 by James Thompson of Wisconsin and Shinya Yamanaka of Kyoto University, who both led teams that were able to take run-of-the-mill skin cells and, by adding four genes to the cells, produce what acted like embryonic stem cells. Li is exploring the ability of adult stem cells to do this more easily. His experiments look promising, and he has anticipated several of Rubin’s questions already.

Despite his obvious excitement, Rubin still checks an e-mail on his phone while they talk—he’s monitoring the status of the day’s experiment. Then he shifts back to focusing on the potential for a paper to be done by late spring.

Rubin says, “Have you decided yet on Science or Nature?”

Li laughs and says, “I haven’t confirmed it yet!”

Rubin suggests he move quickly. “Someone else is probably thinking about it right now.”

Rubin didn’t start out wanting to be a plastic surgeon, in part because his father, Leonard Rubin, was an accomplished plastic surgeon who had done groundbreaking work on soldiers during World War II. Like many children, Rubin wanted to do something different than his father. In college, he considered writing or anthropology, but he wound up on track for medical school.

Once there, he found that he loved surgery. And while he strongly considered cardiothoracic surgery, he felt drawn to plastic surgery. At the time, postbariatric surgery was just emerging as a field. Plus, it had a dramatic impact on patients.

“Not only were these cases very technically challenging and very fertile ground for innovating new techniques, but you were also helping people through a truly amazing transition in their lives. People who, a couple of years ago, could hardly walk up a flight of stairs, and now their lives were completely different,” he says.

Rubin links his research with his clinical and operating room time. That combination is an important one, says Adam Katz.

“Peter has been a visionary pioneer in the ‘life after weight loss’ concept.

“He’s pioneered the way to organize it into a clinic and practice and research setting. He’s intertwined a significant health problem with significant clinical challenges with novel basic science research, and he’s

a surgeon and a molecular biologist. Han comes in a few moments later, and Rubin starts the meeting by asking Huaping Tan to talk about his “great news.” Tan is working on developing a biodegradable gel that could be an injectable carrier for the fat stem cells in work that might someday provide an alternative to silicone implants. Tan, who came over from China in January, has achieved something. It’s not clear at first, but with Li translating between Mandarin and English, Rubin and Tan converse. Rubin is excited by what he hears. Tan has developed a compound that won’t solidify too quickly, a major step forward for the project.

“As soon as you can, make some modifications. Maybe in a week or 10 days, maybe we can test some cells,” he says. Rubin thinks this work will certainly yield a meaningful paper, and he’s almost bubbly.

“This is great. This is goodgoodgood!”

Rubin also talks to the other two researchers at the meeting and makes suggestions for both of them to consider. He then turns
### ANESTHESIOLOGY
- Giel, Brian
- University of Pittsburgh Medical Center
- Haselkorn, M. Lee
- New York–Presbyterian Hospital/Columbia Univ.
- Hui, Sijing
- New York–Presbyterian Hospital/Columbia Univ.
- Kelley, Ashley
- Yale–New Haven Hospital, Conn.
- Melhem, Sameer
- University of Pittsburgh Medical Center
- Shah, Vipul
- Beth Israel Deaconess Medical Center/Harvard University, Mass.
- Tarazi, Paul
- University of Pittsburgh Medical Center

### DERMATOLOGY
- Serrao, Rocco
- Wright State University, Ohio
- Stickert, Joseph
- University Hospitals Case Medical Center, Ohio
- Veloz, Nicole
- University of Pittsburgh Medical Center

### DIAGNOSTIC RADIOLOGY
- Donichus, Brian
- University of Washington Affiliates Hospitals
- Laffrery, George
- Yale–New Haven Hospital, Conn.
- Lee, Vincent
- Robert Wood Johnson University Hospital & Saint Peter's University Hospital/UMDNJ–Robert Wood Johnson Medical School, N.J.
- Mezger, James
- University of Pittsburgh Medical Center
- Shiferman, Gennady
- Loma Linda University Medical Center, Calif.
- Thomas, Ernestine
- UPMC Mercy

### EMERGENCY MEDICINE
- Basarab, Jennifer
- University of Pennsylvania Health System
- Fish, Jesse
- University of Connecticut Health Center
- Inamdar, Utpal
- Yale–New Haven Hospital, Conn.
- Knauss, Courtney
- Sentara Norfolk General Hospital/Eastern Virginia Medical School
- Laughner, Julie
- Christiansa Care Health Services, Del./Thomas Jefferson University, Pa.
- Mossar, Drena
- University of Arizona Affiliate Hospitals
- Penn, Joshua
- Brigham & Women's Hospital/Harvard University, Mass.
- Reynolds, Joshua
- University of Maryland Medical System
- Weber, Emily
- Oregon Health & Science University Hospital
- Webster, Benjamin
- Vanderbilt University Medical Center, Tenn.
- Wong, Eric
- Beth Israel Deaconess Medical Center/Harvard University, Mass.
- Yangcina, Anna
- University Hospital/UMDNJ–New Jersey Medical School

### FAMILY MEDICINE
- Arora, Giselle
- UPMC St. Margaret
- Bowers, Shaun
- UPMC St. Margaret
- Leonard, Erica
- Swedish Medical Center/University of Washington
- Lim, Suzy
- San Francisco General Hospital/University of California, San Francisco
- Martinez, Jacob
- McMonigal County Medical Education and Research Foundation/U. of Texas Southwestern at Dallas
- Overlease, Ruth
- University of Colorado Hospital & Denver Health Medical Center
- Rhode, Diane
- UCLA Medical Center, Calif.
- Scopac, Kristin
- UPMC St. Margaret

### INTERNAL MEDICINE
- Adelamin, Adelotun
- Yale–New Haven Hospital, Conn.
- Baker, Matthew
- Rhode Island Hospital–Lifespan/Brown University
- Bayor, Christina
- Rhode Island Hospital–Lifespan/Brown University
- Borling, Jonathan
- Massachusetts General Hospital/Harvard University
- Chuahan, Chirag
- University of Pittsburgh Medical Center
- Christiand, Amanda
- University of Pennsylvania Health System
- Cullen, Nicole
- University of North Carolina Hospitals
- Dekosky, Alison
- University of Chicago Medical Center
- Fisher, Andrew
- University of Pittsburgh Medical Center
- Harris, Drew
- Emory University, Ga.
- Hoffman, Paul
- University of California Davis Health System
- Hu, Douglas
- Beth Israel Deaconess Medical Center/Harvard University, Mass.
- Huang, Alina
- Rhode Island Hospital–Lifespan/Brown University
- Hudson, Matthew
- Rhode Island Hospital–Lifespan/Brown University
- Johnson, Jennifer
- Thomas Jefferson University Hospital, Pa.
- Larson, Jennifer
- Emory University, Ga.
- Lerrutlanakum, Apinya
- McIlwaine Medical Center/Northeastern University, III.
- Mehta, Nihit
- University of Pennsylvania Health System
- Niles, Kathleen
- Emory University, Ga.
- Pabalan, Melissa
- Rhode Island Hospital–Lifespan/Brown University
- Patel, Anuj
- University of Pittsburgh Medical Center
- Pena, Jennifer
- William Beaumont Army Medical Center, Texas
- Prasanna, Vikram
- University of Pennsylvania Health System
- Shah, Alshih
- University of Michigan Hospitals and Health Centers
- Soobae, Kaeby
- New York–Presbyterian Hospital/Cornell University
- Storch, Emily
- Yale–New Haven Hospital, Conn.
- Sultan, Khalef
- University of Pittsburgh Medical Center
- Trible, Ronald
- Emory University, Ga.
- Zeman, Joseph
- National Naval Medical Center/Uniformed Services University of the Health Sciences, Md.

### INTERNAL MEDICINE – PEDIATRICS
- McGaughey, Annie
- University of Michigan Medical Center
- Case Western Reserve University, Ohio
- McTr, Shal
- University of Michigan Hospitals and Health Centers
- Raghuwanshi, Mithila
- University of Massachusetts

### INTERNAL MEDICINE – PRELIMINARY
- Truslow, Russell
- University of Pittsburgh Medical Center

### INTERNAL MEDICINE – PREVENTATIVE MEDICINE
- Gou, Haimin
- Kaiser Permanent Medical Group/University of California, San Francisco

### INTERNAL MEDICINE – WOMEN’S HEALTH
- Gluck, Melissa
- University of Pittsburgh Medical Center
- Silk, Ann
- University of Pittsburgh Medical Center

### NEUROLOGICAL SURGERY
- Chow, Brandon
- Allegheny General Hospital/University of Pittsburgh Medical Center

### NEUROLOGY
- Robb, Jessica
- Strong Memorial Hospital/University of Rochester, N.Y.

### OBSTETRICS/GYNECOLOGY
- Barkett, Kelley
- Fletcher Allen Healthcare/University of Vermont
- Kari, Sofia
- Oregon Health & Science University Hospital
- Patel, Kanoo
- Rush University Medical Center, Ill.

### OPHTHALMOLOGY
- Chang, Diane
- Mount Sinai School of Medicine, N.Y.
- Leath, Janet
- George Washington University, D.C.
- Mokriyati, Emily
- Georgetown University Hospital/Washington Hospital Center, D.C.
- Shah, Veeral
- University of Pittsburgh Medical Center
- Zhang, Amy
- Strong Memorial Hospital/University of Rochester, N.Y.

### ORTHOPAEDIC SURGERY
- Elerman, Jesse
- UCLLA Medical Center, Calif.
- Henry, Sarah
- University of Pittsburgh Medical Center
- James, Eric
- Orlando Regional Healthcare/Fla.
- Urash, Kenneth
- Milton S. Hershey Medical Center/University of Pennsylvania State University
- Woods, Barrett
- University of Pittsburgh Medical Center

### OTOLARYNGOLOGY
- Chai, Raymond
- Johns Hopkins Hospital, Md.
- Yang, John
- Baylor College of Medicine–Houston, Texas

### PATHOLOGY
- Elwood, Hillary
- Johns Hopkins Hospital, Md.
- Franco, Zachary
- University of Texas HSC at San Antonio
- Laguna, Stephen
- New York–Presbyterian Hospital/Columbia Univ.
- Shih, Michael
- University of Utah Medical Center

### PLASTIC SURGERY
- Bielska, Wiktoria
- New York University
- Christian, Nicole
- Massachusetts General Hospital/Harvard University
- Driscoll, Henry
- University of Pittsburgh Medical Center

### PHYSICAL MEDICINE & REHABILITATION
- Games, Anna
- UPMC Mercy
- Hassaini, Shafiq
- University of Pittsburgh Medical Center

### PLASTIC SURGERY
- Saghinomina, Nima
- University of Pittsburgh Medical Center

### PSYCHIATRY
- Biswas, Wiktoria
- New York University
- Christian, Nicole
- Massachusetts General Hospital/Harvard University

### RADIATION ONCOLOGY
- Garma, Arac
- Washington University Medical Center, Mo.

### RESEARCH:
- Jindal, Rishi
- UPMC Division of Plastic and Reconstructive Surgery

### SURGERY – GENERAL
- Chen, Jerry
- Stanford Hospitals and Clinics, Calif.
- Chau, Wen-Ting
- University of Illinois at Chicago
- Klune, John
- University of Pittsburgh Medical Center
- McCarney, Jeremy
- University of Pennsylvania Health System

### SURGERY – PRELIMINARY
- Eidson, Kasey
- University Hospitals Case Medical Center
- Jahn, Shuna
- University of California, San Francisco

### TRANSITIONAL MEDICINE
- Jain, Shorna
- University of Pittsburgh Medical Center

### UROLOGY
- Rappaport, Christopher
- Wake Forest University Baptist Medical Center, N.C.
The Tuskegee Airmen painted their aircraft with distinctive red tails. Inset: Higginbotham in his flight gear as an 18-year-old cadet in Tuskegee, Ala., circa 1945.
A SORT OF
DEFIANCE

SOMETIMES IT'S ENOUGH TO GET BACK
UP IN THE AIR  |  BY CHUCK STARESINIC

Robert Higginbotham was the cream of the crop. The tests said so, and that's probably why he initially reacted with confusion upon being told that his services were not wanted.

The scene was Sewickley High School in April 1944. Higginbotham (MD ’57) was a high school senior who, like many of his peers, wanted to serve his country and make something of himself. He enlisted before graduation. With test scores like his, he was told he could be a cadet in the air corps of either the army or the navy. He took one look at the crisp, white uniform and the gold wings on the chest of the naval officer and chose the navy.

At the front of the line, the sergeant looked at him in the middle of a wide, open field. Higginbotham reacted with confusion upon being told that this fellow airman came in for a landing too close to another plane.

Persistence is a sort of defiance. He followed his brother Mitchell Higginbotham into the U.S. Army Air Corps and boarded a train leaving Pittsburgh that summer. He was bound for Mississippi for basic training. The train stopped in Cincinnati, where he and six of his friends were told to move to one of two cars right behind the engine; they were reserved for Blacks.

That train rumbled south through the night. Somewhere in Tennessee at daybreak, it stopped in the middle of a wide, open field. Higginbotham and others looked around to find out the reason for the stop and saw a group of soldiers ready to board. Everyone in Higginbotham’s car was ordered to move up to the next car, where there were no available seats. They stood from Tennessee all the way to Kessler Field in Mississippi.

In basic training, the soldiers were put through more physicals, tests, and exams that finally ended with a select group of cadets sent to Tuskegee, Ala., to join the now-famed Tuskegee Airmen of the 332nd Fighter Group. Higginbotham was among them.

Formed in 1941, the purpose of the program was to support the Army War College’s conclusion that Blacks were not fit to operate complicated machinery such as aircraft. It was a project set up to fail. It did anything but.

By the end of the war, the 332nd Fighter Group had flown 15,553 combat sorties on 1,578 missions and racked up 150 Distinguished Flying Crosses, 744 Air Medals, eight Purple Hearts, 14 Bronze Stars, and three Distinguished Unit Citations.

Even the training was dangerous. Higginbotham was at the airfield when one of his fellow airmen came in for a landing too close to another plane. Roughly 700 feet off the ground, the pilot drove his propeller into the tail section of the plane in front of him.

The first plane landed safely, but the one that caused the accident crashed, and the pilot was killed instantly.

Nowadays, an incident like this might result in all planes being grounded. But this was 1944. “Automatically, when somebody crashed, everybody was to get back in the air,” says Higginbotham. “You were called out, even if it was 10 o’clock at night. You have to get back in the air, so that you won’t get that feeling that you might be next.”

He was 18, and he had no fear in the air, even after witnessing a crash. As part of their training in PT-17 biplanes, they did loops and spins. They stalled the aircraft, listened to the rush of air as the engine went silent over Alabama, then fired it up again. Flying was absolutely wonderful, he says.

He received his pilot’s license, but the war was over before Higginbotham completed his flight training. He was discharged in 1946, then served two years stateside during the Korean War.

He guarded his G.I. Bill educational support like a precious inheritance. If a term ended mid-month, he would find a way to pay out of pocket rather than squander an entire month of the stipend. He studied civil engineering at Howard University, transferred to the University of Pittsburgh, and signed up for premed when it became clear that engineering jobs were drying up in the postwar period.

Higginbotham received his bachelor’s of science in 1951. When he entered Pitt’s School of Medicine, he was the only African American in his class. On the one hand, he always felt a bit like he was not a part of the class—he studied alone. On the other hand, he has good friends to this day from that class, three of whom he regularly meets for lunch. He points out that the faculty always treated him with respect.

After a few years of family practice, he decided that orthopaedics fit perfectly with his mechanistic interest in civil engineering. He moved with his wife and children to Cleveland for a residency, then on to Southern California, where he began a long career as a general orthopaedic surgeon, eventually serving on hospital boards in Inglewood and heading up the credentials committee in Hawthorne. He stopped performing surgery several years ago and now works one day a week in a clinic.

And he continues to attend reunions of the Tuskegee Airmen, who have received a lot of attention lately, including a feature film; a WQED documentary called Flyboys: Western Pennsylvania’s Tuskegee Airmen (made possible with support from the University of Pittsburgh), in which Higginbotham appears; and a 2007 Congressional Gold Medal.

The things he learned in Tuskegee have stayed with him throughout his life, he says, including the notion that when things appear grim, it’s enough to simply get back up in the air.
When a young breast cancer patient came to Francene Mason (MD ’77) to design a fitness plan, the woman was a self-avowed couch potato struggling with self-esteem after a mastectomy. Months later she was racing her bike up the steepest hill in town—with Mason right behind her. “This is a woman who was too embarrassed to go to the gym, and she did this bike ride in a Barbie-pink sports bra,” Mason says. “At the top, she takes off her bike helmet and says, ‘Look at me. I’m strong. I can do this.’”

Mason is a clinical instructor at the University of Colorado School of Medicine in Denver and medical director of a cancer survivorship program, designing custom exercise and nutrition plans for her patients. She’s also an oncology adviser for Runner’s World and a grant reviewer for the Lance Armstrong Foundation.

On a typical day, Jeffrey Lewis (MD ’82) patients may self-medicate with ceremonial tobacco and smudgings of cedar, sweetgrass, and sage. As head of the Red Cliff Chippewa clinic in Bayfield, Wis., Lewis understands and encourages these alternative remedies. “There’s the question of whether some of the social and economic burdens on the reservation are because of a loss of their cultural connections, so I certainly don’t want to be part of losing that connection,” he says. Lewis serves as both a family physician and palliative care doctor, overseeing four hospices in northern Wisconsin.

When he has a chance, Lewis shares his love of sailing with children who otherwise might not have the opportunity through North Coast Community Sailing, a nonprofit program he launched in 2001.

When a 34-year-old leukemia patient stopped responding to treatment, William Hicks (MD ’74) came to him with an alternative. “I said, ‘Listen, there’s a new drug that’s being tested, but I don’t know how good it’s going to be,’” Hicks says. That patient entered a clinical trial of the drug now known as Gleevec, which blocks the protein that causes abnormal white blood cell production in bone marrow. It worked like nothing else had, and eight stable years passed before financial difficulty threatened the man’s health anew—he lost his job and considered discontinuing the prescription he could no longer afford.

“I wasn’t going to let him drop out,” says Hicks, a professor of clinical medicine at Ohio State University. “We had to gather some forces and get him back in the fold.” Hicks is the principal investigator on a $1.8 million grant from the National Cancer Institute to address the underrepresentation of African Americans and other minority groups in clinical cancer trials. A disproportionate number of Blacks are affected by certain cancers. Hicks codirects Ohio State University’s Diversity Enhancement Program. He put together a video following five patients from diverse socioeconomic backgrounds through the process of clinical trials.
Twelve years ago, Jonathan Gitlin (MD '78) cloned the gene for Wilson's disease, a disorder of copper storage. It was one of many discoveries in his research on developmental nutrition and neurodegeneration.

“When you understand something new about nature and see the potential of it helping someone, you are really exquisitely wonderful,” he says.

Gitlin, a professor of pediatrics and of genetics at Washington University in St. Louis, leaves in June to take over as chair of pediatrics at Vanderbilt University.

The summer after his second year of medical school, David Mallott (MD '78) walked into a windowless examination room in the schizophrenia outpatient clinic at the Western Psychiatric Institute and Clinic. The minute he crossed the threshold, his patient screamed that she was sorry.

“She apologized for yelling so loudly, but explained that she had two heads, one of which was a dog barking loudly. She told me she had to yell so I’d hear her over the barking dog,” Mallott says. “I fell in love right on the spot, and I said, ‘This is the world for me.’”

Although he pursued internal medicine after his MD, Mallott knew he’d end up in psychiatry. “I think whatever we can do for these patients is more than the rest of the world is going to do for them. They are society’s neglected people in all sorts of ways,” he says.

Now the associate professor of psychiatry is also associate dean of medical education and director of the office of medical education at the University of Maryland, Baltimore.

“I didn’t realize at the time just how forward-looking the education at Pitt was,” Mallott says, pointing to Pitt’s focus on biochemistry before it was popular, as well as today’s requirement for independent research. “There are ‘new things’ that people talk about in medical education these days that seem awfully familiar going back to when I was at Pitt.”

Andrew Burger (MD '78) swapped his cap and gown for a wedding tux when he married classmate Mary Fleet two days after graduating from Pitt. After a whirlwind honeymoon, the two plunged into residencies at the University of Connecticut. Back then, he says, the couple learned to use the little time they had together wisely.

After more than a decade at Beth Israel Deaconess Medical Center, Burger recently relocated to the University of Cincinnati, where he’s professor of clinical medicine and associate division director of cardiovascular disease. Burger, whose funded research focused on natriuretic peptides and heart failure, plans to return to the lab after helping to expand the cardiology division at his new home institution.

Though Mary Burger (née Fleet, MD ‘78) did seven years of cardiology research with her husband, Andrew, at Beth Israel Deaconess, pediatrics is Burger’s first love. “I like educating the parents of newborns and trying to show them the things their baby is capable of, that their baby actually has a personality,” Burger says. She is currently the consultant on a National Institutes of Health-funded stroke onset study at Harvard. —MD
When Edwin Fisher (MD '47) started studying breast cancer in the 1950s, there was only one course of treatment—radical mastectomy. He helped change that.

Fisher was a professor of pathology at the University of Pittsburgh from 1958 to 1985, as well as the chief of laboratory services at the VA Hospital and director of laboratories at Shadyside Hospital. Working with his brother, Bernard Fisher (MD '43), he was among the first to show that cancer was systemic and could not be treated by tumor removal alone. The Fishers helped establish that lumpectomy and follow-up therapy worked at least as well as radical mastectomy. Their work led to the use of more systemic treatments like chemotherapy and tamoxifen, which have greatly improved survival rates and treatment options.

“He was dedicated to trying to make some contribution for the betterment of mankind,” Bernard Fisher says. “He helped to transform the way in which cancer was thought about.”

Edwin Fisher died in Florida, where he was undergoing treatment for pancreatic cancer. Throughout the course of his career, he authored or coauthored more than 600 scholarly articles and received numerous awards, including the 1992 Philip S. Hench Distinguished Alumnus Award from Pitt.

Fisher trained hundreds of pathologists at Pitt during the three decades he was on the faculty. For more than 30 years, he also served as principal pathologist for the National Surgical Adjuvant Breast and Bowel Project. —RRF

Frank Dixon was 31 years old when he arrived at the University of Pittsburgh in 1951 as the new chair of pathology. An MD who trained at Harvard University, Dixon brought with him a new experimental technique. He had developed a way to tag proteins with radioactive iodine and trace them through a living organism. He would apply it to autoimmune kidney disorders, helping to establish the field of immunopathology. While at Pitt, he was named the nation’s leading medical researcher under the age of 35 by the American Association for the Advancement of Science. Dixon left Pitt after 10 years to establish the Department of Experimental Pathology at the Scripps Clinic and Research Foundation in La Jolla, Calif. This was the core of what would become the Scripps Research Institute, which Dixon founded and led until 1986. In 1975, he was awarded the Albert Lasker Award for Basic Medical Research.

Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, notes, “He’s a very important person in human biomedical research, because at a time when people were not necessarily making extrapolations from the experimental situation to human disease, the one thing that Frank Dixon was always very passionate about was how a particular process that he was working on relates to real human disease.”

In a 2001 interview, his daughter Janet Dixon Keller said, “The quintessential memory of my dad is climbing up a high peak in the Tetons or Yellowstone—a real challenge—but having him stop on the way and appreciate the beauty of the scenery, maybe put out his hand to quietly draw my attention to a moose. It’s a competition with himself and with that darn mountain, but it’s joyful.” —Leah Kauffman
There’s a lunch box printed with Leonardo da Vinci’s “The Last Supper” in Susan Blank’s office. She noticed, not long after she won it in the holiday gift swap at work, that everyone who saw it invariably opened it.

“What to put into a da Vinci lunchbox that everyone opens? Condoms, of course!” she says. “When you’re a carpenter, everything is a nail.” She snaps the lunchbox shut with a mischievous grin and scurries over to her desk. “And this, of course, is my penis,” she says, picking up a small, phallus-shaped squeeze toy on her desk. “It’s amusing how frequently colleagues stop in and play with it before realizing what they’re doing,” she says, drumming the toy on the table for dramatic effect.

Blank’s career path from aspiring engineer to pediatrician to assistant commissioner at New York City’s Department of Health and Mental Hygiene, where she directs the Bureau of Sexually Transmitted Disease Control, hasn’t exactly been by the book. But her direct approach has helped her make a big impact on the sexual health of the city’s 8 million residents.

Blank (MD ’87) became interested in medicine after spending a few years studying chemical engineering. “I just missed human contact,” she says. She chose the University of Pittsburgh School of Medicine, in part, because of how friendly everyone was. “I didn’t expect to like it, but I did,” she says. Blank decided on a pediatrics residency because, well, it fit her—literally. “The patients are smaller,” she says. (Blank is not even 5 feet tall). Though she’s still a card-carrying pediatrician today, a visit to Tanzania during a clinical rotation drew Blank in yet another direction: public health.

In East Africa, Blank cared for children dying of diseases like measles—infestions that have been all but eradicated in the United States thanks to widespread vaccination programs. Upon returning home, she was shocked to come across parents refusing to vaccinate their children for these same infections. “I just saw these incredible inequities and what seemed like very backward priorities,” Blank recalls. Public health, she realized, was where she really wanted to make a difference.

After her residency and a fellowship at the Centers for Disease Control and Prevention’s Epidemic Intelligence Service (“sort of a disease-hunting group,” she explains), Blank started working at the New York City Health Department, on assignment from the CDC. She remains there today.

From January to September 2007, reported chlamydia and syphilis cases in the city rose by 20 percent compared to 2006. Blank’s team has been tracking down each syphilis case to learn more about the types of behaviors that put people at risk. From these interviews, Blank and her team have found that most of the city’s syphilis cases occur among men—in particular, men who have unprotected sex with other men—and that half are HIV positive. Her department is now working to ensure that city outreach programs target such residents and that providers likely to treat them know about the heightened risk of syphilis. Blank’s department has also launched an online service allowing people to anonymously warn previous sexual partners of potential STD exposure. This year they plan to screen (and, if necessary, counsel and treat) 30,000 high school students for gonorrhea and chlamydia for free.

“We’ve had really a lot of excellent support from the [city health] commissioner and especially from the mayor to do the work that we think is going to save lives,” she says, gesturing to the top of her filing cabinet, where a newspaper clipping of the commissioner’s face smiles back from the front of a Wheaties cereal box. (She decorated it with his picture one day for fun.) “Our successes are premised on hard work and persistence,” she says of her many 15-hour workdays. Then she adds, “and a good sense of humor.”
In September 1925, a man died of septicemia that flared from an infection in the right knee. Records state that the infection arose when he scratched at a pimple with a pin.

In the late 1930s, a man cooking pancakes for his friends ran out of flour. The previous resident had left powdered rat poison in an unmarked bag in the cupboard and, mistaking it for flour, the man mixed it into his batter. His friends scraped by with stomachaches, but, because he ate more pancakes than the lot of them, the cook’s poisoned breakfast did him in.

After a hotel burned down in Homestead in November 1932, neighborhood men Peter and Adam Ratkiewicz and August Brezicki rushed in after the firefighters to hack off pieces of firewood for their houses. They unintentionally chopped into the support beams, and the building collapsed on them.

When a man robbed a single mother of $20 during the Depression, she chased him down the street with a revolver, screaming, “Give me back my shoe money!” Her bullets missed the thief, but she shot five innocents accidentally, she said. The woman turned the gun on herself and discovered that she’d used the last of the bullets. She was arrested.

—Meaghan Dorff

To learn more: www.coronercasefile.pbwiki.com
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MEDICAL ALUMNI WEEKEND 2008 MAY 16–18
Reunion Classes:
1943 1948
1953 1958
1963 1968
1973 1978
1983 1988
1993 1998
2003

SENIOR CLASS LUNCHEON MAY 16
11 a.m.
Soldiers & Sailors Military Museum and Memorial

LEMONADE SOCIAL MAY 16
1:30 p.m.
William Pitt Union Lower Lounge

ALUMNI WEEKEND OPENING RECEPTION MAY 16
5:30 p.m.
Pittsburgh Athletic Association

REUNION DINNERS MAY 16
7 p.m.
Pittsburgh Athletic Association
Classes Dining:
1943
1948
1953
1958
1968
1983

CME LECTURE MAY 17
8:30 a.m.
“Update on Resuscitation 2008”
Peter M. Winter Institute for Simulation Education and Research

ALUMNI BRUNCH & MEDICAL SCHOOL TOUR MAY 17
10:30 a.m.
Scaife Hall

REUNION GALA MAY 17
6 p.m.
LeMont Restaurant

SCOPE AND SCALPEL’S “THE FULL MONTEFIORE” MAY 17, 7 p.m.
MAY 18, 4 p.m.
Hillman Center for Performing Arts
Shady Side Academy
For Information:
WWW.SCOPEANDSCALPEL.ORG

CLASS OF 2008 COMMISSION MAY 19
10 a.m.
Carnegie Music Hall

LEY LECTURESHIP OCTOBER 10
Gary Firestein, MD, Speaker

MUSGRAVE LECTURESHIP OCTOBER 17
5:30 p.m.
Magee-Womens Hospital Auditorium
Rodney Rohrich, MD, Speaker

HOME COMING WEEKEND OCTOBER 23–26
Pittsburgh vs. Rutgers
Saturday, Oct. 25
For Information:
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Thomas E. Cadman (MD ’56) was tenacious. The late doctor (shown here with a childhood chum) played the piano and organ in local churches to help with expenses during his undergrad studies at Pitt. (As far as we know, however, the pup was a kept canine.) He lived at home during med school, commuting on the bus or with his dad’s Studebaker.

He would become a caring and meticulous pediatric neurologist. Today, he’s remembered warmly by colleagues as the dignified doc likely to take a child’s hand and skip down the hallway. Dr. Cadman also looked after Pitt med students, making sure they would have a leg up on the future by establishing the Thomas E. Cadman Endowed Scholarship at the School of Medicine through his estate.

Consider making a planned gift to the school yourself; it can be directed toward scholarship funds or other meaningful projects.

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