Children who play after dark

Put DNA in a new light
A CAMPUS RESPONDS

On Wednesday, September 12, the magazine received this letter from the Chancellor, as did the rest of the campus community.

Stop and Consider! Life is but a day;
A fragile dew-drop on its perilous way . . .
(from “Sleep and Poetry” by John Keats)

Yesterday, we all were reminded, in the most terrible way, of life’s fragile nature. For most of us, as the news arrived from New York and Washington and Somerset, it produced a state of disbelief.

We were stunned that our nation’s security systems could be breached so effectively.

We simply could not comprehend the magnitude of the carnage and destruction. Perhaps more than anything, we were shocked that human beings could deliberately and coldly inflict this kind of suffering on others.

It seems very unlikely that those initial feelings will be changed by the arrival of new information. From what we now know, when a final death toll is released and other damage is quantified, the staggering size of the numbers almost certainly will make this tragedy even more incomprehensible. And, given those numbers, as the news becomes more specific, members of our University community almost certainly will be personally touched by the tragedy, further deepening our collective sense of loss.

In the midst of yesterday’s unfolding crisis, it was concern for others that characterized this community. Certainly, that was true of the members of the University’s staff. Capable and dedicated members of this group quickly mobilized. Over the course of the day and through the evening, they worked to upgrade security, to ensure that there was a smooth sharing of available information, to provide comfort and counseling to those who needed it, and to ensure that essential services continued to be delivered to our students.

A selfless focus on the needs of others also was characteristic of our students. Even as the events of the morning were unfolding, small groups of students periodically came to my office, and I later talked to others on campus. Particularly after the plane crash in Southwestern Pennsylvania, students had some reason to be apprehensive for their own safety. However, in conversations with me and with others, what they wanted most to know was how they could be of help, especially to people in the Pitt community with loved ones who lived or worked near any of the disaster sites.

The fact that the absence of humanity in some could bring out the most generous of human qualities in others is one of life’s great ironies. Looking forward, it also is our greatest source of hope.

Today, we return to what might be called “normal” routines under the most abnormal of circumstances. For the foreseeable future, there will be regular and graphic reminders of the horrors of September 11, 2001, as well as commentaries on how those destructive events have permanently changed our lives. Presumably, there will be ways for some of us to be of help to those dealing most directly with the tragedies, and we clearly should offer whatever assistance we can.

And as we move forward with our own lives, we all should do so with a renewed sense of commitment to civility and to community. Our actions should reflect the fact that we care about and respect each other. We should listen to and try to understand differing points of view. We should actively pursue ways of resolving conflicts that ultimately strengthen, rather than destroy, our common bonds and that elevate, rather than demean, our humanity.

In a sense, there can be no silver lining in a cloud as dark as the one that cast its long shadow across America yesterday. But there are lessons that can be taken even from such a terrible experience. And those lessons, if we embrace them today and consistently apply them in the future, can make this community, this country, and even this world, better places.

Mark A. Nordenberg
Chancellor, University of Pittsburgh

ON THE ROAD

Now the med school is coming to you.
Expect sizzling speakers and significant schmoozing when Pitt comes to your town.
We’re fueling up for programs in Florida (this January), Philadelphia, New York City, and California.
To volunteer to help with a program in your area, contact Jennifer Rellis at 877-MED-ALUM or jrellis@medschool.pitt.edu.

SECOND OPINION
DEPARTMENTS

OF NOTE 3
Fainting may point toward more serious conditions. BioMedical Security Institute established. An ABC health correspondent can’t deny her lineage.

INVESTIGATIONS 8
Students catch the research bug—despite the mosquitoes. Mysteries of a vital cellular process, now appearing in 3-D. When every second counts.

98.6 DEGREES 32
Keeping people healthy at a ripened age.

ATTENDING 33
Dr. Rogers’s neighborhood. Some begin med school sure the MD life is meant for them; others think, Have I lost my mind?

ALUMNI NEWS 36
Angioplasty in Myanmar. Carol Shields explores “black silences.”

LAST CALL 40
Einstein slept here.

FEATURES

Culture Samples 12
Life at a new transplant center in Sicily is like a start-up—a successful one. What students get from rotations there is more valuable than any stock option.

BY ROBERT MENDELSON

The Oval Wave 18
Stewart Sell wanted some answers, so he turned to an assay developed by his sophomore microbiology professor at Pitt. The results helped lead to his spending the next several years challenging conventional wisdom about the root of liver cancer.

BY REBECCA SKLOOT

Challenging Cowboys 22
It’s a good thing that the late Niels Jerne, Nobel prize winner and former Pitt prof, didn’t let bed bugs or James Watson deter him. Some say the task of describing the biology of the immune response for the past few decades has been a matter of refining his ideas.

BY ERIKA LLOYD

Moonlit Research 26
DNA requires constant tinkering to stay in smooth running condition. When its maintenance contract wears out, there’s trouble.

COVER STORY BY EDWIN KIESTER JR.
As I write this, on September 11, 2001, I’ve just learned that nine MedEvac helicopters en route to the United Flight 93 crash in Somerset County have turned around. The well-equipped Pitt emergency personnel on those copters had received word from Somerset’s local emergency services professionals: No survivors. There’s nothing you can do.

That thought numbs. “Doing nothing” is antithetical to the constitution of the professionals on those helicopters, just as it is antithetical to the American mind-set. What tomorrow will bring, we don’t know, except this: There will be many, many heroes. I expect that more Pitt people than I could hope to trace have already found ways to lend their talents at this horrific time.

As we welcomed the Class of 2005 this August during our annual White Coat Ceremony, I reminded them that they are entering the medical profession during an unpredictable era, and that they will be counted on for their strength and creativity. A small consolation is that those challenges appear more manageable in light of what we will likely soon face together as a nation. Still, the climate could be defined by a series of paradoxes, which are both stark and daunting: About 45 million people in the United States have no health insurance and very limited access to health care. Most of these 45 million work full-time. Further, the cost of health care continues to rise, largely explained by the cost of drugs, litigation, the nursing shortage, and the very costly focus of care on the end of life, rather than on care for infants and children. And managed care, though it has devoted a needed emphasis to evidence-based medicine and to prevention, has turned out to be excessively bureaucratic and expensive. The university itself is fraught with paradox: Academic physicians have found less time for scholarship and teaching as solvency issues of academic medical centers demand that they increase their clinical productivity. Moreover, while the promise of biomedical research now is almost beyond imagination, that promise stands to be compromised by the political process (both a strength and a weakness of our particular form of government). Finally, the need for physician-scientists has never been greater, yet the ever-growing debt of our graduates decidedly dampens the appeal of a research career—or a career in primary care.

During this summer’s White Coat Ceremony, I also let our students in on a secret. Though the white coat is a somewhat new tradition for physicians—dating back 120 years to when doctors first embraced science and the uniform of the lab—taking part in a fecund scientific community is not the MD’s greatest honor. The true privilege of donning that symbolic coat is being invited into another’s life, hourly and daily. Once invited to bear witness to our patients’ stories, we are humbled to reflect on our own mortality and reconsider whether we are living lives that are true to our own potential. That message has just been tragically reinforced as we are again reminded that the veneer of our civilization is thin indeed.
OCTOBER 2001

3

O F N O T E

Devoted to noteworthy happenings at the medical school . . .

To stay abreast of school news day by day, see http://www.
health.pitt.edu

MONKEY SHINE

Gerald Schatten got a lot of attention last winter. That's when the media learned he had inserted a jellyfish gene into the egg of a rhesus monkey, leading to the birth of the first genetically altered primate. (The monkey doesn't glow; the hope is it will produce fluorescent proteins that are easy to track.) Schatten arrived at the University of Pittsburgh School of Medicine from Oregon Health Sciences University in July. He is a professor of obstetrics, gynecology, and reproductive sciences. At Pitt, he hopes eventually to develop primate models of select diseases. For some illnesses, he explains, mouse models have limited usefulness. Breast cancer is one such disease, because mice don't have monthly menstrual cycles and their mammary tissue is unlike that of humans. The scientist will also examine a dizzying array of other issues, including the age-old question of nature versus nurture. By splitting monkey embryos to create identical twins, triplets, and quadruplets, he will be able to observe how genetically identical monkeys develop in different environments. Schatten will direct the new Pittsburgh Development Center, which is part of the Magee Womens Research Institute; it focuses on areas such as reproduction, stem cells, and transgenics. —DH

BIG TOBACCO PAYS

The revelation that tobacco company staff knew smoking was a health risk as early as 1960 was one of the more dramatic moments during the lawsuit against the tobacco giants. Now that the industry has signed the first checks in compliance with the multistate master settlement agreement, Pennsylvania will award about $9 million to the University of Pittsburgh each year for biomedical research. Those millions will be invested in research infrastructure, cancer research, “new biology” programs, and biotechnology applications in the wake of the Human Genome Project. Pennsylvania is one of the few states allocating all of its settlement money to health care and research. —MH

As we were finalizing this magazine, America awakened to a heartbreaking new reality. We are sure that many Pitt people were touched by the recent events, through personal loss, in mobilizing to ease the suffering, or in other profound ways. We encourage you to share your September 11 story.

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The first genetically altered primate is developing with a jellyfish gene.
BEYOND SMELLING SALTS
BY DOTTIE HORN

Almost a third of adults report having fainted at least once in their lifetime—it’s a common problem seen by internists, cardiologists, and neurologists. Last year when the New England Journal of Medicine wanted a review article on fainting, it turned to Wishwa Kapoor. He is the Falk Professor of Medicine at the University of Pittsburgh School of Medicine.

Kapoor’s December 2000 article guides physicians through the process of determining the particular cause of a patient’s fainting. It’s an important issue, Kapoor asserts.

When someone faints, it’s because blood flow to the brain suddenly decreases or briefly ceases. More than half the time, people faint in situations involving anxiety, panic, pain, extreme heat, or other stressors. Blood pressure or heart rate drops suddenly because of a reflex, in the same way that an adrenaline rush results from a reflex. This is called vasovagal syncope, and is generally not indicative of underlying disease. (Syncope is the medical term for fainting.)

In other cases, fainting can result from medications or can be symptomatic of serious or life-threatening heart disease. Conditions such as arrhythmia and arteriosclerosis can disrupt blood flow to the brain and cause fainting. “There are conditions such as aortic stenosis, which is narrowing of the aortic valve, in which syncope can be a precursor to sudden death,” says Kapoor. “The next time the patient has syncope, he may not wake up from it—may die suddenly.

“What’s critical for people to know is that if they’re on medications, or if they have heart disease, they should talk to their doctor if they faint,” he says.

Faculty Snapshots

Five percent of women of childbearing age stop menstruating or have very irregular periods, even though their reproductive system is physiologically normal. The condition is called functional hypothalamic amenorrhea (FHA). Over the long term, it can cause bone loss and affect fertility and brain function. Sarah Berga, a professor of obstetrics, gynecology and reproductive sciences and of psychiatry, has found that women with FHA have higher-than-normal levels of the stress hormone cortisol. She treated an FHA group with cognitive behavior therapy and dietary counseling to reduce stress and improve nutrition. Six of the seven women treated began menstruating normally within the study period of 20 weeks.

Young males from families that have abused alcohol for generations have differences in their brains that make them prone to abuse alcohol themselves, according to a recent study by Shirley Hill, professor of psychiatry, psychology, and human genetics. The brain differences are in the amygdala, a walnut-sized structure that has already been linked to other addictive behaviors, including cocaine use and gambling. Hill’s study was published in the June 1 issue of Biological Psychiatry and was profiled in the New York Times.

Pharmacology faculty members John Lazo and Radosveta Koldamova have found that Apolipoprotein A-1 (Apo-A), which occurs naturally in the body, binds to a protein associated with Alzheimer’s disease, called amyloid beta. Increasing the amount of Apo-A in blood may reduce levels of amyloid beta in the brain and may benefit Alzheimer’s patients. One way to raise Apo-A levels is through diet; fruits, soybeans, and coconut oil are among the foods that can stimulate cells to produce more Apo-A, according to Lazo. The study was published in the March 27 issue of Biochemistry.

Simon Watkins, professor of cell biology and physiology, and collaborators recently discovered a new protein (shown right), which they named desmuslin. It interacts with dystrobrevin, one of a complex of proteins that in turn interacts with dystrophin, the protein whose absence causes Duchenne muscular dystrophy. Watkins used a technique called immunoelectron microscopy to provide high-resolution images of single molecules. The research was published in the May 22 issue of the Proceedings of the National Academy of Sciences. —DH
Icons and Placebos

_The Agnew Clinic_, painted by Thomas Eakins in 1889, is considered an icon of the progress of surgery. It depicts Philadelphia surgeon David Agnew (solitary figure on left) just after he has completed a mastectomy. According to Maarten Ultee, a historian from the University of Alabama who gave the annual Mark M. Ravitch History of Medicine Lecture at Pitt, Agnew appears here as a brilliant angel. Yet, his operations for breast cancer were rarely a triumph. “You, the viewers of the painting, would be misled if you thought Agnew was trying to effect a cure,” said Ultee. “Agnew provided palliative or placebo surgery.” He believed mastectomies shortened rather than prolonged life and performed them to improve the morale of patients, even though he calculated that one in 10 died during the operation from loss of blood and none was cured. “Why did he operate? Because his patients demanded it,” said Ultee. —DH

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**B I O M E D I C A L  S E C U R I T Y  E M P H A S I Z E D**

Known instances of the attempted use of biological agents to inflict harm have been few and far between on American soil. The threat, however, is real according to federal officials. Technological advances in the handling and dispersal of agents employing viruses, bacteria, or toxins have spurred deep concern in public health and other circles. So have intelligence reports throughout the past decade of hidden stockpiles.

At Pittsburgh’s new BioMedical Security Institute—an ambitious University of Pittsburgh/Carnegie Mellon University collaboration—faculty members are helping the nation take precautions against potential bioattacks. Much of their work also will be translatable to naturally occurring biothreats such as West Nile Virus. Pitt researchers, for example, are creating systems able to detect and analyze, in real time, possible clues of outbreaks that range from increases in toilet paper sales to upper respiratory infections reported.

The institute, which was established last fall, is funded by the Centers for Disease Control and Prevention and the Agency for Healthcare Research and Quality. —EL

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**F L A S H B A C K**

As a rheumatology fellow, Alexander M. Minno, MD ’47, worked next door to Philip Hench, MD ’20, at the Mayo Clinic, where Hench discovered cortisone. One day Hench suggested that they catch a Western at a local movie theater. The name of the flick escapes Minno today, and Hench probably wouldn’t have remembered either: In the middle of the shoot-em-up, Hench’s wristwatch alarm went off; he stood, announced he had another appointment—then left his astonished guest.
Thwarting Head and Neck Cancer

Traditional chemotherapy saves lives, yet since it affects both tumor cells and healthy tissue, patients experience side effects such as hair loss and bone marrow suppression. Molecular targeted therapy allows for a drug to be more specific, affecting the tumor, but sparing other cells. Dong Moon Shin, a professor of hematology/oncology and otolaryngology at Pitt’s School of Medicine, is a leader in developing molecular targeted therapy against head and neck cancer.

Shin, who came to Pitt this year from MD Anderson Cancer Center in Houston, Texas, now codirects the Head and Neck Cancer Program with Jennifer Rubin Grandis, MD ’87. In this role, he plans to emphasize three areas of research for the program: molecular targeted therapy, the preservation of organs affected by head and neck cancer, and chemoprevention. Of the 40,000 people in the United States who are diagnosed with head and neck cancer each year, most have a history of long-term, heavy exposure to tobacco or a combination of tobacco and alcohol. Shin is helping to develop drugs that may prevent head and neck cancer in this high-risk group. Such agents may also help those who have survived head and neck cancer.

“If you survive the cancer, and even stop smoking and drinking, the chance of developing a second head and neck tumor gradually increases every year, by four to six percent,” says Shin. —DH

FOR MORE INFORMATION:
http://www.upmc.edu/NewsBureau/upci/bio_shin.htm

SUPERCALIFRAGI-COURSE

The expertise of 4.5 thousand scholars from across the globe is now online at Supercourse, a website created by Ron LaPorte and Akira Sekikawa, both professors of epidemiology at the University of Pittsburgh. The site offers free access to hundreds of lectures dealing with medical and public health topics, with more being added regularly.

Supercourse—the site is also known as Epidemiology, Global Health, and the Internet—means that anyone with online access can refer to lectures on topics such as type 2 diabetes in Japanese Americans or AIDS in Africa. Contributors to Supercourse hail not only from far-flung corners of the world but also from the Centers for Disease Control and Prevention, National Institutes of Health, and Pitt’s School of Medicine. —EH & SD

FOR MORE INFORMATION: http://www.pitt.edu/~super1

A 45,000 square foot “green design” building erected on Pittsburgh’s South Side (left), next to the Hot Metal Bridge, will soon be the site of hushed “Eurekas!” It’s the new home for the medical device component of the McGowan Institute for Regenerative Medicine, an organization born out of the McGowan Center for Artificial Organ Development. Investigators throughout the expanded McGowan Institute will be teasing apart possibilities of using biological building blocks (like stem cells and genes) as well as bioengineered solutions for repairing and replacing tissues and organs. Collaborators from the Center for the Neural Basis of Cognition will also pursue research in the new South Side building.
As far as Nancy Snyderman, Res ’83, knows, her grandmother was the first woman in her family to hold down a job. There was no way that lady was going to just sit and worry about how to stretch the little money her family had. So when her husband went to work, she would sneak out during the day to make extra cash as a milliner. She scooted home just in time to put dinner on the table. Her husband eventually found out. And he didn’t like the idea of his wife making hats or holding any job. *This has to stop,* he told her. She said she understood, then kept working anyway.

The women in Snyderman’s family have a strong sense of self.

In the ‘60s, her mother planned a getaway with some girlfriends. This wife of a prominent otolaryngologist in Fort Wayne, Indiana, had decided, after years of attending to four children and a husband, she would attend to herself for a weekend. Her husband declared, *No,* she wasn’t going. *Her place was with her family.*

Yes, Snyderman’s mom went anyway (after stocking the fridge with meals and securing a sitter), which incensed her husband. He conspired to embarrass her on her return by lining up his children at the airport with forlorn homemade signs; little Nancy’s said, *“Mommy, Mommy, why did you leave us?”*

It’s a good thing that Mrs. Snyderman has a sense of humor.

Nancy Snyderman takes pride in this lineage of folk full of “piss and vinegar” in their veins, as she puts it. Like her mom and grandma, she doesn’t get tired, which may, in part, explain her success: Snyderman is known to millions of *Good Morning America* viewers and *Good Housekeeping* readers as a medical reporter, is a best-selling author, and has a surgery practice in San Francisco, California.

It was no surprise to anyone that Snyderman became a doctor. Her father had taken her on rounds since she was a girl. She attended med school in Nebraska, then came to Pitt for her residency. As much as she admired her father, Snyderman had decided not to become an otolaryngologist. Pediatrics was her chosen specialty, and that was that.

During an Eye and Ear rotation, she realized that otolaryngology must also be in her blood, as part of that vinegar concoction, perhaps. She speaks of training under Eugene Myers and Jonas Johnson as a gift.

She remembers one time Myers called all his residents together. Something was up. Myers never arranged a meeting just to check in. It turned out, not everyone’s performance on the inhouse exams was acceptable. *I’m accused of having favorites,* she recalls him saying, *and I want you to know that’s right. Those of you who work hard are my favorites.*

“*I got it,*” she says. “*I busted my chops for him, and I got paid back in spades. You just couldn’t have had a better residency.*” She’s now a head and neck surgeon, which is, she says, the best job in the world. And she’s able to help more people than she ever imagined as a public personality. In her TV appearances, books, and speaking tours, Snyderman teaches women about their bodies and how to care for themselves in other ways. Some of this, she’s still figuring out herself, she confides: *I think it’s analogous to being on an airplane. When the flight attendant says, grab your oxygen mask first then give [oxygen] to those around you, we nod, but we don’t do that as women.*”

Growing up, Snyderman was told that because the snooty daughters of doctors had horses, she would not. But now, during Marin County’s early hours, Snyderman can be found running one of her horses, guiding it without getting in its way, keeping in mind what every good rider knows: The key is remembering to breathe.
INVESTIGATIONS

Explorations and revelations taking place at the medical school
If it hadn’t been for the mosquitoes, Lestina Clay, MD ’04, might have thought she was in heaven. The University of Pittsburgh medical student was one of 24 who capped off their first year of med school by jumping on a plane, the day after finals, to travel to an island off the rugged coast of Maine. They were there for a week to dive into basic science research.

The beauty of the setting dazzled Clay—the laboratory is right on the shore. But what put the whole experience over the top for her was the drama that unfolds bit by bit, every day in the labs of intent researchers: the satisfaction of asking a good question, hanging in there until you have an answer, talking over what the results mean with your colleagues.

The trip itself—to Mount Desert Island Biological Laboratory (MDIBL), a working retreat on Salisbury Cove, near Bar Harbor and Acadia National Park—was an experiment. Ray Frizzell and Mark Zeidel organized and developed the curriculum for the intensive laboratory experience. “This is part of a larger initiative that we’re developing to stimulate more students to go into research,” says Zeidel, chair of the Department of Medicine.

The decline in the number of physician-scientists—those who will combine clinical practice with research—is cause for concern nationally. “There are often barriers to people becoming involved in research,” says Frizzell, chair of cell biology and physiology. Some of it is economic—a med student’s debt burden and the uncertainty of research funding play roles. Many times, students just might not have had a chance to catch the bug. “They don’t know where to start,” says Frizzell.

Clay is a prime example. She majored in social welfare at the University of California at Berkeley, and her exposure to science was limited to the courses she took in order to apply to medical school.

“I had never done research before,” she says. “I had no idea what research even meant.”

The week on Mount Desert Island would change that.

Study days began early and ended late, often stretching until midnight. Throughout the week, students worked in teams that moved through three lab rotations, each related to the polarized epithelial cell. It’s no accident that MDIBL is perched beside the Atlantic. “Fish tissues resemble parts of our organs, such as the kidney,” says Zeidel. “But the fish tissues are big. The cells are big. And the effects are huge. So, it allows you to study it easily.”

In one project, students worked with frog eggs to study protein expression (specifically epithelial ion channels); this allowed them to consider how protein structure affects function within a specific cellular system. In another, they perfused a shark rectal gland to measure the effect on salt secretion from the gland. After many hours in the lab, the students would present their findings the following day.

There were discoveries—both scientific and personal. Witness the triumph of Hameed Aziz, MD ’04. One of the highlights of his week was when his group, after a 13-hour-day in the lab, discovered a protein in a shark. They named it “sunc-18,” since it’s analogous to a protein called “munc-18” found in mice.

There was also the realization made by Josh Olstein, MD ’04. “The week opened my eyes to how much work goes into a discovery,” says Olstein. “It’s easy to take it for granted when you’re just given the results.”

And there were intangibles—time spent in beautiful, rustic simplicity (even the lab walls were knotty pine) and the collegiality among faculty and students.

“It’s important for students once in a while to be able to have an easygoing conversation over breakfast, lunch, dinner, with a mentor, someone who can provide guidance,” says Allyson Pitt, MD ’04.

Clay’s final impression? She has caught the bug—as long as the mosquitoes stay out of the lab.
10

DEFIBRILLATORS GO PUBLIC

BY EDWARD HUMES

John Dellorso, a veteran of the Korean War, marched in a Memorial Day parade this year in Canonsburg, Pennsylvania, proudly carrying the colors of VFW 191. He felt good afterward, maybe a little tired. Then, while riding away from the parade in his car, he collapsed from a sudden cardiac arrest. His heart had stopped beating.

At that moment, a statistical clock began to tick. Four to six minutes following collapse, most people will suffer permanent brain damage; at the ten-minute mark little hope is left for survival. Ninety-five percent of the victims will die. Virtually the only way to save someone in sudden cardiac arrest is by using a defibrillator, which gives an electrical shock to the heart. The sooner the shock is given, the better chance there is of restoring normal rhythmic beating. “Every minute, every second, counts,” says Vincent Mosesso, MD ’88, assistant professor of emergency medicine at the University of Pittsburgh.

When someone collapses from cardiac arrest, bystanders should call 911 and begin CPR, which plays the crucial role of buying the victim more time, circulating oxygenated blood throughout the body and keeping cells alive, in the hope that medical personnel will soon arrive. But after a call to 911, it typically takes six to eight minutes for an ambulance to arrive on the scene with a defibrillator. For many, help does not arrive soon enough.

Mosesso, medical director of Pitt’s new National Center for Early Defibrillation (NCED), believes earlier access to automated external defibrillators, AEDs, would save lives. Police often arrive at the scene of a sudden cardiac arrest before emergency medical services (EMS), so in 1992, Mosesso began a study involving police officers in the South Hills of Pittsburgh. He gave the officers AEDs and trained them in their use. During the three-year study period, police officers were asked to use the AED if they arrived first on the scene. When those police applied the shock, patients survived in 26 percent of cases. They received the shock a mean time of 6.8 minutes after the call to 911. When EMS arrived first, patients survived 10 percent of the time (mean time 9.4 minutes). When the police arrived first, but waited for EMS to use the AED, patients survived in 3 percent of cases (mean time 10.3 minutes).

Mosesso was impressed by his study’s results, but far from satisfied. Even if all the police officers in the country had AEDs, that wouldn’t be preparation enough for him. It takes time to arrive on the scene. Precious minutes are lost.

What Mosesso wants is for AEDs to be as common as fire extinguishers, to be hanging on the walls of buildings where people live, work, and congregate. He wants the man or woman on the street, who happens to be on the scene of an emergency, to use one, shortening the time from collapse to defibrillation.

Their ease of use helps make his goal feasible. “Not only are AEDs easy to use,” says Mosesso, “they are very difficult to misuse.”

An AED, which is about the size of a laptop computer, contains retractable pads that adhere to the chest. The pads analyze the heart’s electrical activity to determine what action to take. Do not touch patient. Analyzing rhythm, the AED may say in an automated voice. In two-thirds of sudden cardiac arrest cases, the electrical patterns are of the kinds that may respond to an electrical shock. If the AED determines a shock is needed, it might say, Stand clear. Push flashing button to rescue. When the user pushes the button, an electrical current runs between the electrodes contained in the two pads, attempting to give control back to the heart’s natural pacemaker.

Now Mosesso is part of a nationwide trial, supported by a $20 million National Institutes of Health grant, that analyzes the effectiveness of AEDs in the hands of laypersons. There will be 1,000 study sites in the United States and Canada, including office buildings and apartment complexes, golf courses and concert halls. People who live or work at each site, a total of 15,000 volunteers, will participate. Half will be trained in current emergency response techniques, such as contacting 911 and performing CPR. Half will receive AEDs and be trained to use them in conjunction with calling 911, CPR, and other current emergency response methods. Will the people with AEDs save more lives?

Mosesso hopes so. And he’s optimistic that, eventually, AEDs will become inexpensive enough (they are currently priced around $3,500) that they will be given as Christmas gifts.

After Dellorso collapsed on Memorial Day, a police officer with an AED arrived on the scene. The first shock had no effect, and the AED recommended another. With the second shock, Dellorso’s heart was jolted back into beating. His daughter and son-in-law have since purchased an AED for the Canonsburg police department in his name.

FOR MORE INFORMATION: http://www.early-defib.org
Linton Traub keeps a pair of 3-D glasses in his desk. They look like a toy, their shiny lenses, one green and one red, caught in a paper frame. When asked about his work, the assistant professor of cell biology and physiology doesn’t take long to bring out the glasses. But first he defines, for the uninitiated, the cellular process that has been the focus of his career for the past decade—endocytosis. It is the most common way cells bring extracellular particles, like nutrients, into the cell. A deepened understanding of such basic cellular biology will leave scientists better poised to tackle a wide spectrum of diseases.

“One of the things I really like about endocytosis is that it’s very visually compelling,” Traub says.

But the 39-year-old researcher doesn’t grab his glasses immediately. First, he paints a picture with words. “If you were suspended, like from a hang glider, over a cell, and you were looking down at the surface of the cell, you’d see these little indentations in the surface,” he says. These are the pits involved in endocytosis.

“Then, switch your perspective,” he says. “Imagine you plunged into the cell and were inside the cell and were looking up at the membrane, like at the ceiling.” Now, he reaches into his drawer. “I’ll show you a picture,” he says. “See you have to wear these glasses, because it’s actually in three dimensions.”

From inside the cell, the pit is like a bulbous, intruding growth. The surface of the pit is not smooth or continuous, but like a cage or a honeycomb, a hollow, geometric frame. The 3-D glasses make the geometric bulbs (the endocytotic pits) jump toward the viewer.

Having looked at the pits from inside and out, Traub begins to explain how they work. A protein called clathrin is the fundamental component of the pits. Clathrin is drawn to the site on the cell membrane where a pit will form. First, the clathrin is flat, but then it forms a geometric lattice and starts budding in toward the cell. Caught between the clathrin and the membrane is an AP-2 adaptor. This adaptor is like a mail sorter—it selects from the external environment the particular particles it wants to bring into the cell. Once the AP-2 adaptor has bound to the selected particles, the clathrin surrounds the particles, forming a transport vesicle that breaks off from the membrane. The vesicle, which Traub likens to a mail truck, travels inside the cell, deposits its cargo where it needs to go, then disintegrates.

While these basics are clear, Traub has been working to solve some of the mysteries surrounding endocytosis. One puzzle involves the AP-2 adaptor, which binds to clathrin, but only weakly. Given this weak affinity, how does the AP-2 manage to bring the clathrin to the site on the membrane where a pit needs to form?

Traub helped uncover the answer by looking at the handful of accessory proteins that bind to AP-2. When it’s time for a pit to form, these accessory proteins, which also have a strong affinity for clathrin, summon AP-2.

“Accessory proteins together with AP-2 create a much more powerful signal to recruit clathrin onto the membrane than the AP-2 by itself,” says Traub. But, once the clathrin has formed the transport vesicle, it must break off. How can it leave when it has such a strong affinity for the accessory proteins?

“Clathrin binds and very quickly forms this lattice,” says Traub. “But once it has done that, these accessory proteins depart, because their job was just to bring the clathrin, to make it form the cage.”

Each time a mystery is solved, another rises in its place. “These accessory proteins bind to AP-2 and clathrin very well,” notes Traub. “So how do they actually disentangle themselves after they’ve done their job? Actually, we have no clue how they do that.”

He believes his microscopic images will help reveal the answer: “You peel away layers at a time.”
Fourth-year students roll up their sleeves at a new and badly needed transplant center in the Mediterranean. ABOVE: Cristiana Bertocchi, MD ’01, (middle) at ISMETT with colleagues. RIGHT: Heather Hollowell, MD ’01, was the first Pitt student to be transplanted to Palermo.
When the Italian airliner’s wheels touched ground in Palermo, Sicily, one of its passengers—a fourth-year medical student from the University of Pittsburgh—felt a bit overwhelmed. Heather Hollowell had never before ventured outside the United States. She spoke no Italian and knew no one who wasn’t an ocean away. Yet, for two months this island city would be her home while she completed a rotation at a UPMC affiliated transplant center whose name she couldn’t pronounce: Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione (ISMETT).
Months earlier, in the fall of 2000, Hollowell received a scholarship funded by the Italian company, Nuovo Istituto Sieroterapico Milanese, that would make her the first medical student to do a rotation at ISMETT and let her glimpse a different way of life: “I had really hoped to expose myself to some cultures outside America during my undergrad days. But then it was either research or go abroad, and I figured research was more important for getting into medical school.” As a result, she spent a summer in the University of Delaware’s chemical engineering department learning about the crystallization of cholesterol in model bile and how it affects conditions such as gallstones. She didn’t learn, however, to say, “How are you feeling?” in Italian.

So, in preparation for Palermo, Hollowell purchased several Italian language tapes and books, but her fourth-year medical rotations kept getting in the way of her language study time. About a week before her trip, she felt more than a twinge of panic. ISMETT staff spoke English, she had been told. But she wondered, how would she communicate with the rest of Sicily? During a call back to her home in New Jersey, she said to her mom, “I can’t believe that in a few days I’m going to Italy for two months, and I haven’t had time to learn the language. I don’t know what I’m going to pack, and I don’t know where I’m staying.”

Hollowell relaxed a little after her mother—a college English professor and frequent traveler—reminded her that English was a second language in most countries. Hollowell was able to get along fine, as her mother had predicted, when her flight from the States landed in Rome. Courtesy of the terminal’s bilingual Partenze/Departures monitors, she was able to check on the status of her upcoming flight to Palermo. However, when she began that final leg of her trip, her panic returned. There was no English translation on the flight. Oh my God, she thought, what am I doing?

Cristiana Bertocchi, MD ’01, wasn’t doing anything special to prepare for her two-month rotation at ISMETT, which would begin in March after Hollowell, a classmate, returned to Pittsburgh. Bertocchi didn’t need to make special preparations. She was going home. Not home to where she was born and raised. That was Kittanning, Pennsylvania.

Italy, though, was the home she always heard about. Her mother had come from a small Tuscan city called Avenza. Wanda Micheli never had any intention of leaving Avenza, not until—just like in the movies—she met a handsome American soldier who was stationed in Italy. It was the mid-1950s and during a weekend leave when Herman Bertocchi decided to travel around Tuscany; his parents had emigrated from the region. One day, as he visited with cousins, aunts, and uncles, he was introduced to a family friend, Wanda Micheli. It didn’t take long for a courtship to blossom between the soldier and the young woman. The couple was soon taking in operas performed in ancient coliseums and spending afternoons at nearby freshwater lakes. They fell in love, but were separated when Bertocchi’s two years of duty ended.

It took nearly 10 years of convincing, but Herman Bertocchi finally enticed Wanda Micheli to join him in Kittanning, where he had become a successful certified public accountant. She became his wife and the mother of their four children.

“My mom said she was happy,” says Bertocchi, “but in many ways it was a huge culture shock for her—the fashion, the food. And she spoke little English at first; she told me that neighbors thought she came from some third-world country in the dark ages.”

Speaking in Italian to her only daughter, Bertocchi’s mother would reminisce about walking out her door and taking in views of the Mediterranean or the Apuan Alps and its famous quarries that provided the white marble for Michelangelo’s sculptures. She would recount the neighborhood open-air markets where she could buy the freshest vegetables, cheeses, meats, and fish. She would describe the readily available yards of leather, wool, cotton, and linen that she turned into the most elegant clothing. Mrs. Wanda Bertocchi missed all of it; and although her daughter had never known that way of life, part of her began to long for those days, too.

Once on the ground in Palermo, Hollowell was greeted by Claudia Cirillo—ISMETT’s administrative coordinator for international relationships. When they hailed a taxicab to take Hollowell to her studio apartment, she realized the cab driver didn’t speak English.

Hollowell quickly learned that Palermo’s cabbies make New Jersey’s seem like chauffeurs. Generally, Sicilian drivers tend to ignore stop signs and pedestrians. Their bumper-car size Micras typically race through the city’s cobblestone streets—streets that were built hundreds of years ago for horse-drawn carriages and now make up an inner-city beltway with a distinctly NASCAR flavor.

Along Hollowell’s inaugural journey, she did manage to peek out the window a few times. It was like riding into a travel brochure—uninhabited, jagged mountains rising majestically from the island, the Mediterranean looming in the distance. In the heart of Palermo, the streets were shuttered on either side with centuries old three- and four-story edifices bordered by flower beds; laundry fluttered in the breeze.
from second-floor balconies like some kind of national flag.

The next day, Hollowell officially began her rotation. She survived another cab ride, this one to the hospital. Once there, she tried to figure out where to report. Nobody was sure. The transplant center had admitted its first patient in July 1999 so protocols for the English-speaking hospital were at a minimum. Hollowell sought out Ignazio R. Marino who is on the transplant team at UPMC Presbyterian in Pittsburgh as well as director of ISMETT. Marino effectively told her to make herself at home, Hollowell recalls:

“He said, ‘Just talk to different people [on the staff] and figure out what you want to do and just let us know. Whatever you decide, it’s no problem.’” Then, he flashed a welcoming smile and dealt with the three or four hospital employees vying for his attention to discuss some pressing concern.

ISMETT’s atmosphere, with Marino at the helm, could be compared to that of a small start-up company. People juggle multiple roles and incredible responsibilities. Pathology is a good example. Marta Ida Minervini is not just the chief pathologist. She is the only pathologist. (On some tough cases she consults with pathologists in Pittsburgh via a secure Internet connection.) The center rushed to open its doors before it had its own doors, for good reason. Until 1995, southern Italians in need of liver and other organ transplants would have them performed abroad because the procedures weren’t available in the region. All expenses were paid by Italy’s national health care. In 1995 alone, Italy spent for Sicilian transplant migrations more than 252 billion lira (more than $125 million). It may not have been the most cost-efficient system, but lives were saved.

The situation changed dramatically in 1995 because of an ongoing donor organ shortage. That’s when the US Congress stipulated that 95 percent of all transplant recipients had to be US citizens. At that time, more than 50,000 Americans were on organ waiting lists. Marino, who was born in Italy, witnessed firsthand that decision’s impact as a transplant surgeon at UPMC Presbyterian (where he was recruited after his residency at the University of Cambridge). There were scarce opportunities for Sicilians in need.

“How could you tell people from Pittsburgh they would have to wait their turns while some patients from Italy were given organs from American donors?” he reasons.

Europe reacted even more dramatically to the shortage. “Belgium, England, France, and Germany decided to go suddenly to zero [foreigner transplants],” Marino recalls. “And in Rome or Milan, they had a subtle way of taking care of the people of northern and central Italy first.”

Nobody, it seemed, was looking out for southern Italians. “These people started to be desperate,” Marino says, “because even though the government would pay for their transplants, they had nowhere to go.” Italian government officials decided something had to be done. In 1997, they formed a working partnership with UPMC to create a facility with transplant capabilities, along with specialized surgical and diagnostic services. The plans call for Marino to oversee four operating rooms, 14 ICU beds, and 44 acute care beds, to be operational by 2002.

It became clear though that southern Italy couldn’t wait that long, so on July 21, 1999, ISMETT’s first patient was admitted in a temporary location on the second floor of the Palermo hospital Civico. Marino and his staff oversee two operating rooms, four ICU beds, and 16 acute care beds there.
“In our first year and a half,” notes Marino, “we did 63 transplants, 84 liver resections, more than 600 difficult cases, and more than 900 interventional radiology procedures. This was from nothing! And our survival rate is within the best five transplant centers in the world.” Marino is understandably proud.

Like any bright new employee at a start-up, Hollowell quickly immersed herself into the hospital’s culture. She decided to spend her first two weeks in the ICU, followed by two weeks in surgery, and the final four weeks in infectious disease. She saw some cases she would never come across in Pittsburgh, including a man enduring a mysterious inflammatory reaction in his liver and lungs.

“He was on a ventilator. We didn’t think he was going to make it. We were talking to experts around the world, and there was a lot of prayer going on,” says Hollowell. She watched the staff systematically rule out various causes.

At last, they figured it out. He had strongyloides from stepping on a rare worm that thrives in the Sicilian climate. The parasite had entered his body through his foot, and made its way to the lungs and liver. “We gave him dozens of different antibiotics,” Hollowell says. “One of them finally worked. He didn’t lose his liver or lungs, and he ended up being fine. In the morning, I would have him sit up so I could listen to his lungs. I would always ask him in Italian how he was feeling, whether he was in any pain, if he felt he was breathing better.” The questions, by design, called for succinct responses. When the response became more than a yes or no, Hollowell would head to the hallway for help.

“By the fourth week, I could speak functional Italian; I was finding my way around Palermo without any problems. I could go to the market, things like that, but I couldn’t speak well enough to have true conversations with the patients. I could ask them simple questions like ‘Do you have pain?’ ‘Do you feel better—on a scale of one to 10?’

“I must admit it was a little frustrating. It made me realize the importance of doctor-patient communication.”

The Italian that once flowed so easily in the Bertocchi household became stilted when Cristiana Bertocchi was 14.

“My mother was thinking words, but she just wasn’t able to say them, and it upset and frightened her,” she notes.

Wanda Bertocchi was diagnosed with a brain tumor. “It was developing on her left frontal lobe, and the left side is what controls speech,” Bertocchi explains. Her mother underwent treatment, to no avail. In 1986, about a year after her diagnosis, she died.

Bertocchi excelled in science and had thought about becoming a doctor in college; instead, she majored in Italian during her undergraduate studies at Pitt, with a minor in French and Spanish. After working for a few years as an interpreter for Pittsburgh companies involved in international business, she spent a year in France teaching English to high school students. While there she had an appendicitis attack. For many people, the prospect of being admitted to a hospital in a foreign place would be frightening. Bertocchi’s experience rekindled her desire to become a physician. When she returned to the States, she took the necessary premed courses and
Bertocchi never missed a word, often taking notes on the _modulo disposizioni medicine_ (physician order sheet). After the morning rounds, she and some of the Italian trainees would drift into Italian before returning to English. Bertocchi never missed a word, often taking notes on the _modulo disposizioni medicine_ (physician order sheet). After the morning rounds, she and some of the Italian trainees would often hustle to a nearby diner (called a _bar_) to grab a quick espresso and maybe a cornetto filled with apricot jam.

**The patient slipped out of bed and started shuffling down the hall in his bathrobe, tow ing his IV line.**

During rounds, patients sometimes would become anxious, lying in bed unable to understand doctors and nurses as they discussed their cases in English. One man with a treatable liver problem found the staid stares of medical professionals caring for him disquieting. So one afternoon as the attending physician and his sober throng of trainees moved on to the next room, the patient slipped out of bed and started shuffling down the hall in his bathrobe, towing his IV line. Bertocchi spotted him and broke off from the group. _Signore, stia attento alla linea!_ She convinced him to return to his bed.

“He wanted to make sure he was going to be okay,” Bertocchi says. “I told him that barring any complications he would be fine, and he said, ‘God bless you’.”

During their respective two-month rotations, Hollowell and Bertocchi found time to enjoy Palermo’s opportunities to participate in transplants. “I didn’t get to see a liver transplant, bad timing on my part,” quipped Hollowell, “but I did get to see a couple of living-donor kidney transplants.” One sticks out in her mind. A mother was donating her kidney to her adult son. Once the transplant was completed, the son wanted to be discharged.

“He didn’t want to stay there, even though he still was recovering. I think it was just the whole euphoria of getting a transplant. We were concerned about whether he would comply with the regimen and medications necessary after a transplant.” Hollowell, in her functional Italian, and the doctors on staff regularly reminded the patient that his operation was more complicated than something like having a hernia repaired.

After his discharge, he returned days later with a serious urinary tract infection. Doctors speculated that it resulted from his forgetting to take his medication. Hollowell sat down next to him and reiterated the importance of regularly taking his medication. The way she phrased the message must have clicked.

“He finally realized how sick he was,” says Hollowell. “You never wish sickness on anyone, but this episode helped him understand what we were telling him.” He had no further recurrences while Hollowell was at ISMETT.

Bertocchi won’t quickly forget a transplant that came up during her rotation:

“We were supposed to do a big abdominal case, but then we were alerted about a liver. I had stayed on call the night before, but I wasn’t going back to my apartment.” While a team went to harvest the organ, Bertocchi and the others waited.

“We were going to be there all night, so we kind of rested and looked forward to it.” The operation started around 5 p.m., with a Phil Collins CD playing in the background. “There were six of us: two attendings, two fellows, a scrub nurse, and me. Dr. Marino was heading it up,” says Bertocchi. “There was a lot of commotion throughout the evening; people were coming in and out of the OR, music was playing, and there was an aura of camaraderie. It was just a lot of fun.”

At 4 a.m. the sleep-deprived student scrubbed out. Bertocchi had a cold piece of pizza that had been ordered in the middle of the night, then went back to her flat, convinced more than ever that she wanted to be a surgeon. The operation concluded around 5:30 a.m. Another ISMETT success.

Both alumnae are settled into their residencies now: Hollowell in emergency medicine at the University of Virginia and Bertocchi in surgery at Allegheny General Hospital in Pittsburgh. Each speaks fondly of days at ISMETT and the emotional good-byes from the little island in the Mediterranean.

“My hands were flying every which way on my last day,” says Hollowell. “My speech had become a lot more visual in two months. I guess I fit right in.”

When Bertocchi began to say good-bye to one of the Italian nurses, a handshake didn’t seem appropriate. They hugged and gave each other a kiss on both cheeks. That established Bertocchi’s departing modus operandi. Handshakes for the Americans. Hugs and kisses for the Italians.
In the 1970s, Stewart Sell suggested certain stem cells cause liver cancer. Now some people are thinking he was right.
very now and then, as dusk fell on the San Diego coast, Stewart Sell swam out to sea, children in tow. As the shore dwindled in the distance, Sell would stop, bobbing in the water to wait for the perfect wave. He had a special talent for spotting the good ones, and wouldn’t give up until he found one that would take them all back to shore. As it crested behind him and his children, he would yell for them to swim hard, arch their bodies, and ride the wave as far as they could. After a good ride, they would pull themselves onto shore and head home, where Sell then climbed into bed, spread out his papers, and dove into some of the most pivotal research in stem cell history. It was the 1970s and 1980s, and Sell (MD ’60) was riding the biggest wave of his life: the oval cell, a tiny liver cell that may provide researchers with a key for treating cancer, cirrhosis, diabetes, and any number of other disorders. But people said he was wasting his time.
cipitated malignancy. Farber’s group found that in the earliest stages of liver cancer, the primary liver cells—called hepatocytes—develop small foci. The foci then grow to become actual nodules on the liver, which grow into cancer.

Sell followed these developments with each meeting, until Garri Abeler, a young researcher in Moscow, found something called alpha-fetoprotein (AFP), a protein required for fetal development that disappears later in life, then reappears mysteriously in animals with liver cancer. That news hit Sell like a wave, and he knew he had to ride it.

“I just had to find out how the production of this protein related to those early changes that Dr. Farber was studying,” he says.

Sell figured the best place to start was by developing a test for its presence. So he turned to his notes from sophomore microbiology at Pitt. His former instructor, Richard Farr, had developed what’s known as the Farr Assay, which utilizes antigen and antibody binding as a way to measure proteins, even in miniscule amounts. Using Farr’s technique, Sell developed a test for AFP and discovered that animals exposed to cancer-causing agents had elevated AFP levels long before they actually developed liver cancer. (Incidentally, Sell’s test for AFP is now used to screen for some birth defects, in which AFP leaks from the fetus into the mother’s system.) To truly understand his findings, Sell needed to know exactly where the AFP came from. So he began looking in liver foci and nodules for cells that produced AFP. But he couldn’t find them.

Imagine the liver is a house made of bricks. Tucked within the layers, within the mortar that holds them together, are a few scattered stones: The bricks are hepatocytes; the stones are oval cells. Oval cells are a fraction of the size of hepatocytes, and if you’re not looking for them, chances are you’ll never see them. They were actually discovered by Emanuel Farber, but since he was sure cancer arose from hepatocytes, he didn’t give oval cells much thought. Initially, neither did Sell.

After taking a faculty position at the University of California, San Diego in 1970, Sell would spend his Saturday mornings in a darkroom, scanning countless liver samples for AFP traces. He stained samples with a marker that fluoresced green in the presence of the protein, and he was stumped when
they didn’t seem to fluoresce, even when the sample had already tested positive for AFP. But one day, a tiny spec of green light caught his eye and he yelled, “Oh boy, there it is!” To his amazement, the light came from oval cells, not hepatocytes. The more he looked, the more his amazement grew: Oval cells were tiny, completely undifferentiated cells with no organelles (the organized structures within cells), all of which are characteristics of stem cells.

In 1976, Sell announced that oval cells were the source of AFP, and therefore liver cancer. People smirked. The field of stem cell research had yet to take hold. When he said oval cells were stem cells, people told him he was ridiculous. But he kept at it, developing markers to trace their development, showing that they proliferated wildly as cancers grew, and publishing papers saying stem cells were the root of liver cancer. Finally, a few researchers caught on and began replicating his findings.

“This opened a new view of liver carcinogenesis as potentially being a problem of stem cell development as opposed to the mutation of hepatocytes,” says Hyam Leffert, professor of pharmacology at the University of California, San Diego, and a long-time collaborator. “That really shifted thinking around and got a lot of people focused on understanding oval cells.”

A few years ago, decades after researchers told Sell he was crazy for thinking liver stem cells existed, Bryon Petersen, then a Pitt faculty member, made headlines around the world when he took stem cells from bone marrow and created liver cells. Before becoming full-fledged liver cells, they became oval cells. Now Petersen, an assistant professor of pathology at the University of Florida, has shown that liver stem cells can become various cell types.

So what does Sell—who started out looking for the root of liver cancer—think of the way science has embraced the therapeutic promise of stem cells? “I think it’s fantastic,” he says. And he has helped set the pace with researchers like Petersen by developing his own lines of oval cells he will attempt to grow into liver, lung, and a multitude of other tissues. “Hopefully we’ll use them to replace damaged organs someday,” he says, “or we’ll insert genes and use them for gene therapy. . . it all depends. But right now, these cells are hot.”

George Michalopoulos, chair of pathology at Pitt, speaks of oval cells as a phenotypic bridge: “Hepatocytes and cells of the bile ducts can change into each other, and they do so by going through the oval cell route. Cancer can come from all three types [of liver cells], but when it does, it looks very often like oval cells.”

Though the scientific community still awaits formal proof, many now suspect those little cells lie at the root of liver cancer. But back when Sell first said this was so, few believed his findings.

“It was a violation of the dogma at that time,” says Leffert. “But he really showed that the dogmatic models of liver cancer may well be wrong.

“That iconoclasm, that persistence, was so important to the field.”

“Stewart was one of the pioneers in this field,” says Petersen. “By making antibodies to help identify oval cells, he made it possible to find them and pull them out to work on them.”

“He’s tenacious; he doesn’t give up,” notes Leffert.

Sell always told his kids that holding out for the best wave will take you far. At the age of 66, he’s been riding oval cells for more than three decades: He has yet to hit the coast, and he’s not heading home just yet. In 1964, as a postdoc with Philip Gell in Birmingham, England, Sell discovered that antibodies react with proteins called immunoglobins on the surface of normal rabbit lymphocytes (arrows in A). This reaction activates the cells, causing them to change into larger “blast” cells (arrows in B). This was one of the first documentations of lymphocytes with immunoglobins on their surface (a cell type that later became known as B-cells), and an early demonstration of how immunoglobins activate cells.
It’s hard to name a thinker more important to shaping modern immunology than former Pitt professor Niels Jerne. Shown here, Jerne with the Queen of Sweden at the Nobel prize ceremony in 1984.
Sometimes during the Eisenhower era, somewhere in the Rocky Mountains, a traveling European scientist stood at a cowboy bar with a couple of colleagues and did the unthinkable. Niels Jerne turned to a few locals standing next to him and, uninvited, said something like this: *You probably think that your Colorado countryside is pretty wonderful. Actually, all these mountains and forests are very boring compared to the Champs Elysées.*

His buddies managed to rush him out of the tavern before he was clobbered. Jerne escaped unscathed and went on to serve as the chair of what was then the University of Pittsburgh School of Medicine’s Department of Microbiology. In 1984, while director of the Basel Institute, he received the Nobel prize for his theories that jump-started the modern understanding of the immune response. An assay he developed at Pitt went a long way toward refining that understanding. This same man who displayed startling hubris over a beer was considered a nobleman, in the finest sense of the word, among scientists. His nobility has little to do with social circles—although the London-born Dane spent the last years of his life in a French castle near Avignon, where one can see the
ancient Pont du Gard aqueduct from the library. (For years after he died in 1994, his widow kept his room there as he left it.)

He may have acted like a punk in that bar, yet the late Niels Jerne is remembered for elevating the behavior and pursuits of those around him. The University of California at Berkeley's Gunther Stent, who also survived the cowboy incident, was moved to write the following about him:

_He brought order to immunology by becoming its conscience. “What will Niels think of it?” had become the Gretchenfrage of the immunological psyche, and to receive his praise counted for his colleagues' self esteem more than prizes, promotions and election to academies._ The immunologists' ambition to receive Niels' approval kept order, and especially good manners, in a discipline that had been contentious and disorderly.

Though his ideas were prolific and prophetic—"too numerous to mention" wrote one journal editor—Jerne put his name on few papers. This was, in part, because he was largely a theorist. But also because honorary authorships were not to his liking—not during his days at Pitt in the '60s, nor when he led the Paul Ehrlich Institute in Frankfurt, Germany, nor later when he directed the Basel Institute for Immunology in Switzerland for two decades.

Jerne also knew how to pick a fight. He certainly upset an order, or lack thereof, in the field of immunology.

By 1950, Jerne probably suspected the status quo wouldn't do. He had discovered something that no one could explain: An antibody response becomes more effective the longer an animal is exposed to an antigen. Each antibody seemed to evolve so that it "fit" the antigen better. Jerne had seen it happen in rabbits when he was doing his MD dissertation work in Copenhagen in a lab shared with Stent and James Watson (the same James Watson who later found the "secret of life" with Francis Crick). In this group, which had been handpicked by the revered Max Delbrück and was inventing the field of molecular biology, Jerne was a bit of an outsider. As he studied the immune response of rabbits, the others were investigating bacteriophages (viruses that infect bacteria). As Jerne put it: "The air was filled with the phage particles that Delbrück had picked out as one of the weakest spots in the armour behind which Nature guards her secrets."

Jerne couldn't see how what he'd found in Copenhagen fit into the reigning explanation for antibody formation espoused by Linus Pauling. Pauling and other "instructionists" believed that when an antigen was introduced, it somehow taught proteins in the body to transform themselves into antibodies; these new structures would fold around the antigen, like an enzyme might, to destroy it. What else could explain the immune system's capacity to fight off an infinitely wide range of antigens? When news eventually spread of Jerne's finding that antibodies grew in effectiveness, it caught people off guard. Some thought: Well, maybe the proteins learn to fold better—or something.

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This line of thinking didn't sit well with Jerne. He didn't know why antibodies got better at their jobs in the course of the immune response, as he'd seen, though this goodness-to-fit phenomenon seemed to have Darwinian overtones. He began to develop a new theory of the whole system. Looking back years later, he compared how he saw the immune system to a glove shop—to be a successful proprietor, one would need a wide variety of sizes and styles in stock to fit the preferences of anyone who walked through the door. A proprietor didn't just magically produce whatever a shopper needed. Jerne believed the body was preprogrammed to have the appropriate antibodies; further, those antibodies existed before the antigen was even introduced. The antigen, in effect, selected the glove that fit it best.

When Jerne was a postdoc at the California Institute of Technology, he managed to secure a personal audience with Pauling to describe his idea, what would come to be known as the "natural selection theory.” Pauling took it in, understanding it completely within minutes. Then he dismissed it entirely. When Jerne met up with James Watson at one of Pasadena’s all-night eateries, he asked him what he thought of the theory. Watson was succinct: “It stinks!”

Jerne was anxious to get people to take his approach seriously. He and a colleague traveled across the States in a Studebaker, giving scholarly talks along the way (which covered their expenses). The men were not paid especially well; fortunately Jerne's traveling companion was lecturing on the eyes of beetles and claimed to be able to tell if a motel had bed bugs by smell alone. Six dollars a night appeared to be the rate the bugs couldn't afford. Along the way, Jerne got enough encouragement to write a paper on his theory—longhand, he never typed—which Delbrück had offered to submit to the Proceedings of the National Academy of Sciences. “Do not make any changes in the text, but please leave it as it stands,” Jerne the postdoc requested on a note to one of the fathers of molecular biology. Delbrück added a comma and sent it off; it was published in 1955.

The instructionists were wrong, as it turns out. Jerne wasn't precisely correct either, but he had the right idea. Antibodies were not molded by an antigen directive as the instructionists believed. Instead humans have billions of precommitted antibody-forming cells (lymphocytes) in their systems waiting to be selected and employed. In 1957, the Australian scientist Sir Macfarlane Burnet and others described how each of these billions of antibody-forming cells spawned antibody clones that put down certain antigens. This made sense to Jerne. He delighted in nature's elegant organization—not its apparent randomness, which he'd felt he had witnessed in the Rockies.

Confering order on the messy field of immunology took up much of Jerne's efforts. As a director at the World Health Organization (WHO), he became known for adding precision to its muddied terminology. He felt the WHO work was important; however, he was eager to see the early immune response
When Jerne met up with James Watson at one of Pasadena’s all-night eateries, he asked him what he thought of the theory. Watson was succinct: “It stinks!”

measure the end result of a full-blown antigen response in animals. To try to use those methods to figure out what the body was doing cell by cell was pointless—you might as well be asking a gorilla to put away the china. The job required a delicacy that no existing technique offered.

Jerne’s idea was to take a diluted set of antibody forming cells, poised in a “lawn” of red blood cells, and entreat them to release antibodies. The antibody would then puncture and explode those red blood cells. You would end up with antibody-forming cells highlighted because the blood cells once surrounding them would be gone—leaving a clear ring of nothingness, called a “plaque.” Then you would finally have cells that you could actually count and study.

Albert Nordin, a promising Pitt postdoc, was charged with making this dream plaque a reality. Ole Rostock, a superb technician from the Copenhagen lab, had been recruited as well to help his friend Jerne set up shop. Rostock consented to do this though he had never been further than 80 kilometers outside Copenhagen. One day, after a little jaunt through the western Pennsylvania mountains, Rostock dined with the other hikers at a Chinese restaurant near the med school. All this newness was too much for the homesick Rostock. Looking at a huge, exotic mushroom on his plate he began to weep. He left soon after.

Jerne, Henry, and Nordin were sad to see Rostock go, but the work proceeded. The seventh floor of Scaife soon became a venue for spontaneous colloquia—usually in Jerne’s office, with him at a blackboard sketching out an idea with Henry, Nordin, Hiroshi Fuji, Stewart Sell, MD ’60 (see p. 18), Aurelia Koros, and anyone else able to contribute.

In Pittsburgh, Jerne was still stirring things up, though now more successfully than he had in that cowboy bar. At local gallery exhibit openings, he was likely to look at a piece and ask the gallery owners, “Could you turn that upside down so we can see how we like it that way?” They would always do it, for some reason. They were happy to. One had the sense that something interesting was about to happen around Niels Jerne. That was usually the case. By 1963, the Pittsburgh group was watching the primary immune response unfold before you could actually count and study.

As Burnet would have predicted, there was a tremendous increase in the number of cells making antibodies—an expansion of clones. Aaron Stock, a bacteriologist, suggested staining the plaques with benzidine. Jerne proclaimed that the view was like taking in the stars in the heavens.

The group was rewarded with intriguing findings: In a control group, mice were producing antibodies without being injected with antigens. (Jerne had seen something similar in horses in Copenhagen.) And the instructionist notion that the antibody destroyed the antigens was finally put to rest altogether. They found antigens still floating around the bloodstream after antibodies had done their jobs.

The plaque was soon adapted in labs everywhere pursuing problems of cellular immunology. It begot exciting new techniques and expositions on the biology of the immune system. Jerne, of course, found much to say.

His plaque window underlined how dramatically the immune response typically shuts down. He went on to develop his network theory, which pointed out how the immune system imbeds “internal images” of the outside world via antigens. The recognition pattern is like a series of ripples in a lake, he noted: Antigens are recognized by antibodies that are recognized by antiantibodies and so on. And those antiantibodies must then look a bit like—or have characteristics of—the original antigen. Jerne suggested that these internal images help healthy individuals build powerful and self-regulating immune systems that are uniquely appropriate for their environments.

The idea was enticing and important to further thinking in clinical and experimental immunology. It was maddening to model mathematically though. By the ’80s, immunologists seemed less interested in describing biology and more interested in genetics. “I feel that the immense crowd in that field are suffering from the universal DNA disease,” Jerne wrote his old friend Henry in 1993. “If you ask them what happens to an antigen when it enters into your tissues, they look like rabbits that don’t know what way to flee.”

Some are still captivated by the hypothesis. Leonore Herzenberg of Stanford University is, though she thinks Jerne was wrong, and said so in a paper she submitted to the European Journal of Immunology. She postulated that such a network would work more like a circuit board than interacting ripples. Through the grapevine she heard that Jerne, who was on the journal’s editorial board, had been arguing with the other board members—he thought it was important to publish her paper. Herzenberg didn’t see it appear, and began to think it wasn’t going to run. Finally, it came out: volume 10 (1980), issue 1, page 1—the exact same page that one of Jerne’s landmark papers appeared nine years earlier. She likes to think Jerne was behind that.

“This,” she says, “I would consider a singular honor.”
Children with a rare disease who are only able to go outside after sunset gave Rick Wood an extraordinary view of how DNA maintains itself. They also demonstrate some of the sad consequences when it doesn’t.
Rick Wood is not exactly a car buff. “To me, an excess of cars is a modern tragedy of the USA and Europe,” declares Wood. “I hate driving, and the only reason we even own a car is that Enid needs it when she goes to Carnegie to give her violin lessons. I don’t even know what make of car it is.”

At first, Wood, who holds the University of Pittsburgh School of Medicine’s Richard M. Cyert Chair in Molecular Oncology, backs off from his previously published quotations using the mechanical maintenance of cars as a metaphor for his research interests. While his wife is loading the car to teach an across-town Suzuki violin lesson, Wood is likely to be thinking about how human cells fix damage to their DNA—how they keep these crucial life threads in tip-top condition.
Wood's research has contributed significantly to a fundamental understanding of that process, as well as what can happen when things go wrong: i.e., damaged DNA plus poor repair leads to mutation leads to cancer. (The repair process affects cellular aging as well.)

Discussing DNA in terms of Mr. Goodwrench is an oversimplified analogy but a helpful one, so Wood gamely concedes. “Your DNA chromosomes are a machine, like a car. DNA is a very stable molecule. That’s why it was selected to be the genetic material. But it does fall apart over time, like a car, or like all of us. One of the reasons we fall apart is because our DNA does.”

At any moment—as you walk your dog or read this article—every cell in your body is shedding some of its three billion chromosomal base pairs, the building blocks of DNA, at the rate of 20,000 per cell per day. DNA is under relentless attack from such aggressors as sunlight, cigarette smoke, and toxic chemicals. It is further assailed by substances normally considered benign but that participate in molecular breakdown at body temperature—including oxygen, water, and the by-products of metabolism. The onslaught keeps an intricate and elaborate repair system scrambling to contain and correct the damage and replace the missing or damaged parts to keep the machine running. Neglected DNA maintenance or a botched repair job becomes a mutation, throwing the normal DNA sequence out of whack, with potentially dire results.

Wood, 46, came to Pitt in March after 16 years at the Clare Hall Laboratories of the Imperial Cancer Research Fund, the leading cancer research institute in the United Kingdom. The laboratories are just north of London. There he built a worldwide reputation in a once little-explored field, the genetics of DNA repair. He was elected a fellow of the Royal Society (the UK academy of sciences) and is one of only two Pennsylvania-based academics who have been elected to the European Molecular Biology Organization. (The other Pennsylvania member is Ivett Bahar, who joined Pitt this year to direct its new Center for Computational Biology and Bioinformatics.) Wood’s recent review article in the landmark issue of Science devoted to the human genome (February 16, 2001) illustrates how far DNA repair research has advanced since he entered it in the 1970s. The article listed 130 distinct DNA repair genes identified by various laboratories, and some of the key discoveries were made by Wood and his coinvestigators.

It was at Clare Hall that Wood first turned his attention to the sad plight of the "children of the moon," which led directly to a major breakthrough in his understanding of DNA repair. These children suffer from a rare but tragic genetic disease, xeroderma pigmentosum (XP), which affects one in 100,000 persons in the United States and Europe. From birth, those with XP are extremely sensitive to ultraviolet light; to avoid it, they play outside only after sunset. By age 2 or 3, their small bodies may be covered with freckling and skin tumors, which can develop into massive skin cancers. Many die of rampant, invasive skin cancers while in their teens.

In 1968 James Cleaver of the University of California at San Francisco pinpointed the cause of XP as a case of faulty DNA repair.

At the simplest level of DNA repair is the mechanism of base excision repair, abbreviated BER, in which a single base pair wears out or becomes damaged and must be replaced. This kind of basic maintenance, "like replacing the sparkplugs," Wood explains, is going on continuously: "The system comes in, finds the damage, takes it out, replaces it, and everything is fine."

Lying too long under a scorching sun at the beach or forgetting to apply sunblock when spring skiing calls for a larger repair job. In this process, tagged NER (nucleotide excision repair), segments of 25 or 30 DNA building blocks called nucleotides are removed and replaced. Cleaver’s work showed that when XP patients are exposed to ultraviolet radiation, their DNA’s biochemistry is not able to snip away and replace the damaged segments. Neither Cleaver nor subsequent investigators, however, could readily explain what caused the repair system to fail.

NER had piqued Wood’s curiosity since graduate school, where he says he came into it “sideways.” How solar radiation damages cells had long been a fascination of his, perhaps because he came from the Four Corners area of the Southwest. Wood attended high school in Farmington, New Mexico. (It was there, he recalls, that he developed his disdain for automobiles: “I had a 1961 Ford Falcon that had an unfortunate habit of dropping its driveshaft at red lights. I would have to crawl under and lift it back into the transmission.”) He went on to Westminster College in Salt Lake City, Utah, where he met his wife: “She had the highest score in Introductory Biology, I remember.” He then did graduate work at the University of California at Berkeley. His thesis adviser there was Jack Burki—who was a visionary, says Wood. “He was one of the first radiation biologists to explicitly say that DNA repair was an important modulator of radiosensitivity.” Burki convinced Wood to change the direction of his research—told him that he should be investigating DNA repair processes rather than the damage itself. Then Wood was left to complete his PhD without his adviser’s insightful guidance. Burki died of prostate cancer at 40.

At Yale as a postdoctoral fellow and later at Clare Hall, Wood remained focused on the basics of DNA repair, especially NER. He began to see that studying the damaged cells of XP patients might lead not only to fuller knowledge of XP, with possible future applications for the disease’s victims, but...
Science increasingly views breakdowns in DNA repair processes as key to many cancers, in part because of the stellar work coming out of Wood’s lab. (Shown here: Federica Marini and Beate Koeberle with Wood.)
also to understanding the biochemistry of how NER also works and why it sometimes doesn’t. And that fundamental knowledge, he recognized, could have implications for other processes and conditions as well, such as aging and skin disorders.

The cooperation of XP patients and their families made the experiments to come possible, Wood notes gratefully. He was able to obtain protein from XP cells to try to reconstruct NER in a test tube. Wood combined damaged DNA with the protein from the XP cells, and after several years of trying was rewarded by seeing the NER process develop almost before his eyes.

“Once a biochemist is able to get a reaction to happen outside cells, it can be teased apart in order to figure out the detailed mechanism,” he says. Beginning in the late 1980s, Wood published a series of scientific papers on NER that caught the attention of the research community, showing how different proteins do their work at different steps in the repair process. Eventually he identified about 25 proteins that make up components of what he calls the “NER machine,” and investigated how they act on damaged DNA. “Our major contribution has been in finding out how NER actually works,” he says.

Wood was primed to return to the States when Pitt’s offer came. “The initial plan had been to go to London for two years, and it ended up 16,” he says. “But I always had it in the back of my mind to move back. ICRF Clare Hall was a wonderful research institution with nine interactive labs. But I was ready to work in an environment with ready access to a large university and to hospitals.”

He points out an architect’s rendering of the new Hillman Cancer Center under construction in the Shadyside section of Pittsburgh, admiring the design features that encourage interaction with other scientists. The center will be Wood’s headquarters, where he will lead the University of Pittsburgh Cancer Institute’s program in molecular and cellular oncology. In addition to the Cyert chair, named for the late president of Carnegie Mellon University, Wood will hold appointments as professor in the Departments of Pharmacology and of Biological Sciences.

The 130 genes named in Wood’s review article represent only a portion of the important genes that govern the DNA repair process in organisms ranging from viruses to humans. Wood and others believe many have yet to be identified or fully described.

“Everyone knows that cigarette smoking is a huge risk factor for lung cancer,” Wood says. “And everyone also knows that So-and-so’s grandfather smoked two packs a day and lived to be 85.”

Wood’s team was surprised to find that a gene known to be linked to damaged DNA replication in yeast turns out to be somehow necessary for normal development in mammals. Mouse embryos lacking the gene (REV3L) only survive halfway through gestation.

Slide A shows a normal healthy embryo; B shows a mouse with one copy of REV3L disrupted; in C both copies are disrupted—that embryo died.

Repair genes instigate and direct an exquis-ite series of chemical pathways that both monitor the condition of DNA and guide its repair. Some of these genes govern routine maintenance, typified by BER and NER. Others—Wood accepts another car analogy with a shake of the head—are cases where you might “call AAA, consider the car totaled, or get a new one.”

Because cells vary, the biochemical repair process can become specialized. “Sometimes you have to call in a transmission expert, sometimes a carburetor expert, and so forth,” notes Wood.

Sometimes that expert isn’t available, in a biochemical sense. And sometimes our bodies instead employ “cowboy mechanic” techniques.

“Oftentimes, the damage isn’t repaired right, but you still need something to make the car run,” Wood says. “You develop a hole in the radiator hose, and what you really should do is replace it. But if you’re
out in the middle of nowhere, maybe you put tape around it and try to keep going. You don't have it repaired correctly, and soon—well, that's a mismatch. In DNA, a mismatch can cause a mutation or a change in DNA sequence."

Other times, DNA suffers from neglect. “The DNA replication apparatus sees the damage but doesn’t repair it,” says Wood. “The car still functions, but it’s changed in some critical way. Six months later, it’s found that a big mistake has been made.” Such instances, known as DNA damage bypass, may be relevant to many types of cancer.

At Pitt’s Cancer Institute, Wood’s group will be looking at several intriguing questions about DNA repair and cancer, especially the biochemical aspects. (Wood’s group includes six “superb” postdoctoral fellows who came with him from London: Beate Koeberle, Federica Marini, Nagun Kim, Mike Seki, and John and Birgitte Wittschieben.) Science is linking many cancers to a breakdown in DNA repair. Two rare forms of breast cancer trace to defective repair genes, as does a form of familial colon cancer.

As with many bodily processes, DNA repair plays both Jekyll and Hyde roles. While it maintains the DNA of normal cells, it also, even-handedly, bolsters the DNA of tumor cells, thus helping them to proliferate. Many chemotherapies and radiation therapies for cancer operate by attacking the DNA of cancer cells. Unfortunately they also attack healthy cells, producing the well-known unpleasant side effects associated with these treatments. “The idea [with chemotherapy] is to give the maximum dose you can tolerate to wipe out the cancer without wiping out you,” notes Wood.

Cisplatin is a chemotherapeutic drug used against many forms of cancer that often produces harsh side effects, with one exception. Cisplatin cures 80 to 90 percent of young men with testicular cancer, with far fewer side effects. What accounts for that miraculous record?

“Nobody really knows,” Wood says. “It’s a very active area of investigation, with thousands of papers, and one we’re directly involved in with a project led by Beate Koeberle.” The working hypothesis is that testis tumor cells have an inherently low level of NER so that when DNA is damaged by cisplatin, the tumor cells are affected much more than healthy cells. If that’s the case, researchers like Wood might be able to identify the reason for the low repair capacity of testis tumor cells and find ways to inhibit DNA repair in other forms of cancer.

“If that basic mechanism could be understood, it could be an increasingly important element in cancer therapy,” he says.

And, as the XP example shows, DNA repair capability is a highly individual matter. Some people have more or less effective DNA repair systems than do others.

“Everyone knows that cigarette smoking is a huge risk factor for lung cancer,” Wood says. “And everyone also knows that So-and-so’s grandfather smoked two packs a day and lived to be 85.” Despite the nonstop assault on his DNA, Grandpa So-and-so’s repair system was strong enough to overcome it.

“That’s something we want to look at.

“The relevance of DNA repair to cancer is clear,” Wood says. “Cancer is caused by mutation, by changes in the base sequence. Mutations only arise if DNA repair is not operating properly. The more we understand DNA repair, the more we will understand how cancers arise and why the protective mechanisms aren’t always adequate.

“DNA repair is our frontline defense against cancer, and it’s very important to understand every aspect of it. That’s what we’ll be trying to do here.”
THE GOOD OLD DAYS
ADVANCING GERIATRICS
BY ROBERT MENDELSON

Every July there would be the same telephone call to Evelyn Granieri: "Evelina, Evelina" her Italian grandmother would exclaim, "Come and pick the cherries!" Off went the young girl to her grandmother’s house. "First, we would get stones to shoo away the birds; then we would go up on the ladder and pick cherries for three weeks," recalls Granieri, who is now an associate professor of medicine in the University of Pittsburgh’s geriatric medicine division.

Granieri never considered her grandmother old even though she was in her mid-seventies during those cherry picking days. Years later, as a dietetic student at Syracuse University, the fact that not all grandmothers are so full of life became woefully apparent. “We were told to go mingle in the day room of this nursing facility,” says Granieri. “I was hooked up with this one woman who was in her seventies. All she said to me the entire time was, Take me home, take me home.” Granieri realized then she wanted to help people in their later years.

Andrea Fox didn’t start out as a geriatrician, either. Something happened during the last leg of her internal medicine residency. Because of space constraints, one of her older patients was moved to a geriatric floor.

“It was the first time a care plan for a patient in the hospital ever made sense to me,” she says. “This patient had been lingering, depressed, kind of wasting away in the hospital bed. Everyone had been focused on getting him out of the hospital. No one spent time talking to him.”

The general internists Fox had worked with were focused on diseases and organ systems; the geriatricians, however, talked extensively to the patient about his home life, including what he enjoyed for breakfast, what kind of shoes he wore, even what he liked to watch on television. Then they accurately diagnosed him with hypothyroidism. He returned to good health. Fox became a geriatrician.

Granieri and Fox began their careers here 10 years ago. They started on the same day and haven’t separated since. The two know each other so well that when one begins a sentence the other can finish it. That close working relationship contributes to their success in caring for elderly patients with multiple needs, as Granieri sees it: “Working as a team is an optimal way to care for frail older adults. We show students you don’t need to be a lone ranger. You can trade on each other’s skills.”

Even if students decide not to become geriatricians, Granieri and Fox make sure they understand what good geriatric care is. Students shadow them in the clinic and on house calls. The duo also organizes formal and less formal didactic sessions and has student groups over to their homes a few times a year. “We’re not shy about showing them what it’s really like. They see us at work and at home,” notes Granieri.

Neil Resnick, chief of geriatrics and gerontology, commends the dedication the two have shown in engaging students at a number of levels. Their success, he says, also stems “from their own passion for teaching and nurturing bright and idealistic young adults who are thrilled to see idealistic role models so happy with the course they’ve chosen.”

This year Granieri received the American Geriatrics Society’s highest honor for advancing geriatrics education; and Pitt’s division has been lauded with awards. A five-year grant from the Jewish Healthcare Foundation will turn the Granieri-Fox duo into an expanding team. Each year, $30,000 will go toward training a faculty member in the ways of mentoring medical students in geriatrics. The first recipient is assistant professor of geriatrics Hollis Day. Ultimately, the grant’s real beneficiaries will be the elderly. Cherry trees beware.

HIGH MARKS FROM HARTFORD

The United States has more than 34 million people over the age of 65, but only 800 fellowship-trained geriatricians. Each year, a mere 125 physicians specialize in geriatrics—fewer than 10 of those pursue careers in research. “We desperately need to train scientists who can do research in geriatrics,” says Neil Resnick, chief of the School of Medicine’s Division of Geriatric Medicine and Gerontology. The John A. Hartford Foundation agrees—and believes that Pitt is a great place to do that training. The foundation has designated Pitt’s division a Center of Excellence in Geriatric Medicine—recognizing its teaching and research accomplishments. Only 21 such centers exist in the country. The $500,000 grant accompanying the designation will help train tomorrow’s geriatrics researchers and educators. –DH
A man with cancer receives his first chemotherapy treatment, and it sends him into seizures that won’t stop. Jolene Seibel, MD ’02, who was then a third-year medical student, watched as a team of doctors and nurses handled the emergency, wondering, As a medical student, if I came across this alone, what would I do? “It was a very scary thought at that point in my training,” she says.

Paul Rogers, associate professor of anesthesiology/critical care medicine, understands what students like Seibel experience. At least, the 45-year-old professor remembers how he felt when he was in training: Though he might have known what was wrong with a person and why, he wasn’t likely to know the specifics of what to do when a patient becomes unstable.

He remembers that no one ever gave him the step-by-step instruction he wanted on how to care for a patient in a crisis situation. “Nobody said to me, This is how you hook up the oxygen. This is when you call for the crash cart. This is how you evaluate a person in respiratory distress,” says Rogers.

After reading many textbooks and journal articles to add to his growing experience, Rogers eventually mapped out a methodical approach to caring for patients in an emergency.

“It occurred to me that if someone had taught me all of this, it would have been a whole lot easier,” says Rogers.

When Rogers finished his fellowship and arrived at Pitt as an assistant professor in 1987, he began giving students the kind of instruction that he had never had. Since then, teaching awards have accumulated on his CV. “I make someone’s learning my responsibility,” Rogers notes.

Just this year, he was honored by the administration of the medical school, its alumni, and students: He received both the Dean’s Master Educator Award and the Alumni Faculty Recognition Award. Students also chose him to receive the prized Golden Apple Award for Excellence in Clinical Education (it was his second time winning that honor). His fourth-year elective in critical care medicine is more difficult than any other elective to get into. By means of a lottery system, 24 students get a place in the class he teaches at the Veterans Administration hospital each year. But you don’t have to win the lottery to meet Rogers. Every medical student at Pitt takes the small-group sessions he teaches during the third year.

During one morning class, students gather around a computerized mannequin, named Sim Man, who is hooked to a heart monitor. Rogers shows the students pattern after pattern on the heart monitor. “This is one of the rhythms you’ll see when someone is getting ready to die from hypoxemia,” he says. He shows them more detailed printouts of the rhythms, arranging the strips on the blanket-covered legs of the mannequin so that everyone can see.

“This is scary,” he says of one strip, telling students that when he sees that rhythm, his heart rate becomes about as fast as the patient’s.

He stresses the knowledge and skills needed to save lives, including speed. “Evaluate the airway, breathing, and circulation within 10 seconds,” he urges. The goal for the course is to teach students how to evaluate a patient in distress and how to initiate a resuscitation.

Once the teaching portion of the class is over, it’s time for an evaluation. Students come in individually to resuscitate the mannequin and to get feedback. Before they begin, Rogers offers them reassurance: “Students are way too hard on themselves. My goal is that by the time you finish today, you’re better than you were last week.”

His favorite day of his courses is the very last day: “We run through various scenarios, and I see how they are excited about their abilities to tackle problems and initiate therapies that they will say they couldn’t have done before they went through my course.”

For Rogers, the reward for his efforts is seeing his students make that progress. “I made this a remarkable responsibility.”
COATED IN WHITE

OR, “WHAT AM I DOING HERE?” | BY TODD GREEN, MD ’01

A first year student isn’t sure that white coat will fit him. (On the cover of the latest edition of *On Doctoring*, an anthology that all med students receive as they begin school, this Rockwell illustration appears.)
Backstage in alphabetical order, 148 of us sit in ties and dresses. Coat racks at the front of the room hold 148 white coats. These are short white coats, the length of a blazer, not the long white coats that one might wear in a lab. Their shortness signifies that we are students, not physicians, though in our case, as they hang at the front of the room, they are signifying that we are about to become students. Right now we are in the liminal world, but when this ceremony ends we will have crossed the threshold, moving from whoever used to be to medical students.

The woman at the front of the room is from the Office of Student Affairs. She is friendly, and before we arrived she learned all of our names from our photographs. She instructs us to look around at our neighbors, and I wonder if this is the old “look to your left, look to your right; one of you won’t be here in four years” routine. But no, she is telling us what a great group we are, how diverse, and then something about how well we are going to get to know our alphabetical neighbors throughout the next four years.

Four years. Suddenly it sounds so long.

Four years ago I was graduating college as an English major whose only science course was a class called “AIDS and Society,” about to start my first job teaching at a boarding school, full of enthusiasm and certainty about spending my life with young people and books. This ceremony was nowhere in sight. “Don’t let it eat you.” That was my friend Greg’s mantra during the year we took premed courses. We’d heard the statistics about doctors and substance abuse, doctors and depression, doctors and divorce. Greg described his father, a retired physician, still startling when the phone rings at home, always expecting the call that will pull him from wherever he is back into the hospital. We are afraid of losing ourselves.

And now I am paralyzed by the realization that there are many useful and worthwhile things you can do with your life, all of them a clear second to medicine. I do not believe this, did not anticipate this career path from birth, but here I am.

The Robert Wood Johnson Foundation provides every medical student in the country with an anthology called On Doctoring, and we have received ours today. On the cover of our 1995 edition a Norman Rockwell doctor in a white coat and bow tie bends over a little girl with his stethoscope. Her back is to us; we see red pigtailed and her shirt around her waist. The doctor’s hands rest on her back; his expression is soft and serious, comforting. A letter from the president of the foundation, Dr. Steven Schroeder, comes along with the book. “Congratulations on your admission to medical school,” Dr. Schroeder writes. “You have now entered a profession that has as its purpose the relief of suffering and the caring for others. Your studies will quickly introduce you to sciences and technologies that have saved many lives and lessened much human misery. But it is the knowledge of people—the insights into the human condition—that is the essence of the practice of medicine. This, too, is the challenge and the privilege of being a physician.”

Our names are called in alphabetical order, and I climb the stage steps to greet Dr. Musgrave. Flashbulbs go off in the audience where my family sits. A second-year student helps with the ceremony. She holds a white coat open to me, and I work my arms into the sleeves. It feels like polyester, tighter, stiffer than I imagined. I walk to the opposite side of the stage to descend the stairs and go back to my seat. I smooth the pockets with my hands as I move, trying to make it fit.

Todd Green, MD ’01, is now a pediatric resident at Maine Medical Center in Portland. He and his wife, Cindy Green, are the parents of six-month-old Jonah.

Mayer Green, MD ’32, Todd’s grandfather, offered a steadfast example. Before he died in 1997 he reminded his anxious grandson, who was then a freshman, “Medical school is supposed to be hard.”
Eugene Cutuly, MD ’47, the son of an Italian emigrant shoemaker, continues to practice at the age of 91. Cutuly was accepted to the School of Medicine in 1930, but, lacking money for tuition, chose instead to pursue a master’s in experimental morphol- ogy because of the accompanying assistantship in Pitt’s Department of Zoology. He would finally attend Pitt’s medical school years later, in 1946, after earning a PhD in anatomy and completing his first three years of medical school at what was then called Wayne University in Detroit, Michigan. After graduation he started a general practice in Clairton, Pennsylvania, where he still makes house calls today.

Robert Berk, MD ’55, is a professor emeritus and gastrointestinal radiologist at the University of California, San Diego. His research improved X rays of gall bladders prior to ultrasound. Berk also helped start one of the first magnetic reso- nance imaging facilities in California, which is named in his honor. He was the 1986 recipient of Pitt’s Hench Distinguished Alumnus Award. Berk also wrote the book “30 Minutes to Shrink Your Stomach” in 2014.

James Kushner, MD ’62, is a professor at the University of Utah in Salt Lake City and director of the university’s General Clinical Research Center. Kushner recently published in Nature “Physiology: Mining the Genome for Iron.”

Anne Little Wedemeyer, MD ’62, a pediatric cardiologist, learned the Tibetan language in 1996 for the express purpose of giving the dedication for the grand opening of Katsel clinic in Tibet, which she secured the funds to build. She retired a year later to start the Kathmandu Children’s Heart Project at the Kanti Children’s Hospital, the only children’s hospital in Nepal. She esti- mates some 500,000 Nepalese children have rheumatic or congenital heart disease and that the rheumatic cases could have been prevented through access to basic health care. Wedemeyer spends a few months each year in Nepal training physicians and treating thousands of children.

Robert Hardesty, MD ’66, is director of the University Diabetes Treatment Center and Diabetes Outpatient Clinic at Parkland Memorial Hospital. He is a professor of internal medicine at University of Texas Southwestern Medical Center in Dallas. Raskin and his staff helped develop many new diabetes treatments including the insulin pump.

Barbara Weiser, MD ’75, codirector of the HIV Research Laboratory at the Wadsworth Center in Albany, New York, discovered that combina- tion antiretroviral treatments change not only the quantity but also the quality of HIV, contributing to the success of therapy. The center also is developing a test to measure the characteristics of the virus in a person’s system. Says Weiser: “This is good news because it opens up a new area of monitoring . . . . We can watch the progress of the virus and the effects of the treatment.”

The chief of cardiology at Yagon General Hospital approached Michael Miller, MD ’85, with a problem: A patient needed angioplasty. Her health was deteriorating. She was on a ventilator. Miller told the doctor they should perform the procedure together. The doctor protested, fearing culpability. If the patient, the mother-in-law of an important government official, died, the government could shut down the first cardiac catheteriza- tion lab in Myanmar (formerly Burma). Miller reluctantly performed the operation alone.

The next evening, as Miller dined with colleagues, a convoy of government cars raced toward the restaurant. Miller, realizing they had arrived on his account, anxiously waited as several military officers headed toward his table. Perhaps the patient had died; perhaps his own health was now in danger. Instead the officers presented Miller with a jewel- encrusted painting, a reward for helping the official’s mother-in-law survive.

Miller, an associate professor of medicine at East Carolina University, in Greenville, North Carolina, spent January in Myanmar as a visiting cardiologist with the World Health Organization. “The only reason I would consider something like this is because of my experience in Nigeria in medical school at Pitt,” Miller says. He points out how that trip’s success made it easier for him to put his life in the States on hold again this year.

The Owl, 1963
Paul F. Worley, MD ’80, professor of neuroscience and neurology at Johns Hopkins University, in Baltimore, Maryland, is working to identify the molecular mechanisms of neuronal plasticity in relation to protein synthesis. His last paper in Nature suggests that a protein known as Homer may have a role in long-term memory.

Edward Giovannucci, MD ’84, is associate professor of medicine, nutrition, and epidemiology at Harvard University. Giovannucci’s research at Brigham and Women’s Hospital in Boston, Massachusetts, focuses on how nutritional, hormonal, and genetic factors relate to malignancies such as prostate and colorectal cancer. Giovannucci’s recent work shows that carcinogens from tobacco that reach the colorectal mucosa through either the digestive tract or the circulatory system increase colorectal cancer risk.

Robert D. Dowling, MD ’85, General Surgery Resident ’88, Cardiotoracic Surgery Fellow ’89, General Surgery Chief Resident ’91, Cardiotoracic Surgery Resident ’93, Cardiotoracic Surgery Chief Resident ’94, performed the first self-contained artificial heart implant at Jewish Hospital in Louisville, Kentucky. He credits Hank Bahnson, Bartley Griffith, and Thomas Starzl with reinforcing his budding interests in surgery as a career: “There was so much depth to what they were doing.” Dowling recalled for the New York Times the first time he participated in a heart transplant. Pitt doctors cut out the heart, revealing an empty chest: “It was the most unbelievable, neatest, coolest, mind-boggling thing I had ever seen.”

Theresa Guise, MD ’85, is an associate professor of endocrinology and an attending physician at the University of Texas Health Science Center at San Antonio, where she is researching the effects of cancer on the skeletal system. She recently received the Fuller Albright Award, which recognizes outstanding bone researchers under the age of 41.

Margalit Rosenkranz, MD ’98, has started a three-year fellowship at the Cornell University—Hospital for Special Surgery in New York City where she is researching pediatric rheumatology and immunology. —SD and MH

THE WAY WE ARE

BY EDWARD HUMES

THE CLASS OF ’51 accepted World War II; they’ll tell you they saw it as their responsibility. So their college-age years were spent fighting some of the world’s worst battles. Everything else was put on hold, including, of course, medical school. “We were practically all veterans of World War II,” says Edward Farrell, MD ’51, a quartermaster on a Navy ship carrying troops and equipment to the beaches of the South Pacific during three invasions.

On the other side of the world, John Bucur, MD ’51, operated intelligence equipment during almost every major battle in Europe, often from behind German lines. His unit pinpointed enemy guns by calculating the distance by their sounds, then relayed the coordinates to awaiting American artillery. “We just devastated them,” Bucur says.

Stanley Hendry, MD ’51, treated the wounded. A combat medic, he went into battle armed with saddlebags stuffed with bandages and morphine syringes. When the fighting subsided, he would help carry the wounded out on stretchers, treating them in makeshift infirmaries. During some nights, a dizzying stream of soldiers staggered into the battalion hospital.
Robert Bragdon, MD ’73, began college in the 1960s amid the flash of antiwar demonstrations. Yet the studious Bragdon never felt the lure of social upheaval while attending Mt. Union College in Alliance, Ohio. After recently being elected president of the University of Pittsburgh’s Medical Alumni Association (MAA), he shared memories of those school days.

His father, Floyd Bragdon, MD ’31, a prominent neurosurgeon and a clinical professor at Pitt’s School of Medicine, had made it clear. The young man would have to prove himself as an undergraduate in order to get into the medical school. Bragdon heard him loud and clear.

After his freshman year, Bragdon traveled to Europe with his father, who was presenting a paper at a conference. During that trip, Floyd Bragdon suffered a fatal heart attack. Bragdon returned to Mt. Union the next fall, shaken but determined. He studied harder. He began to spend his summers assisting his father’s colleagues at Mercy Hospital. He finished his undergraduate work a semester early.

Then Bragdon attended medical school at Pitt: “I think I was one of the few guys who owned a tie.” His focus occasionally waned, his thoughts slipping to his father or the Vietnam War. Those who knew and admired his father encouraged him to stay focused. “That was very important, especially in a time when there were so many free spirits,” says Bragdon, now a prominent Pittsburgh plastic surgeon. Such lessons no doubt will help him keep the MAA on track.

Bragdon keeps this photo of Pitt's original plastic surgery faculty in his office.
One might assume that Carol Shields, MD ’83, could afford to leave little to chance. She has seven children as well as a premier ocular oncology practice that has her attending to patients three times a week, performing surgery three other, and putting out reams of publications that are considered trusted references. Yet she has found it wise at times to have faith in serendipity. Even a simple piece of paper can be a turning point, she’ll tell you. One such leaf, tacked to a dormitory wall at the University of Notre Dame, read: Women’s Basketball Team Tryouts.

“That eight by eleven announcement made a whole difference in my life—on all levels,” says Shields. “Being on the team gave me confidence, inspired me to trust myself so I could extend myself . . . know I could do anything.”

In the ’70s Shields turned the “ball club” at Notre Dame into a varsity sport, then became its captain her senior year. She was the first woman at that university to receive the Byron Kanaley Award, which is given to a varsity athlete for excellence in academics. As an MD, she has been recognized as one of Philadelphia’s “Top Docs” in Philadelphia Magazine for four years running, though her reputation is by no means confined to one metro area. Along with her husband, Jerry Shields, she runs the oncology department at Wills Eye Hospital and a practice that regularly gets referrals nationally for eye cancer treatments.

Cancers of the eye caught her imagination when she was a resident on call in the emergency department at Wills. Shields got her share of eye trauma that evening. One patient had a knife wound; another, a torn retina—from the blunt force of a fist. Still waiting was a woman who couldn’t see from one eye. Had she lost a contact? By the time Shields examined her, the night had grown late. Shields breathed deeply, then dilated the eye:

“When I looked in the back of the right eye there was silence. Just black silence. Under her retina there was a large melanoma. She hadn’t lost her contact; she had a tumor.”

The next day, Shields was part of a team of doctors who, along with the woman, decided to remove the eye. A month later, while on pathology rotation, Shields was asked to examine a specimen—it was that very same eye.

“I went through the whole process with this one woman, from initial diagnosis to treatment to pathology, and, finally, with her as a patient whose life I followed until she died,” says Shields. “That experience gave me a real feel for cancer of the eye—what it can do, what I could do.”

Because of a desire to help children and “focus on one thing and excel in it,” Shields now treats more than half of the infants with eye cancer in the United States.

The eye care community has come to rely on the expertise of Carol and Jerry Shields to, in a sense, fill in those black silences—to advise them about tumors that most ophthalmologists come across only once or twice in their careers.

“Theyir combined clinical experience is unparalleled,” Michael Gorin, chair of ophthalmology at Pitt notes. “They consistently have been major contributors to multicenter trials and are able to offer personal experience that allows them to really appreciate the nuances and variations within each case.

“Dr. Carol Shields, in particular, is beloved by the families and patients she guides through these very frightening times—times in which vision, appearance, and lives are at stake,” continues Gorin. “The trust that she builds is no less therapeutic than the treatments that she administers in the operating room or through radiation or chemotherapy.”

Each night Shields and her husband are home for dinner at six. Later, when it is quiet and still, she gathers her children in a circle, pulls out a book or talks about one of their soccer or basketball games. Here is a place to muse on the magic waiting to happen around the corner, about believing they can do anything.
He sure was good at posing interesting questions. Albert Einstein once said: “What I’m really interested in is whether God could have made the world in a different way; that is, whether the necessity of logical simplicity leaves any freedom at all.” Shown here: Einstein visits Pittsburgh in 1934 for an American Association for the Advancement of Science meeting. His talk was titled, “An Elementary Proof of the Theorem Concerning the Equivalence of Mass and Energy.”
CHAIR’S ROUNDS
OCTOBER 18
Eye & Ear Institute, 4 p.m.
5th Floor Board Room
Pittsburgh, Pennsylvania
Harvey Lincoff, MD ‘48, Speaker
“Changing Patterns in the Surgical Repair of Retinal Detachment: 1929-2000”
For information
Rika Beckley
877-MED-ALUM
rbeckley@medschool.pitt.edu

NEW ENGLAND ALUMNI RECEPTION
OCTOBER 19
Harvard Club, 5:30 p.m.
374 Commonwealth Avenue
Boston, Massachusetts
For information
Jennifer Rellis
877-MED-ALUM
jrellis@medschool.pitt.edu

M ARSHALL S. LEVY, MD MEMORIAL LECTURESHIP
NOVEMBER 1
Shadyside Hospital
West Wing Auditorium
5 p.m. Reception, 6 p.m. Lecture
Henry J. Mankin, MD ‘53, Speaker
“Tuberculosis of Bone and Joint: The Red King is Back”
For information
Ross H. Musgrave, MD ‘43
412-648-9090
medalum@medschool.pitt.edu

OREGON ALUMNI RECEPTION
NOVEMBER 2
Ashland, Oregon
Musical: “Wings”

CLASS OF ’66 REUNION
NOVEMBER 3
Pittsburgh, Pennsylvania
For information
Ross H. Musgrave, MD ’43
412-648-9090
medalum@medschool.pitt.edu

DC ALUMNI RECEPTION
NOVEMBER 4
Washington Hilton and Towers, 6 p.m.
Washington, DC
For information
Jennifer Rellis
877-MED-ALUM
jrellis@medschool.pitt.edu

ROSS H. MUSGRAVE LECTURESHIP
NOVEMBER 9
Carl R. Hartmann Jr., MD, Speaker
“My 25-year Experience in Breast Reconstruction—Disappointments and Joys”
Lecture, Magee-Womens Hospital Auditorium, 5 p.m.
NOVEMBER 10
Surgery Grand Rounds
“Defining Plastic Surgery, Past and Future”
Lecture Room 6, Scaife Hall, 10 a.m.
For information
412-648-9090
medalum@medschool.pitt.edu

PETER AND EVA SAFAR LECTURESHIP
DECEMBER 6
Michal Schwartz, MD, Speaker
“Protective Autoimmunity After CNS Trauma and in Chronic Neurodegenerative Disorders: A Paradigm Shift”
Lecture Rooms 5 and 6, Scaife Hall
4 p.m.
For information
Linda Amick
412-383-1900

PITT MED: ON THE ROAD
JANUARY 14, 15, AND 17, 2002
Florida locations to be announced
For information
Jennifer Rellis
877-MED-ALUM
jrellis@medschool.pitt.edu

ANNUAL ALUMNI DINNER DANCE
MAY 17, 2002
Pittsburgh Athletic Association
Pittsburgh, Pennsylvania
For information
412-648-9090
medalum@medschool.pitt.edu

SENIOR CLASS LUNCHEON
MAY 17, 2002
The Twentieth Century Club
Pittsburgh, Pennsylvania
For information
412-648-9090
medalum@medschool.pitt.edu
STAY THE COURSE FOR THE MOON

Members of the School of Medicine's Class of 2001 graduated with an average debt burden of nearly $110,000. Costs for tomorrow's graduates won't soon come back to Earth. For that reason, fewer new doctors will choose careers in primary care or clinical research, opting instead for more lucrative fields to keep their finances from wobbling toward the outer limits. Help them stay the course for the moon. Call 877-MED-ALUM to contribute to a scholarship fund.