“MY FATHER HAD FORGOTTEN HOW TO MAKE COFFEE.”

4.5 MILLION AMERICANS HAVE ALZHEIMER’S DISEASE
SECOND OPINION

PENKOWER CARED FOR THE CARETAKERS
Thank you so much for the article regarding Dr. Lili Penkower in the November ’04 issue [“Not Alone”]. When I was a naïve first-year med student facing a world of total unknowns called medical education, Dr. Penkower helped me. She taught me to hold my humanity as a framework as I built my medical knowledge.

I am truly grateful. She contributed as much to my education as the many legends of medicine at Pitt. I regretted not having a chance to thank her when graduation came and I was pulled into the whirlwind of a medical career.

Kam Fai Pang (MD ’85)
Overland Park, Kan.

THIS KING STILL REIGNS
I just wanted to tell you that I have had a number of telephone calls and notes from people who routinely receive the magazine commenting on how well written the article is on my late husband, Klaus Hofmann [“King of Peptides,” February 2005].

Frances Finn Reichl
Princeton, N.J.

Thanks for your wonderful article on Klaus Hofmann. It brought back memories for me. I was ill in 1976 with a bout of colitis. I was in Presby, bleeding badly, losing weight, and getting weaker by the day.

To this day, I don’t know whether Dr. Hofmann had direct input, but my physician marched into my room and announced they were going to try something new. I was put on an IV of synthetic ACTH and, almost like a miracle, my condition improved dramatically. My appetite returned, and I am fine to this day.

Many years later, I did thank Dr. Hofmann.

Sam Zacharias
Pittsburgh

WILEY APPRECIATED
Many thanks for mailing me Pitt Med. It has made me feel closely connected to Pitt.

To complete my residency training in combined anatomic pathology and neuropathology, starting in 1996, I spent two years as a neuropathology fellow with Dr. Clayton Wiley at Pitt studying HIV encephalitis. I returned to my home country, Thailand, right after completing my training. Now I am a practicing pathologist with a subspecialty in neuropathology in Bangkok Hospital. I was very glad to see Clayton’s photo in the November 2004 issue.

One belated correction: In the April 2002 issue, on page 13, an article mentioned “the 497th Tactical Fighter Squadron in Ubon, Vietnam.” Actually, Ubon is one of largest provinces in Thailand. During the Vietnam War, there was a U.S. Air Force base there.

Virawudh Soontornniyomkij (Fcl ’98)
Bangkok, Thailand

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

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

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

MAGAZINE HONORS 2004
CASE District II Accolades
Gold Medal, University Magazines
Gold Medal, Periodical Staff Writing
Gold Medal, Best Article
Women in Communications
Matrix Award, Feature Writing
Honorable Mention, Feature Writing
American Association of Medical Colleges
Robert G. Fenley Writing Award
IABC Golden Triangle Awards
Award of Excellence, Magazine Design
Award of Honor, Magazines
Award of Honor, Writing

DID YOU NOTICE?
A typo on the cover: That certainly tops the list of reasons editors might wake up in a cold sweat, hoping to tell themselves, “It was only a dream.” The glitch with our February issue—an extra “c” in the word “vaccine”—was caught right before our printer was to drop the issue off at the post office, on its way to you. Rather than reprint at significant expense, the dean chose delivery “as is.” Frankly, we hoped you wouldn’t notice. But now, we’re owning up.

It’s been pointed out to us that this incident could be treated as a cue for a discussion delving into medical errors. An extra “c” in the medical world—what prescription snafu might that have wreaked? (Alternatively, might an extra half cc of the Salk vaccine been a good thing?) Taking tips from the quality-control world, we’ve examined the process that led to the incident to prevent such a typo from occurring again.

Other charitable souls have suggested this is a terrific opportunity for talking about how the mind works—how we see what we want to see, rather than what is really there. The typo really was there, however.
DEPARTMENTS

OF NOTE 3
The ABCs of autism.
A special kiss brings on puberty.
Sights set on eradicating polio in India.

CLOSER 7
Scaife’s Grammy nominee.

INVESTIGATIONS 8
What goes wrong in the “boy in the bubble” disease?
Certain cancers can’t be fought with radiation—and now we know why.
New insight on health disparities among African Americans.

98.6 DEGREES 33
Heartache spurs understanding.

ATTENDING 34
The history behind a silent office mate.

ALUMNI NEWS 36
In adoption medicine, the pregnancy is in the paperwork.
Abraham Twerksi left his father’s congregation to pursue the work he thought he’d do as a rabbi.

LAST CALL 40
French lessons.

CONTRIBUTORS
It was a treat to work with writer CINDY GILL—[“How to Make Coffee”]. It’s not every day you get to assign something to your “big sister.” Gill is the editor in chief of our sister publication, Pitt Magazine. In the Thomas Detre era, she was on the staff of Health Sciences Review magazine. (She recalls being interviewed for that job by Detre, giant of psychiatry and longtime Pitt administrator, who was “both charming and imposing.”) When you read her essay, you’ll get a sense for her dad’s Pontiac. She still thinks about that old car. “That door, it never did open. We ended up junking the whole thing,” she says with a smile.

If you call photographer MYRANDA ZARLENGO-VARGAS [“So You Want to Change the World?”], you’re likely to hear the roar of a train in the background. The Chicago native and self-declared city girl lives next to the El. She loves her location—which perhaps because of where she can be next to so many people so quickly, and photographing people is her first professional love. She’s currently working on a project about generations of women that she hopes will become a book. A “huge women’s libber,” she was thrilled to meet Pitt alumna Catherine DeAngelis, editor in chief of the Journal of the American Medical Association. That said, a large part of her strategy as a photographer is to go into a shoot unbiased. “People are often categorized,” she says, “and it’s so great to unravel some of those layers—to bring out part of a soul. That’s a great photograph to me.”

COVER
The toll neurodegeneration takes on our communities is staggering. In this issue, we focus on two heavies: Alzheimer’s and Parkinson’s diseases. In a follow-up story, we’re invited along on a father-daughter journey. (Illustration © Michael Lotenero.)

FEATURES

Stolen Lives 12
Alzheimer’s and Parkinson’s: 5.5 million Americans afflicted, and that figure’s slated to increase. Is there no stopping these diseases? Our neurogurus respond. In a follow-up story, we learn how bugs might save our brains. (It makes more sense than you’d think.) In another, a Pittsburgh writer takes us on an eye-opening journey with her father.

Twin Portals to the Brain 24
An astounding new surgical procedure was kept quiet at Pitt for five years. Why? Because you’d better have your act together before you tell people you can remove brain tumors the size of baseballs through the nose.

So You Want to Change the World? 28
Some people might say Catherine DeAngelis has reached a point in her life where she’s no longer afraid. “But I’ve never been afraid,” clarifies the editor in chief of the Journal of the American Medical Association.
In 1963, the renowned physicist Richard Feynman wrote (The Feynman Lectures on Physics) that the most important hypothesis in all of biology was that “…all things are made of atoms, and that everything that living things do can be understood in terms of the jigglings and wigglings of atoms.” Not long before Feynman wrote this, Perutz, Kendrew, Crick, Watson, and others in Cambridge—mainly physicists—determined the first macromolecular structures (e.g., a double helix) by analyzing the diffraction of x rays through crystalline solids. Shortly thereafter, Pitt established a Department of Crystallography—then the only one of its kind in the United States. (Pittsburgh also has a rich history in nuclear magnetic resonance, or NMR, another method that allows us to glean structural information on macromolecules important in biology. Paul Lauterbur, a Pitt alumnus, won the 2003 Nobel Prize for work that eventually led to the development of magnetic resonance imaging.) Now, we are establishing a Department of Structural Biology in our medical school; only a handful of American universities have such a department.

At atomic resolution, structural biologists shed light on the 3-D structures and dynamic properties of proteins, nucleic acids, and carbohydrates, illuminating secrets of their biologic activity like function, recognition, and toxicity. X-ray crystallography presents static structures, just as NMR presents dynamic conformations, and cryo-electron microscopy, large structures, e.g., viruses and organelles. As they combine structural findings with other data, these scientists gain insight regarding cellular events and how these events translate into the form and physiology of entire organisms. That can save lives. When x-ray crystallographers at Merck elucidated the structure of the HIV protease, their work immediately led to the design of the first protease inhibitor, yielding an extraordinary increase in the length of survival of patients with AIDS. In the next decade, many new drugs for cancer, infectious and neurologic diseases, and disorders of the immune and cardiovascular systems will follow in the wake of structural biologic studies—for bargain prices. It is estimated that half the cost of drug discovery could be saved if we had structural knowledge of drug targets early on in the process.

The creation of our department is particularly timely, given that what we know of biological 3-D structures is far behind our knowledge of gene and protein sequences. Our new Biomedical Science Tower will house practitioners of the various structural methods in one venue, encouraging their overlapping techniques to yield exciting composites. This new department will also neighbor the Pittsburgh Institute for Neurodegenerative Diseases (see our cover story), fostering what I believe will be landmark studies on the aberrant proteins in Alzheimer’s and Parkinson’s diseases. I anticipate the department will have 10 full-time primary faculty within a few years, wiggling and jiggling together. Led by Angela Gronenborn, a preeminent structural biologist, they’ll address the enormous challenge of relating our one-dimensional knowledge about DNA sequences to the 3-D architectures that they encode and to the complex chemical and physical transformations that underlie all living systems.

Arthur S. Levine, MD
Senior Vice Chancellor for the Health Sciences
Dean, School of Medicine
Autism’s ABCs

Some children with autism can recite the alphabet backwards as easily as they can say it forwards. “That’s something that even brilliant normal children can’t do,” says Nancy Minshew, an MD professor of psychiatry and neurology. A new study by Minshew and collaborators shows that people with autism don’t process the alphabet in the same region of the brain as other people do. They use the brain region normally reserved for understanding shapes when dealing with the alphabet, rather than the brain region involved in language, reports Minshew in her study, published earlier this year in Neuroimage. “They see the letter ‘A’ as a picture. They don’t see the letter ‘A’ as the ‘A’ sound,” says Minshew. Because children with autism often have an apparent facility with language, parents and teachers may talk over the child’s head and then become frustrated when the child doesn’t do what’s requested.

“The comprehension part of their brain is not developing normally,” says Minshew. There’s a disconnect between what autistic people can say and what they can understand, she adds. —Dottie Horn

ON THEIR HONOR, THEY WILL TRY

The woman was in preterm labor. She’d been beaten by her boyfriend and was worried that she’d miscarry because of the abuse. She was high on cocaine, agitated and crying, and kept calling her mother, who wasn’t answering the phone. She kept saying, “I don’t want to be alone. I don’t want to be alone.” For about an hour, Laura Warren (Class of ’05) sat beside her, not saying much, as doctors and nurses came in and out of the room, providing care. The next day, the woman said to Warren, “Miss, I remember you. Thank you for not leaving me.”

The medical school recently created the Humanism in Medicine Honor Society to recognize students, like Warren, who show exceptional sensitivity, respect, compassion, altruism, and other such qualities toward patients and colleagues. Each spring, third-year med students will nominate their classmates, as well as faculty members and residents, for membership in the society. —DH

FLASBACK

What folks were humming 90 years ago:

Drinking water’s just as risky
as the so-called deadly whiskey,
And it’s often a mistake to breathe the air.
Some little bug is going to find you some day.
Some little bug will creep behind you some day.
Then he’ll send for his bug friends,
and all your earthly trouble ends.

—“Some Little Bug is Going to Find You”
B.H. Burt and R. Atwell, c. 1915
Faculty Snapshots

An African American woman had a curable breast tumor but didn’t go to a surgeon to have it removed. Nine months later, she came back to the doctor who’d diagnosed the cancer. The disease was now much more serious—she had metastases. “The reason why she didn’t follow up with a surgeon is she didn’t have transportation to get back to the hospital,” says Dwight Heron, assistant professor of radiation oncology, who treated the woman. Heron, who is an MD, is now the principal investigator on a $3.5 million National Cancer Institute grant—he’s seeking to better understand why African Americans have worse outcomes from cancer than Caucasians. He’s also trying to develop models for programs to reduce the disparities. He’ll be looking at the impact, for example, of offering cancer patients free transportation to their appointments.

About 20 percent of National Institutes of Health–funded geriatric psychiatrists are trained at Pitt, according to Charles Reynolds, professor of psychiatry. And that impressive number is increasing. The John A. Hartford Foundation recently named Pitt a Center of Excellence in Geriatric Psychiatry (one of only two such centers in the country). As part of this recognition, Pitt will receive $450,000 throughout three years to support fellowship training—increasing the number of geriatric psychiatry fellows trained each year at Pitt from seven to nine.

What sets off puberty? Tony Plant, a PhD professor of cell biology and physiology, has shown that a receptor previously known only as a tumor suppressor plays a role. In 2003, scientists first reported that several patients who didn’t experience puberty had a mutation in the GPR54 gene. In a February Proceedings of the National Academy of Sciences paper, Plant and his colleagues showed that, in monkeys, activating the gene’s receptor induces early puberty. Plant also found that reaching puberty increases a normal male monkey’s production of a protein known as kisspeptin (its gene aptly shorthands to KiSS-1 and activates GPR54). When females reach puberty, they also turn on KiSS-1; in addition, the number of their GPR54 receptors increases. No one knows why females are different. —DH

A&Q

With Gretchen Dickson

“I just never thought that sitting in meetings for eight hours a day would energize me,” says Gretchen Dickson (Class of ’05), the only medical student in the country on the board of the American Academy of Family Physicians. At the meetings, Dickson delves into a variety of issues: How can the academy influence politicians and increase public understanding of the specialty? Should there be greater diversity among students entering medical school? Why is health care in some geographic areas insufficient? It’s a chance to discuss topics that often aren’t considered in med school, says Dickson. “You spend so long doing biology and chemistry that you forget about all the nice social science stuff that you left behind in undergrad,” says the Latrobe, Pa., native. “It’s a chance to revisit that.”

On the inspiring people she has met through the board:
There’s a physician on the board who said, “Are we likely to have more people go into family medicine if we have more [family physicians] on [medical school] admissions committees?” That may or may not be true, but he said, “I can apply to be on my admissions committee.” He did and got on.

What was interesting about that to me is this is someone who’s already busy and has a lot of responsibilities. But he was willing to say, “I can do one more thing.” It’s not necessarily something that’s ever going to be on 60 Minutes. ... But it’ll probably change someone’s life. There will probably be somebody who goes to medical school, maybe becomes a family physician, because of him. I think that’s the whole point of advocacy—getting people to say, “I can do this one little thing.”

It makes me realize that saying, “I don’t have enough time” is not an excuse. You can do it. You can find the time.

Her questions for us:
Why don’t people choose to get involved with their specialty society or the American Medical Association or the group that they feel close to? Why don’t they take on leadership roles? Why don’t they sit on commissions and committees? —Interview by Dottie Horn

Heron

Plant
No Stone Unturned

Rumors circulating in the Indian state of Uttar Pradesh that the polio vaccine transmits HIV and makes boys infertile hasn't helped eradication efforts. Maggie McDonald, associate vice chancellor for academic affairs, health sciences, saw some of the fallout from such untruths herself this February when she participated in the Global Polio Eradication Initiative's immunization program there. She also saw how determined the vaccination teams were to meet their 2005 worldwide eradication goal. McDonald was impressed by the "absolutely exhaustive, detailed planning" the teams employed. They made detailed maps of neighborhoods. They enlisted women and children in targeted neighborhoods as volunteer informants to alert them to where young children and pregnant women lived and whom they might have missed. And they were pretty darned persuasive, too. When one mother came to the doorway and said, of her 1-month-old daughter, that the girl didn't need to be immunized, she was told, "But Dr. McDonald has come from America to give your child the drops." The mother then invited the team inside.

When McDonald arrived back at Pitt, she put together the final touches for a multiday program commemorating the 50th anniversary of the announcement that the Salk vaccine was "safe, effective, and potent." As part of the festivities, more than 400 people who'd participated in Pittsburgh field tests or had polio came together on April 10 in the Commons Room to be honored for their crucial contributions to abating the scourge.

Will the eradication initiative meet its 2005 goal? McDonald hopes so but wouldn't be surprised if it took a few more years. One thing is certain. If they don't wipe out polio this year, it won't be for lack of trying. —Erica Lloyd

MED STUDENT COURTSIDE

Stephen Esper rocks in his chair at the side of the basketball court, slapping his legs to the beat of the horns from the Pitt band playing in the corner. Then, he slips his head-phones on and welcomes an invisible audience back to his broadcast. As he talks while watching the women on the court fight for control of the ball, he throws his hands up passionately. He seems to describe every movement of every player on the court. "Since the listeners aren't watching the game, I have to make them see exactly what I'm seeing," he explains.

Esper is a second-year med student and volunteer sportscaster at WPTS 91.2, Pitt's radio station. Four years ago, he did an internship with Steelers and Panthers announcer Bill Hillgrove. "He taught me everything I know," says Esper. This school year, Esper will broadcast 16 games. On this February day, it's women's basketball; he also covers men's football and basketball. He typically spends several hours preparing for each game: making charts listing each player's stats, memorizing names and numbers.

As Esper stumbles over a fact, he shakes his head and sticks out his tongue. (He encourages friends and family to listen in and help him improve.) It's looking like Pitt could catch up to Villanova, and Esper starts shouting out movements and baskets at the pace of a possessed auctioneer. He can't help getting excited when the game intensifies. He knows he should be studying for a test, but instead he's nearly out of his seat following Marcedes Walker's trek down the court. "If you need to get psyched," he says, "you shouldn't be doing this job." —JD

HEALTH UPGRADE

When Vioxx was recalled, thousands of UPMC patients needed to be notified that they would have to use a replacement medication. It only took one day for doctors to track down and contact all of those patients.

Abilities like this compelled Information Week magazine to name UPMC number one in information technology among healthcare organizations and number five among all U.S. companies. What's the medical center's secret? A software network made up of more than 15 programs integrating records from UPMC hospitals and physician offices.

The network, called eRecord, was developed by the medical center. Daniel Martich, vice president of eRecord and codirector of cardiothoracic intensive care at UPMC Presbyterian, compares the old way of doing things to a game of Telephone. The game stops being fun when, for example, the word potassium gets mixed up with phosphate. "Person-to-person communication is error filled," says Martich, an MD. "Systems like eRecord have reduced medication errors by over 50 percent nationally." —Jen Dionisio

Watching polio immunizations in Uttar Pradesh.
Appointments

In 2000, Mitchell Fink, chair of critical care medicine, started a company, Critical Therapeutics, with two other professors. Within four years of its creation, the new company had an initial public offering; it's now listed on NASDAQ, employs about 100 people, and has licensed an asthma treatment from Abbott Laboratories that will be on the market soon. As the new associate vice chancellor for translational research and commercialization, Fink will help other Pitt researchers become entrepreneurial. He'd like to increase the number of invention disclosures made by health sciences faculty as well as the number of faculty technologies being licensed. “It starts with helping people plan their research so that they actually end up with an invention,” says Fink.

This summer, James Conway will bring a new way of seeing to the medical school. The PhD works with the structural biology technique called cryo-electron microscopy. Conway is originally from New Zealand; he comes to Pitt from the Institut de Biologie Structurale Jean-Pierre Ebel in Grenoble, France, and will be an associate professor in Pitt’s new Department of Structural Biology. Cryo-EM lets researchers create 3-D models of proteins as they interact with one another. It’s especially useful for looking at complexes of proteins, like the outer coats of viruses (capsids), which may be composed of five or six different proteins. Conway studies the capsids of the HK97 bacteriophage (which infects bacteria) as well as the human hepatitis B virus.

Susan Dunmire (MD ’85, Res ’88), award-winning teacher and associate professor of emergency medicine, will serve as the executive director of the Medical Alumni Association. Students get to know the MAA through programs such as the White Coat Ceremony and, of course, scholarships—where 80 percent of all MAA contributions are invested. The MAA is eager to play a more significant role in the lives of the school’s graduates as well—beyond reunions. So the association is developing new education programs for alumni. Dunmire also wants to boost scholarship contributions. She has already lined up 200 enthusiastic students who will call alumni in an October telethon. She asks, “Please do not hang up or tell them you are out of town for the next decade. Only 25 percent of alumni contribute anything to the MAA or any part of the medical school. Our goal is to increase this to at least 50 percent participation.” —DH & EL
WHAT A FEELING

This past December 7, what started as a typical day for Scaife Hall housekeeper Frank Gibala turned extraordinary. Gibala was preparing the conference rooms on the 11th floor for a series of meetings when his wife called with news: His band’s self-released album *Come on Over* had been nominated for a Grammy in the best polka band category.

“I guess I let out a scream,” says the affable, salt-and-pepper ponytailed Gibala. “I just couldn’t believe it.”

Gibala has played clarinet and saxophone for Henny & the Versa J’s for 11 years. The group plays a Chicago-style polka with a mix of influences—“a touch of jazz, a touch of country,” Gibala says.

Despite his excitement, Gibala wasn’t sure he would attend the Grammys. He had never flown before and wasn’t sure he was ready to try. His wife made him buy a black suit just in case he changed his mind. At the urging of many, Gibala found himself in L.A., receiving a commemorative medal during the nomination ceremony the night before the awards show. That evening, as he and the other band members were parading around the room, taking pictures, Gibala accidentally bumped into Kevin Bacon.

“I was hoping to see Shania Twain, but she didn’t show up,” Gibala laments.

The next day, Henny & the Versa J’s lost to the faster Tex-Mex flavor of Brave Combo. But Gibala savors his near win.

“Everybody that’s in polka, I wish this on them,” he says, showing off his medal. “Because you can’t believe the feeling. It’s just incredible.” —JD

PHOTO | C.E. MITCHELL
These cells growing in tissue culture in Lisa Borghesi’s lab are destined to be B cells—the immune system’s antibody factories. Borghesi is figuring out what drives and what stops antibody production.
S
tonds after David Vetter was
born, in 1971, he was placed in
a specially designed crib. Plastic
encased it—only sterilized items
and filtered, germ-free air could enter. Vetter
had severe combined immune deficiency
(SCID). His immune system was so severely
crippled that any infection could become
life threatening. Doctors hoped that they’d
develop a cure for his disease within a few
years; they were unsuccessful. As the boy
grew, he lived in larger and larger plastic
bubbles, cut off from any direct physical
contact with other people. Vetter died at the
age of 12, known to the world as the “boy
in the bubble.”

These days, isolating children in a bubble
is almost never used as a therapy for this rare
disease.

“The cost of the bubble and the emotional
toll, it’s just so extraordinary, that’s not
usually an option,” says Lisa Borghesi, assis-
tant professor of immunology.

Some children can be cured with a bone
marrow transplant—which is particularly
successful if performed in the first three-and-
ahalf months of life. But only about 30 per-
cent of SCID patients can find a matching
bone marrow donor, and, among those who
receive transplants, not all survive or have
successful grafts. Children who don’t receive
a transplant often die before the age of 2.

Experimental gene therapy has yielded
mixed results for a decade. In 2003, French
researcher Alain Fischer administered gene
therapy to 10 children whose SCID was
caused by a single genetic defect. The treat-
ment cured them of the disease—but three
of the children developed cancer as a result
of the therapy. Even so, many researchers
regard gene therapy as having promise as a
cure for SCID.

But gene therapy depends on knowing
which defective gene is causing the disease.
Although several genetic mutations linked to
SCID have been discovered, in 20 to 30 per-
cent of cases, it’s not known exactly what
causes the disease. In these mysterious cases,
we at least know that the cause has to do with
B cells, which are vital to immune function.
And research on B cells conducted by Pitt’s
Borghesi is paving the way toward answers.

B cells are created and developed in the
bone marrow. When they mature, they exit
the marrow and circulate throughout the
body. Once a B cell circulates, it releases
thousands of Y-shaped antibodies. Those
thousands of antibodies are unlike the anti-
bodies released from any other B cell in the
body. The twin tips of the Y are the distinc-
tive part of the antibody. That’s where the
antibody’s receptors, which enable it to
detect and grab hold of an invading particle,
are found.

At any given time, millions of different
types of antibodies circulate in our bodies.
We have antibodies that would recognize
SARS, avian flu, Ebola. Our bodies’ strategy
is to randomly produce millions of flavors of
antibodies, so that no matter what the invad-
ing particle is, there will be a corresponding
antibody whose receptors will recognize and
latch onto surface proteins on the particle.

Those distinctive Y-tip sections make the
immune response work. They are created by
a process known as recombination, which
takes place inside the nucleus of the B cell.
Through recombination, the cell chops up
and reshuffles hundreds of tiny gene seg-
ments to form myriad patterns on a portion
of the genome. Although changes to genes in
any other cells might have grave conse-
quences—like disease and death—these
changes inside the B cells are essential to cre-
ate the diversity of antibodies needed to
defend our bodies against a wide array of
invaders. Some people with SCID cannot
make many antibodies because their recom-
binations process is somehow blocked.

“Recombination is unique to the
Genome Project showed that the body has
between 20,000 to 25,000 genes, yet we
have millions and millions of different anti-
bodies. So it’s not possible that each gene
encodes an antibody, because we don’t have
even a few genes. But through recombination,
the body takes the three genes that code [for
antibodies] and turns them into millions of
protein receptors.”

In the Journal of Experimental Medicine in
2004, Borghesi and her colleagues identified
the stretch of B-cell DNA where the recom-
binations process begins.

More recently she has learned that mice
without a certain protein (transcription
factor E47) show a 90 percent decrease in recombi-
nation activity, indicating this protein plays an
important role in the process, yet there must
be another factor at work as well.

“Once we know the specific factors that
turn recombination on and off in the mouse
model, we’ll look in patients and see if they
have those factors.

“With gene therapy, there may be an
opportunity to correct that defect if they
don’t,” says Borghesi.
C
ells make mistakes. And who could blame them? According to the Human Genome Project, which mapped the minutiae of our DNA, there are perhaps 25,000 genes within each of our cells. As cells copy that huge volume of information in preparation for division, there’s bound to be a clerical error or two.

Fortunately, there’s a rigorous copy editor at work in most of us. As cells progress through the cycle of DNA replication and cell division, several checks assure that DNA is faithfully reproduced. Protein proofreaders scan lengths of DNA, checking for errors and omissions, alerting other proteins to drop in to make repairs. And if the DNA damage is too severe to be fixed, defective cells are discarded entirely.

“Proteins that are involved in these responses are actually genome protectors,” says Pitt molecular biologist Baskaran Rajasekaran. So there’s a lot of interest in how the process works—or doesn’t. When these proteins stumble, cells with mutated DNA continue to replicate. By picking apart the subtleties of this protective process, Rajasekaran has revealed why radiation therapy is not always effective in warding off certain cancers.

For all our complexity, our 25,000 genes are made of just four molecules bound together in a specific way: adenine to thymine, cytosine to guanine. And for all the immutability of this pattern, sometimes cells have been known to muddle things, say by joining an adenine to a guanine. Lucky for us, aptly named mismatch-repair proteins can catch these errors and correct them. Rajasekaran, who is an associate professor of molecular genetics and biochemistry in the School of Medicine, is interested in fully illuminating the function of these proteins.

Mismatch repair, though important, has been thought of as junior copy-editing stuff for proteins, like correcting punctuation. But in a 2003 Nature Genetics paper, Rajasekaran and colleagues described another, even more vital role for these proteins: They point out broken DNA to proteins equipped to bring cell replication to a halt and destroy the defective cell.

Those cell-killing heavies can’t recognize DNA damage on their own. As Rajasekaran sees it, because the mismatch-repair protein has to look for damage anyway, it may as well hang out a flag to alert the big guns. (Although the current model of cell cycle proteins gives just one function to each kind of protein, “in reality this is not the case,” Rajasekaran says. “It’s much more complicated than that.” The newer model being built by him and others describes a myriad of functions for a protein, depending on which molecules it communicates with at which point in the cell cycle. These proteins are, in fact, jacks of many trades.)

Rajasekaran’s findings explain why cell lines from certain inherited forms of cancer are resistant to radiation therapy. In garden-variety cancer cells, treatments like chemotherapy and radiation aim to jump-start DNA quality control, rendering cancer cells defective enough that they’ll be marked for destruction. But in some forms of colorectal and endometrial cancer, the crucial mismatch-repair protein pennant is missing, so cells ravaged by radiation continue to chug through the cell cycle and divide: “They don’t even know that they’re damaged,” says Rajasekaran. When the mismatch-repair protein is restored, news of damage is correctly communicated down the line, and the cell replication cycle functions as it should: Irradiated cancer cells cease to replicate, arrested just before their chromosomes separate. While this approach is still a long way off, Rajasekaran imagines one day dosing radiation-resistant cancer cells with the missing protein prior to therapy, so that chemo- and radiation therapies can do their work.

By revealing the secret lives of mismatch-repair proteins (shown here in intranuclear depots known as PML bodies), Rajasekaran has, among other things, told scientists why radiation and chemotherapy aren’t effective against certain cancers.

HOW CELLS FLAG DOWN THE BIG GUNS
AND WHY RADIATION ISN’T ALWAYS AN EFFECTIVE CANCER THERAPY
BY LEAH KAUFFMAN

By revealing the secret lives of mismatch-repair proteins (shown here in intranuclear depots known as PML bodies), Rajasekaran has, among other things, told scientists why radiation and chemotherapy aren’t effective against certain cancers.
When it’s time to be born, the fetus usually emits a chemical communiqué, signaling to the mother’s body, *Let me out*. At the receipt of this signal, the mother’s immune system goes into action. It activates white blood cells in the uterus and cervix and liberates agents that bring about inflammation. This immune response ultimately makes the uterus contract and prepares the cervix for birth. Inflammation drives labor.

But in some cases, the inflammatory process starts too soon. Twelve percent of babies in the United States—nearly 500,000 each year—are born prematurely. Pitt research suggests that African American women may be genetically predisposed to premature labor because of subtle variations in their immune systems.

Hyagriv Simhan, assistant professor of obstetrics, gynecology, and reproductive sciences in the School of Medicine, conducted a study focused on a polymorphism in the gene for IL6, which often plays a role as an inflammatory protein. A polymorphism is a small peculiarity in a gene that typically is found in 1 to 10 percent of the population. We all have polymorphisms of one kind or another—thousands of them, in fact. As it turns out, people who carry this IL6 variant produce less of the natural inflammatory agent than people with the more typical version of the gene. (Other research has found that solid organ transplant recipients with this variant are less likely to reject an organ. Less IL6 seems to translate into a less robust immune response.)

Simhan found that women with the IL6 variant have a much lower risk of premature delivery. He also discovered that African American women are less likely than Caucasian women to have the protective polymorphism. This helps explain why preterm birth is almost twice as common among African American women than among Caucasian women.

So how can the medical community help these women and their babies? For the most part, efforts to prevent preterm birth have focused on mothers during the 11th hour—when they’ve already begun to go into labor—usually by administering uterus-paralyzing drugs. Now research is taking some impressive baby steps in a new direction. Scientists like Simhan, an MD who received his MS in clinical research from Pitt in 2001, are attempting to identify women at risk of early delivery so doctors can intervene before labor starts.

“We’ve explored using the body’s own anti-inflammatory products as candidate pharmacologic agents,” he says.

By this summer, he will begin testing these natural immune suppressors in rodent models of preterm birth.

**WHY PRETERM BIRTHS ARE HIGHER AMONG AFRICAN AMERICANS**

By Dottie Horn

**RACIAL DISPARITIES LINKED TO INFLAMMATION**

Are Blacks genetically predisposed to inflammation-associated conditions? It appears so. A recent study by Roberta Ness, Pitt’s chair of epidemiology in the Graduate School of Public Health as well as professor of medicine, offers more clues to racial health disparities. In line with the findings of Pitt’s Hyagriv Simhan (see “So Soon?”), she’s concluded that the answers seem to lie in genetic polymorphisms, slight variants encoded in DNA. Ness found that African American women are more likely than Caucasian women to have polymorphisms that result in pronounced immune and inflammatory responses.

Says Ness, “African Americans suffer disproportionately from a variety of diseases, and many of those diseases are thought to be at least partially mediated by inflammation—heart disease, diabetes, preterm delivery, transplant rejection, autoimmune diseases [where the body goes into hyper-immune mode].”

“Everything we found suggested that Blacks had a more revved up inflammatory response on the basis of genetics.”

But such genetic variants are only part of the story.

“Genes don’t act in a vacuum. Environment plays a huge role and probably plays a greater role, frankly, than genes do in predicting racial disparities,” says Ness. “I don’t think genetics is destiny. We need to think about how to alter the environment in such a way that this predisposition doesn’t get triggered.” —DH
Considering the toll Alzheimer's and Parkinson's takes on our communities, we prodded Pitt's neurogurus with questions: Who is the most vulnerable? What causes these diseases? What's the next best hope?
Losing the ability to move or think or remember. Being caught in the grip of an inevitable, progressive decline. Not knowing which symptoms you’ll develop or when. Neurodegenerative diseases are among the most-feared illnesses.

Four-and-a-half million Americans have Alzheimer’s disease and another 1 million have Parkinson’s, the two most common neurodegenerative diseases. Because of the aging population, as many as 14 million Americans could have Alzheimer’s by 2050.

Alzheimer’s causes memory loss and dementia by disrupting the physiology of the brain and altering neurotransmitter levels. In Parkinson’s, the dopamine neurons die, resulting in movement problems, such as telltale tremors, stiffness, walking difficulties, and other symptoms. Both the suffering these diseases bring and the societal cost of caring for those affected are staggering.
In 1999, the School of Medicine created the Pittsburgh Institute for Neurodegenerative Diseases (PIND) to foster a community of scientists focused on these two enormous disease burdens as well as Huntington’s, ALS (amyotrophic lateral sclerosis), and other conditions. In 2000, PIND received a $10.8 million gift from the Scaife Family Foundation and the Scaife Charitable Foundation, one of the largest gifts the University has ever received. Ten million of the gift (matched by $10 million from UPMC) is being used to construct a PIND floor in the new Biomedical Science Tower 3. (The Scaife money also funds a seed grant program, supporting new neurodegeneration researchers.) PIND moves into its new home later this year. The institute’s “open lab” layout, where one scientist’s space is contiguous with another’s, is designed to spark freer exchange of ideas among investigators of different backgrounds. Add Pitt’s all-star faculty lineup to that equation, and the prospects for the school to make even more substantial contributions to efforts to understand and treat these debilitating diseases start to look very good indeed.

In November, Timothy Greenamyre, professor of neurology, took over the leadership of PIND, following in the footsteps of Steven DeKosky, chair of neurology. DeKosky, an MD, heads Pitt’s Alzheimer’s Disease Research Center and just won the Ronald and Nancy Reagan Research Institute Award. Greenamyre, an MD/PhD known for his work on pesticides and other causes of Parkinson’s, came to Pitt from Emory University. He has served on numerous National Institutes of Health committees and on the scientific advisory boards of the Michael J. Fox Foundation for Parkinson’s Research and the Parkinson’s Study Group. Other Pitt neurology professors instrumental in the development of PIND include Michael Zigmond and Robert Moore. Zigmond, a PhD, is an expert on why cells die in Parkinson’s and how they might be protected. Moore, an MD/PhD, is interested in biomarkers for Parkinson’s.

Considering the toll Alzheimer’s and Parkinson’s take on our communities, we prodded these neurogurus with questions: What sets off these diseases? Is there a way to prevent the development of Parkinson’s, as well? In people with this disease, the protein alpha-synuclein forms abnormal clumps within the brain’s dopamine cells. This brings up a chicken-or-the-egg question: Do the clumps themselves cause trouble, or is the disease caused because the protein—which is taken out of the cell of aggregating protein. Scientists have also identified “susceptibility genes.” These genes don’t cause Parkinson’s but, when mutated, increase a person’s risk of developing the disease.

A rare and particularly devastating form of Alzheimer’s, which strikes decades earlier than most cases, is caused by inherited gene mutations. The more typical late-onset Alzheimer’s is often associated with a gene called APOE4, but not everyone with it gets the disease. Most cases are not attributable to heredity—yet. DeKosky says it’s unlikely that a gene as powerful as APOE4 remains undiscovered, but that “there probably are other genes out there that have effects.” To accelerate this research, the National Institute on Aging sponsors a bank of genetic material from families with two or more cases of late-onset Alzheimer’s.

ROGUE PROTEINS

In Alzheimer’s, “We know that two different kinds of proteins in the brain are processed in a way that they aren’t supposed to be,” says DeKosky. A protein called tau forms tangles within neurons; and at some point, a protein known as amyloid-B amasses into plaques between neurons. It’s thought that the plaques probably contribute to the formation of tangles. Indeed, recent research shows that when plaques are cleared from mouse brains, so are very early tangles.

BANDING TOGETHER FOR NO GOOD

Proteins get together in suspect ways in Parkinson’s, as well. In people with this disease, the protein alpha-synuclein forms abnormal clumps within the brain’s dopamine cells. This brings up a chicken-or-the-egg question: Do the clumps themselves cause trouble, or is the disease caused because the protein—which is taken out of action once it bands into the clump—no longer does its usual job? No one knows.

DOES IT RUN IN THE FAMILY?

In 5 to 10 percent of Parkinson’s patients, the disease is inherited—what’s known as familial Parkinson’s. In these cases, the disease is caused by a single genetic mutation. So far, researchers have identified five genes that, when mutated, cause the disease. Scientists have also identified “susceptibility genes.” These genes don’t cause Parkinson’s but, when mutated, increase a person’s risk of developing the disease.

A rare and particularly devastating form of Alzheimer’s, which strikes decades earlier than most cases, is caused by inherited gene mutations. The more typical late-onset Alzheimer’s is often associated with a gene called APOE4, but not everyone with it gets the disease. Most cases are not attributable to heredity—yet. DeKosky says it’s unlikely that a gene as powerful as APOE4 remains undiscovered, but that “there probably are other genes out there that have effects.” To accelerate this research, the National Institute on Aging sponsors a bank of genetic material from families with two or more cases of late-onset Alzheimer’s.

PESTICIDES

People who are exposed to pesticides at work as well as those who live in a farming area and drink well water are three to seven times more likely to get Parkinson’s than the population at large. Pitt’s Greenamyre has shown that chronic, low-dose exposure to the pesticide rotenone causes Parkinson’s disease in rats and monkeys.

FREE RADICALS

Oxidative stress—the damage caused by free radicals—is probably part of the process that causes protein clumping seen in Parkinson’s patients. Free radicals can make proteins bind together and can also throw a wrench into the garbage-removal system that normally rid the cell of aggregating protein.

Unusual oxidative stress is apparent in Alzheimer’s, too, but it isn’t clear if that’s a cause or a symptom.

DYSFUNCTION WITHIN CELLS

Mitochondria are the major source of the free radicals that are generated within a cell. When mitochondria aren’t working properly, they produce many more free radicals than when they’re functioning normally. Accumulating evidence suggests that dysfunctional mitochondria are linked to the oxidative stress associated with Parkinson’s. But there’s a mystery involving the mitochondria. Parkinson’s patients have a defect in a certain mitochondrial enzyme (called complex 1) throughout their bodies—yet, apparently, only the dopamine cells in the brain malfunction. No one knows how a systemic defect can have such a selective effect.

HEAD TRAUMA

Several teams, including DeKosky’s, have described Alzheimer’s-like plaques in patients with traumatic brain injury, even as soon as two hours after an injury. What’s the connection? DeKosky and colleagues have shown that plaque-forming proteins increase after injury; they may leak from traumatized neurons.
AGING
The biggest risk factor for typical late-onset Alzheimer’s disease is advanced age. Just about 3 percent of Americans ages 65 to 74 suffer from Alzheimer’s, but up to half of those who are 85 or older may have it.
Parkinson’s strikes at an average age of 60 and is most common in those in their 70s and 80s.

SMOKING
Repeatedly, studies have found that smokers have a decreased risk of developing Parkinson’s. No one knows why. “Obviously we don’t want to recommend to people that they smoke, but if we could find out what it is about smoking that decreases risk, that would be important,” says Greenamyre.
And nicotine, curiously, reduces the plaques found in Alzheimer’s; however, in a mouse model it promotes the formation of tangles.

EXERCISE
Lace up those tennies. Exercise stimulates the growth of new neurons and increases the number of synapses and capillaries in the brain. (More capillaries mean better distribution of nutrients.) Exercise also increases the concentration of naturally occurring protective agents in the brain. In a 2001 paper published in the Journal of Neuroscience, Zigmond and his collaborators were the first to show that, in a rat model, exercise helps protect the brain against Parkinson’s. In his current studies with rats, Zigmond is examining how exercise protects the brain and what sort of exercise regimen is best. (Rodent pilates?) He’s also part of a small pilot study examining the impact of exercise on Parkinson’s patients.

CAFFEINE
Consuming caffeine decreases your risk of developing Parkinson’s. The more caffeine ingested, the less your risk. But before you make another pot of java, keep in mind that there are good reasons to kick the caffeine habit. For example, those with coronary artery disease or chronic renal disease should stay away from the brown stuff. There’s also data showing adverse effects of caffeine use during pregnancy and with other conditions.

GENDER AND HORMONES
Men develop Parkinson’s up to twice as often as women. Why? We don’t know. Some researchers are exploring whether estrogen helps protect against Parkinson’s.
There is no definitive evidence of a higher incidence of Alzheimer’s in either men or women. Although studies have shown less cognitive impairment in women who used hormone replacement therapy after menopause, estrogen treatment did not slow the course of Alzheimer’s when given early on and actually slightly increased the risk of dementia when studied as a preventative.

BAD BLOOD
One Pitt study found that cardiovascular disease results in a 30 percent increase in Alzheimer’s; another study found a 39 percent increased risk of Alzheimer’s in people with diabetes and elevated insulin. Accordingly, the Alzheimer’s Association asks you to “Maintain Your Brain,” that is, adopt healthy habits as a means of postponing Alzheimer’s.
“For all we talk about prevention, what we’re really talking about is delaying the manifestations of the disorder,” says DeKosky. “Could we push it back five years? That would halve the number of cases in this country. That’s our strategy until we have a very specific way to stop it from occurring.”
STOLEN
**CURRENT TREATMENTS**

**WHAT'S THE STANDARD OF CARE?**

**PARKINSON'S**
In 1961, Oleh Hornykiewicz, a Viennese pharmacologist, discovered that dopamine neurons died in the brains of people with Parkinson’s. In 1967, levodopa, a naturally occurring enzyme, was first used as a Parkinson’s treatment. Ingested orally, levodopa is transported to the brain, where it is converted to dopamine. It replaces the dopamine no longer produced by the damaged neurons and reduces Parkinson’s motor symptoms, including slow movement, stiffness, and tremors. More recently, drugs that mimic dopamine’s molecular role have been used to treat the disease, often in conjunction with levodopa. These “dopamine agonists” generally improve motor symptoms. Levodopa and dopamine agonists are the most commonly prescribed treatments for Parkinson’s.

**ALZHEIMER’S**
Among other treacheries, Alzheimer’s disrupts a network of cells that use the neurotransmitter acetylcholine. Although acetylcholine can’t be given medicinally, levels of it are increased by drugs that interrupt its normal breakdown, resulting in improvement or temporary stabilization for patients.

A newer drug holds promise, as well. Cells responsible for memory storage and learning rev into high, sustained activity when powered by the neurotransmitter glutamate. But too much glutamate floods Alzheimer-afflicted brains, overstimulating receptors and killing cells—imagine how a moped souped up for jet propulsion would rip itself apart. The newest drug approved for the treatment of Alzheimer’s, memantine, blocks one kind of glutamate receptor, permitting enough activity for cognition while protecting neurons from overstimulation.

---

**RARE TREASURE**

Nuns and priests from more than a dozen Catholic orders are volunteers in two long-term studies of aging and Alzheimer’s, one run by the University of Kentucky in Lexington, the other by Rush University Medical Center in Chicago. Participants not only undergo yearly cognitive and physiological testing, but also donate their brains at death whether or not they have Alzheimer’s—meaning scientists now have a stable supply of diseased and healthy brains to study—a rare treasure.

Nearly 700 Roman Catholic School Sisters of Notre Dame from chapters all over the country volunteer in Kentucky’s so-called Nun Study. You may recall one of their most surprising—and widely reported—findings: In the ’80s it was reported that women in their 20s with the least facility with written language, as demonstrated in archived autobiographical essays, had more cognitive impairment in old age and more culprit tangles among neurons in their brains at autopsy than their eloquent contemporaries. But what does this really tell us? Does exercising your brain when young protect against Alzheimer’s? Or does Alzheimer’s cause subtle cognitive deficits as early as one’s 20s? We can’t answer that yet, says Pitt’s Steven DeKosky.

But then there were other findings that appeared to link learnedness and late-life lucidity. The Religious Orders Study at Rush found that the more years of formal education participants had, the higher the level of cognitive function they were able to maintain, even when their brains were riddled with plaques associated with Alzheimer’s. DeKosky, who collaborates with the Rush team, reminds us again that correlation is not causation: Formal education may train people’s brains to solve problems like the ones in neuropsychological tests in novel ways, ways that work around damaged neurons. And animal studies have shown that mental stimulation builds thicker brains with more synaptic contacts; perhaps people with similarly bulked-up brains maintain cognitive function even as they lose tissue to disease.

“When we look at... a population and come up with a finding that says, ‘Yes, [education] is protective,’ the explanation is in fact that which made us hypothesize that we might see this in the first place,” says DeKosky. “But we certainly can say, ‘Look, this will not hurt you.’”

One of DeKosky’s roles in the Religious Orders Study is to characterize the brain pathology of mild cognitive impairment, which is often a precursor to Alzheimer’s. To his surprise, a brain enzyme that was thought to be deficient in mild cognitive impairment is actually overabundant, probably produced at higher levels to compensate for dying neurons. Another finding is that a type of neuron thought to be completely devastated by Alzheimer’s actually dies off in a certain pattern; some of those neurons even persist through the worst of the disease. In a disease with such a long course, these findings will help doctors know what to treat and when. “It’s helping us to map out the most vulnerable areas,” says DeKosky, “[to understand] at any specific level of severity of the disease, what is the underlying structure of what’s left? What’s dead, what’s hurt, and what needs to be saved?” —LK
SHOOT TO CURE
Alzheimer’s has no cure and few palliative treatments. So when Elan Pharmaceuticals announced in 1999 that its vaccine cleared Alzheimer’s plaques from mice, it seemed that there would finally be a new, robust therapy for the disease. A limited trial of the vaccine began in 2001—the company suspended it a year later when four of the 97 participants showed signs of encephalitis. The good news? In the two years after they were immunized, the patients who mastered the highest anti-body response had less cognitive decline than controls, and autopsies of participants who have died since treatment confirm clearance of plaque from the brain.

Seeking a safer alternative than stimulating the patient’s own immune system, Elan developed a treatment of lab-made antibodies to thwart plaque. Pitt’s Alzheimer’s Disease Research Center was one of just four centers participating in safety trials last year and will now participate in Phase II trials to judge the antibodies’ effectiveness.

PARALLEL PLAQUES
People who use cholesterol-lowering drugs have a reduced risk of developing Alzheimer’s—perhaps by a whopping 70 percent. DeKosky’s team is participating in a National Institute on Aging–funded multicenter trial of Zocor to study how it influences cholesterol and Alzheimer’s risk; similar trials are under way on other statins. It appears that statins promote the normal breakdown of the protein that is mismetab-

CUT AND PASTE
Alzheimer’s plaques result when the wrong enzyme clips a protein in the wrong place. Eli Lilly has successfully completed a safety trial of a drug that shuts off that errant enzyme. Therapies aimed at other enzymes are in earlier stages of development.

Alzhemed, a new drug developed by the Canadian firm Neurochem, inhibits the action of a sticky carbohydrate molecule that helps protein bind into plaques. Pitt’s Alzheimer’s Disease Research Center will participate in efficacy trials of the therapy.

PRO ANTI-INFLAMMATORY
Large-scale studies of other diseases show that people who took nonsteroidal anti-inflammatory drugs for several years had a reduced risk of Alzheimer’s. In 2001, the National Institute on Aging embarked on a prevention study involving up to three years of treatment with the anti-inflammatories celecoxib and naproxen but halted it in December 2004 when an unrelated cancer trial linked celecoxib to increased risk of heart attack and stroke. The search for anti-inflammatories from other drug classes continues.

THOSE MUCH-TALKED-ABOUT STEM CELLS
Replacing the cells that die in Parkinson’s with new dopamine neurons derived from stem cells may one day cure the disease—but this avenue of research is probably the furthest from realization. Why? For one, getting stem cells to turn into dopamine neurons is tricky. “Right now, we have very little control over how stem cells differentiate,” says Greenamyre.

SPECIAL DELIVERY
Delivering genes into Parkinson’s-afflicted cells could stimulate the cells to produce more naturally occurring protective agents, which might revive dying neurons. But there’s at least one problem with this approach. Once a gene therapy treatment is delivered, it can’t be reversed. What if the cell starts pumping out so much of the protective agent that the patient has unexpected side effects? Researchers are now trying to develop reliable methods to turn the gene on and off once it has been delivered into the cell.

Similar strategies are being applied to Alzheimer’s: A small safety and tolerability study of a compound called CERE-110 is happening now. In the study, patients receive a shot of the compound. The needle is placed in the basal forebrain (the site most often affected by Alzheimer’s), where the compound ushers into cells a gene for nerve growth factor. Another gene, APOE2, confers protection from Alzheimer’s. Lilly Research Laboratories recently reported that when mice with Alzheimer’s-like plaques had the gene injected into their brains, 30 to 50 percent of the plaques were cleared from the brain’s memory center.

LOOK WITHIN
Our bodies may already manufacture solutions for staving off neurodegeneration. The brain produces compounds that promote cell survival; they’re called trophic factors. Studies suggest that boosting the levels of trophic factors within neurons might help shield them from Parkinson’s. One trophic factor in particular—GDNF—has been the focus of much Parkinson’s research. Pitt’s Michael Zigmond studies how GDNF protects neurons. Other researchers are trying to find ways to effectively deliver GDNF, which doesn’t cross the blood-brain barrier, to patients. So far, clinical studies have shown mixed results.

Along the same lines, researchers may already have their hands on the first neuroprotective drug for Parkinson’s. Patients treated with coenzyme Q10, an antioxidant produced normally by the body, showed improvement. When patients took the enzyme orally in high doses, they had fewer disabling symptoms—the higher the dose administered, the more the patient benefited. The enzyme appeared not only to relieve symptoms but to actually slow the progression of the disease. Yet the study of 80 patients was too small to be conclusive.

“The treatments that we have right now for Parkinson’s, as far as we know, just treat the symptoms,” says Greenamyre. “They don’t keep the disease from getting any worse. So the Holy Grail right now is neuroprotective therapy, treatments that are either going to slow or prevent the progression of the disease.”

VITAMIN ENRICHED
In 1998, after a large clinical trial, researchers reported that high doses of vitamin E, an antioxidant, showed no benefit in slowing the progression of Parkinson’s. Afterward, the idea of treating Parkinson’s patients with
antioxidants fell out of favor, says Greenamyre: “People assumed that because vitamin E didn’t work, that no antioxidant would work. But it turns out that vitamin E doesn’t get into the brain very well, and the researchers might not have used high enough doses.” If there were a way to deliver more vitamin E into the brain—through higher doses or by modifying the molecule so that it crosses the blood-brain barrier more easily—E might be just the thing.

Vitamin E may do double brain duty. When taken with vitamin C, at levels a bit higher than the U.S. recommended daily allowance, it reduces the risk of sporadic Alzheimer’s.

And as it turns out, vitamins that keep our cardiovascular system in balance may keep us sharp as well. An amino acid called homocysteine is metabolized with help from folate and vitamins B6 and B12. When these vitamins are deficient, too much homocysteine circulates as the brute in a broad swath of cardiovascular destruction. In one study, people with the highest levels of this amino acid had nearly twice the risk of developing Alzheimer’s within a decade or so. Pitt is participating in a study of folate, B6, and B12 to see whether these vitamins reduce cognitive decline in early Alzheimer’s.

**GO HERBAL?**

While ginkgo biloba is hawked as a memory enhancer, Alzheimer’s researchers are interested in it as a powerful antioxidant and therefore, a potential preventative. To determine whether daily ginkgo intake maintains cognitive function, DeKosky is heading a five-year, multicenter study of 3,000 elderly people without dementia.

**CURRY CURIOUS**

Mary Ganguli, a Pitt professor of psychiatry and epidemiology, was the first to report on the low incidence of Alzheimer’s in the Indian subcontinent. She compared populations in Ballabgarh, India, and the Monongahela Valley, where the rate of Alzheimer’s is nearly four times higher. A new study shows that the Indian diet may contribute to this difference. Curcumin, the tasty stuff that gives curry its amber glow, prevents plaque buildup in rodents. When injected into the veins of mice with Alzheimer’s-like plaques, curcumin was able to cross the blood-brain barrier. (Bridging this divide has been a big challenge to the development of new therapies.)

By the time people develop symptoms of Parkinson’s, 80 percent of their dopamine neurons have already been damaged. If researchers can develop therapies that prevent or slow degeneration related to Parkinson’s, doctors will want to administer them early—before symptoms develop. But how can anyone diagnose Parkinson’s before a patient has symptoms? The clues may be just a sniff or tap away (see “Do You Smell That?”).

Likewise, as research reveals aspects of the Alzheimer’s disease process that begin long before cognitive decline is obvious, the window for intervention widens. But, here again, it isn’t always clear who needs treatment, though Pitt researchers are making great strides in this area. Last year, with collaborators in Sweden, William Klunk and Chester Mathis, of the departments of psychiatry and radiology respectively, were the first to view plaques in living brains. They just received the prestigious MetLife Foundation award for that work.

And there are other clues to the presence of the disease. Alzheimer’s patients often first experience mild cognitive impairment, which includes subtle deficits that don’t interfere with everyday living—like more memory loss than is typical for one’s age. DeKosky’s autopsy studies of people with mild cognitive impairment (who succumbed to other illnesses) show that about 60 percent had Alzheimer’s pathology in their brain tissue, so there are compelling reasons to begin neuron-preserving therapies early. Unfortunately, a PIND study shows that mild cognitive impairment is recognized by primary care physicians just 23 percent of the time. Now researchers are looking into what variants of the condition are likely to progress to Alzheimer’s. They’re hoping to find biomarker and imaging tests that are sensitive and cost-effective enough for mainstream clinical use. And they’re assessing neuropsychological tests for detecting mild cognitive impairment. For example, Judith Saxton, a PhD associate professor of neurology and psychiatry, is developing a test that runs on a tablet PC; patients can take it while they wait to see a doctor.

“I think it’s extremely important to diagnose [these diseases] early,” says Greenamyre, “particularly if we are on the track of neuroprotective therapies. The earlier you begin it, the better.”

---

**IF WE CAUGHT IT SOONER**

**COULD WE STOP NEURODEGENERATION IN ITS TRACKS?**

Early detection may come down to a puzzle of the proboscis. Your ability to detect certain odors may help your doctor determine whether you have Parkinson’s disease—before you ever develop symptoms. Another clue may be how fast you can tap your foot. Pitt neurologists discovered that these two markers correlate well with impairment of dopamine pathways in the brain. Robert Moore and Nicholas Bohnen, assistant professor of neurology and radiology, figured this out by studying people who had an inherited form of Parkinson’s but hadn’t reported any symptoms.
In a glass vial, fruit flies climb the walls. They’re gnat-like specks, the same flies likely to gather around ripening fruit left on a kitchen counter. Today, Michael Palladino’s lab is nearly filled to capacity—up to 200 flies per vial, 60 vials per metal rack, dozens of racks arranged on shelves that line the walls. All total, he’s looking after about a million flies. There are a few normal flies, and 500 different types of mutants, mutants galore. This PhD assistant professor of pharmacology wants to help find new drugs to treat neurodegenerative diseases. To help him in this endeavor, he has enlisted this made-to-order army of Drosophila.

Palladino’s fly-brain story starts back in 2000. That’s when he treated some flies with a chemical to “mutagenize” them. Mutagenizing a fly means you introduce a random mutation into one of its genes. Palladino’s lab came up with and examined about 600,000 flies, each with a different single random mutation. He’d produced flies that had a strange eye color or were missing a bristle—those didn’t interest him. Palladino was looking for flies that behaved abnormally.

He picked out the flies that were acting oddly. Some didn’t walk well, had problems flying, or couldn’t mate normally. Others appeared fine at first but became paralyzed if you raised the room temperature to 98 degrees Fahrenheit. Some didn’t respond well to being “vortexed.” Vortexing flies means taking the little vial they’re in and shaking it. A normal fly is unfazed, but Palladino found that some mutants were temporarily paralyzed by the shake-up. Altogether, out of 600,000 flies, he found 200 that had some kind of behavioral problem.

One by one, Palladino started looking at the brains of those 200 flies. The aberrant behaviors were really just a screening device. (He kept in mind the behavior might have been caused by brain damage.) His underlying goal was to find mutants with neurodegeneration. Of the 200, he found 15.

A fly neophyte visiting his office looks at the numbers—600,000 to 15—and makes the mistake of saying, “Only 15?” “You say ‘only,’ but that’s great,” the young scientist replies with a laugh. Finding those 15 mutants monopolized a year and a half of his scientific life.

But finding the mutant flies was just the first step. His next challenge was to use them to investigate what might protect the brain. For one study, he picked out a strain whose mutation resulted in neurodegeneration. These flies were paralyzed by heat. Two generations and mutations later, he’d created a brood of flies—about 100,000—with the initial neurodegenerative mutation and a second random mutation. Palladino was hoping to find flies among this generation whose second mutation somehow compensated for the first. He wanted flies that had inherited the mutated neurodegeneration gene but didn’t exhibit neurodegeneration. Examining all 100,000 brains would have taken ages, so he looked for flies that no longer became paralyzed when he raised the temperature. Of the 100,000, he found 30 that could continue moving in a heated vial.

Now he’s in the process of inspecting the brains of those 30. If he finds one with a normal brain or with minimal damage, he will look for the gene that conferred the protective effect. His hope is to find proteins, and perhaps a whole pathway of biochemical events in the brain, that can offer protection—even in the face of adverse events like a mutation that might contribute to a disease like ALS.

He and others could then look for chemical compounds that would make this protective pathway more active.

“Using that approach for studying neurodegeneration is a great idea,” says David Featherstone, assistant professor of biological sciences at the University of Illinois at Chicago. “It does two things—it identifies potential drug targets, but it also sheds light on the process [of neurodegeneration] itself. So, in a way, it kills two birds with one stone.”

“If there’s a pathway that you can modulate that acts as a general neuroprotectant, then it wouldn’t matter whether we’re talking about Alzheimer’s, ALS, Huntington’s—it’s all the same; neurons are dying,” says Palladino. “If we can find a way to slow or stop that process, that’s exactly what we need.”
One Saturday when I was 8, my Dad began loading his saltwater fishing gear into the trunk of our family’s Ford Fairlane. I must have been watching him pack with pleading eyes. I loved riding in the car with him, whether it was short drives to the grocery store or longer trips to visit my grandparents in New Jersey. There was something about his confidence in the driver’s seat that made me feel safe and happy.

Whatever the reason, I was thrilled that day when he asked me to tag along—just me, not my pregnant Mom, not my little brother. After lunch, we left our suburban ranch house on the outskirts of Richmond, Va., and headed for the salt air of Virginia Beach. When the weather was good, he liked to drive with the window down and the breeze gushing in. He would gently guide the steering wheel as if he were a wizened captain at the helm of a boat he had piloted for years. I can still see him behind the wheel, a handsome 34-year-old, with blonde short-cropped hair, in a white cotton crew shirt and khaki pants.

When he drove, he was relaxed, even joyful. I think driving pushed his worries aside. It pulled him out of his life as a struggling industrial salesman and father with too many bills, two children, and a baby on the way.

On the road, he was free. To be allowed into that world was special, and I knew it, even then.

I don’t remember a lot of specifics from that all-night fishing trip. Just a long, long pier, a sense of dark humps of water moving, and the whooshing beat of the ocean against the shore. I don’t even remember how many fish Dad caught, or if he caught any—that wasn’t the point, really. It was just to be out there, together, under a canopy of stars.

Through the night, he drank black coffee from white Styrofoam cups. He started drinking coffee as a teenager in the navy, standing watch on the deck of a destroyer escort in the North Atlantic. At home, I rarely saw him without a cup nearby—and that never changed in all the years I knew him, until one day toward the end of his life.

As I approached his place, it was mostly dark. The porch light was off, even though I had called him during the workday to say I would visit. I knocked on his door. It took several knocks for him to answer. “Oh!” he said, as he opened the door. “This is a nice surprise. I didn’t know you were coming.”

The dining room and kitchen lights were off. He had been in the living room watching TV. More than a year ago, I’d taped the remote control so that only the power button and the up-down buttons for volume and channel selection were usable. It had become clear that Dad couldn’t handle anything more complicated. He’d already stopped collecting and listening to music and comic recordings. (When I was a kid, the voices of Andy Williams, Julie London, Bill Cosby, and Ray Stevens kept us company.) Now, even a manual radio tuner befuddled him.

I flipped on the kitchen light. The sink was nearly empty. No pans. No glasses. No coffee cups. It had been two days since my last visit, and usually the sink held a pile of unwashed dishes.

“Dad, have you been eating?” I asked.

“I think so,” he said, then chuckled. But it was clear he was uncertain.

“What did you have for supper?”
He hesitated, looking at me blankly, then said, “I’m really not sure.”

Then I noticed his Mr. Coffee brewer, with its patina of stains from constant use. The machine wasn’t in its usual place on the counter. A few clean coffee filters were strewn nearby. A red Folgers can sat on the Formica, unopened. No coffee cups. My father had forgotten how to make coffee.

In this small moment, I understood the ferocity of Alzheimer’s. The disease had been whittling away at him, and the whittling had deceived me. It had started simply enough. Repeating comments made only minutes earlier. Forgetting to pay bills. Leaving milk and meat in the refrigerator too long. At one point, he began telling my brother, my sister, and me that he felt like “a short boy in tall grass.” He’d laugh about it, but I could tell it scared him. He was getting lost.

Then he began really getting lost on drives to familiar places. Eventually his doctor insisted that he give up his car. On the spot, Dad gave me the keys to his decade-old Pontiac Grand Prix, which still amazes me. Driving was his last great love, his final shred of independence.

He slipped further and further into some fog, where time had stopped. He couldn’t tell you the day, or the year, or much else. He was reduced to a craggy, silver-haired man sitting at a small kitchen table, drinking coffee and smoking cigarettes.

But then his disease took even that away from him. Not long after he forgot how to make coffee, we moved my father to an assisted-living setting that specialized in Alzheimer’s disease. Less than a year later, he was dead.

On the day he died, I was driving his battered Grand Prix. When I left his bedside and returned to the parking lot, the afternoon sun lingered in a sea of white clouds. It was a Saturday much like the one we’d shared at Virginia Beach. I walked over to the Pontiac, but the driver-side door wouldn’t open. The lock had inexplicably jammed. Nothing I tried would open it. Despite many attempts over several weeks, that door never opened again. I like to think it’s because my Dad has reclaimed what was his. He is driving his very own car on a scenic road, past fields and woodlands, toward salt air. He has the window down, the radio on, and he remembers everything.

Cindy Gill is editor in chief of Pitt Magazine.

If you have a story to share about how neurodegeneration has changed your life, we encourage you to send us a letter about it (medmag@pitt.edu).
How can anyone perform brain surgery without manipulating critical arteries, cranial nerves, or the brain itself? Without even making an incision? Pitt surgeons have figured out a way that involves fewer complications than traditional methods: They work through the nostrils with minimally invasive tools.
Peruse the back issues of a few medical journals, and you will find detailed accounts of surgical innovations performed, at the time they were written, on just a few occasions or perhaps a single time. Spreading the word early on is how the science and art of surgery advance. Being first and publishing first ensures that credit is given where credit is due.

Why, then, did a handful of surgeons in the University of Pittsburgh School of Medicine not say a thing for five years about a new procedure they knew would astound their peers? They were removing cranial tumors the size of baseballs without leaving a scar. They were sending patients home and sometimes even back to work in a matter of days, with no outward sign that these men and women had undergone major brain surgery. They’d performed hundreds of procedures, most of which had the potential to set the neurosurgical field on its cranium, and still not a peep. Forget publishing—they wouldn’t even discuss what they were doing with colleagues from other academic medical centers.
“You try to explain to a neurosurgeon that you took out the upper part of the spine through the nose, and they think you’re certifiable at that point.”

Amin Kassam, a Pitt associate professor of neurological surgery and one of the key conspirators, explains, “We understood that when we brought the work out, it had to be at a level that it could withstand a lot of important criticism.” Then he adds, “The work is just so unimaginable for most neurosurgeons.”

This is what was previously unimaginable: using minimally invasive technology to work inside the skull through the nostrils. No incisions. No manipulation of the brain, critical arteries, or cranial nerves. Just one or two long telescopic instruments in each nostril, plus an endoscope. For starters, the surgeons drill a hole the size of a thumbnail through the bottom of the skull. Depending on where they create this opening, they gain access to points inside the skull from behind the brow to the top of the spine and out toward the temples.

Reaching the base of the skull has always been problematic. The gamma knife does it with radiation and no incision, but it won’t work for all tumors or all patients. Sometimes, a neurosurgeon has no choice but to reach inside the skull with surgical tools. For years, this has required very large openings in the skull. Going in from above, surgeons use long metal retractors to pull the brain aside and hold it there. The risk? Permanent damage to this sensitive brain tissue.

Another approach goes by strikingly blunt, mechanistic monikers: facial disarticulation or facial disassembly. Surgeons peel skin back from most or all of the patient’s face. They remove large chunks of the skull and the facial bones to access the skull base from beneath (which means the patient must later endure extensive reconstruction). The brain is not manipulated, but other complications associated with this approach can be devastating. It can damage nerves and structures related to facial expression, swallowing, and breathing.

When Kassam came to Pitt in 1997, surgeons like Carl Snyderman and fellow Pitt otolaryngologist Ricardo Carrau were learning to navigate the sinuses with endoscopes. They removed tumors and other malformations right up to the skull base. “We would stop at the bone that separates the sinuses from the brain,” says Snyderman (Res ’87, Fel ’89). “We were working between the eyes and below the brain. That was what many people were doing, but then we started to take the tissue off the bone around the eye. We started to take the bone off below the brain but not go into the brain, and so we just slowly progressed.”

Kassam, fresh from a neurosurgical residency in Ottawa, saw what they were doing and realized these head and neck surgeons were on the doorstep of minimally invasive skull base surgery. To figure out how to transform Kassam’s vision into reality, the surgeons cleared their schedules one day and sat down in a room in UPMC Presbyterian to identify obstacles and plot a course for overcoming them. After several hours and numerous containers of takeout, they laid out a long series of steps—such as partnering with industry to design new instruments—that they knew would take years to accomplish. They agreed that progression would be slow and systematic, and that nobody would publish a word until they had 300 cases under their belts.

The approach from below was so foreign that the first task was to define the anatomy from that perspective. Surgeons were unable to look at the bottom of the skull and know which bump of bone hid the optic nerve or carotid arteries. These Pitt surgeons made it their business to map the skull base. As patients who could benefit from this approach arrived at the Department of Neurological Surgery, the team stepped cautiously, methodically, and gradually into the skull base. One of their first cases was a pregnant woman losing vision because of a grape-sized tumor compressing her optic nerve. They removed it through her nose. It took about two hours, and she regained her vision the next day.

“But we knew we hadn’t changed the world,” says Kassam, reviewing case histories in his office, “because we knew that if we went to neurosurgeons and said, ‘We removed a grape from this space,’ they would say, ‘Come back when you have to take an orange out.’ So here’s an orange.” He gestures to a brain scan on his computer screen. “It’s a cylinder, and all this white stuff you see is engorged brain. Swollen. So if I have to manipulate this brain, this brain has a high likelihood of not functioning right when I’m done.” Instead, he says, his team removed the tumor through the nose, bit by bit, without touching the brain.

A typical operation proceeds with Snyderman and Kassam on either side of the patient. They hold pistol-grip instruments; thin cables snake into the patient’s nostrils. Snyderman, 49, an associate professor of otolaryngology and of neurological surgery, is slight of build with a narrow face. With angular spectacles perched between his surgical cap and mask, he seems the more professorial of the two. Kassam, at 10 years younger, could pass for an entrepreneur of the dot-com generation. He has the friendly intensity and demeanor of someone who just left grad school, framed his MBA, and took his company public all in the same week. The two are codirectors of Pitt’s new Minimally Invasive Neurosurgical Center.

To reach a tumor resting on the skull base, the surgeons will drill through the base of the skull and land right on the tumor without manipulating the surrounding brain tissue, nerves, or arteries. Snyderman drives the endoscope and periodically taps a pedal with his foot to flush the lens clean with water. Kassam manipulates a device for suctioning blood and other fluids through one nostril; through the other, he controls an ultrasonic aspirator, which disrupts tissue and sucks it out all at once. An observer might momentarily forget the patient on the table, because both surgeons’ eyes are glued to a video screen showing a patch of red flesh and the steel tips of Kassam’s instruments. With the ultrasonic aspirator, Kassam strips away tumor, working outward until he can peel the last layer right off the brain.

Speaking at an annual congress of neurological surgeons in November 2003, Kassam let the cat out of the bag. He and his colleagues had performed 312 endoscopic approaches to the skull base in the previous five years. The initial reaction: denial. As Kassam described case after case of progressively more difficult and complex skull-base surgeries, the denial changed to anger. Maybe you’re doing it, but you shouldn’t.

“There has been a lot of resistance and skepticism from what we would consider the giants or the very senior people in this area of surgery,” says Snyderman.

“You try to explain to a neurosurgeon that you took out the upper part of the spine through the nose, and they think you’re certifiable at that point,” quips Kassam. But this exact procedure, for an elderly woman whose spine was impaling her brain stem after years of spinal degeneration, was a natural extension of their endoscopic abilities. It was the safest way to proceed—an open procedure would have required splitting open the back of her mouth, potentially compromising her ability to breathe and swallow.

“I think the misconception is that we’re just going in blindly and pulling out tumor without seeing the brain or nerves or blood vessels,” says Snyderman. “There’s nothing blind about what
Amin Kassam (left) and Carl Snyderman

we’re doing. We see everything.”

“At first people would send their residents here to spend some time with us to find out what the gimmick was,” says Kassam. “And the resident would go back and say, ‘There’s no gimmick. They are really doing it. They are doing this through the nose.”

What was so hard to comprehend? Meet Sandra (not her real name), who was referred to them when she was a little slip of a girl, not yet 4. Sandra suffered nosebleeds so terrible they sent her parents rushing for bath towels, because tissues weren’t enough. One night, she lost most of the blood in her body and landed in the ICU. The culprit: a mass of abnormal arteries and veins growing within her skull base. “Like a bag of worms hiding in a moth-eaten bone,” was how Snyderman described this arteriovenous malformation (AVM). As it grew, it stole blood from her carotid arteries. Inevitably, it developed weak spots that periodically burst.

Typically, a tumor has a number of vessels supplying it with blood. Each can be clipped and cauterized to isolate the tumor for removal. (The notion of handling vessels in the skull base endoscopically set off alarms with Snyderman and Kassam’s peers. Eventually, you’re going to get bleeding you can’t control, they’d say. You’ll be handcuffed, and the patient will die on the table.) In Sandra’s case, the entire mass consisted of blood vessels.

Some say that surgeons are conservative by nature. (The endoscope has revolutionized several areas of surgery, points out Snyderman, but it has always been met first with resistance.) Carrau, a professor of otolaryngology and of neurological surgery, is sympathetic to the initial reactions of some of his colleagues: “You have to understand what this is like for the people who have not done this before.” He explains that most neurosurgeons are used to manipulating instruments through sizeable wounds—space enough to move their hands to clamp vessels or cut away tumors with traditional instruments. This work has never been easy, but “when you are going through the nose,” says Carrau, “you have a limited scope and the instruments are very small. You have to change your technique. For someone who doesn’t understand how that’s done, and who’s not familiar with the instruments, it would seem like an impossible task.”

The Pitt team had always advanced cautiously, developing the tools and the skills to deal with aggressive bleeding before it even happened. But this little girl and her AVM made them especially wary. They’d worked in this area of the skull base, but not with so many blood vessels. They tried an open procedure first, removing a chunk of skull at her forehead to reach into the skull base without manipulating her brain. But she was so tiny that before the surgeons had made a significant dent in the AVM, she had already lost too much blood. They had no choice but to do it through the nose.

After a few weeks of recovery from the open procedure, Sandra went back to the OR. Snyderman (or “Dr. Spiderman,” as Sandra sometimes calls him) began by inserting the endoscope in one tiny nostril. Through the other, he used forceps to take down the soft honeycomb-like sinuses and reveal the bone that hid the AVM. Kassam and Snyderman inserted a diamond drill to begin removing the bone. It whirred softly in the little girl’s head as they watched the video screen. Her skull base was like Swiss cheese, with every hole filled with blood vessels. The finer ones sealed automatically with bone dust. For the larger vessels, Kassam worked with a suction device in one hand and an electro-coagulator in the other. As he cauterized each vessel, a bit of smoke went across the screen and into the suction. Sandra’s blood pressure dropped as he suctioned blood away. He talked with the anesthesiologist as he proceeded. Kassam’s end of the conversation essentially consisted of the question, How much time have we got?

They had enough time. The AVM was repaired in several stages, a few weeks apart. The before-and-after images are like aerial shots of a river during and after a 100-year flood. In one frame, the fluid of life flows everywhere and in every direction, inundating every available space. In the final image, it is restored to one central artery with an orderly series of tributaries. Sandra is doing well and is in first grade now.

D enial and anger are giving way to serious interest. A few other groups are now experimenting with the approach. In September, Pitt will host the first world congress of endoscopic skull-base surgery. The Pitt team teaches a course for surgeons three times a year—an astounding nine chairs or section chiefs came in the first year. But developing proficiency takes a long time, probably four years of additional training.

The most difficult problems to overcome can be the most basic. Sometimes, when Snyderman momentarily hands the scope to a resident or junior surgeon, the surgery cannot proceed because it’s so difficult to maintain a view without getting in the way. Manipulating instruments that you only see on a video screen is “like playing Nintendo,” notes Kassam. But it’s not child’s play. Kassam seems to have a preternatural ability to use both hands to navigate space that he cannot see—talents he traces back to his father, an automobile mechanic. His dad made him change spark plugs without using his right hand and oil filters without looking at them. This was the only way to become a good mechanic, from the elder Kassam’s point of view. It also turned out to be great basic training for an endoscopic surgeon.

It’s now approaching two years since these Pitt surgeons went public with the expanded endonasal approach. They are in high demand as surgeons, teachers, and now as private consultants, regularly rushing from appointment to appointment, from operating room to airport. “We’re victims of our own success,” Kassam says now, moments after being informed he’s already running late for the airport, but he says it with a smile.
Here comes Dr. De, hustling down the hall on the 10th floor of the American Medical Association building in downtown Chicago. She’s about 5-foot-4 in those low-heeled shoes and black pants. Where’d those chalky fingerprints come from? she’s asking herself, brushing at her legs furiously. She’s missing an earring. It’s 8 a.m., and the editor in chief of the *Journal of the American Medical Association*, one of the most influential publications in the world, looks like she’s already gone into battle. She likes to be at her desk by seven. On days when she feels a little sluggish (or she senses her staff does), she blasts the *William Tell* Overture from her corner office to rally her troops. Today, there’s no need. She’s moving so fast to her office, it’s hard to keep up.

"Some people might say I’ve reached a point in my life where I’m not afraid. But I’ve never been afraid," says Catherine DeAngelis.
DeAngelis thinks journal editors working together can “keep the drug companies honest.”

Catherine DeAngelis—she prefers Dr. De—is the first woman to be editor in chief of *JAMA*. A graduate of Pitt’s School of Medicine, member of Pitt’s Board of Trustees, and a professor of pediatrics at Johns Hopkins University, she was born and raised in Old Forge, Pa., the granddaughter of Italian immigrants. You can hear that heritage in her accent, the way she punctuates her sentences with “You’re outta your mind!”—her version of fuggedaboutit.

You can hear it when she calls out to each of her 80 employees, offering a friendly wave while passing his or her desk, or pausing to talk for a moment before burrowing on through the maze of cubicles to her back corner office, rubbing her hands together the whole time as if warming them before a fire. She passes a wall of framed, mostly black-and-white 8-by-10 photographs—displaying the faces of all the men who have held her position since *JAMA* published its first issue 121 years ago. Bearded and expressionless, they seem like an intimidating bunch. She gives them an appraising look. *The boys,* she calls them.

The last “boy” on the wall is George D. Lundberg. The physician editor was fired in 1999 for publishing a study on how adolescents define sex, which the AMA said inappropriately brought *JAMA* into the controversy surrounding President Clinton’s impeachment trial. At the time, DeAngelis was the vice dean for academic affairs and faculty at Johns Hopkins and the editor of the *Archives of Pediatrics & Adolescent Medicine*, one of *JAMA*’s nine specialized publications. She says she and the other eight archives editors were infuriated by Lundberg’s firing, which they saw as a violation of *JAMA*’s editorial freedom. While the administration searched for Lundberg’s replacement, she championed a proposal that said *JAMA*’s future editor would report to a 17-member journal oversight committee, not the association’s managers. She took it upon herself to rally the other editors: “I said, ‘Guys”—cause they’re all guys—‘let’s get them to sign this, or we’ll all resign.’”

The editors agreed, and to her surprise, so did the AMA. Then—surprise again—she was asked to become *JAMA*’s new editor in chief. She accepted.

In her regular editorials, she has become one of the loudest and most persistent critics of the healthcare and pharmaceutical industries. She’s also increased the journal’s influence. Its “impact factor,” or the number of times *JAMA* articles are cited, has doubled in the last five years.

In 2004, she led the International Committee of Medical Journal Editors’ (ICMJE) efforts to stop pharmaceutical companies from suppressing scientific studies that reveal the negative effects of their products. Drug companies rely on the major medical journals to make the results of their studies public, so DeAngelis suggested that journals should refuse to publish any study unless the results of all related clinical trials are published on a public registry, such as www.clinicaltrials.gov. DeAngelis thinks journal editors working together can “keep the drug companies honest.”

In 2002, she showed how much influence the major medical journals could have when she published groundbreaking findings by the Women’s Health Initiative. The study revealed that estrogen-progesterone hormone replacement therapy was linked to increased risk of invasive breast cancer, coronary heart disease, stroke, and pulmonary embolism. (Her colleague at Pitt, Lewis Kuller, professor of epidemiology, was an investigator on the study.) *JAMA* published subsequent findings that the therapy made breast tumors difficult to detect and contributed to urinary incontinence and dementia, particularly in women older than 65. The study was widely cited in the media, and doctors throughout the world reconsidered what they prescribed for postmenopausal women.
Of her tendency to speak freely and passionately about her opinions on the state of health care and to tackle everything from the pharmaceutical companies to the FDA in her frank editorials and media interviews, she says, “Some people might say I’ve reached a point in my life where I’m not afraid.” (DeAngelis turned 65 in January.)

“But I’ve never been afraid.”

“Everything that I value has very little monetary worth,” she explains. “They can’t take my family. They can’t take my knowledge. What are they gonna take, my job?” She laughs.

“Take it! I’ll get another one.”

After all, this was not the trajectory she’d envisioned when she started her career. She wanted to be a medical missionary and surgeon, but “somebody who didn’t know what he was talking about” told her women became doctors by studying nursing first, so she got her RN.

She started out in nursing with every intention of joining the Maryknoll Missioners, an order of Catholic nuns who devote their lives to service overseas. But taking a year of religion classes, as the sisters suggested, didn’t appeal to DeAngelis. Instead she went to Wilkes College, in Wilkes-Barre, Pa. (now Wilkes University) as a premed student. Then she applied to medical school at Pitt. She’d still minister to the sick, but not exactly according to plan.

“You make plans, and God laughs,” she says.

DeAngelis still attends Mass every Sunday, even when she’s at a JAMA meeting in a far-flung corner of the world. (Her husband, a Protestant, usually helps her find the nearest church). She says that the humility, social concern, and openness to divine providence that have distinguished her career grow from strong Roman Catholic roots.

Her warmth puts visitors at ease. In fact, until she eyes your lunch plate with concern, and reminds you that you shouldn’t eat so much red meat, you might forget that you’re eating a medium-rare hamburger in front of one of the most powerful people in health care, a woman who has been breaking down barriers in the profession since she walked through the doors of Pitt’s School of Medicine in 1965.

Even fearless Dr. De was a freshman in medical school once—unsure of herself, hungry for that nod of approval from her teachers and a perfect score on her physiology research project. By the time she enrolled at Pitt, DeAngelis was already a nurse with a year of experience at Columbia Presbyterian Medical Center in New York. She’d also spent a summer working with Monto Ho in Pitt’s Graduate School of Public Health. “I knew my way around a lab,” she says. So she was shocked when her first research paper came back marked zero.

“Remember that this was the ’60s,” she says. DeAngelis was one of nine women in a graduating class of 88, and the medical profession in general was skeptical of the potential of any woman to be a competent physician.

That night, she became so depressed that she contemplated giving up everything—her dream of being a doctor, even her life. Then she decided to return the paper to the teacher unreviewed and demand that he grade it again.

She said: “Either you give me the proper grade on that, which is—at a minimum—a B, or let’s go down to the dean’s office right now. Because I want you to pick any five papers from our class plus mine, unmarked, hand

DeAngelis still attends Mass every Sunday, even when she’s at a JAMA meeting in a far-flung corner of the world. (Her husband, a Protestant, usually helps her find the nearest church). She says that the humility, social concern, and openness to divine providence that have distinguished her career grow from strong Roman Catholic roots.

Her warmth puts visitors at ease. In fact, until she eyes your lunch plate with concern, and reminds you that you shouldn’t eat so much red meat, you might forget that you’re eating a medium-rare hamburger in front of one of the most powerful people in health care, a woman who has been breaking down barriers in the profession since she walked through the doors of Pitt’s School of Medicine in 1965.

E

DeAngelis misses her clinical work in underserved communities, but she feels she has the most far-reaching impact on patient care in her current position.

right. So you wanna change the world overnight, he observed.

“Well, yeah, she thought. I do.”

Today, she realizes that the late Rogers understood her perfectly. “This was where I’d wanted to be all along,” she says. She was finally a medical missionary.

During her third year at Pitt, DeAngelis went on to work in a hospital in rural West Africa. Years later, she organized immunization programs and taught nurse practitioners in Peru and in the West Indies. She decided that despite her childhood dream—she used to cut open her rag dolls and stitch them back together—she wouldn’t be a surgeon after all; she could do more to improve the overall health care of the young and the poor by specializing in general pediatrics and researching ways to improve medical education. After her pediatric residency at Hopkins, she was granted a National Institutes of Health fellowship to study health law and economics in Harvard’s School of Public Health, where she earned a master’s degree in 1973.

While at Harvard, she wrote a curriculum and a textbook teaching MDs and RNs how to work together to improve critical care. In both, she insisted that RNs were undervalued and underused. Nurses don’t have the same knowl-
look them in the eye. Even when she became a physician, her own patients sometimes refused to believe she was a doctor, not just because she was a woman, but because of the way she treated them.

“Compassionate care” and “care of the whole patient” have become catch phrases in medical education. But when she started out, DeAngelis reminds us, they certainly weren’t.

Can compassion be taught? Some of Pitt’s current best-loved teachers think so. Basil Zitelli, a professor of pediatrics, cites DeAngelis as his inspiration. He remembers her as an intern at Children’s Hospital of Pittsburgh, comforting even the sickest patients with her easy demeanor. These days, even though DeAngelis is still officially a general pediatrician, some of her patients are nearing 35 years old. They are unwilling to make the transition to another doctor.

It’s easy to see why you’d never want to leave her when she lays a hand on your arm.

Johns Hopkins, where she has held a faculty appointment since 1978, she logged countless hours in the free clinic.

DeAngelis feels that in her current position, she’s had the most direct and far-reaching influence on patient care. JAMA is published in 14 languages and read in 120 countries. Under her direction, the journal has focused international attention on many of the causes and issues she holds dear, including global health, depression in children, and gender-based health care. (This recent trend says diseases and treatments affect men and women differently; DeAngelis will only publish research data broken down by gender.) She has also continued the journal’s tradition of publishing poetry and, on its covers, fine art reproductions.

“Doctors should know about art,” says DeAngelis. “They should be well-rounded people.”

A week after Halloween, the JAMA office decorations as one of her Thursday meetings adjourns. If she had her way, they’d leave the set up all year. DeAngelis tries to keep things light. She throws food at people when they get too serious. Usually gummy bears, she says. Sometimes peanuts and chocolate.

DeAngelis feels she’s doing her part, making sure that this influential journal is scholarly, compassionate, profound, even amusing. She’s proud that doctors can look to it for advice on patient-care decisions and that the media and the public can look to it for accurate, honest information about medical issues. She’s also proud that it’s a pretty cool place to work.

But when her second five-year contract is up in 2010, DeAngelis says she’ll be looking for a new challenge. “Ten years at any job is long enough,” she says.

What’s next? That’s up to the wind. “What’s there to be nervous about?” she asks. “You’re not getting out of this life alive, and if you have a soul, you shouldn’t care.”

For now, it’s back to battle. She says goodbye to this writer in the bustling lobby of the office tower on State Street. On her way to the bank of elevators that will take her back to her castle, she pusses to chat with the security guards and read the sign posted near their station: MEDICAL ETHICS DAY. She throws her hands up as she walks away.

“How many times do I have to tell you people?” she shouts to nobody in particular, shaking her head but not looking back.

“Every day is medical ethics day here.”
HEARTACHE SPURS UNDERSTANDING

MOM FURTHERS TUMOR RESEARCH IN SON’S NAME
BY CHUCK STARESINIC

Nick Wichman of Ellicott City, Md., was 7 years old when he complained to his parents of a stomachache. Seven weeks later, just after his eighth birthday, he was dead. A malignant glioma, among the deadliest of brain tumors, killed him. There was little anyone could have done.

Nick’s family announced that, in lieu of flowers, friends and family could donate to a fund in his name. Nothing causes an outpouring of grief like the death of a child. A week later, the Wichmans had to figure out what to do with several thousand dollars. They wanted to support research that would help other boys and girls recover, so they held fundraisers and accepted donations from people moved by the plight of children with brain tumors. Within a year, the Nick Eric Wichman Foundation was ready to give a grant of $40,000 to support medical research.

But Karen Wichman, Nick’s mother and a 1985 legal studies graduate of the University of Pittsburgh, almost gave up when she approached a renowned neurosurgeon in another state who seemed interested only in finding out whether there was more money beyond the 40 K. “Worst day of my life,” she says. “Worse than when my son died.” He made her feel like she and her son weren’t important unless they were relatives of Bill Gates. That money came from kids with lemonade stands, she says now, barely suppressing her anger. “When a woman gives me a thousand dollars and says, ‘I want you to have this,’ and her husband doesn’t even have a job, I know it matters.”

In February of 2002, a friend e-mailed her an article from the *Pittsburgh Post-Gazette*—“Study finds clue to deadly childhood brain cancers.” The article described how Ian Pollack, chief of pediatric neurosurgery at Children’s Hospital of Pittsburgh and Pitt’s Walter E. Dandy Professor of Neurosurgery, had led a study that found a protein that was highly expressed in the deadliest pediatric brain tumors. The discovery offered some hope for better diagnosis and treatment. Perhaps inhibiting the protein would make tumors less deadly.

The foundation asked Pollack to submit a proposal, which eventually was selected for the first of its annual $40,000 grants. Wichman, who has visited Pollack several times, was moved by his commitment to patients and to long-term research.

In each year since, the annual grant has supported Pollack’s work with Marie Beckner, research assistant professor in the Department of Pathology. The two are trying to understand the sort of process that killed Nick—the invasive migration of tumor cells into healthy tissue, which is different from a tumor that presses against, but is essentially separate from, nearby tissue. In a recent paper, the Pitt collaborators identified, in vitro, the rich assemblage of proteins that make up the leading edge of a tumor cell—a pseudopod—as it protrudes through a small opening in search of fertile territory. Understanding the pseudopod’s makeup, says Beckner, is the first step to stopping it.

Beckner adds that the foundation’s support is absolutely invaluable, because though there are lots of research dollars for studying proliferation or other aspects of tumor cell behavior, there is little funding directed specifically to tumor cell migration. “I’m just a mom with a broken heart,” says Wichman. “I don’t want anyone else to go through this.”

BOOSTER SHOTS

Each August, the Medical Alumni Association, with help from generous alumni and with great ceremony, presents entering Pitt med students with white coats, marking their entry into the hallowed realm of medical apprenticeship. In response to overwhelming demand from students, there was one difference this year in the coats themselves—bigger and better pockets. We were moved to ask the question: Now that students have publicly declared their intention to pursue the medical profession with integrity and honor, what have they got in those pockets?

Our poll revealed these ample pockets are where students store tools of the trade (at least that’s what they told us): stethoscopes, oto-ophthalmoscopes, reflex hammers, penlights, *Bates’ Pocket Guide to Physical Examination and History Taking*. One student confessed her stethoscope rarely sees the inside of her pockets because she enjoys having it around her neck so much—a reminder that she is on her way to becoming a doctor. Other intelligence reveals that personal items—including hair ties, cough drops, and tissues—are filling said pockets. And one student, clearly too busy studying to do laundry, admitted that the only thing in his white coat, which is hanging in his anatomy locker, is a strong and pervasive odor.

Of the more than a million HIV-positive people in Kenya, 100,000 are children. The Kenyan Pediatric HIV Project, run by first- and second-year Pitt med students, intends to work with Kenyan groups providing medicine and clinical care to infected children. Founder Kate Dickman (Class of ’07) and other students are now raising money to acquire antiretroviral medicine for infected children and for an assessment trip in June. They recently received news that the dean’s office will match any donations from School of Medicine faculty. —Jen Dionisio

FOR MORE INFORMATION ON THE KENYAN PROJECT:
www.pittmed.pitt.edu/KHPH
RE OTHER GIVING OPPORTUNITIES: 1-800-MED-ALUM
The late Pitt med prof Lewis Etter (MD ’27) donated this rare translucent Spalteholz skull to Pitt. Its origins and history have kept another prof pondering for a decade.
HEADY PURSUIT

THE HISTORY BEHIND A SILENT OFFICE MATE

BY MOLLY KENEFICK

Dennis Ranalli needn’t look far to enliven a humdrum day. Behind his office chair is a translucent human skull; and though Ranalli is arguably the living expert on such rare Spalteholz skulls, when this DDS, MDS turns his gaze toward “the Pittsburgh specimen,” he’s reminded that his investigations throughout the past decade have yielded almost as many questions as answers.

His office mate has a complete, perfect set of teeth that must have served someone very well until she died at about 28 years old. For perhaps five decades, this skull has rested in an 11-inch Pyrex glass sphere that is held rigid by glass rods. The sphere sits upon roller bearings on top of a truncated nose cone from a guided missile.

Ranalli, who is a professor of pediatric dentistry and senior associate dean at the dental school, encourages inquirers to consider what such a skull meant to understanding internal anatomy before the age of x rays and CAT scans. “We can look at the nerve canals in 3-D. We can see how the various bones of the skull fit together,” he says.

The specimen had gathered dust in the dental school’s learning center until the early ’90s, when Ranalli, as chair of that school’s centennial committee, set out to understand its history.

This is not the first extracurricular mystery that has intrigued Ranalli. He is perhaps best known for his investigations on detecting child abuse through dental clues and preventing traumatic dental injury in athletes. But he also has written about topics such as cleft lips and palates in ancient art; the history and depiction in art of St. Apollonia (patron saint of dentistry); and famous American historical figures who were also dentists. (The list includes Paul Revere, Old West outlaw Doc Holliday, novelist of the Old West Zane Grey, and football legend Jock Sutherland.)

Ranalli didn’t have much to start with except a 1973 Pitt Alumni Times article, which said that Lewis E. Etter (who was awarded his undergrad degree from Pitt in ’24 and his MD in ’27), professor of radiology at the medical school, gave the skull to Pitt—he also placed it atop the missile nose. Etter received the skull from Gustav Becky, who invented the Becky x-ray grid and was an associate of Werner Spalteholz, the renowned German doctor and anatomist who prepared the skull. Spalteholz’s Hand Atlas of Human Anatomy, a classic text that is still highly regarded, is in its 14th edition.

The Times reported that two other such skulls existed—one in New Canaan, Conn., and one in Dresden, Germany, and that the Pittsburgh specimen had been appraised at $50,000. But there is no byline on the article. (No writer to follow up with), and the appraisal company named in the article seems to be key. “It’s like I’m looking for A through D, and I have B and C,” Ranalli says of this puzzle.

Another breakthrough came in August 2002, when a colleague from the University of Bonn located the second skull. It was not in Dresden, as expected, but in the anatomy collection of the University of Leipzig.

In Ranalli’s office, nicknamed “The Tomb” for its temperature (he likes to keep it chilly) and its mysterious occupant, the professor considers the specimen he has rescued from obscurity. Although his sleuthing has yielded some satisfying answers, questions continue to haunt him: Whose skull was it, and where did Spalteholz get his specimens? Where are the other remaining pieces of Spalteholz’s collection? Why did Etter choose a truncated nose cone from a guided missile for mounting the Pittsburgh specimen?

Ranalli started with the New Canaan lead. He might as well have asked his office mate where to look. Contacts at the University of Connecticut, the local Chamber of Commerce, and the museum of the Hartford Dental Society led to dead ends. So he set his sights on Germany, where the archives of the Deutsches Hygiene-Museum yielded promising articles—in Old German. After Ranalli found translators with sufficient scientific knowledge, he learned that Spalteholz had prepared the Pittsburgh skull as one of at least three for the 1911 International Hygiene Exhibition in Dresden. (He’d prepared 375 human anatomical specimens in all.)

Ranalli also learned that Spalteholz’s early research led to the discovery that tissue transparency depends primarily on the refraction index of the permeating liquid. His innovative formula rendered the skulls translucent without dis-integrating them and laid the foundation for the slab-plastination preservation technique used today. A World War II air raid severely damaged Spalteholz’s Leipzig laboratory. For a while, Ranalli feared that the formula for translucence went to the grave with Spalteholz in 1940. Then, happily, his investigation yielded ingredients in the formula—benzene seems to be key. “It’s like I’m looking for A through D, and I have B and C,” Ranalli says of this puzzle.

He’s still looking for the third Spalteholz skull. He imagines a reunion of sorts.
‘50s

As a teenager in Punxsutawney, Paul Pifer (MD ’52) worked as a soda jerk in a drug store. The pharmacist encouraged Pifer to pursue a career in pharmacy. Pifer obtained an apprentice’s license and began working, but soon he left Pennsylvania to serve in the U.S. Army Air Corps as a radio engineer and gunner in World War II. He flew more than two dozen missions with his crew, and they were shot down several times flying over enemy territory. Luckily, they were rescued each time. When Pifer returned after the war he entered Pitt as an undergrad, eventually deciding that he preferred medicine to pharmacy. Pifer had a long career as a private practice ob/gyn in Ohio, Pennsylvania, and Louisiana. He retired in 1994 and moved to Pensacola, Fla., where he is a consultant for the Naval Hospital.

‘70s

As a teenager in Punxsutawney, Paul Pifer (MD ’52) worked as a soda jerk in a drug store. The pharmacist encouraged Pifer to pursue a career in pharmacy. Pifer obtained an apprentice’s license and began working, but soon he left Pennsylvania to serve in the U.S. Army Air Corps as a radio engineer and gunner in World War II. He flew more than two dozen missions with his crew, and they were shot down several times flying over enemy territory. Luckily, they were rescued each time. When Pifer returned after the war he entered Pitt as an undergrad, eventually deciding that he preferred medicine to pharmacy. Pifer had a long career as a private practice ob/gyn in Ohio, Pennsylvania, and Louisiana. He retired in 1994 and moved to Pensacola, Fla., where he is a consultant for the Naval Hospital.

As an intern at Children’s Hospital of Pittsburgh, Martha Turner (Pediatric Intern ’73–’74) and her colleagues watched helplessly as the wards filled with children suffering from brain swelling and delusions. The children had Reye’s syndrome, and no one knew how to treat it or what the cause was (a bad reaction to the flu virus and aspirin). Turner says she enjoyed her time at Pitt, but her experience with the Reye’s epidemic made her decide that she didn’t want to become a pediatrician after all. Instead, she pursued psychiatry. She tailored her practice to treat alcohol and drug addiction, and in the early 1980s, an alcohol-addicted patient shocked Turner by revealing she had another addiction—sex. Turner developed “a big love” for treating addiction. The psychiatrist is now senior physician and director of substance abuse services at a small drug abuse detoxification facility in Middle Georgia. He also does outpatient rehab at two other centers. For himself, Giannini finds science fiction has great therapeutic value.

G. Michael Deeb intended to be a pro baseball player. But the summer before his freshman year at Pitt, he had surgery on his arm, ending his career. So Deeb (MD ’75, Surgery Intern ’75–’76, General Surgery Resident ’76–’80, Cardiothoracic Surgery Resident ’80–’82), who loved biochemistry, decided to pursue endocrinology. When he was an intern with Dave Steed (MD ’75, now a professor of surgery at Pitt), Steed recommended he do a surgery rotation with Hank Bahnson. Again, Deeb’s career path changed, but that was the last time. He is the newly minted Herb Sloan Chair of Cardiac Surgery at the University of Michigan, Ann Arbor. For the past five years he has been researching Marfan syndrome, a genetic disease that weakens connective tissues in the cardiovascular system. Those with the disease are more susceptible to aneurisms. He found that beta-blockers decrease the chance that the aorta will burst.

Dartmouth Medical School changed its program from four years to three when Daniel Walsh (MD ’76) was a sophomore there. Knowing that he wanted the clinical experience accompanying a longer program, Walsh scrambled to find a great med school to resume his training. He found Pitt. He recalls the gratitude he felt when the school “took a total stranger under its wing.” He was impressed with the unexpected kindness and acceptance of his fellow classmates and the caliber of the faculty, especially in the surgery department. Walsh is now a consulting surgeon at Veterans Administration Hospital and Central Vermont Hospital, in White River. He’s also a professor and vice chair of surgery in Dartmouth Medical School. He says the reason he teaches and acts as an adviser is because of Charles Watson, Hank Bahnson, and Charles Cobb; these men, he
As a kid, W. Timothy Ward (MD ’77) was interested in two things: science and sports. So he decided to become an orthopaedic surgeon. Although he eventually lost interest in sports as a specialty, Ward never lost interest in orthopaedics. His work at Children’s Hospital of Pittsburgh (where he’s chief of pediatric orthopaedic surgery) was highly specialized—fixing spinal deformities, clubfeet, and orthopaedic trauma. Looking for a change of pace, Ward took a sabbatical a few years ago to train at Case Western Reserve University in adult spinal orthopaedics, learning to fix such degenerative problems as ruptured disks, fractures, and spinal tumors. Now, the Pitt associate professor of orthopaedic surgery splits his time equally between his child and adult patients. He laughingly admits the best part of his Pitt School of Medicine experience was meeting his wife, Lynne Bobbette (Doepker) Ward (MD ’77).

‘80s As a student in an accelerated med school program at Ohio State University, Douglas Chen (Otolaryngology Resident ’81–’85) picked out a residency program before he completed his rotations. He decided on otolaryngology because he wanted to treat adults and children and also have the opportunity to perform surgery. He laughs now at his hasty choice, but he doesn’t regret it. He also trained in L.A. at the House Ear Institute, where he met Bill and Howard House—two men who devoted their careers to developing tools to help the deaf hear. It was there that Chen learned extensively about cochlear implants, before they were even approved by the FDA. As co-director of the Hearing and Balance Center at Allegheny General Hospital, Chen regularly recommends cochlear implants for profoundly deaf patients. These implants help his patients hear and oftentimes speak—as though they never were deaf. Although Chen loves helping people hear, he realizes that his work is controversial in the deaf community, which feels that cochlear implants are a threat to deaf culture.

Some of Roger Albin’s (MD ’82) most valued colleagues at the University of Michigan, Ann Arbor, are mice—mutant mice, to be precise. These creatures model diseases and aid the neurologist in his research on Parkinson’s disease, Huntington’s disease, and Tourette syndrome (TS). Using PET scanning for his most revealing study on TS, Albin found evidence that those with the syndrome had too many nerve cells containing dopamine. Although this research is not yet clinically useful, Albin is expanding his study to confirm his finding in the hope it could lead to more effective treatments. Thinking back to his days in med school, he remembers Pitt’s John Moossy, professor of pathology and neurology, as a demanding but also a kind and outstanding teacher. In 1995, when Richard Kennedy (MD ’85) started as the senior medical officer at the World Bank Group’s headquarters in Washington, D.C., he was shocked that there were no emergency protocols in case of incidents like heart attacks. The primary purpose of the clinic for the 12,000 staff members of the World Bank and International Monetary Fund is to treat the busy professionals who acquire tropical diseases when working in developing countries. Kennedy convinced the medical staff that everyone at the World Bank should have Advanced Cardiac Life Support skills.

Larkins-Pettigrew holds baby Margaret, who is her namesake, with (from left) Margaret’s grandmother, mother, and a nurse in a Liberian refugee camp in Ghana.

Kennedy is likely to get to know Paul Wolfowitz. Part of his job has been to travel with the president of the bank as his personal medical escort.

‘90s After working many years as a nurse and educator, M. Delaere Larkins-Pettigrew (MD ’94, Ob/Gyn Resident ’95–’98) enrolled at Pitt as a med student. In her fourth year, she chose a rotation with Morris Turner (MD ’73), the late Robert Kisner (Ob/Gyn Resident ’73), and Robert Thompson (MD ’73). The three practiced ob/gyn in East Liberty. She admired the men for many reasons, most of all because they accepted patients regardless of their ability to pay. In 2002, Larkins-Pettigrew joined their practice. Since then, she has treated patients in jails, low-income government housing, and a home for runaway youth. And though Larkins-Pettigrew enjoys working in Pittsburgh, she has also traveled extensively throughout Africa to treat patients there.

—CB, JD, & MH

Sarah Springer with her children, Jonathan and Natalie.
Reflecting on his days as a med student, Terry Puet (MD '80) opines that the Class of '80 was closer than most. "We broke out of the competition mode that you need to get into med school," he says. The cooperation and camaraderie karma he was blessed with at Pitt has followed him into his career as a physician and medical director of Hillside Rehabilitation Hospital in Warren, Ohio. He works hand in hand with other doctors and therapists as they attempt to improve or restore cognition in patients suffering from injuries and degenerative diseases. He remembers one irritation from his Pitt med days: having to draw in Nikolajs Cauna's gross anatomy class. "I was a terrible artist," he says. Now he laughs about how helpful the class was. "A week doesn't go by that I don't draw what's happening for a patient's family," he says. "Nothing explains things quite like it."

Jon Watchko (MD '80) also remembers Cauna fondly, but for reasons not so academic. Watchko is still grateful that the professor let him and some fellow students take an afternoon off to go to a Pirates opener. He believes that the closeness the Class of '80 enjoyed improved their studies. "If you enjoy the people you're working with, you do better," he says. Watchko is currently a senior scientist at Magee-Womens Research Institute and Pitt professor of neonatology; of pediatrics, and of obstetrics, gynecology, and reproduction sciences. He's pursuing work on the mechanisms of unconjugated bilirubin transport in the central nervous system as a means of decreasing bilirubin-induced brain injury in newborns.

Watchko chose the field of neonatology because his patients have a lifetime to look forward to after treatment. Carl Gartner, professor of pediatrics and "a real gem," also had a major impact on the direction he took in his career.

For Raya Armaly (MD '80), one of her biggest influences in med school was surgeon Norman Wolmark (Surgery Res '76): "It was fascinating to see his thought processes." Today, the surgical aspect of her work as an ophthalmologist is her favorite part of the job. She has a private practice at the Greater Baltimore Medical Center and is an instructor at Johns Hopkins and the University of Maryland schools of medicine. She specializes in glaucoma, which she calls "the internal medicine of ophthalmology." Her husband is Charles Harrison (MD '82).

Andrea Draisen (MD '80) still laughs about her fellow classmates singing and dancing in their Scope and Scalpel production, Saturday Night In Vivo. She recounted the favorite lines from the "Dr. Rogers' Neighborhood" skit—Children, say prophylactic! Speaking of children, Draisen decided to go into pediatrics after becoming disillusioned with her adult patients. She eventually tired of treating chronic illnesses caused by lifestyle choices. Pediatrics and her private practice in Anderson, S.C., are more immediately satisfying, she says. The late pediatrician Lois Pounds-Oliver (MD '65) influenced her as a med student at Pitt. She remembers Pounds-Oliver as both a compassionate doctor who was encouraging to students and as a role model who happily balanced a career and a marriage—exactly what Draisen is doing now. If you see Draisen at the reunion, remind her of the lyrics to the song for the Anus Equinus award. She's forgotten, though she remembers the prof who won the award quite clearly. —JD
A

braham Twerski set out to be a rabbi like his father—a daunting challenge, given his father’s considerable charisma and reputation among congregants. “People flocked to him for counseling,” says Twerski, a man of small stature and large presence. His beard obscures the top half of his necktie, and a gray suit hangs loosely on his slight frame. He reclines easily in his chair, stretches his legs, and props his elbows on the armrests as he speaks. He was ordained at 21, then began to assist his father, but he felt like a functionary who performed bar mitzvahs, weddings, and funerals. In those postwar days, professional analysts were becoming the norm, and Twerski realized that he was never going to be sought out like his father. “That’s not where the cloak is anymore,” he says now. “The cloak of counseling is in psychiatry and psychology.”

So Twerski (Res ’63) became a psychiatrist. He attended medical school at Marquette University in Milwaukee, graduated in 1959, and came to the Western Psychiatric Institute and Clinic for residency. After a few years in Pittsburgh, Twerski became the clinical director of the Department of Psychiatry in St. Francis Hospital—“an impossible position,” he says now. “The cloak of counseling is in psychiatry and psychology.”

He left his father’s congregation to pursue the work he’d always wanted to do as a rabbi. Twerski hesitates to say that psychiatry is the most spiritual of all medical specialties, but he believes it could be.

“People have confused spirituality with religion, and the doctrine is that the psychotherapist does not get involved in the patient’s religion in any way. So they scoot around all religious issues, and at the same point they avoid dealing with the spiritual issues that are not of a religious nature. Unfortunately, they are missing the point because many patients, even if they are not religious, are missing a spiritual goal in life.” Twerski believes this lack of purpose is at the root of most unhappiness. Ask him about this, and he pounces.

“I think spirituality is fulfilled when one looks for an ultimate purpose,” he says that as long as it’s not “animalistic,” it matters not what your purpose might be—caring for children, fighting famine, saving redwoods—“even if you don’t find anything. So long as you’re looking for it!”

Psychiatry could become the most spiritual of all medical specialties, says Twerski.
Claude Bernard’s *Leçons de Physiologie Opératoire* (Lessons in Surgical Physiology), published posthumously in 1879, detailed his controversial experimental procedures, such as heart catheterization (in animals) and vivisection. In 2002, the School of Medicine donated this rare book, which features 116 fine woodcut illustrations, to the Falk Library of the Health Sciences in honor of Daniel Paul Greenlee (MD ’24) on the occasion of his 100th birthday. Before his death this March at the age of 102, Greenlee was believed to be the school’s oldest living alumnus (see page 38).
CALENDAR
OF SPECIAL INTEREST TO ALUMNI AND FRIENDS

Unless otherwise noted, for information on these events, contact the Medical Alumni Association: 412-648-9090 or 1-877-MED-ALUM
medalum@medschool.pitt.edu

MINORITY ALUMNI WEEKEND
MAY 12–15
For information:
Office of Student Affairs/Diversity Programs
412-648-8987
diversityaffairs@medschool.pitt.edu

MINORITY ALUMNI REUNION DINNER
MAY 14
7 p.m.
Keynote: Jeannette South-Paul (MD ’79)
Alumni Hall Gallery
For information:
Office of Student Affairs/Diversity Programs
412-648-8987
diversityaffairs@medschool.pitt.edu

MEDICAL ALUMNI WEEKEND 2005
MAY 20–23
Classes Celebrating:
1940  1950  1955  1965
1955  1980  1990

SCOPE AND SCALPEL’S BEDSIDE STORY
MAY 20 & 21
7 p.m.
The Antonian Theater
Carlow University
Pittsburgh
For information:
www.scopeandscalpel.org

SENIOR CLASS LUNCHEON
MAY 20
11:30 a.m.
Twentieth Century Club
Pittsburgh

THE 1787 SOCIETY LUNCHEON
MAY 20
11:30 a.m.
Schenley Park Visitor Center
101 Panther Hollow Road
For information and reservations:
Clare Flanagan
412-647-0515
fclare@pmhsf.org

SCHOLARSHIP APPRECIATION TEA
MAY 20
3:30 p.m.
William Pitt Union

DEAN’S BREAKFAST & REUNION GALA
MAY 21
8:30 a.m. and 6 p.m.
Sheraton Station Square
Pittsburgh

GRADUATION CEREMONY
MAY 23
10 a.m.
Carnegie Music Hall
Pittsburgh
For information:
Student Affairs Office
412-648-9040
student_affairs@medschool.pitt.edu

CLASS OF 2009 WHITE COAT CEREMONY
AUGUST 14
3 p.m.
Lecture Rooms 5 and 6
Scaife Hall
For information:
Student Affairs Office
412-648-9040
student_affairs@medschool.pitt.edu

TO FIND OUT WHAT ELSE IS HAPPENING AT THE MEDICAL SCHOOL, GO TO www.health.pitt.edu
THE WORLD AT YOUR FEET

Remember those times when you felt 70 stories tall and you could see opportunity coming from miles away? Help tomorrow’s medical students reach the same heights with a planned gift to the School of Medicine. This much-needed support for your alma mater can also be a smart way for you to provide an annual lifetime income stream for yourself or a loved one.

If the School of Medicine is already in your will, and you haven’t let us know, please contact us so we can make sure that your gift will be used as you intend it to be.

FOR MORE INFORMATION:
School of Medicine
University of Pittsburgh
Kathleen Helling
Medical Arts Bldg.
Suite 400
3708 Fifth Ave.
Pittsburgh, PA 15213
412-647-4220
khathleen@pmhsf.org