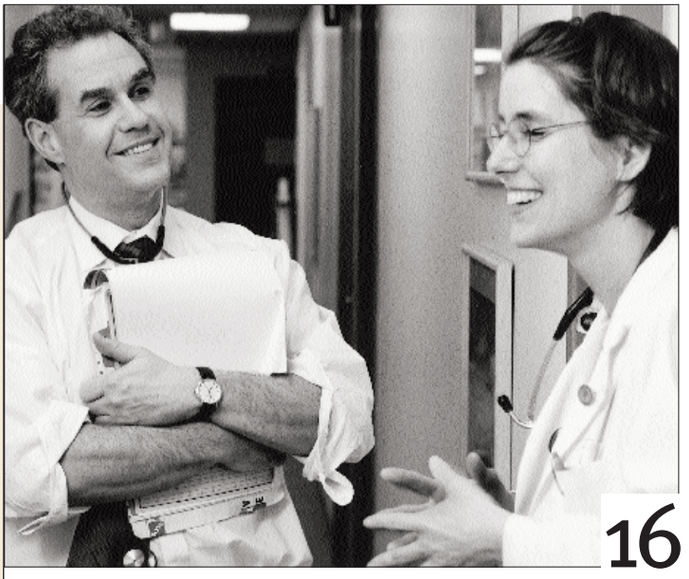
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UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE | APRIL 2000, VOL. 2, ISSUE 2



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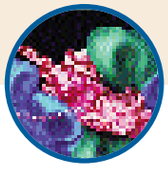
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REBECCA SKLOOT—["First Contact," "In Search of Chimeras," "The Art of Swallowing," and much, much more] Rebecca Skloot is a freelance science and medical writer. Skloot was the assistant editor of *Pitt Med* until this spring, when the call of her book in progress became too loud to ignore. Fortunately for us, her fear of flying keeps her either close to home or on trains with plenty of time for writing feature stories. She will continue to contribute to *Pitt Med* as our favorite freelancer until Oprah steals her away.

RICHARD KELLY—["First Contact"] Richard Kelly is an environmental portrait photographer who has been living life in the fast lane. He recently finished photographing race-car drivers for a book he expects to publish next year. His work has appeared in *Sesame Street Parents* and *Fortune*, and he is the official photographer for *Mister Rogers' Neighborhood*.

COVER

Combinatorial chemistry is giving Peter Wipf (left) and John S. Lazo the ride of their lives. This chemist and pharmacologist (respectively) can't think of a better way to explore uncharted regions of chemical space. (Portrait by Alex Bellotti; protein image compliments of the School of Medicine's whiz-bang Cellomics Array Scan II.)

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JULIA MAROUS STRAUT

We do not live in a necessarily cerebral world. It seems the outcomes of scientific research often are more prized than the work itself. Certainly, the number of students choosing careers in academic medicine is alarmingly low. It has come to the point where we need to seriously ask the question—will there be a generation after this one to fill the role of medical school faculty?

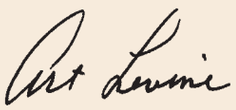
We are establishing a program here at the medical school to abate the debt of those who choose careers as physician-scientists. But an interesting question remains: How do we know which applicants, students, and young MDs are creative enough to pursue and enjoy fruitful research careers? One thing is clear, GPA is not a telling indicator of future success as a scientist.

It also is easy to imagine that achievement in science may not depend only on mathematical/logical intelligence. One needs to reach some threshold of global intelligence. Wordsmithery (linguistic intelligence) helps, though it is not enough to promise an inspired scientific research career. How one theorizes about the trafficking of intracellular organelles may depend, in part, upon a spatial or even a kinesthetic intelligence. And as Thomas Starzl's work with microchimerism so well illustrates (see story on page 31), to move from creative scientist to the realm of paradigm shifter, one must have all of this as well as the independence of thought to remain steadfast in the face of contention.

So, for the School of Medicine to grow the ranks of inspired physician-scientists, we must ourselves be creative. As a starting point, our admissions committee is looking beyond typical parameters when winnowing through medical student applications.

Once we entice young people to choose academic careers, we must foster their creativity. The current state of academic medicine—which requires managing competing clinical, teaching, business, and research demands—can tax the most fertile mind. And a recent study of women's faculty issues here has revealed other concerns that are applicable to both men and women: The logistics of the two-career family can put research careers in peril. Many young faculty members are dealing with child-care issues while contending with the pressures of the tenure track system. Consequently, we are establishing an office to address these and other career development issues of our health sciences faculty.

Not only must we value and encourage creativity, we must give faculty—and future generations of faculty—the opportunity to cultivate it.

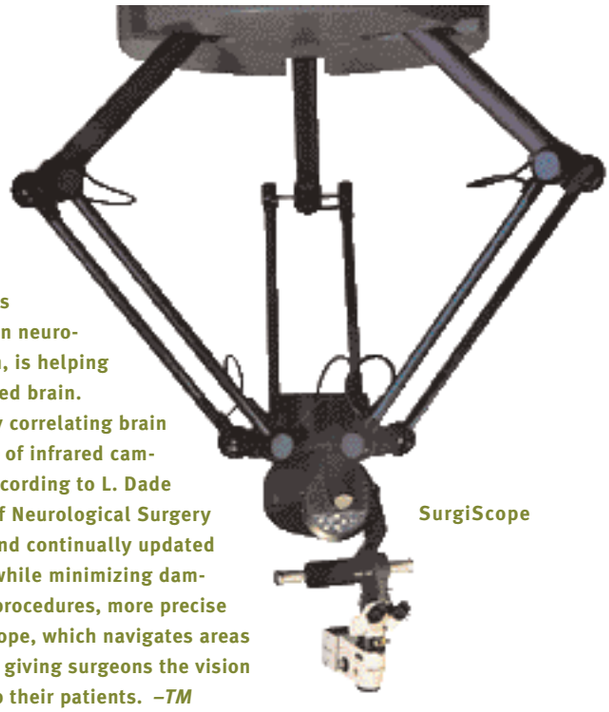


Arthur S. Levine, MD
Senior Vice Chancellor for the Health Sciences
Dean, School of Medicine



ILLUSTRATION: BECKY SMITH

Devoted to noteworthy happenings at the medical school. . . Also, to stay abreast of Pitt health sciences news, including info on faculty and research, see http://www.health.pitt.edu



SurgiScope

Delicate Terrain

Suspended above a stainless steel surgical table, its long spidery legs dangling toward the floor, hangs the newest member of Pitt's precision neurosurgery team. SurgiScope, a ceiling-mounted robotic guidance system, is helping neurosurgeons steer through the most delicate of terrain—the damaged brain.

SurgiScope guides surgeons through the intricacies of the brain by correlating brain scans with a high powered microscope and robotic arms. With the use of infrared cameras, the microscope is lined up and calibrated to a patient's head. According to L. Dade Lunsford, Lärs-Leksell professor and chairperson of the Department of Neurological Surgery at the School of Medicine, this system, with its interactive software and continually updated visual images, allows neurosurgeons to pinpoint and remove tumors while minimizing damage to healthy tissue. The results: smaller incisions, shorter surgical procedures, more precise removal of lesions, and an overall decreased risk for patients. SurgiScope, which navigates areas of the brain that are otherwise impossible to behold during surgery, is giving surgeons the vision to tackle new approaches and expand the realm in which they can help their patients. *–TM*

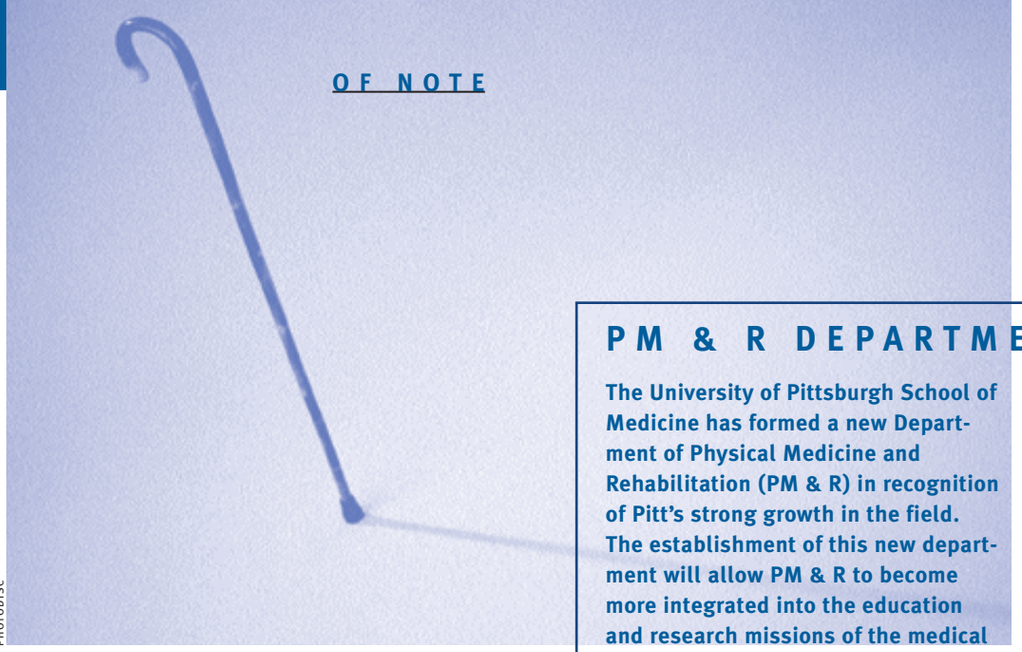
FOOTNOTE

"If women and men can be embarrassed by studying medicine together, then their places are certainly not in the medical profession."

—Dr. Amelia Dragna, Women's Medical Society, 1912, during the protest for women's readmission into the School of Medicine

NIH PUTS PITT'S MED SCHOOL AMONG NATION'S TOP 10

The *New England Journal of Medicine* reports that the University of Pittsburgh School of Medicine is solidly among the top 10 med schools receiving National Institutes of Health funding. From 1989 to 1998, Pitt's annual share rose to $170 million and 580 grants a year. This news puts Pitt in the company of institutions such as Johns Hopkins, Yale, and the University of Pennsylvania. The only other new entrant to the list is Case Western Reserve University in Cleveland.



PHOTODISC

PM & R DEPARTMENT FORMED

The University of Pittsburgh School of Medicine has formed a new Department of Physical Medicine and Rehabilitation (PM & R) in recognition of Pitt's strong growth in the field. The establishment of this new department will allow PM & R to become more integrated into the education and research missions of the medical school, while moving Pitt into a position to compete with other PM & R departments for grants and highly qualified faculty.

In addition to its role in the medical education of both residents and medical students, PM & R will cover inpatient and outpatient services and, in collaboration with several other University departments, will offer electromyography and nerve conduction studies, spinal cord injury rehabilitation, traumatic brain injury rehabilitation, and more. Louis E. Penrod (MD '84), assistant professor of PM & R, has been named acting chairperson of the department. ***—RS***

FOR MORE INFORMATION:
http://www.upmc.edu/rehabmed

Faculty Snapshots

A SAMPLING OF SOME OF THE PITT SCHOOL OF MEDICINE FACULTY'S WORK:

Eugene N. Myers, chair of the Department of Otolaryngology at the University of Pittsburgh School of Medicine, received an $11.2 million grant from the National Institute of Dental and Craniofacial Research to establish an Oral Cancer Center. During the last three decades, there has been little change in the success rate of oral cancer therapies—the available treatments are often painful and disfiguring for the patient. Myers, director of the center, hopes to improve treatment and diagnostic options and increase awareness of oral cancer, which will affect almost 30,000 people in the United States this year.



Samples from the Chart Engine desktop

Henry Lowe, associate professor of medicine and director of Pitt's Clinical Multimedia Laboratory, received a grant from the National Library of Medicine for further development of the Chart Engine System. The project, a multimedia electronic medical record system, integrates clinical images—like X rays, MRIs, CTs, and clinical photos—with text data and laboratory test results using a secure, Internet-based architecture. Ultimately this system may allow clinicians to consult on specific cases while allowing researchers and teachers to access anonymous images for studying diseases and their clinical presentation.

John A. Horton III, assistant professor of physical medicine and rehabilitation, won the 1999 Ernest Bors Award from the American Paraplegia Society for his research on the management of urinary tract infections in patients with spinal cord injuries.

And by the way, Pitt now has three Robert Wood Johnson Foundation Generalist Physician Faculty Scholars. These awards are given nationally to support research in primary care. Pitt's current scholars include **Amy Justice**, assistant professor of medicine, who specializes in primary care of patients with HIV, **Joseph Conigliaro**, assistant professor of medicine, who focuses on prevention of alcohol problems through brief interventions, and **Melanie Gold**, assistant professor of pediatric and adolescent medicine, who specializes in strategies that focus on prevention of teen pregnancy and STDs. *—RS*



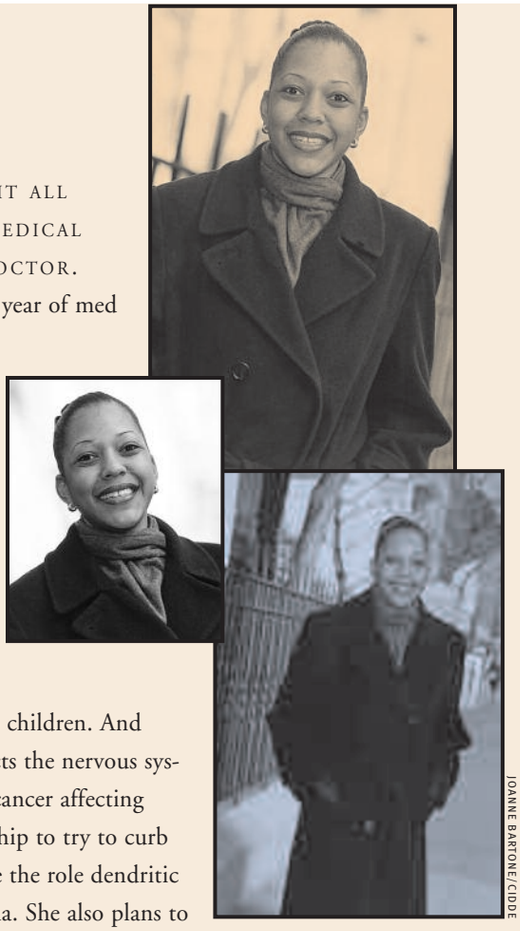
Gold

FOOTNOTE

Just so you know, one of the largest collections of rare hernia repair books is under lock and key in the Historical Collection at Pitt's Falk Library. *Treatise on Dislocations* and *Hernia and its Radical Cure* are just a few of more than 500 titles, some dating back to the sixteenth century.

THOMAS RECEIVES NATIONAL MEDICAL FELLOWSHIP

FOR KEYNE THOMAS (MD '01), IT ALL STARTED AT AGE 3 WITH A TOY MEDICAL KIT AND A WISH TO BECOME A DOCTOR. Since then, she has finished her second year of med school, researched diabetes in Barbados, and participated in Merck studies on the HIV drug Crixivan. Most recently, Thomas was one of 26 minority medical students nationwide to receive a research fellowship from National Medical Fellowship, Inc., a nonprofit organization encouraging students to pursue careers in academic medicine.



JOANNE BARTONE/CIDDE

Thomas is driven by a desire to help children. And since neuroblastoma, a tumor that affects the nervous system, is the most common extracranial cancer affecting children, she decided to use her fellowship to try to curb it. Thomas designed a study to examine the role dendritic cells play in the spread of neuroblastoma. She also plans to specialize in pediatric and adolescent medicine. As if that wasn't enough, she and her husband recently founded an outreach organization to provide health care and counseling to underserved youth. After all, she says, children need all the help they can get. —*TM*

Flashback

"War broke out on December 7th, 1941, when we were freshmen, so everyone in the class of '44 who passed the physical was in the army or the navy—those who weren't got drafted into service. As part of the program, we used to jump from the second floor of Trees Gym into the pool, you know, to simulate jumping off of a ship. Then we'd run to the stadium, down to Panther Hollow, around it once, and back up again. I tell you, we were dragging when we got up there. The whole way we'd sing a song about six pence. . . *I've got six pence, jolly jolly six pence, I've got six pence to last me all my life. . . two pence to spend and two pence to lend and two pence to send home to my wife.*"

—Albert William Corcoran, MD '44

THE OWL, 1943



PHOTODISC

X Chromosome Linked to Lung Cancer Risk

More than 170,000 lung cancer cases are diagnosed in the United States each year—women comprise the majority.

Jill Siegfried, professor and vice chair of pharmacology and codirector of the University of Pittsburgh Cancer Institute's lung cancer basic research program, has found a compelling explanation for why more women than men develop lung cancer, caused from their own smoking habits or secondary smoke. She and her research team recently found a gene on the X chromosome that codes for a lung-cell receptor—a receptor stimulated by nicotine. Through this receptor, this gene causes cells to grow and multiply, potentially triggering tumor formation. Since women, of course, have two X chromosomes, they are twice as likely to express the gene that can ultimately lead to lung cancer.

A man would have to smoke one pack of cigarettes per day for 25 years to match a nonsmoking woman's risk of expressing the gene.

"Hopefully, our study will present a powerful argument against smoking in the work place," says Siegfried. "This should also warn parents, especially with daughters, that smoke exposure is causing harm." —*ST*

Appointments



Fechter



Kanter

George A. Fechter was appointed associate vice chancellor for external relations for the health sciences. He has served on the council of the University of Pittsburgh Cancer Institute since its inception in 1985 and as its chair from 1994 to 1998. Fechter, who most recently was CEO for the University's McGowan Center for Artificial Organ Development, will represent the Office of the Senior Vice Chancellor for the Health Sciences and Dean in all philanthropic development activities, government relations, and commercial collaborations.

Arthur S. Levine, senior vice chancellor for the health sciences and dean of the School of Medicine, has further expanded his office. **Steven L. Kanter** now serves as senior associate dean, overseeing academic and faculty affairs, and **Charles F. Reynolds III** continues as senior associate dean, assisting Levine with special projects. ***—RS***



JANET KURJAN/FIBERART INTERNATIONAL 1999

FRANK AND STARZL ELECTED TO INSTITUTE OF MEDICINE

Ellen Frank, professor of psychiatry and psychology, and Thomas Starzl, professor of surgery and director of the Thomas E. Starzl Transplantation Institute, have been elected members of the National Academies' Institute of Medicine (IOM).

Frank, whose work has broadened the scope of treatments available for psychiatric illnesses, most notably for depression, will serve as a member of the IOM. And Starzl, who pioneered the science of organ transplantation and immunosuppression, has been elected a senior member. *—RS*

PANTS ACROSS AMERICA

Yes, that's what we said. To raise awareness of the problems of the severely and morbidly obese, Philip Schauer, assistant professor of surgery at the medical school, brought an exhibit called "Pants Across America" to UPMC Presbyterian this winter. It included more than 50 pairs of oversized trousers. The roomy wardrobes were no longer needed by patients who had undergone surgery to reduce their stomach capacity and bypass parts of their intestines. Schauer is also codirector of the Mark Ravitch/Leon C. Hirsch Center for Minimally Invasive Surgery.



Mind over Matter



JOANNE BARTONE/CIDDE

Matthews

IF YOU DON'T CALM DOWN, YOU'RE GOING TO HAVE A HEART ATTACK. Lots of us have heard or said that line—many shrug it off under the misconception that it's a myth. But what impact the mind has on the body and *vice versa* is a serious question. It has occupied scientists and philosophers for centuries, and if you ask Karen Matthews, professor of psychiatry, epidemiology, and psychology at the University of Pittsburgh School of Medicine, she'll tell you some serious progress is being made toward answers. With a $10 million grant from NIH, Matthews is now the principal investigator of a five-year collaborative project with Carnegie Mellon University to establish the Pittsburgh Mind-Body Center.

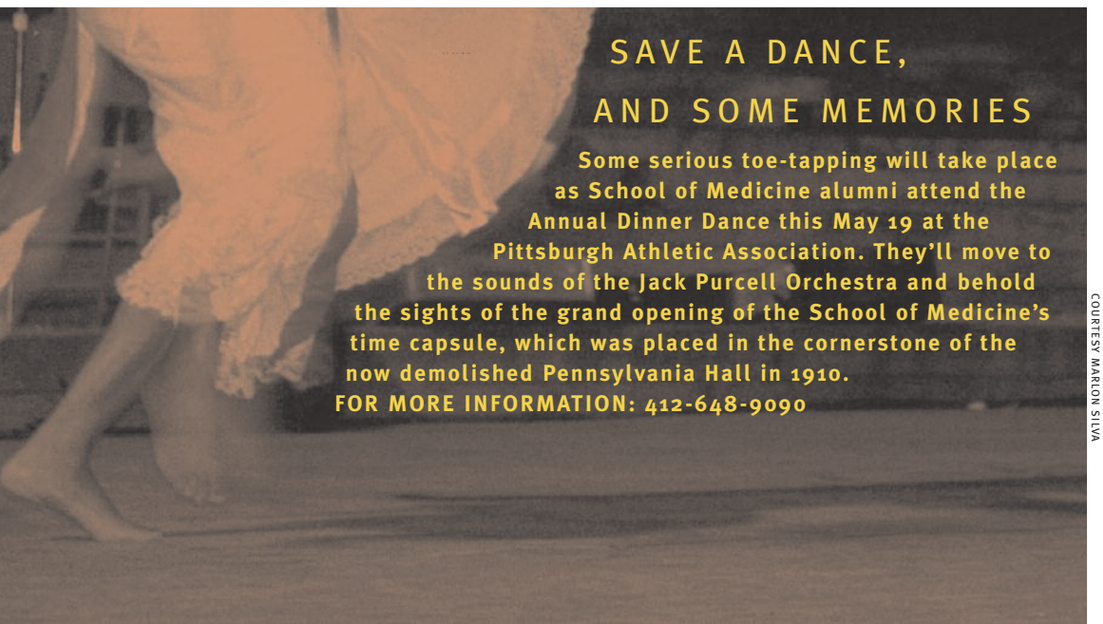
Pittsburgh researchers have been at the forefront of mind-body interactions and health for years. They've shown, for example, that women with increased hostility and aggression are more prone to coronary artery disease, and that a person's risk for respiratory illnesses is affected by his or her personal relationships. But Matthews wants to focus this expertise on a broader approach to the mind-body relationship. She wants to study how stress, personal relationships, and other mind-related factors impact health across the board.

"Studies we did locally found that optimistic people recovered more quickly following bypass surgery. . . and that they live longer after being diagnosed with breast cancer. So here are illnesses that all suggest optimism plays a role in either susceptibility or recovery."

This is what Matthews wants to develop at the center—an understanding of how factors related to the mind influence multiple diseases and how intervention might affect recovery.

In addition to its research efforts, the center will offer training programs for scientists interested in the mind-body relationship, as well as seed money for developing projects. And perhaps, with time, the unanswered mind-body question will exist only in the realm of history. —*RS*

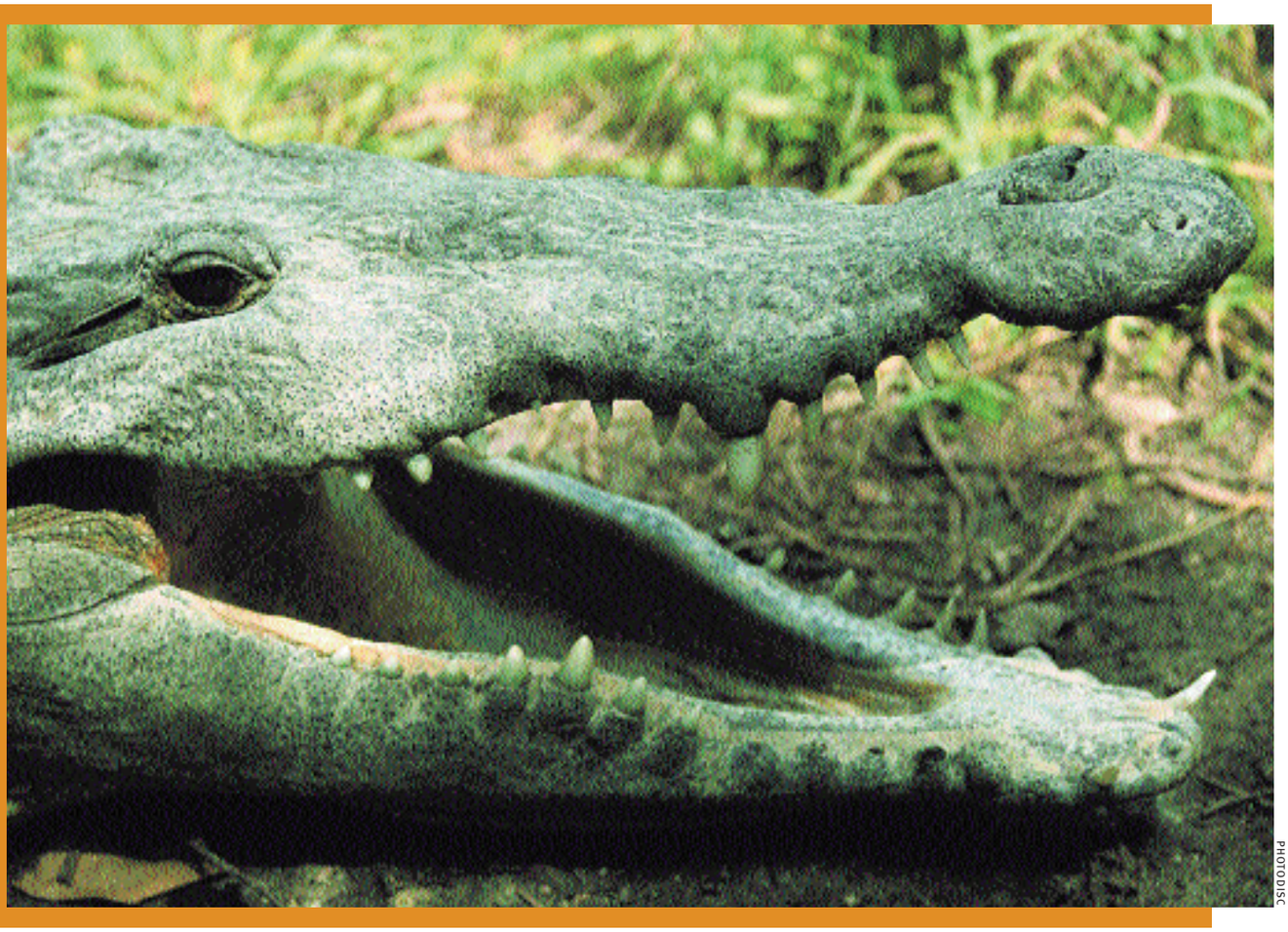
FOR MORE INFORMATION:
http://www.wpic.pitt.edu/behavioralmedicine/



COURTESY MARLON SILVA

SAVE A DANCE, AND SOME MEMORIES

Some serious toe-tapping will take place as School of Medicine alumni attend the Annual Dinner Dance this May 19 at the Pittsburgh Athletic Association. They'll move to the sounds of the Jack Purcell Orchestra and behold the sights of the grand opening of the School of Medicine's time capsule, which was placed in the cornerstone of the now demolished Pennsylvania Hall in 1910.
FOR MORE INFORMATION: 412-648-9090



PHOTODISC

THE ART OF SWALLOWING

A NEW CENTER USES SURPRISINGLY GRACEFUL THERAPEUTICS. | **BY REBECCA SKLOOT**

Swallowing is one of those things you do about 3,000 times a day without thinking much of it. But each successful swallow is, in many ways, an art. A dance of perfectly coordinated performers: the lips, tongue, teeth, palate, vocal folds, and a host of muscles. At any step along the way, if one movement is out of sync, the swallow can go awry. For some, this means a moment of discomfort—a cough during dinner or a cleared throat in a moment of silence—but for others, it can mean malnutrition, dehydration, pneumonia, and even death.

"We all take swallowing for granted until a problem shows up," says Thomas Murry, professor of otolaryngology at the University of Pittsburgh School of Medicine. "People who clear their throat all the time or cough after they drink. . . they're probably unaware that they may have a swallowing problem." According to Murry, director of UPMC Health System's new Swallowing Disorders Center, about 15 million Americans have swallowing disorders. But only some of these problems manifest in clearing throats or coughs.

"We see that group," says Murry, "but the majority of our patients, especially stroke patients and those with neurological disorders, actually needs to be retaught to swallow from the ground up." With a number like 15 million, it's surprising that Murry directs one of the few such centers in the country. But it's true.

The center revolves around what Murry refers to as the swallowing team. The team is led by a speech-language pathologist and relies on professionals focused in specialized areas of swallowing disorders: dietitians, voice therapists, maxillofacial surgeons, neurologists. . . the list goes on. But until recently, says Murry, swallowing disorders weren't treated by a group of specialists as a unified problem.

"Family doctors treated them, then gastroenterologists—and they often treated them successfully. But there haven't been any comprehensive centers simply because treatment was fragmented from the start."

Only 20 years ago, the physiology of swallowing and its role in medicine was a whole new field.

"It was just accepted," says Murry, "that people died in the hospital of pneumonia after stroke." Often, stroke patients couldn't swallow food or liquids—so the materials passed into their lungs instead of their stomach, and they developed pneumonia. Fortunately, the incidence of pneumonia deaths after stroke plummeted as knowledge of swallowing increased.

While other researchers worked toward understanding swallowing physiology, Murry followed his own path to exploring swallowing disorders.

"It all stems back to my fascination with vocal cords," he says. "They're at the top of the airway, so when the vocal cords don't work, the patient can choke or aspirate." This, Murry points out, presents difficult treatment issues. "Now, we may all like to talk, but given the option, you would rather swallow than talk. Trust me."

When a patient walks into the center, Murry's team questions, examines, and searches for the problem's cause. Once they've found it, they begin their delicate work toward the final goal: a healthy swallow. Their therapeutics range from pharmaceuticals to corrective surgery. But for the majority, swallowing therapy is the answer.

If swallowing is a dance of precise movements, swallowing therapy is where each performer learns her part. Oral motor exercises increase strength and range of motion of the lips, tongue, and jaw. Then, when they're ready, patients learn techniques for sending food and liquid in the right direction through methods whose names conjure images of ballerinas in dance—the "Mendelssohn maneuver," the "supraglottic swallow," the "chin tuck," the "head tilt." It's through these graceful therapeutics that the swallowing team begins choreographing a healthy swallow.

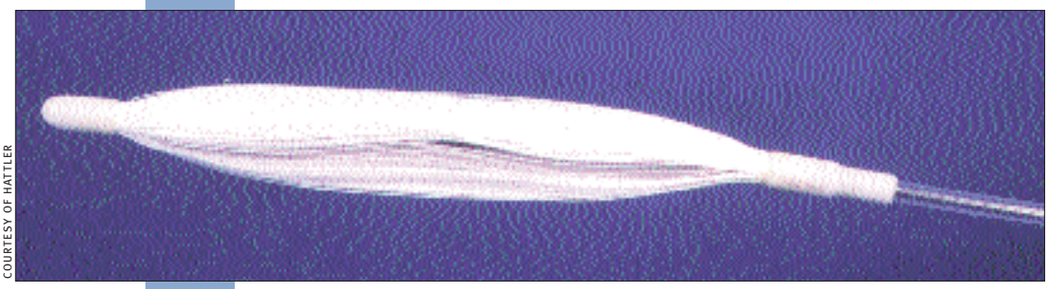
In some cases, therapy isn't effective and the team switches to nutrition management, and as a last resort, surgery. In the end, their work always comes back to coordination—whether it's a well-executed "head tilt" or the bringing together of top-notch specialists. ■

FOR MORE INFORMATION:
http://www.upmc.edu/swallowingdisorders/

BREATHING EASIER

HATTLER INVENTS AN INTRAVENOUS MEMBRANE OXYGENATOR.

BY RICH LORD

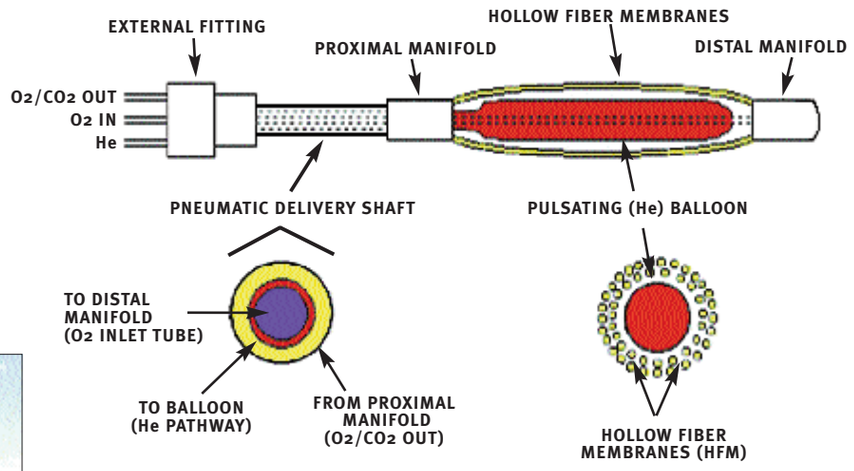


COURTESY OF HATTLER

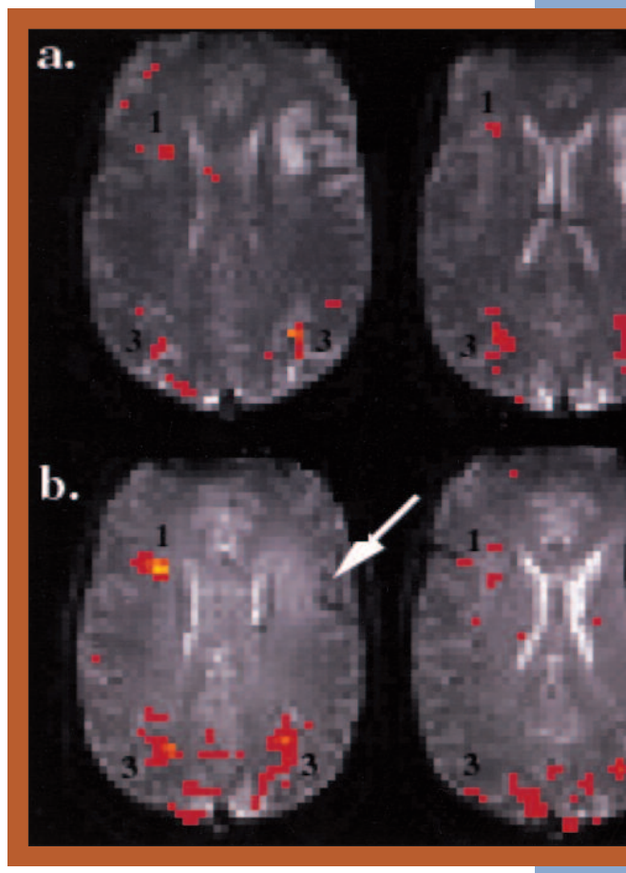
The internal membrane oxygenator is 30 to 40 centimeters in length and consists of about 1,000 hollow fiber membranes. The device would be placed in the superior and inferior vena cava, spanning the right atrium.

For Brack Hattler, one tragedy has spawned 16 years of research. In 1984, Hattler was a surgeon at Denver's Swedish Porter Hospital, where he took care of two men in their early twenties who were in a car accident. Their legs were crushed, causing a flood of proteins that led to acute respiratory distress syndrome. Respirators couldn't help, because the patients' lungs were too distressed to process oxygen. So Hattler, now a professor of surgery at Pitt's School of Medicine, hooked





HOW BRACK HATTLER'S (LEFT) IMO WORKS: Oxygen enters the hollow fiber membranes through an external tube and flows through the fibers under vacuum pressure. Then, within each fiber, oxygen diffuses through tiny pores in the fiber wall into the blood, where it is exchanged for carbon dioxide, which diffuses into the fibers and exits the device through a second tube. Buried within the bundle of fibers is a pulsating central balloon that mixes the blood. By inflating and deflating, the balloon draws blood directly across the fiber. A bonus: Since the balloon pumps the blood over the fibers, the IMO doesn't get in the way of blood flow returning to the heart.



them up to the only equipment available that offered any hope of survival—extracorporeal membrane oxygenators (ECMOs), which remove blood from the body, add oxygen, then return the blood to the circulatory system. Though ECMOs can save lives, they also are associated with high mortality rates, he says.

"Both of those young men died, and at that time I began considering that there might be a better way of doing this," he says.

Now Hattler is putting finishing touches on that better way. The intravenous membrane oxygenator (IMO) should be on the market, "and hopefully saving lives," Hattler says, within a year. Hattler is developing the IMO at the School of Medicine and Pitt's McGowan Center for Artificial Organ Development.

Instead of taking the blood out of the body for a lengthy and potentially problematic journey through oxygenation machines, the 10-ounce IMO fits into the patient's vena cava and adds the oxygen there. Delivery shafts run from an external oxygen source into the body and to the IMO and carry away the carbon dioxide shed by the blood. "It allows the lungs to rest, essentially," Hattler says.

Hattler began working on the IMO in a Denver-area machine shop in 1984. "It was a sort of backyard-type operation," he says. Initial testing looked promising, and at first he expected to have a finished product in a few short years. Then a problem arose that would occupy him for more than a decade: Blood that passively flowed through the IMO's membranes wasn't picking up enough oxygen. By the time he joined the School of Medicine in 1989, there was still much work to be done.

The answer would be to wrap the membranes around a 25-cubic-centimeter balloon, which fills with helium and pulsates at 300 or 400 beats per minute. When the balloon deflates, it creates a vacuum, drawing blood through the oxygen-rich membranes. When it inflates, the blood is pushed away, allowing the membranes to carry away carbon dioxide and then fill with oxygen again, just in time for the next influx of blood.

Hattler and his team—lab director William Federspiel, Tom Merrill, designer/fabricator Brian Frankowski, chief technician Joe Golob, and many others—are now testing the IMO in large animals. FDA approvals and clinical trials are next, followed by production by ALung Technologies, Inc., of Pittsburgh, in partnership with Minneapolis-based Medtronic, Inc.

The IMO may lead to bigger breakthroughs.

"Everything we're learning about oxygenating venous blood in the body would be directly applicable to a long-term artificial lung," Hattler says. In the meantime, patients with acute respiratory distress syndrome, pneumonia, and chronic lung disease could stand to gain, he says.

"We think this device, placed inside humans for five to seven days, can reverse most of the acute processes that cause respiratory distress."

That means up to 300,000 Americans could benefit yearly from the IMO, and many of the 5,000 annual deaths from acute asthma could be prevented.

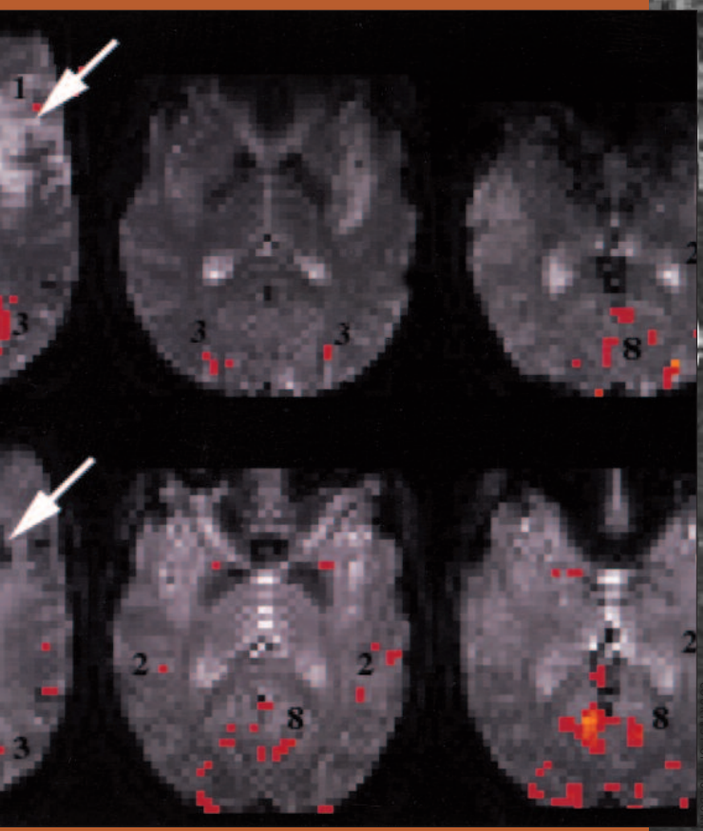
Hattler notes: "Worldwide, the numbers look like they're in the millions." ■

FOR MORE INFORMATION:
http://www.upmc.edu/mcgowan/artlung/hattler.htm

IF YOU COULD SEE WHAT HE SEES

THULBORN SHOWS HOW BRAINS CAN REDISTRIBUTE WORKLOAD AFTER APHASIA.

BY MICHAEL ROSENWALD



ABOVE: Activation maps of right-handed, left-middle-cerebral-artery stroke patient. At 76 hours, the affected Broca's area shows strong shift to right dominance; at six months, shift is total. Wernicke's area (undamaged) shows complete left dominance at 76 hours, and remains strongly dominant at six months. The ability to visualize redistribution via functional MRI offers hope for the stroke intervention and recovery process.

What makes Keith Thulborn have lunch at 4 p.m., work until he falls asleep, and start working again when he wakes up, is the idea that if he works hard enough, long enough, he is eventually going to see over the horizon.

"It's the idea that I'm looking at what nobody else has seen," Thulborn says. "That's an incredibly stimulating process. If you think of adding information to our civilization's body of knowledge, it's only when you look over the horizon that you're actually doing it."

Thulborn, an MD, PhD (neuroradiologist and biochemist), is one of the world's leading magnetic resonance imaging (MRI) brain researchers. He's Australian, easygoing, clearly dedicated, and fascinated with the mystery of the brain. He has certainly seen over a few horizons since coming to Pitt in 1993.

To understand how the brain functions, it's a real advantage to see living tissue in action during cognition. Functional MRI is one of the few ways to do such a thing. Thulborn came to Pitt because it allowed him to build a functional MRI scanner that went beyond 1.5 tesla, all the way to 3.0 tesla, and allows researchers to see any part of a functioning brain as if it were in their bare hands.

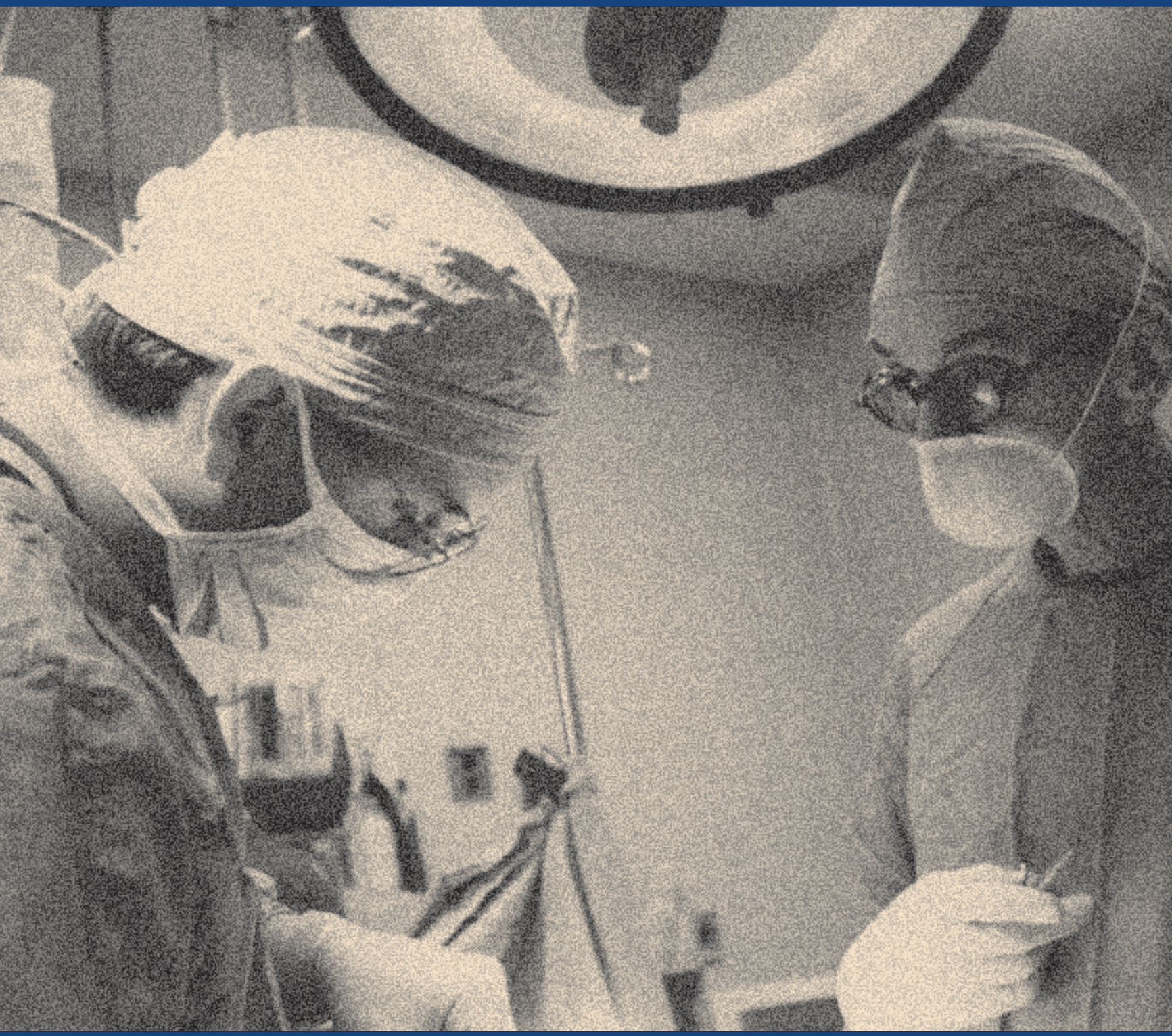
What he has found is astonishing. Thulborn recently published a paper (*Stroke*, April 1999) that could one day change the way physicians treat acute stroke patients. At its simplest, Thulborn can use the souped up scanner to examine what part of the brain is involved when a person is asked to tap her fingers. But Thulborn is interested in far more complex studies: namely, how a person's ability to process language is affected after a stroke.

"They're not just losing a part of their brain," he says of stroke victims unable to communicate. "They're losing a part of their humanity."

Researchers have hypothesized that after a stroke, the brain tries to redistribute functions over existing networks, much like a computer network would have to reroute information if part of its wiring became damaged. By looking at stroke patients through functional MRI and tracking anatomical, physiological, and functional changes in brain activity from five hours to six months after an insult, Thulborn was able to confirm this theory. He also showed that redistribution could in fact happen very quickly and in patients of all ages. It was previously thought that adult brains were too set in stone for such changes to take place.

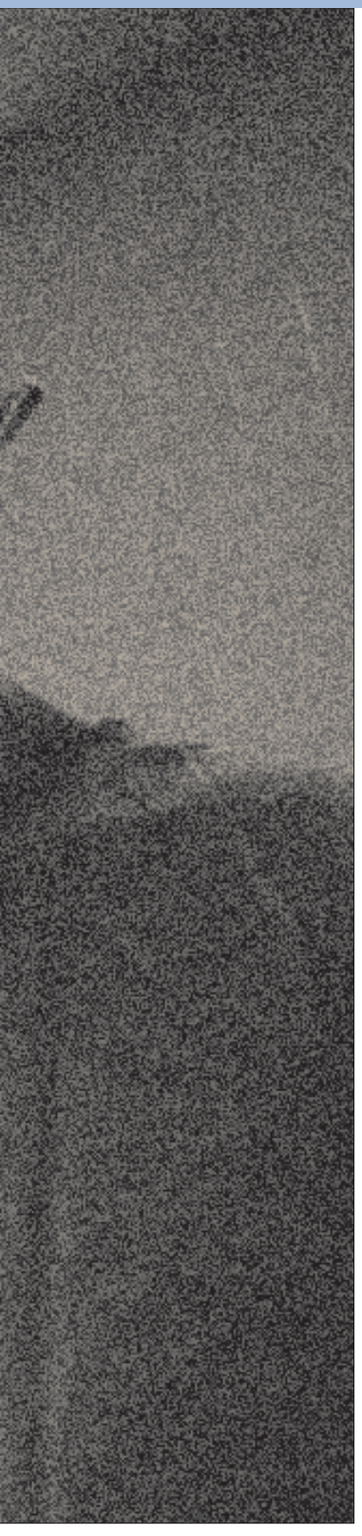
When redistribution occurs, Thulborn also sees some recovery. But why some people don't recover still isn't clear to him, though he surmises (and intends to prove) that extensive involvement of white matter tracts—the network cables, let's say—prevents redistribution.

Thulborn is working with Marcel Just and Pat Carpenter of Carnegie Mellon University's psychology department; he believes their efforts will allow doctors to come up with stroke interventions that enhance the redistribution process. The research has helped at least one patient so far. An aphasia-afflicted man wrote Thulborn to say the findings made it easier to understand what was happening to him. Thulborn's response? Smile. Keep working. ■



For the past century the title "Dr. Watson" referred to at least one stellar Pittsburgh surgeon.
ABOVE: The late Charles Gray Watson supervises son Andrew Watson on a surgery rotation.

THE FAMILY THAT SET THE STANDARD FOR SURGERY IN PITTSBURGH | BY E. DOUGLAS BANKS



DR. WATSON

In Presbyterian Hospital in the 1950s, you could look down the long hall of the old surgical floor on 11 and at any moment, James Rose (J. R.) Watson would swing open the doors at its end. He loomed well over six feet tall, yet he was a giant in more than stature. When he entered a room, people couldn't help but look at him.

You could set your watch by his entrance, which came precisely at 7:45 a.m. on Tuesdays and Thursdays. In 15 minutes, at 8 a.m., the first surgery of the day would begin. Watson would enter his operating room, No. 54, and ask the staff if they were ready. They would answer "yes." There was no other acceptable answer.

Outside the OR, Watson wore a navy blue three-piece suit. For surgery, he wore bright white buck shoes. Always. If you looked down, you would see navy blue or black socks. Always.

For J. R. Watson, the patient came first. He would enter the OR and always—always—put his hand on the shoulder of the patient, say "hello," and ask about her well-being. He used titles when referring to anyone—"Dr. Smith" or "Miss Lynch."

During surgery he would ball a fist and stick out his index finger. That meant: scalpel. If his thumb and forefinger opened and closed: forceps. His hand out, he would open and close his forefinger and middle finger like an alligator mouth: scissors.

"He had a tendency to do what they called signals," recalls Sarah Lynch, the operating room technician for J. R. Watson from 1957 until his retirement in 1973. "I used to love that. I absolutely loved it."

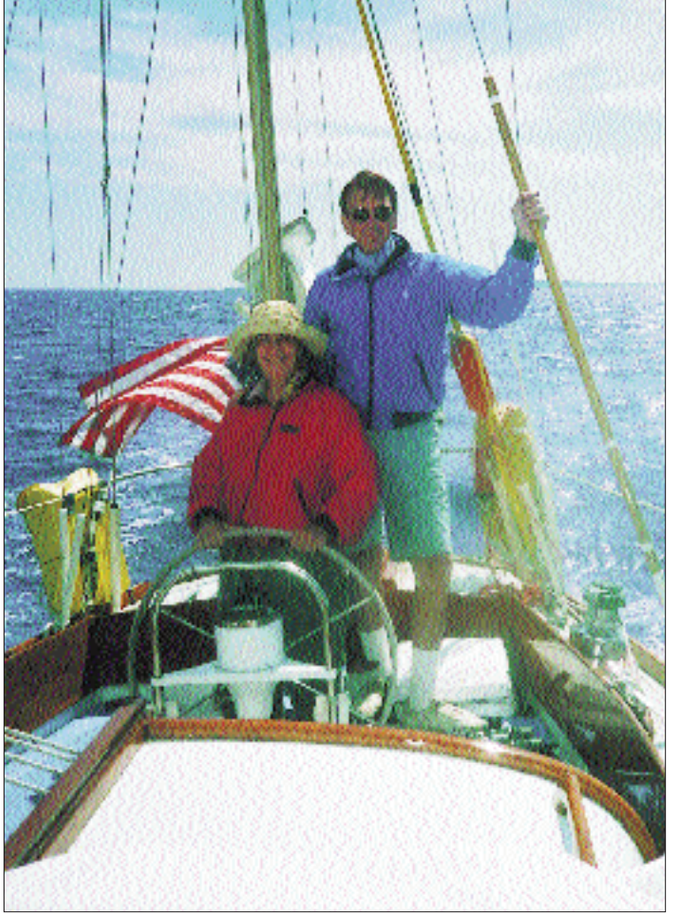
Many others were endeared by the doctor with the commanding presence. As one faculty member recently noted, most great surgeons were feared. J. R. Watson was loved.

With the deaths this winter of J. R. Watson, his son Charles Gray Watson, and nephew Thomas M. Watson (MD '76), the Pitt medical community suffered a blow described by one senior University official as nothing less than the loss of the medical school's soul. Ask anyone who attended the memorial service for Charles and J. R. at Heinz Chapel in late January. Every seat was filled; friends and colleagues stood three across in the aisles, packed into the lobby, halls, and stairs outside. The word heard over and over again was "gentlemen."

To know the Watsons was to see no coincidence that the words "gentle," "gentlemen," and "genteel" all come from the Latin *gentilis*, "belonging to the same clan." They belonged to a clan that, at any point in the past 100 years, has been represented in the Pittsburgh

PHOTOGRAPHY | COURTESY OF THE WATSON FAMILY





J. R. Watson taught surgery at Pitt before a full-time faculty existed in that department. LEFT: **J. R. with scrub nurses Sarah Lynch and Janie Rocheck.** ABOVE: **Charles Watson on one of many high-seas adventures with wife, Nancy.**



J. R. Watson

community of surgeons with the Watson surname. The Watson dynasty began with J. R.'s father, Charles Masena Watson, who graduated from the University of Pittsburgh School of Medicine in 1900, and was further perpetuated by his brother William G., his nephew Thomas M., as well as Charles Gray.

J. R. Watson himself was considered a giant in general surgery. He made national headlines after he performed the first autotransfusion on record to a boy who had been stabbed in the heart and left lung. When he retired in 1973, he was credited for helping build the surgical program at Pitt during the 1950s and 1960s.

These days when most people think of "Dr. Watson" they think of Charles Gray Watson. On his endocrine surgery service, Charles Watson's imperative was not unlike his father's: get to know the patient. And like his father, he stressed precision of thought, action, and purpose.

Charles Watson treated words as surgical instruments, his vocabulary a tray of refined tools, exact and literal in use. When he asked questions of his students he was Socratic, requiring only that the person answering be honest. If you know the answer or think you know it, say it. If you don't know, say you don't know. You see, if you bluffed and were wrong, he would never correct you. He would simply move on. But he always remembered who didn't know and would expect them to know the next day.

What nerves are critical to protect during a thyroid or parathyroid?

To get an answer, Charles Watson would begin with the newest medical students and go up the line, all the way to the chief resident, if necessary. You worked hard to know the answer to questions he was likely to ask, even if it meant a sleepless night poring through books. You simply couldn't bear not knowing about the hard-to-find recurrent laryngeal nerve if asked by Chuck Watson. His purpose was clear: The questions were not about memorizing anatomy. Being central to voice integrity, damage to the laryngeal nerve can lead to permanent hoarseness. To do your job right, you had to think about the patient's quality of life after the surgery.

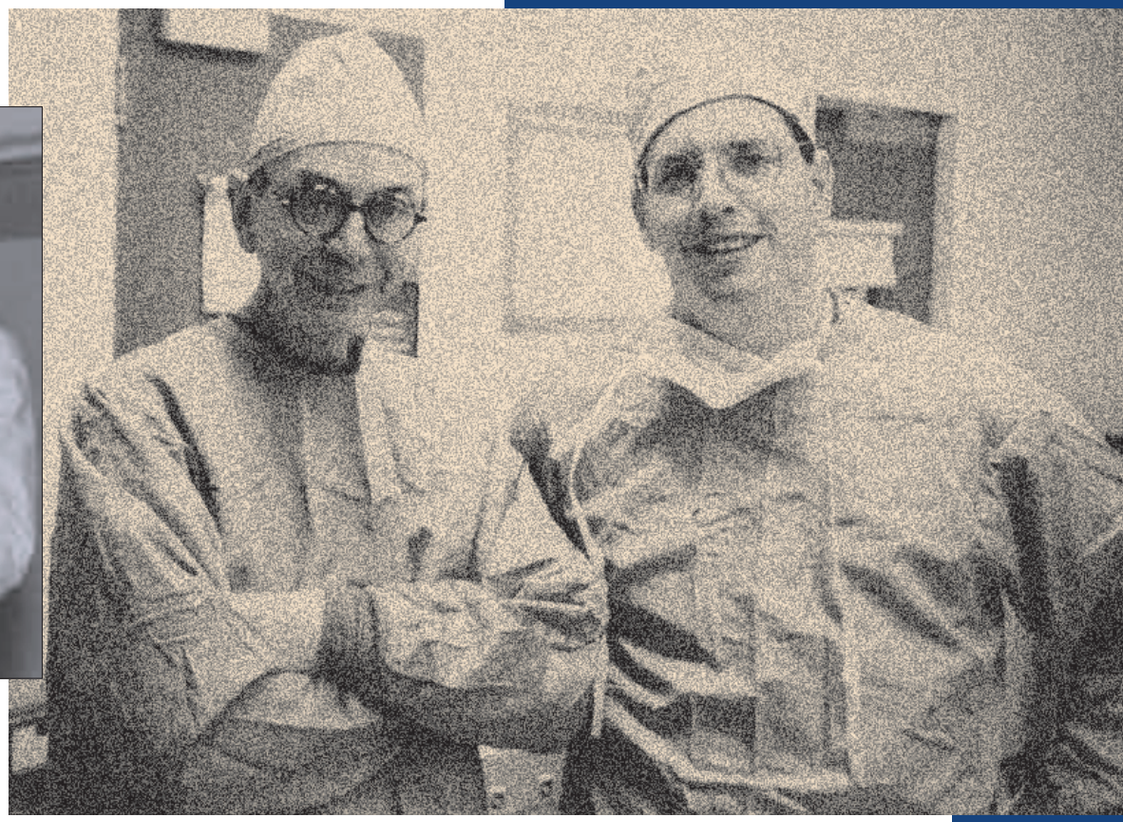
A small crowd of residents follows Charles Watson as he makes his rounds. It is 6:30 p.m., Election Day, some time during the late 1970s. Among the group is David Steed, then a senior resident, today a professor of surgery at the School of Medicine.

"Did all of you vote today?" Watson asked in the formal, aristocratic New England tone in which he spoke.

"No, Dr. Watson. We're too busy," said one harried resident. The others concurred.

If you bluffed and were wrong, he would never correct you. He would simply move on. But he always remembered who didn't know and would expect them to know the next day.







Charles Watson

ABOVE: It seems an understatement to say Charles Watson was a favorite professor. Students dubbed him the "Velvet Harpoon" for his uncanny ability to correct a student decisively yet gently. RIGHT: Charles and son Andrew, who will soon begin a residency in internal medicine at Columbia.

Watson well remembered the dues of getting through such a program. During his own residency, back when he rode a bicycle to the Peter Bent Brigham Hospital in Boston, he once was so exhausted, he actually fell asleep along the way. Right in the midst of Boston's hair-raising traffic he toppled over. Fortunately, he landed on the sidewalk.

"I'll finish rounds," Watson said. "All of you who haven't voted, go out and make sure you do."

For his trademark sensibility, Charles Watson was recognized with three Golden Apple awards, a Chancellor's Distinguished Teaching Award, and the Healthcare Foundation of New Jersey's Humanism in Medicine Award.

His former students claim they are good doctors because he was a great one, and that affinity was returned generously. Richard Simmons, his former department chair, made this observation: Charles Watson always considered the upcoming class to be the brightest, the next resident group the most promising. The grass was always greener where Chuck Watson stood.

The salt seemed stuck in the words as they hung, floating in the air above the *Odyssey*, Charles and Nancy Watson's 44-foot yawl. Sailing in the Bay of Maine a couple of summers ago, Charles had just been asked by a friend, Robert Flory, what he hoped to accomplish in his last few years at the School of Medicine. Charles Watson said he wanted to raise $5 million to endow surgical research fellowships for residents at Pitt. Nancy knew Charles was passionate about the fluctuations of research funding, but still, she thought to herself: "Good grief, listen to this."

It was one of those things that could happen during August, which Charles and Nancy always spent sailing. The peaceful but sometimes challenging atmosphere often led to inspired thoughts and exchanges on the boat. Twenty-four hours after Watson made his wish known out loud, Flory organized a committee that doubled the endowment's goal. The group already is halfway to realizing a $10 million fellowship fund.

For Nancy, who met Charles on a high-seas voyage in 1957 and married him one year later, it is fitting that it was on a boat named the *Odyssey* that this last great part of his legacy was born.

J. R. and Charles Watson practiced together for a while in the late 1960s and early '70s. Like most surgeons, they brought their own preferences to the operating arena. For instance, their styles of suture tying differed: J. R. was a chromic man, Charles a silk man. This was certainly a reflection of the generation in which they trained; yet, Charles was a silk man in dress as well. If you knew Chuck Watson, you could hardly imagine him without a jazzy bow tie, probably custom-made at a company in Vermont. Those ties were his sartorial signature—a detail everyone noticed. What people might not have noticed was why he wore them. Nancy Watson tells how Charles started procuring bow ties after he realized his other ties would droop in the faces of his patients during examinations. He couldn't stand the idea of that. He should be putting people at ease, offering them the best diagnosis, even a bit of consolation and perspective; he did not want to contribute to their discomfort.

Even in dress, Chuck Watson's priority was the patient. ■



Mary Hohenhaus, MD '01, on her way to her outpatient clerkship

THE NEW THIRD-YEAR CURRICULUM HAS STUDENTS ASKING LOTS OF GOOD QUESTIONS.

BY REBECCA SKLOOT

FIRST CONTACT



As the sun warms October's first frosty morning, 20 third-year medical students stand in Scaife Hall, facing the walls, reading small pieces of paper taped to 20 classroom doors. They are restless. They shift back and forth, some bumping their knees rhythmically against the wall in front of them.

"Do you think we can take notes?" one student asks over her shoulder in a loud whisper.

"I don't know," another says softly, "but this is fun."

"Are we supposed to start?" someone yells.

"No, you have to wait for the whistle," Erica Hickey shouts back. Hickey is the curriculum specialist sitting cross-legged in a chair, whistle in one hand, stopwatch in the other.

These students are waiting to begin an exam that marks the end of the first Community/Ambulatory Medicine Clerkship (CAMC), a 12-week program that is a required part of Pitt's new third-year curriculum.

PHOTOGRAPHY | RICHARD KELLY



Mary Hohenhaus with Gordon Handelsman, MD '83, one of her clerkship preceptors

They have completed a three-week rotation in internal medicine, family medicine, and pediatrics as well as a rotation in a "selective" (any of the above of their choosing). Through CAMC, they worked in clinical settings ranging from urban hospitals to small rural family practices and vans servicing low-income urban areas. They have been observed and coached every step of the way by their clinical preceptors but are gathered today for the final evaluation: a performance-based exam and a 100-question written exam. Anything they've learned, in any specialty, is fair game.

A shrill whistle echoes down the hall and Hickey winces, quickly apologizing for the noise. But no one moves.

"You're supposed to go into the rooms when the whistle blows!" yells Hickey, whose slight frame and subdued demeanor are a sharp contrast to her ear-splitting noises. "You go in when it blows once, then you have 10 minutes. When I blow it twice you come out and switch stations."

With that, Hickey wedges the whistle between her lips, covers her ears, and lets out another strident screech. Several doors creak as students enter their classroom-turned-exam-room-for-the-day to greet their simulated patient and a faculty observer.

With the hall barren of students, Mary Hohenhaus peeks her head out of a station to reread her patient's history. Her patient (which is actually a plastic model of a pelvis) is a 35-year-old woman who is experiencing a sense of "heaviness in her pelvis when she lifts things." The note tells Hohenhaus to perform a pelvic examination and reminds her to speak to the model as though it were a real patient. Hohenhaus nods and walks back into the room where Ilene Burns, assistant professor of family medicine and clinical epidemiology, stands ready to observe her and answer any questions she might ask the pelvis. Questions like, *Does it hurt when I squeeze here?* or, *Do you and your sexual partners use condoms?*

When Hohenhaus finishes the physical, Burns will give her feedback until the next whistle blows. If Hohenhaus, say, forgets part of the physical exam, or doesn't ask the right questions, Burns will tell her, and they'll discuss ways to avoid these mishaps in the future. By now, Hohenhaus is accustomed to one-on-one work with faculty—for the past 12 weeks, she and other third-year students have been working closely with CAMC physician preceptors, learning to approach and examine patients.

Note: Patients' names and identifying details have been changed.

During the 1960s, before the phrase *primary care physician* came into vogue, there were *physicians of first contact*. And according to Steven Kanter, senior associate dean, CAMC was designed with that phrase in mind.

"I like it because it describes what we are really trying to do with outpatient medical education," says Kanter. "We want students to learn what happens the very first time a physician sees a patient. Because once the patient has been seen, some thinking has been done, and you can read that in the chart. But without a chart, there are different reasoning processes and issues."

Say, for example, you're a physician doing a routine exam on a patient and the patient's husband, who's just along for the ride, falls unconscious in your waiting room. You don't know whether he has been poisoned, had a stroke or a heart attack, or is suffering from any number of other possible conditions. What you do know is that you need to help.

This situation is worlds different from seeing the man in an exam room the next day, after paramedics resuscitated him and emergency physicians determined that it was a cardiac problem.

"The thinking that goes into that initial assessment of a problem," says Kanter, "is what we want students to see in CAMC."

A few winding miles beyond the Homestead cemetery where victims from the 1892 steel strike are buried, just two days before her CAMC exam, Hohenhaus sat in a small white exam room with nurses rushing past outside the door. She rested her elbows on her knees, and slowly rolled her stool toward Jason, an 8-year-old boy, who hung his head and turned his back to her. She was trying to break the ice.

"So how's school?" Hohenhaus asked as Jason grabbed the sides of the exam table and jerked with all his strength. The table didn't budge.

"Okay. Fine, I guess," he mumbled, yanking the tucked-away metal stirrups from beneath the table.

"Do you have friends there?"

"Yeah. I guess. Well . . . no."

"Where do you live?"

"With him and my grandma," Jason sighed, pointing over his shoulder to the man, who was probably in his 50s, sitting by the door.

"And how is that?"

"Can we just get this over with?"

"Get what over with? The exam? Are you worried about the exam?"

"I'm not worried, I just want to get it over with," he snapped, his back still facing Hohenhaus, his arms now wrapped tightly around his chest.

"Alrighty," she said, hopping up from her stool. "Then you've got to climb up here on the table."

You don't know whether he has been poisoned, had a stroke or a heart attack, or is suffering from any number of other possible conditions. What you do know is that you need to help.

Jason twirled around and jumped on the table. Hohenhaus looked at him and said she needed to check his tickle reflex. She wiggled a finger against his pudgy side, but Jason resisted. She did it again. Hohenhaus leaned in to see his eyes, which were squeezed shut to stifle his laughter.

"Gotcha," she whispered as he let out a low, anxious giggle.

As Hohenhaus circled the table asking Jason to make a muscle for her, puff out his cheeks, take a deep breath, and squeeze her finger as hard as he could, she asked his grandfather, Dave, if he had noticed any problems at home. He hadn't. At school? Nope, none. They just need to get the forms filled out. But Hohenhaus wasn't convinced. She turned to Jason.

"What do *you* think? Is everything okay?"

"Yeah. Fine, I guess."

Something didn't feel right, but Hohenhaus dropped the issue.

Across the hall from the exam room, Gordon Handelsman (MD '83), Hohenhaus's preceptor, sat at his desk waiting. This was part of their regular routine: Hohenhaus would take the patient's history, carry out a complete physical, decide what she wanted to do for the patient, then report it all to Handelsman. He would then question her methods and decisions, carry out his own interview and physical exam with her standing next to him, then they would meet again to discuss everything she had or hadn't done.

"Well?" Handelsman said, leaning back in his chair. Mary was one of the best students he'd ever had; he was eager to hear her take on the situation.

"It's so nice when there's nothing wrong with them," Hohenhaus sighed as she collapsed into a chair. So far that day she had seen patients with problems ranging from kidney failure to excessive overmedication, and Jason was the first who seemed healthy.

"Jason is an 8-year-old male here today with his grandfather. . ."

"Wait. Isn't that his father?"

"No, I think it's his grandfather."

"Where are his parents?"

"I'm not sure."

"So he lives with his grandparents?"

"Yes."

"Why?"

"I'm not sure. The grandfather didn't say."

"How's he doing in school?"

"The grandfather says he's doing fine."

"At home?"

"Same."



Third year student Ryan Levy and William Markle, MD, his instructor for the day's didactic session

"Is he having any social problems?" Handelsman didn't wait for an answer. He jumped up from his desk, ran across the hall, and burst into the exam room with Hohenhaus close behind.

Handelsman knew the man. Dave was a long-time patient. He also knew about Dave's grown children, but he had never seen or heard of young Jason before. Something wasn't right.

"Can you clarify your relationship to this child, Dave?" Handelsman asked with an air of playful confusion.

"I'm his grandfather," Dave replied, amused.

"Where are his parents?"

"Nearby."

"How did he end up living with you?"

"He used to come over to the house so I could help him with his homework. One day, he said he didn't want to live at home anymore and wanted to move in with us."

Hohenhaus leaned against the wall, watching intently as her preceptor moved around the table tousling Jason's hair and poking his belly button. Jason giggled.

"When?" asked Handelsman as he looked in Jason's ear.

"Few months ago," Dave replied.

"How's he handling it?"

"Seems fine."

"Talk to you about it much?" asked Handelsman, moving to the other ear.

"Nope."

Jason sat still, playing with a balled up T-shirt in his lap.

"Drugs? Alcohol?" Handelsman asked putting his stethoscope against Jason's back.

"Some."

"Who?"

"Mother."

"When pregnant?"

"I don't know."

Handelsman looked into Hohenhaus's eyes and nodded.

Physicians of first contact can't afford to be shy with their questions. And the situation with Jason was a perfect example. As the primary physician, it was essential that Handelsman learn more about Jason. His possible exposure to drugs and alcohol *in utero*, and the details of his family life, could shed light on learning, behavioral, or even physical problems that might manifest in the future.

"Part of being a medical student," says Handelsman, "is not just medical training, it's social training."

"When a situation makes you scratch your head, you haven't asked the right questions. And you have to be able to ask the right questions."

"There was something about the situation that just didn't seem right," Hohenhaus says.

"The grandfather was so matter-of-fact about the whole thing, but I knew I was missing something. The thing I learned from that experience was that when a situation makes you scratch your head, you haven't asked the right questions. And you have to be able to ask the right questions, or you won't get the information that determines how you care for your patients."

In her clerkship, Hohenhaus learned she needs to go into a patient's drug history, sexual history, what's going on in the home life. She needs to ask the questions that might make a patient uncomfortable.

She learned that questions are part of the larger art of patient examination, and she'll never forget it. This lesson, which seems like a basic requirement for any med student, isn't one that has been taught across the board. Kanter takes this issue to heart.

"We want every single person who graduates from the University of Pittsburgh School of Medicine to know how to do a good history and physical," says Kanter. To master the art of the physical exam, students must practice. But in order to practice, they must go where there are patients.

"When I was in med school," says Handelsman, "I did *no* outpatient work at all. Zilch. Everything I did was inpatient."

But medicine was different then—patients were admitted for procedures that now involve only a few hours of hospital time. So if students are going to see the scope of modern medicine, they need to do it in outpatient clinics. Through the past few years, outpatient experience started popping up in different areas of medical education—students got a bit of outpatient in pediatrics, a few weeks in family medicine, but it was never coordinated overall. And according to Kanter, this was a limitation. The school's curriculum committee decided to take the majority of the outpatient experience included in the curriculum and put it into one clerkship.

"What we have now," says Kanter, "are representatives from various disciplines working together to figure out the best way to teach primary care as an integrated concept to our students." And the innovation hasn't gone unnoticed: Pitt was awarded a grant from the Health Resources and Services Administration (HRSA) as a national demonstration site for an integrated clerkship in primary care. Students are noticing the change too.

"It used to be that you got your outpatient experience in dribs and drabs," says Hohenhaus. "Now, even though you're doing some internal medicine, some family practice, and some pediatrics, it's all primary care outpatient medicine, so it focuses the program and drives home the important lessons."

During her CAMC experience, Hohenhaus saw about 500 patients in three months. "You never know what's going to be behind each exam door. You just walk into a room and think fast on your feet. It has put me in a great position for the rest of my third year. I can walk through any door into any room and not be thrown too much by what I find."

Even if what she finds is a plastic pelvis and a faculty member who's waiting to evaluate her.



Susan Rubin, MD '01, learns to palpate breast tissue on a plastic model. This sort of one-on-one learning experience takes place during the weekly didactic sessions that are part of the new third-year curriculum.

Hickey, still sitting cross-legged in Scaife Hall, squeezes her eyes shut one more time and lets out a final double-whistle. Hohenhaus and the other students slowly pour out of their last station. They're exhausted. They have 20 minutes to recover before their written exam, while the other half of the class, who has just spent the morning answering the 100 written questions, gets ready for its performance-based test. As the students wander down the hall *en route* to the cafeteria, the faculty gathers in the hall to compare notes.

Basil Zitelli and William Markle approach each other smiling. Zitelli, a professor of pediatrics and the clerkship director, and Markle, an assistant professor of family medicine who organized the performance-based exam, have been pacing the halls nervously for the last hour, going from the written exam to the performance-based stations and back again, making sure everything is running smoothly. They are pleased.

Other than a little confusion over whistles, the exam was a smash success. The students could think of only one way to describe it: "Fun." But beyond having a little fun, more importantly, they got to demonstrate all they'd learned during CAMC while finding places for future improvement.

For Hohenhaus, this meant impressing faculty with her ability to ask the right questions. But the students did have one suggestion for the organizers of CAMC: They wanted more performance-based exams, and they wanted them scattered throughout the clerkship, not just at the end. Because, like the rest of CAMC, the exams presented them with a one-on-one learning opportunity like they'd never experienced before. They wanted more. ■

Pitt was awarded a grant from the Health Resources and Services Administration designating it as a national demonstration site.

FOR MORE INFORMATION:
http://www.dean-med.pitt.edu/HandBook/ACADEMICMATTERS.html

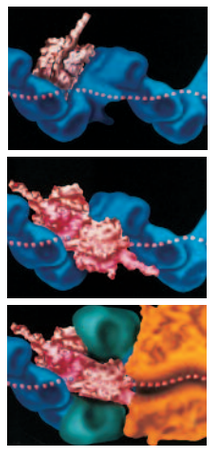


WITH ART LEVINE AT THE HELM, PITT'S SCHOOLS OF THE HEALTH SCIENCES ARE RIGHT ON TARGET.

BY SALLY ANN FLECKER

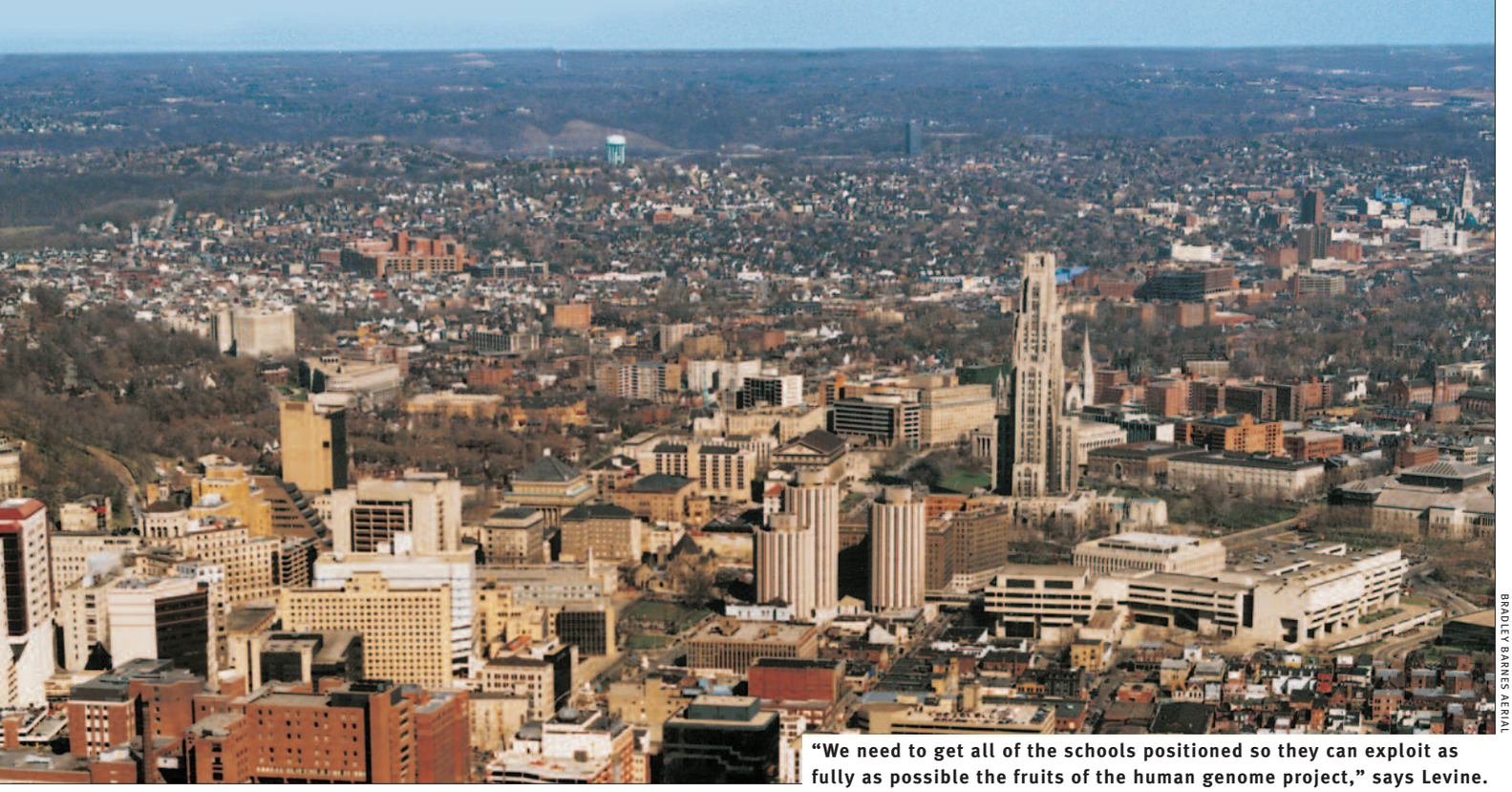
HIS AIM IS TRUE

Post-Depression era Cleveland: Two boys, cousins, one the elder by 10 years or so, are thrown together by the vicissitudes of fortune and familial generosity. The parents of the older boy must work long hours to keep their dry goods business afloat. The parents of the younger child—better situated financially—are happy to play host, to invite the cousin, a budding young scientist, to spend time after school, to enjoy dinners and evenings in their home. It's a sweet scene, one that Norman Rockwell could have painted: the small boy sitting in wide-eyed awe of his older cousin, breathing in the excitement of science, of its wondrous power to untangle so many mysteries, to describe and illuminate what cannot be seen. Art Levine was that young child in Cleveland, and he never forgot what he took in at his cousin's knee. As it turned out, the older cousin, Donald Glaser, lived up to his early promise. He became a physicist and invented a device called the bubble chamber that revolutionized scientists' ability to visualize the invisible—subatomic particles. In 1960, when Glaser was only 34, he was awarded the Nobel prize in physics. So perhaps Art Levine's earliest wise decision was in choosing his first mentor.



Pitt has chosen a leader who was at the heart of the world's premier medical research center for 31 years. LEFT: Images derived from an X-ray crystallographic study of the "mutasome," a highly conserved, multimolecular structure that permits "last resort" replication of damaged DNA, but at the cost of mutagenesis. The work was carried out in Levine's lab at NIH.

PHOTOGRAPHY | ROY ENGELBRECHT



BRADLEY BARNES AERIAL

"We need to get all of the schools positioned so they can exploit as fully as possible the fruits of the human genome project," says Levine.

Present day Pittsburgh: There is a carved Javanese spear on the wall behind the desk where Art Levine carries out his duties as dean of the University of Pittsburgh School of Medicine and senior vice chancellor for the health sciences. It's a beautiful piece, so intricately carved, so carefully hung as if caught in mid-thrust, it seems almost a gentle artifact. "My daughter gave me that when I took this job," says Levine. "She's a lawyer." He laughs. It's the laughter of a man who has no doubts about his ability to use a spear if need be. Levine is a straight-to-the-point kind of guy. He has to be. He has taken on a *huge* job—responsible for the direction, not to mention the vision, of the six schools of the health sciences. He has to be on top of how economics and politics are threatening the very premise of the academic health center in this country so he can lead and strategize in ways that will lessen this threat. And, he's in the process of re-establishing his National Institutes of Health lab and setting it up in Pittsburgh where he can continue to oversee research on the molecular mechanisms of DNA repair and mutagenesis, the processes that govern the fidelity of our genomes and underlie much disease and disorder.

Already Levine is something of a larger-than-life figure on campus. Legend has it that he met with every member of the health sciences faculty upon his arrival here. Not possible, Levine laughs: "I *couldn't* have done that; we have nearly 5,000 members." But like all legends, this one has a toe-hold in reality. While making the transition to Pitt from his post as scientific director of the National Institute of Child Health and Human Development, Levine read—and committed to memory—the CVs and bibliographies of every tenured and tenure-stream professor in Pitt's health science schools. That's 530, for those of you keeping score.

Mark Zeidel, chair of the medical school's Department of Medicine, tells about Levine's first interview at Pitt. Meeting over lunch with the medical school's 23 department chairs, Levine proceeded to wow the group by going around the room and thoroughly describing the research of each individual; he had read in detail the research papers of each chair.

"It was impressive," says Zeidel. "It told us several things. One, that he was serious about the job and came prepared. Second, that he understood how to touch the heartstrings of academics—talk to them about their work. And third, that he was able to follow and understand what people's work was and what its significance was, so that he could make decisions about what kinds of work he wanted to support and put resources into, and what he wouldn't be as interested in putting resources into."

In fact, Levine is particularly poised to strike a balance. Early on in medical school, he understood that he would make his way professionally as a physician *and* a researcher, and he set about the long, slow process of gathering the necessary tools—including board certification in pediatrics and oncology and a post doctoral position with the National Cancer Institute (which he joined as a United States Public Health Service Officer to fulfill his military obligation—then rose to the rank of admiral).

"Physician-scientists have a unique contribution to make; they are trained to appreciate how research that seems very remote from the human condition eventually *does* redound to the benefit of their patients," he points out. In fact he's concerned with the country's current dearth of young physician-scientists and is starting a program at Pitt to encourage promising doctors to pursue careers in academic medicine and biomedical research.

Indeed, members of the health sciences faculty seem to be confident that Levine brings all the right tools: an understanding of clinical medicine, clinical investigation, basic investigation, and leadership. "The medical school is now lifting off more rapidly," says Zeidel. "Dr. Detre made it possible for the school to go from the middle of the pack to the top 10. And now we can see our way, with Dr. Levine at the helm, of getting into the top five."

The medical school now sits among the 10 highest-ranked schools with respect to NIH research grants. Levine's goal is to site the other Pitt health science schools similarly. Within his first year as head, he established the groundbreaking Center for Pharmacogenetics in the School of Pharmacy, one of the first in the nation. Two projects near and dear to his heart—

Already Levine is something of a larger-than-life figure on campus. Legend has it that he met with every member of the health sciences faculty upon his arrival here.

the development of a center for human genetics and integrative biology and the creation of a very high field MRI facility—he says will keep Pitt on the leading edge in research and treatment.

At the medical school, Levine is pushing for an increase in endowed, merit-based as well as need-based scholarships to help relieve the heavy financial burden on medical students. He has high praise for the school's curriculum, which he calls one of the country's most innovative. Yet, he reminds, "Education has a fluidity that we have to respect and cherish—which means that we have to constantly refine the curriculum as we refine our understanding of what the core of a medical education should be at any point in time."

Faculty observers say they like the fact that Levine gets up and talks about the importance of research. And they appreciate the value he has put on good teaching as well as the highest quality of patient care.

"And he's very straight," notes Zeidel. "You ask him a question, you get an answer. And it's extremely well stated and right to the point."

Levine is a man who likes nothing more than to feel that he has got his arms wide around a challenge. The son of a lawyer and teacher, his personality bears the stamp of both of their influences.

"My mother was a very atypical Jewish mother in that she seemed to have little interest in my going to medical school," Levine says with a fond smile. "I think she would have much preferred that I become a poet."

The possibility was not out of the question. Although science was an early and passionate interest, Levine majored in Russian literature at Columbia College in New York. During his junior and senior years, he was editor of the *Columbia Review*. Levine laughs when he admits that he fulfilled his science requirement with a course in spherical astronomy—largely because it was offered jointly with the women's college, Barnard.

The nudge that led Levine back toward a career in science came from his father. "The night before my college graduation, my father reminded me that I would have to make a living," Levine says, his voice carrying the tone of a story he likes to tell on himself. "In an attempt to stall that as long as I could, I said, 'I have a great idea. I'll go to medical school.'" (Levine notes that medical students have the longest period of dependency on their parents of any mammalian species.)

For two years, while he caught up on the required pre-med courses, Levine threw himself into life in New York with the wide-ranging enthusiasms and intense energy already a trademark of his tenure at Pitt. He worked behind the scenes in off-Broadway theater, continued to study Russian lit, translated Russian scientific literature for a technical publishing house. Oh, and lest we forget, he drove race cars. No injuries, unless you count the very first race he won. Lime Rock, Connecticut. He was driving a Porsche—with very low slung doors. "When they handed me the checkered flag," he says, "I leaned over to get it and fell out of the car."

Onward to medical school in Chicago where he intended to specialize in psychiatry and then psychoanalysis. "That seemed to me to allow the sciences and the arts to meet halfway," he says. But a funny thing happened on the way to his second year. "Watson and Crick described the structure of DNA," he says.

"And I was hooked—both on its scientific implications and its aesthetics."

There's another telltale piece of "art" hung on the wall in Levine's office. While the Javanese spear hangs behind his chair, where visitors can appreciate it, another simply framed image is placed so that when Levine looks up from his work his eyes fall upon it. This unassuming piece represents what he proudly calls his earliest significant achievement in biomedical research—the first genetic map of SV40, a mammalian tumor-causing virus that has long been a classic biological model.

Levine's long career at the National Institutes of Health—1967 to 1998—means that Pitt has chosen as a leader a man who has been at the heart of the world's premier center of medical research. Despite times of fiscal hardship, as the National Institute of Child Health and Human Development's scientific director, Levine built one of the most fruitful scientific programs found anywhere. Michael Gottesman, deputy director for intramural research at NIH, underscores the wisdom and enormous breadth of scientific knowledge that Levine brings to Pittsburgh: "We miss him greatly around the table of other scientific directors where he more often than not took the leadership role."

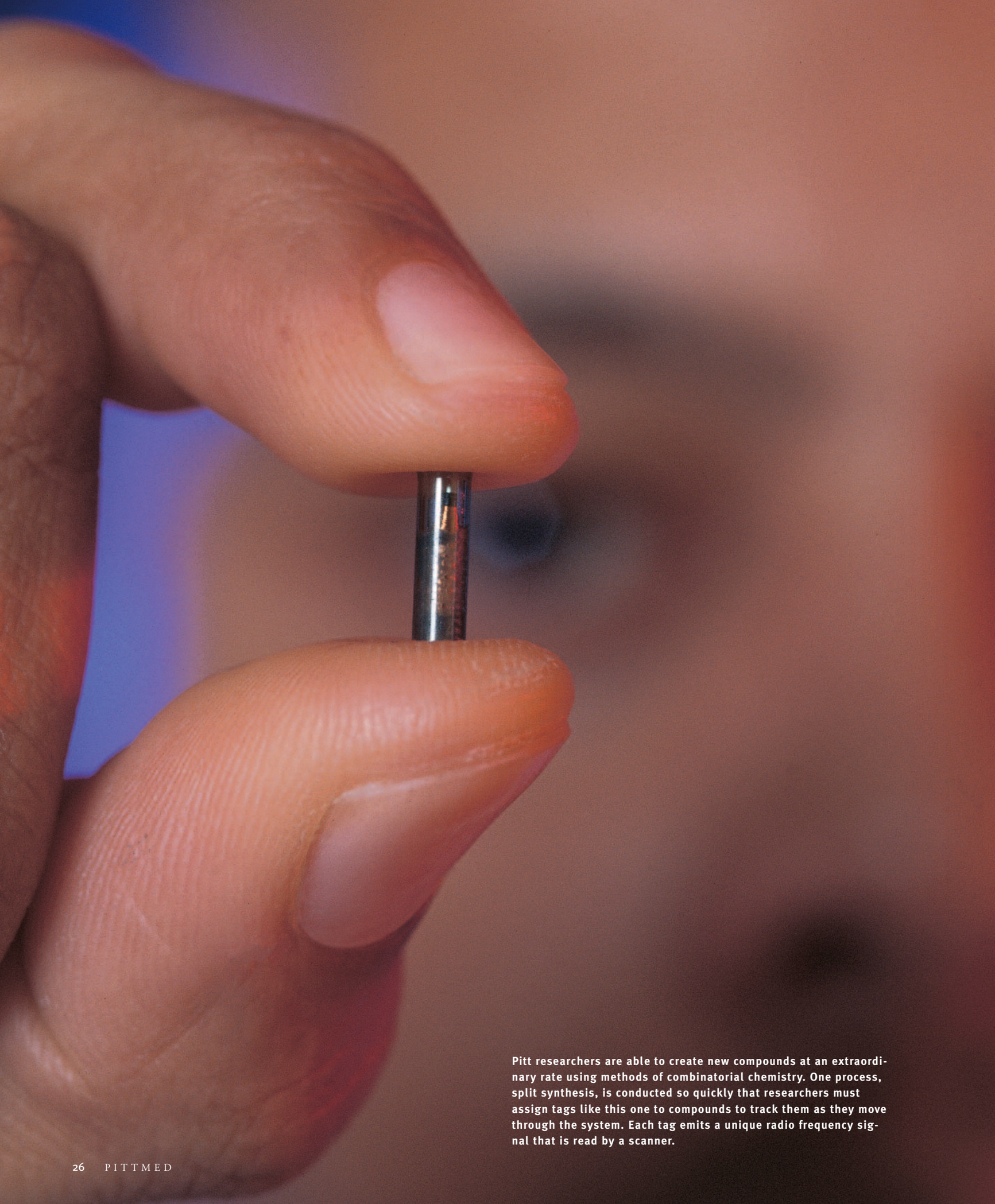
Likewise, Levine's early and deep interest in the double helix makes him well equipped to lead the health science schools into the 21st century.

"The human genome project," Levine says with a touch of mischief, "is like the Manhattan telephone directory. It tells you where everybody lives and how to spell their names. But it doesn't tell you who's sleeping with whom. In other words, the next challenge in biomedical reasearch is to illuminate the interactions of gene products."

Levine has imposed genetics—with its integrated concomitants of molecular, cellular, structural, developmental, and computational biology—as a common theme throughout the health sciences. "We need to get all of the schools positioned so they can exploit as fully as possible the fruits of the human genome project," he says.

The complex, even daunting, research that the genome map will provoke provides just the sort of challenge Levine is equipped to tackle. Levine will bring all of his experiences—from his early days at the feet of his older cousin, to his thrill at Watson and Crick's discovery, to his own elucidation of the genetic structure and function of SV40—to bear as he leads Pitt's health sciences into this new era.

His spear remains secure on the wall. But it appears that Art Levine's aim is as true and accurate as it gets. ■



Pitt researchers are able to create new compounds at an extraordinary rate using methods of combinatorial chemistry. One process, split synthesis, is conducted so quickly that researchers must assign tags like this one to compounds to track them as they move through the system. Each tag emits a unique radio frequency signal that is read by a scanner.

DRUG DISCOVERY LIKE NEVER BEFORE

BY MUBARAK S. DAHIR AND ERICA LLOYD

WHIZ BANG

On the ninth floor of the University of Pittsburgh Chevron Science Center, a computer-controlled robotic arm releases 90 droplets of a sample into a matrix of 90 vials in the same instant. Each receiving vial fills with a different mix of chemical solutions, so that 90 different reactions take place simultaneously with every plunge of the arm. In the seconds it takes the robotic arm to make its dipping gesture, 90 brand new chemical compounds are created. In a day, this device alone could invent hundreds, even thousands of compounds.

This robotic synthesizer is one of many pieces of equipment housed within three bright blue labs at Pitt's Chevron Science Center that is altering the realm of chemical discovery. Here, new compounds undescribed in textbooks and yet unseen by humankind are being created. What's truly amazing is the rate and level of sophistication at which this is happening.

Consider this: There are maybe 50 million known organic molecules for chemists to choose from as they attempt to create new structures. And any 10 of those building blocks could translate to 10 billion new compounds. The diversity of chemical structures is practically unlimited.

Now, imagine you are a pharmacologist or chemist or materials scientist. Of the mind-numbing number of chemical possibilities, you probably have the tools to build one compound at a time. And then once you have synthesized your new chemical structure, you must test it, crossing your fingers that it might actually lead to a new drug or a new fabric or a new building material. If it doesn't, then it's back to the drawing board of organic molecules. The rate of discovery is going to be glacial.



This split synthesis tagging station is a pharmacologist's dream come true.

It's glacial unless, *unless*, you work in one of the very few universities where a single wave of a robotic arm unveils 90 new chemical possibilities. A university that has taken full advantage of advances in robotics and computer technology. Where, in fact, an entire army of high-tech equipment soldiers away at the business of chemistry, materials science, and pharmacology. There aren't many such universities.

Some industries, particularly pharmaceutical companies, began establishing in-house combinatorial chemistry capabilities about six years ago. The Combinatorial Chemistry Center (CCC) in the University of Pittsburgh's Department of Chemistry was founded in 1997 and marks one of the first such labs in an academic setting. Investigators from scientific disciplines throughout the University are welcome to use the center, but it has forged particularly promising collaborations between the School of Medicine and the Department of Chemistry, notes Peter Wipf, a professor of chemistry who also serves

PHOTOGRAPHY | ALEX BELLOTTI



John Lazo (left) and Peter Wipf at the Chevron Science Center

as the Combinatorial Chemistry Center's director. Faculty members in fields such as pharmacology, surgery, medicine, pediatrics, and radiation oncology find this new technology so promising that the medical school has invested in equipment for conducting further biocombinatorial analysis.

In terms of drug discovery, the timing is prime for combinatorial work, says John S. Lazo, Allegheny Foundation Professor, chair of the School of Medicine's Department of Pharmacology, and director of the University of Pittsburgh Cancer Institute's Fiske Drug Discovery Laboratory. He notes that with the completion of the human genome project on the horizon, he and other investigators are anxious to identify drugs that will interact with the molecular and biochemical targets the genome project defines.

Billy Day shares his enthusiasm. Day is an associate professor of environmental and occupational health at the Graduate School of Public Health; he says, "The way I was trained 20 years ago as a medicinal chemist was to make one chemical compound at a time.

"But today, with combinatorial chemistry, we can create a large number of compounds that can be isolated and tested simultaneously. So with the same effort it used to take to build and test one compound, we're looking at hundreds. That's a huge step forward."

Day uses combinatorial methods to more rapidly identify what are called "lead compounds." By lead, Day isn't talking about the metal, he's talking about compounds that have previously unmapped structures or combinations of chemical building blocks and that also demonstrate previously unknown biological activity in cell cultures. Day describes lead compounds as "the first sparks of ideas." He and his colleagues are making some sparks of their own. They've identified a lead compound called discodermalide, which is showing early potential in treating breast, prostate, and ovarian cancer. Discodermalide stabilizes cells' microtubules, which act as the railways for intracellular deliveries and the ratcheting system for pulling apart duplicated chromosomes. Stabilizing these microtubules can inhibit cancer cell division and lead to apoptosis (cellular suicide).

Day sees combinatorial methods yielding "more drugs faster and cheaper."

And Dennis P. Curran, a distinguished service professor and Bayer professor of chemistry, adds another layer to the promise of faster, cheaper drugs: better drugs.

"In the past, it took a lot of work to come up with a structure that passed muster as a drug," Curran says. "By the time we got one, we had a pretty good idea of what the drug should look like, but the process of refining the chemical structure of the drug could be time consuming and costly."

But with combinatorial technology, not only can you discover new lead compounds more quickly, but you can create what were once prohibitively costly iterations to refine the best possible structure of a new drug.

"With the same effort it used to take to build and test one compound, we're looking at hundreds. That's a huge step forward."

"You can easily make 1,000 variations on a basic drug design. Each of the 1,000 copies is similar, but slightly different," Curran points out. Testing will then yield which of the slightly modified structures is the best choice as a drug.

"So we've moved from total trial and error to educated trial and error," he says with a chuckle.

As Wipf and his colleagues synthesize new chemical possibilities, they still may not know exactly what offspring are going to result from the myriad of repeated reactions that go on in robot-dipped test tubes, reaction box flasks, or other such devices. So once a new generation of compounds has been created, it must be tested for its structure.

The CCC buzzes with instrumentation for analyzing, purifying, and controlling the quality of the compounds it creates—and pretty much all of this instrumentation is driven by a generous store of gigabytes. With compounds being generated at this exponential rate, combinatorial work relies heavily on the latest in software informatics to keep straight the hundred or so chemical innovations it generates on a daily basis.

These extraordinary machines tend to look innocuous.

One vaguely resembles a checkout counter at a grocery store, but instead of two-for-one specials, it offers split synthesis tagging. At this station, a computer uses radio-frequency tagging to decipher the contents of newly created compounds. The compounds move through the system in the form of bead-like samples ranging in size from as small as your fingernail to as big as your thumb. The scanner reads radio-frequency chips embedded in capsules placed in each compound. Then the system tells the operator the basic chemical building blocks contained in each bead and even what beads to mix together to synthesize more complex compounds.

Wipf and his students might, for example, use the split synthesis station to create and tag a series of "small organic molecules" (as opposed to large proteins or pieces of DNA) for John Lazo. Lazo is likely to take these compounds back to his lab to analyze their applications on cellular structures as possible drugs.

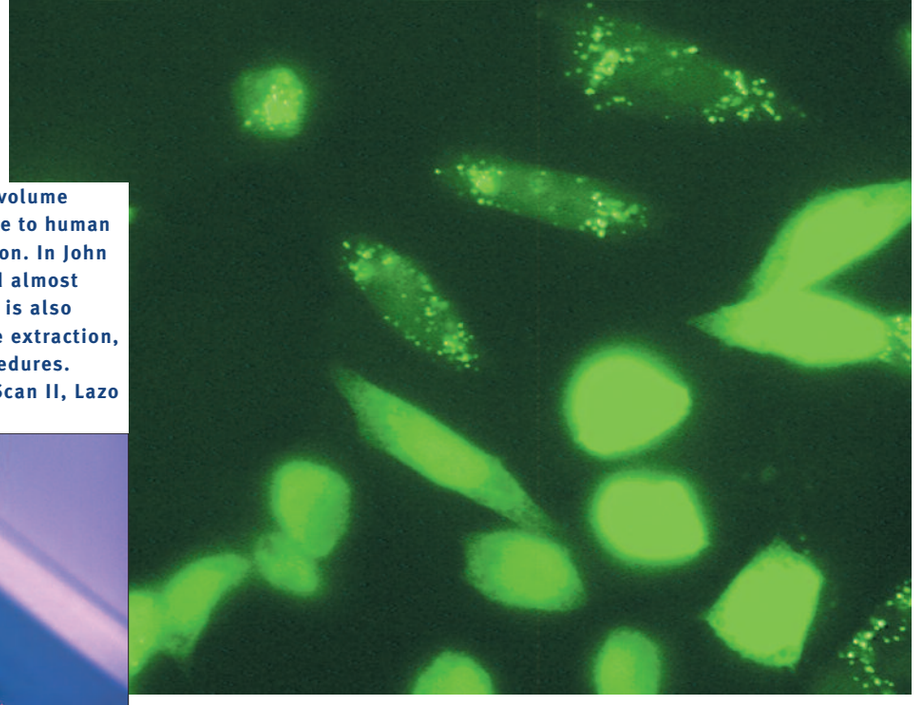
Lazo conducts these studies using some of the School of Medicine's equally whiz-bang equipment that also utilizes robotic and computer technology. His department lays claim to the only Cellomics Array Scan II in a university lab. Using the Array Scan, he is able to conduct cell-based, multiparameter interrogation of chemical libraries. In other words, Lazo can fluorescently tag a molecular target within a cell, then take a library of newly created compounds, or small molecules, provided by Wipf, and map how they interact with that target.

Lazo can do this with 96 compounds at once, examining how they react with up to three molecular targets at a time. This takes him all of about 25 minutes. Doing this "the old way," as Lazo likes to put it, would have taken an ambitious month.

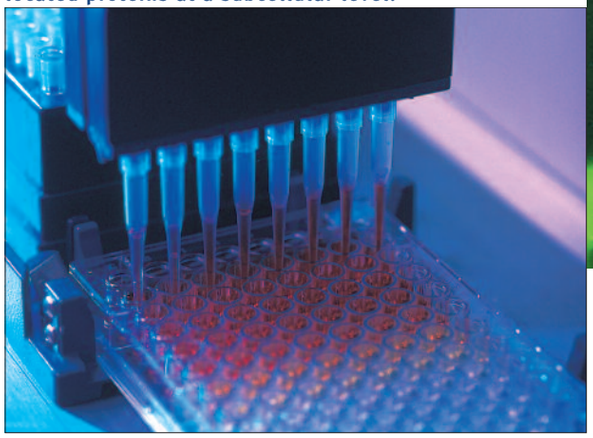
Combinatorial technology has given Lazo and his colleagues front row seats to the inner workings of emerging therapeutics. From this vantage point, they can examine how various compounds affect protein synthesis (which is critical to cellular regulation), ion movement (which can have implications for conditions such as hypertension), apoptosis (a natural phenomenon, which could provide leads to novel cancer therapeutics). . . . In effect, with



As Wipf and others mix solutions at a speed that makes heads spin, you might wonder, does anything ever, you know, blow up? Actually, combinatorial chemistry has taken some of the bang out of the whiz bang. Of course, Wipf's team takes great care to keep the labs safe, but the combinatorial process typically uses smaller quantities of solutions and less glass (some vials are plastic or teflon), so the work of discovery is actually less dangerous. RIGHT**: A parallel synthesizer for solid phase synthesis**



BELOW: The Biomek 2000 is excellent for low-volume liquid handling work that is particularly prone to human error, such as pipetting, mixing, and aspiration. In John Lazo's lab and elsewhere, the Biomek is used almost exclusively in the realm of drug discovery; it is also capable of being programmed for solid phase extraction, the blood test ELISA, and cell-culturing procedures.
RIGHT: Using the School of Medicine's Array Scan II, Lazo located proteins at a subcellular level.



this technology, investigators can learn pretty much anything they would ever want to know about what a chemical compound does at a cellular level.

For a pharmacologist, trial and error never looked so good.

But what of all those newly generated compounds that do not seem to hold any therapeutic promise? Has their creation been a waste of time, the proverbial stack of hay hiding the chemical needle for which everyone has been searching?

Not at all.

Even if a compound doesn't turn out to have an obvious use, its discovery still advances scientific understanding.

Go back to those 50 million organic molecules that constitute the basic building blocks of chemistry. Those molecules, and all the structures that can be built out of their various combinations, can be thought of as making up "chemical space."

"But talking about chemical space is a little like talking about outer space," says Lazo.

"We're not really sure what's out there. We can tell you where a lot of chemical planets and even galaxies are, but there are a lot of black holes, too."

Combinatorial chemistry promises to help fill in many of the black holes. One of its advantages, says Lazo, is that it will allow the University to build its own "library" of known chemicals. This means that the University of Pittsburgh can stock up on tens of thousands of the known and newly identified compounds and keep copies of them "on file" for use by researchers and students. That way, a researcher can go to the center and request her own personal library of 50 or 1,000 chemicals to use in her experiments, Lazo says.

Wipf and Lazo hope to have 100,000 compounds in the library by fall 2000. They also are collaborating with NIH, garnering access to that agency's storehouse of compounds.

"Scientists can then withdraw compounds from it like students check out a book from Falk Library," Lazo says. "You could not have done this stuff two years ago."

Combinatorial advances have invited closer cooperation between researchers in complementary disciplines. Medical scientists, drug researchers, biochemists, and chemical engineers will be able to share their results with one another, and borrow from each other's successes, through the compound library.

As you can imagine, Wipf, Lazo, and colleagues pursue fruitful partnerships with industry. Yet they see themselves upholding a distinct academic mission.

"We don't want to just duplicate what's already being done in industry," says Curran. "We're not here simply to make copies of compounds for industrial use. All of our projects have to have a clear educational component, and all of our work should be done with the idea of heralding new scientific discovery."

Or as Lazo might describe it, their mission is to chart the vast and compelling frontier of chemical space. ■

FOR MORE INFORMATION:
http://ccc.chem.pitt.edu

REINING IN THE ROGUES

Sometimes there *can* be too much of a good thing.

The addition of a high-energy phosphate to particular amino acids is crucial to cellular communication in the body. Many diseases, however—including cancer, diabetes mellitus, arthritis, and obesity—are thought, at least in part, to be due to abnormalities in the enzymes that facilitate this process. John S. Lazo, chair of the Department of Pharmacology, is especially interested in a relatively simple group of proteins that regulate both these signaling pathways and a cell-cycle checkpoint controlling system. Certain variants of this checkpoint system have oncogenic properties and are overexpressed in many cancers such as non-small cell lung, breast, and head and neck cancer as well as non-Hodgkin's lymphoma. Lazo and his colleagues have described the combinatorial synthesis of a library of small molecules designed as inhibitors of the rogue enzymes.

And this inhibition could be a crucial first step in the creation of potential anti-cancer agents. *–PP*



Mythological chimera

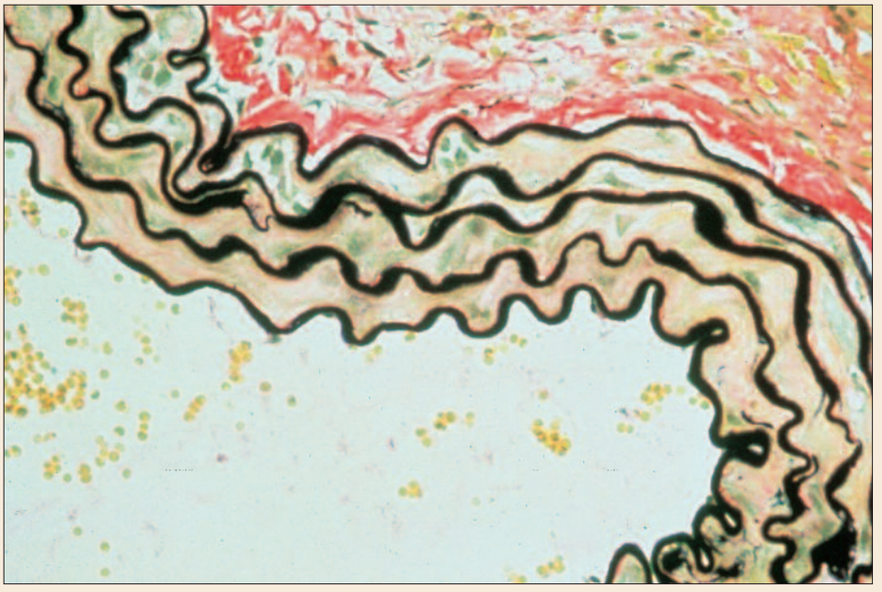
IN SEARCH OF CHIMERAS

A HOPE TO END THE NEED FOR IMMUNOSUPPRESSANTS IS GROUNDED IN MORE THAN MYTH.

BY REBECCA SKLOOT

ILLUSTRATIONS | BECKY SMITH

Thomas Starzl once took 16 transplant recipients off of immunosuppressants on a hunch. His peers thought he was crazy to do it, though they knew he was a maverick, and several decades into a career built on the fringe. Starzl, University of Pittsburgh distinguished service professor of the health sciences and director of the Thomas E. Starzl Transplantation Institute, had proven himself time and time again, but this seemed utter lunacy.



This cross-section of a rat aortic allograft shows no signs of chronic damage. The animal had received a liver from the same donor and become tolerant. Studies in animals that did not receive same-donor transplants did not exhibit normal aortas.

Starzl's hunch started with something he'd seen in animal models: some only needed enough immunosuppressants to overcome the body's initial immune reaction, then the organ mysteriously induced a state called tolerance—peaceful coexistence of donor and recipient tissues.

To other surgeons, his theory seemed unlikely. After all, everyone knows that after any successful transplant, a patient's blood, rich with cells programmed to distinguish self from non-self, floods into a foreign organ full of foreign cells. This point, where the recipient's immune system meets its new organ, is a moment of potentially fatal clash. Mature cells from the donor and recipient recognize each other as foreign and mount their immune attacks. Surgeons keep a handle on this initial reaction with immunosuppressive drugs, but there's a natural process of cell death that must accompany transplantation: All mature immune cells must die. What's left, from both donor and recipient, are young cells, those not yet learned in self versus non-self. As long as their cellular cohabitation is peaceful, the organ isn't rejected, and the patient has achieved tolerance. The field of transplantation is pretty much in agreement on that. What might happen next, however, now is hotly debated.

If you're a transplant surgeon, and you're *not* Starzl, when your patient reaches this initial state of tolerance, chances are you'll exhale a sigh of relief and write a prescription regime for immunosuppressants that he'll be on for, oh, the rest of his life. The belief has been that it takes an arsenal of medication to maintain the necessary peace between the donor organ and its recipient. Transplant surgeons have done this for years, and the resulting amity is still called tolerance. But if you ask Starzl and his colleagues, this is not *true* tolerance.

"We can't go on thinking that immune suppression is the best solution," says Massimo Trucco, a professor of pediatrics at Pitt. "It's the worst solution, but right now it's the only solution we have." It's the worst solution because humans lead active, sometimes destructive, lives: they get drunk, they get the flu, and they need an immune system that can keep up. Unfortunately, immunosuppression doesn't just inhibit an immune response to the foreign organ, it inhibits *all* immune responses, even those necessary to withstand day-to-day exposures. And for a transplant patient on immunosuppressants, one case of the flu or another infection can kick off organ rejection. And that's saying nothing of the kidney failure, lymphomas, and other side effects that can come with immunosuppressants.

According to Starzl and John Fung, an MD, PhD and Pitt professor of surgery, by chemically inhibiting the immune system of the recipient, physicians induce a state that *mimics* tolerance, but actually prevents true tolerance from developing. True tolerance, if you ask them, is a state of perfect natural harmony. No drugs. And it starts with those two populations of young cells that remain after the initial immune response. If all goes well, and they're allowed to rebuild an immune system together, the young cells mature, never learning the other is truly foreign, and in doing so, train the body that the transplanted organ is not foreign. And that, say Fung and Starzl, is true tolerance. So, if you're Starzl, once your patient passed through that initial immune response, you might take him off medications to see if his body could take over.

Of the 16 patients Starzl took off immunosuppressants on a hunch, 11 started to reject—he quickly put them back on medication. But five made his hunch seem far from lunacy: They had no immune reaction. To this day, they're walking around with transplanted organs and aren't taking immunosuppressants. According to Starzl this true tolerance has only one explanation: chimerism.

According to the ancient Greeks, a creature once roamed the earth with the body of a lion, tail of a serpent, and head of a goat.

According to the ancient Greeks, a creature once roamed the earth with the body of a lion, tail of a serpent, and head of a goat. They called it a chimera. The beast actually had a number of configurations in ancient myth, and the term "chimera" lingers today with many meanings. If you look up "chimera" in the dictionary, you'll see that it's more than a mythical creature. It's an unrealizable dream, a fabrication of the mind, or a person with tissues



ABOVE: Systemic chimerism. The stars represent donor cells that migrated throughout the patient's body from a transplanted organ.

of diverse genetic composition. And with a Starzl-sized step further, "chimera" could mean the end of immunosuppressants and organ rejection, and the beginning of true tolerance.

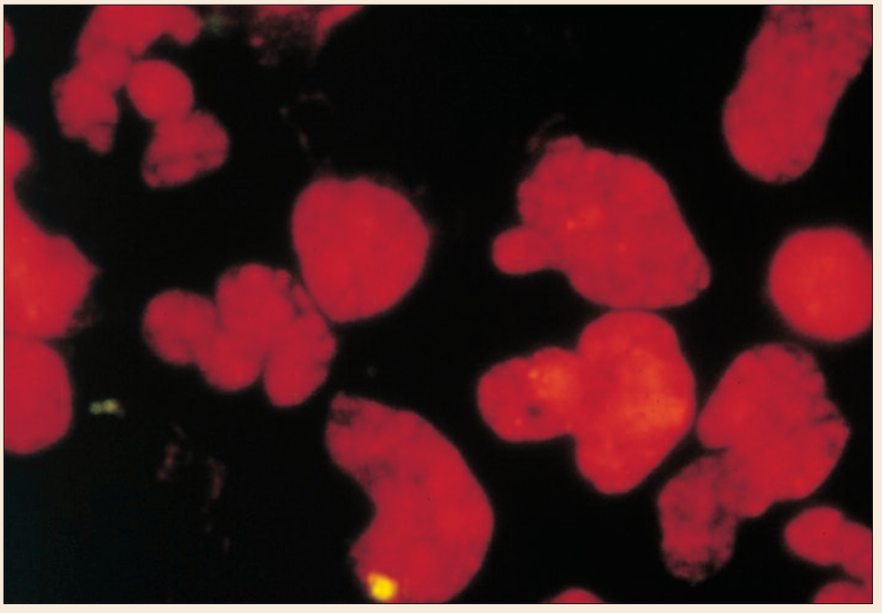
"By definition," says Fung, "if you get a transplant, you're chimeric." In the transplant world, a chimera is a patient with two cell populations, one from her own body, one from that of an organ donor.

But no one besides Starzl thought too much about what chimerism could mean until a Festschrift in 1990, when he and a colleague were each asked to write a chapter for a book on heart and lung transplantation. Starzl was to write a chapter on the mechanisms for whole organ acceptance; the other chapter was to cover tolerance.

When Starzl caught wind of this idea he looked at his colleagues and said, "Well hell, they're the same thing." They all looked at Starzl, told him he'd lost his mind, for real this time, and dared him to prove it.

Starzl went home and began searching for his chimera. He called Trucco, an expert in polymerase chain reaction, which can be used to test cellular identity based on DNA, and Pitt's Anthony Demetris, whose expertise was in identifying cells through HLA antibody testing, which utilizes dyes that fluoresce in the presence of certain cellular proteins. And he called 30 of his longest-term patients. He needed them for samples, he said, and they came from around the world to help.

One patient, we'll call her Susan, received an organ from a 4-year-old boy when she herself was 4. Susan was a wife and



ABOVE: Microchimerism was detected in a female recipient's lymph node more than 10 years after she received a male kidney. Yellow dot represents Y chromosome.

mother by the time Starzl called. She and patients like her, those who had transgender transplants, offered particularly hard-hitting evidence for Starzl. When Starzl, Trucco, and Demetris presented their lab results, complete with images of Susan's cells, there was nothing much their opponents could say:

Susan had Y chromosomes on approximately .1 percent of the cells in her body. The donor's cells had actually *migrated* and remained in her tissue.

"That means," says Starzl, "she's closer, in a physical sense, to that donor than she's been to anyone in her life, with only one exception: when she was a baby in her mother's womb." And in case that wasn't evidence enough, Starzl offered many other examples.

"I always knew those cells were there, I had just never looked for them myself," he says.

To Starzl, the lingering of donor cells was a key to understanding how his early animal models developed true tolerance. These cells, as Starzl and his colleagues discovered, don't live just in the donated organs. They can live peacefully throughout recipients' bodies: in their lymph organs, in their skin, and in other sites. And it's not that the donor gives cells along with, say, a liver, it's that the donor's cells actually move from that liver, or lung, or any other organ that was transplanted, out into the surrounding tissues. Once this happens, these patients are chimeric, or more accurately, microchimeric. At this point, the highest level of chimerism anyone has seen in a transplant patient is about what Susan reached—.1 percent. But most importantly, even if only on a micro-level, these patients have accepted *some* donor cells as self. This means, to a degree, that they've accepted the donor organ as self also. If only this micro-level of acceptance could be increased, says Starzl, true tolerance could be reached.

According to Starzl and Fung, by chemically inhibiting the immune system of the recipient, physicians induce a state that mimics tolerance, but actually prevents true tolerance from developing.

According to Demetris, it's clear that Starzl was on to something with his hunch about chimerism: "Microchimerism gives you a form of tolerance;" he says, "it's just not quite robust enough because there are not enough donor cells [in a microchimeric's body]." So Starzl, Demetris, and Fung are all trying to find ways to move from micro to macro.

They started by infusing large quantities of donor blood cells, and later infused about 2 billion donor bone marrow cells, at the time of transplantation to increase chimerism. But without fail, patients came out microchimeric at best. Researchers have tried irradiating the recipients to suppress their immune systems and increase chimerism. But in the end, that's no step-up from immunosuppressive drug therapy: "You can irradiate heavily and give donor bone marrow," says Demetris, "but you pay a price for that irradiation down the road. And that's not quite acceptable." So, researchers are trying to boost chimerism through less morbid procedures.

Some Pitt researchers are trying to identify which donor cells remain in recipients' bodies and have tolerance-inducing properties. Once they've succeeded, they hope to grow those cells in culture to be used in new infusion therapy trials. Another group is developing what they call "co-stimulatory molecule blockers," which are designed to thwart the body's immune response, preventing it from killing the cells deemed essential for tolerance.

"Figuring out how to induce tolerance is the Holy Grail in transplantation," says Fung.

He, Starzl, and a few other Pitt researchers say they found the map to the Holy Grail back in 1991 after the Festschrift, though no one believed them at the time. But that was then. Today, there's essentially no question as to whether chimerism plays a role in tolerance. Some argue that the role is unclear, that there's no way to know which came first, the tolerance or the chimerism. Starzl hears these objections, and has one reply: You have to prove me wrong, then I'll believe you. And he'll tell you, so far, no one has even come close. ■

LITTLE LOSSES

WHEN A PHYSICIAN IS THE "INTERESTING CASE"

BY JOSIE FISHER



MATT BULVONY

Carol Congedo, MD '76

With a dinner to prepare for Shabbat and a temple choir rehearsal to attend, Carol Congedo, MD '76, took time to meet in the sunlit gallery of Pittsburgh's Jewish Community Center to talk about a life reclaimed. Forty-nine-year-old Congedo spends much time in this building, aerobicizing to big band music with the seniors ("That's all I can keep up with," she says, laughing), stepping to water aerobics in the warm-water pool ("Much easier on the joints!"), or attending a monthly lupus patient support group, of which she is both participant and facilitator.

As half a dozen toddlers are wheeled by in a buggy, Congedo smiles. She then tells how, after the birth of her second child, she began experiencing profound fatigue and arthritis in her hand and jaw. "Stress," her internist told her. But Congedo could not concur. She had managed stress for 10 years as sole practitioner in her McKeesport, Pennsylvania, otolaryngology practice. An elevated ANA titer confirmed a physical problem with an autoimmune base, but Congedo's rheumatologist could give it no name. Within a year, Congedo's symptoms compounded until, at age 41, she found herself flat on her back. This time the prednisone prescription was for her. The diagnosis: systemic lupus erythematosus. Her arthritis and weakness were so debilitating she couldn't even drive. Within four months, she closed her practice.

A rheumatologist told Congedo that since her lupus hadn't expressed itself in early reproductive years, her case was not serious.

"Not serious to whom!" says Congedo, incredulously. "When I was a freshman in medical school, I remember professor Alexander Minno telling us to pray every night not to become an interesting case. My response when I first realized I had lupus was: 'Well, I blew it!'

"When I graduated from Pitt, all the lupus patients we heard about were dead in five years. With no dialysis, they presented in end stage renal failure." Of course that's not the case nowadays.

"The first thing I tell people newly diagnosed with lupus is that this is a survivable and manageable illness. I tell people to learn to say 'no.' Pacing is the name of the game with lupus." That had been a hard lesson for Congedo. The former surgeon says she has learned to deal with "little losses." Chronic fatigue. Weight gain. Facial rashes. Arthritic pain. . . "They're not permanent, but it gets to you," she says. "It's hard for me today to even go into McKeesport where I had my practice."

Congedo also speaks of what her illness has given her. She's now able to be a full-time mom and study and teach Judaism. And she has six or seven quilting projects in progress. "Now, instead of sewing people, I sew cloth.

"I still very strongly feel the call to healing," she says. And so Congedo is active locally and nationally with the Lupus Foundation of America; she wrote two booklets published by the foundation.

"In the United States," she says, "a patient expects a doctor to provide medicine to get a cure. We, as physicians, are taught to cure. But with lupus, it's balancing chronic symptoms with medicine and its side effects.

"I know I could never top what Minno said," says Congedo, with a wink. "But if I have one bit of advice to offer my medical colleagues, I would have to say, 'Remember that at some point in life you're going to be on the receiving end.' "

A young, dark-haired man calls out as he walks briskly through the gallery. Congedo and he talk a bit about a special performance the choir is preparing for tonight's service. Afterward, Congedo says, "Singing is important to me, as a form of prayer."

She pauses for a moment, then says, "I think part of me inside wants to dance. I'm really only limited by my body." ■

THEY COME IN DROVES,
AND THEY COME TO LEARN



PATRICIA NAGLE/CIDDE

PITT'S MINI-MEDICAL SCHOOL

BY JENNIFER ANDREWS

The night has been difficult. Heavy winds and rain whip at cars, pull at umbrellas, and open jackets to the cold. There will be snow tonight, deadlocks and slow rides home. Despite all this, they still come. Wrapped in layers, the class rumbles in. The Brendlingers, a retired couple, stop at registration, shake out the rain, and grab an information packet. Tonight they will learn about the brain—how it develops and how it functions with changes they call Parkinson's or Alzheimer's. Seconds later, Cindy Ciocca, a registered nurse, pushes through the door. She is still thinking of the son at football practice, her daughter's homework, and the Halloween costume she has yet to make. But within minutes, she relaxes and remembers why she's here. Like the 500 others who attend the University of Pittsburgh School of Medicine's Mini-Medical School, she has come to get answers to difficult questions, to hear talk of innovation, therapies, hope. Like her classmates, who are caretakers and college students, professors and retired professionals, she has come to learn.

Ciocca finds her way to the middle front of the auditorium and settles in.

"You have to get here early for the best seats or fight your way over legs to get a good one," she says.

Though only in its first year, the response to the mini-med school has been overwhelming. Originally designed for 300 students, this free, two-and-a half month program, paid for in large part by Pfizer Inc., offers community members the opportunity to find out what's happening today in medicine. Because enrollment was so staggering, organizers, including Pitt's Loren Roth, "dean" of mini-med, and Maggie McDonald, "associate dean," made room for 200 more. Even still, the waiting list continues to grow.

Over the course of seven seminars, participants learn about the human infrastructure, the heart, the immune system, the brain, human genetics, and infectious diseases such as AIDS. Students are shown how science is translated into new techniques and applied to clinical medicine—grounded in ways general audiences will understand. Tonight, two brains are projected onto a screen; one is healthy, the other, damaged. Both have been injected with an infrared substance that lights up the brain in places where there is activity. The healthy brain lights up like a Christmas tree, while the other, affected by Parkinson's, is dark. The audience gasps, then goes silent.



Ciocca scribbles quietly in her notebook. Others bend over theirs. These students are learning that many of the people who were thought to have Alzheimer's are instead experiencing something that, in some respects, is similar to what happens in Parkinson's patients. They are learning that nerve cells die in both diseases, and when they do, the cells contain an abnormal accumulation of proteins called a Lewy body. They are learning that scientists are working to develop ways to protect the nerve cells from dying. And, they are learning that doctors know more about these diseases today than just very recently.

For Ciocca, who has worked on and off as a nurse for 25 years, mini-med gives her a chance to get the very latest information on many topics. "Medicine is in my blood. I had a nurse's costume on at three, and I never wanted to be anything else."

For Thurman and Marie Brendlinger, graduates of Pitt's business and nursing schools, mini-med helps keep their minds young and their hope strong. Thurman Brendlinger has prostate cancer and heart disease. These classes give the couple the opportunity to discover what's out there and get the answers to questions they might sometimes be afraid to ask.

In slow waves, the class files out and into the lobby. Thurman Brendlinger tucks his sweater into his coat. His wife is still inside. Others mill around munching cookies, sipping soda, and filling each other in. *Levodopa, I gotta tell my father about it. Maybe it'll do something for my mother. . . . If they could find a way to repair the Lewy body, wouldn't that be something?*

The night is still howling. It's bitter cold and trees are down. It doesn't matter. This class, generations and races and religions apart, will stay late to talk, ask questions, exchange ideas and information.

Ciocca folds her coat under her arm. The costume and homework can wait—like the others, she's staying a while, to learn. ■



ILLUSTRATION: BECKY SMITH

CLASS NOTES

'40s

FRANK E. SCHWARTZ, MD '43, of Toledo, Oregon, recently retired from nearly 50 years of private practice as an ophthalmologist. Schwartz served in the US Marine Corps as a battalion surgeon during World War II, participating in the invasion of Okinawa, Japan, where he earned a Purple Heart and a Bronze Star. He also served in the Korean War as an ophthalmologist at a US Army evacuation hospital near the front. After the war, he began a private practice that relocated several times before landing in Newport, Oregon, where he practiced until his retirement. Schwartz was a diplomate of the American Board of Ophthalmology and is a fellow of the American College of Surgeons.

MARTIN H. KALSER, MD '46, has been honored by the University of Miami School of Medicine with an endowed chair. His research on inflammatory diseases of the small intestine and gastrointestinal cancers brought him national and international acclaim when he demonstrated that removing large sections of small intestine resulted in low absorption of nutrients by patients and that conservation of the small bowel was possible in many cases. Kalser, the founding chief of Miami's gastroenterology division, joined their faculty in 1959. Prior to his Miami appointment, he completed an internship at UPMC Montefiore and a two-year stint as a US Army medical officer in Tokyo, Japan. He trained in internal medicine at Cook County Hospital in Chicago, Illinois, completed a doctorate in physiology at the University of Illinois, and spent six years on the faculty of the University of Pennsylvania School of Medicine's graduate studies program.



The Owl, 1950

Among his many professional activities, Kalser served as chairman of the editorial board for *Bockus Gastroenterology* and administrator for grants from the National Institutes of Health (NIH). He is president of the medical staff at Jackson Memorial Hospital in Miami.

'50s

JOHN L. HUMPHREYS, MD '56, has spent the past 31 years in Atlanta, Georgia, where he is the president of Crawford Long Hospital of Emory College and also has a private practice in ophthalmology. He completed his residency at the Cleveland Clinic and was in private practice for six years in Charlotte, North Carolina, before settling in Georgia.

BASIL M. RUDUSKY, MD '59, who operates a private practice in internal medicine, cardiology, and forensic medicine in Wilkes-Barre, Pennsylvania, recently was appointed to the international editorial board of *Angiology*. He continues to serve as editorial and manuscript consultant for *Angiology*, *Annals of Internal Medicine,* and *Chest*. RuDusky's impressive CV also lists his work as a diplomate of the American Board of Internal Medicine and the American Board of Forensic Examiners, developing liquid potassium chloride for Cooper Laboratories, and serving as senior consulting physician for the United States Department of Health, Education, and Welfare.

'60s

STEWART SELL, MD '60, professor of pathology and the laboratory medicine director at Albany Medical College in Albany, New York, is conducting research on the factors that contribute to development of liver cancer. His early research in basic immunology at the University of Birmingham Medical School in England (in '64 and '65) led to the discovery of surface immunoglobulin on a subset of lymphocytes, now known as B cells. In the past year, his research illustrated that liver cells may arise from bone marrow precursors. Among his numerous academic appointments, he was professor of pathology at the University of Pittsburgh School of Medicine in 1965 and chair of the Department of Pathology and Laboratory Medicine at the University of Texas-Houston. Sell received Pitt's Philip S. Hench Distinguished Alumnus Award in 1988, has been funded continuously by the National Institutes of Health since 1965, and has written 13 books and more than 200 articles.

RONALD J. AMALONG, MD '61, recently graduated from Rollins College in Winter Park, Florida, with a master's degree in liberal studies and published *The Doctor is Out: Please Be Seated*, a collection of fictional short stories. He has been in private practice in ophthalmology in central Florida since 1971, following his service in the US Navy as a flight surgeon. Amalong is also medical director of Vision Health International, a volunteer eye surgery organization. During his 26 years with the organization, he has directed projects in Ecuador, Costa Rica, Nicaragua, the Dominican Republic, and Poland. He can be reached at Weyes@worldnet.att.net.

CHARLES J. SEIGEL, MD '67, has grown the obstetrics and gynecology department at Monadnock Hospital in Peterborough, New Hampshire, from a staff of 13 to well over 100. The clinic was ranked among the country's top ten in 1995 by *Child* magazine. A clinician and chair of the department for 27 years, Seigel was recently appointed adjunct assistant professor at Dartmouth University Medical School.

DOUGLAS M. GRODIN, MD '68, recently retired from the US Navy following 27 years of service as a psychiatrist. During his career, he served as chief of psychiatry and medical director at the Newport Naval Hospital in Rhode Island, director of the addictions program at the Bethesda Naval Hospital in Maryland, and associate professor of clinical psychiatry at the School of Medicine, Uniformed Services University of the Health Sciences in Bethesda.



The Owl, 1978

'70s

TAD CASSIDY, MD '79, has delivered medical supplies to Russia since 1992 through a sister-city humanitarian aid program set up by St. Luke's Methodist Church in Oklahoma City, Oklahoma. Cassidy is chief of angiography and interventional radiology at Integris Baptist Medical Center. He completed a two-year residency in general surgery and a four-year residency in radiology, both at the University of Pittsburgh. He also completed a fellowship in angiography and interventional radiology at Johns Hopkins University and was assistant professor

of angiography and interventional radiology at the University of Florida. He can be reached at Tad@mmcable.com.

'80s

WILLIAM G. COMBS, MD '80, recently started a private cardiology practice in Allentown, Pennsylvania, with the Heart Care Group, PC, after spending 15 years at Temple University Hospital.

ALBERT FARO, MD '88, is clinical assistant professor of pediatrics and the assistant director of the pediatric lung transplant program at the University of Florida. He completed pediatric pulmonary fellowship training at UPMC Presbyterian and Children's Hospital in 1996. Faro can be reached at Faroal@peds.ufl.edu.

MARK L. HOCH, MD '88, recently became a full-time family and osteopathy practitioner at the Atkins Center for Complementary Medicine in New York City. Hoch was lead physician at the Arizona Center for Health and Medicine until he took faculty positions at Stamford Hospital and in the Columbia University Family Medicine Residency Program in 1998. Among his numerous publications is a chapter on back and knee pain in *Thriving*, a book on men's health published in 1998 by Putnam.

'90s

LORI HALASZYNSKI, MD '91, spent the last three years practicing general internal medicine with University of Pittsburgh Physicians at UPMC Edgewood Primary Care. She completed her residency at the University of Pittsburgh School of Medicine, where she now holds the title of assistant professor of clinical medicine.

RICHARD J. SAVARINO JR., MD '91, a lieutenant commander in the US Navy, is an orthopaedic surgeon at the Naval Hospital in Groton, Connecticut. He can be reached at Sav3369@aol.com.

DAVID G. METRO JR., MD '94, is an assistant professor of medicine and an anesthesiologist at UPMC Presbyterian, where he finished his residency in 1998. He also is chair of resident selection and recruitment for the Department of Anesthesiology.

LEILA KAHWATI, MD '96, and **RICHARD OH**, MD '96, who are married, recently were stationed at the Hanau Health Clinic in Hanau, Germany. Oh, a captain in the US Army, and Kahwati, a civilian contractor, are family physicians. Kahwati can be reached by E-mail at LeilaKahwati@pol.net and Oh at RichOh99@hotmail.com.

MICHAEL J. METRO, MD '96, is a resident in urology at the Hospital of the University of Pennsylvania.

KRISTINA M. RATH, MD '97, is a resident in obstetrics and gynecology at Yale-University Hospital. —*DE*

***Pitt Med* is eager to publish news of its fellow and resident alumni as well! See attached form.**



PICTUREQUEST

A TREE GROWS FOR FRANK EDWARD SHERMAN, MD '38

OCTOBER 31, 1914 – OCTOBER 24, 1998

There was always a place at Frank Sherman's dinner table for any of his residents and, according to his daughter Missy Hillman, these extended invitations were no rare occurrence. Sherman treated his residents as his own children, and this second family soon branched around the world. He shared his knowledge not only with his residents at Children's Hospital of Pittsburgh, where he practiced pathology and later became the department's director, but with all who sought it. Sherman instructed students of all kinds through his *An Atlas of Congenital Heart Disease*, which served as an essential textbook for numerous medical schools; he also taught pathology at Pitt's School of Medicine for more than 30 years and cofounded the Frank Sherman/Cora Lenox Heart Museum at Children's Hospital. After his retirement, he became a lover of orchids and bromeliads. Now, one year after his untimely death, an epiphyte was dedicated in his honor at the Fairchild Tropical Garden in Coral Gables, Florida. —*ST*

IN MEMORIAM

JAMES V. BALLANTYNE JR. (MD '41)
DECEMBER 28, 1999

WILLIAM H. BURNETT JR. (MD '47)
JUNE 7, 1998

ARNOLD FELDMAN (MD '49)
SEPTEMBER 1, 1999

FRANK D. GEER III (MD '47)
OCTOBER 26, 1999

ROBERT B. GUMP (MD '42)
NOVEMBER 3, 1999

LLOYD M. HORNE (MD '53)
DECEMBER 6, 1999

JOHN A. JOHNSTON JR. (MD '40)
JANUARY 4, 2000

MARSHALL S. LEVY (MD '53)
OCTOBER 31, 1999

ROBERT SHAW MILLIGAN (MD '53)
NOVEMBER 21, 1999

HERBERT J. MORROW (MD '51)
DECEMBER 2, 1999

M. PRINCETON NADLER (MD '40)
JANUARY 11, 2000

JOHN K. RADLER (MD '57)
DECEMBER 24, 1999

W. GLENN REED (MD '46)
NOVEMBER 18, 1999

THEODORE D. SCURLETIS (MD '51)
DECEMBER 29, 1999

HENRY R. SHALLENBERGER (MD '33)
APRIL 11, 1997

HOWARD M. SIMON JR. (MD '51)
DECEMBER 24, 1998

JOHN R. SIMPSON (MD '53)
SEPTEMBER 10, 1998

WILLIAM U. SIPE (MD '43)
OCTOBER 2, 1998

CORNELIUS Y. VEENIS (MD '45)
JANUARY 24, 2000

CHARLES GRAY WATSON (MD FACULTY)
JANUARY 16, 2000

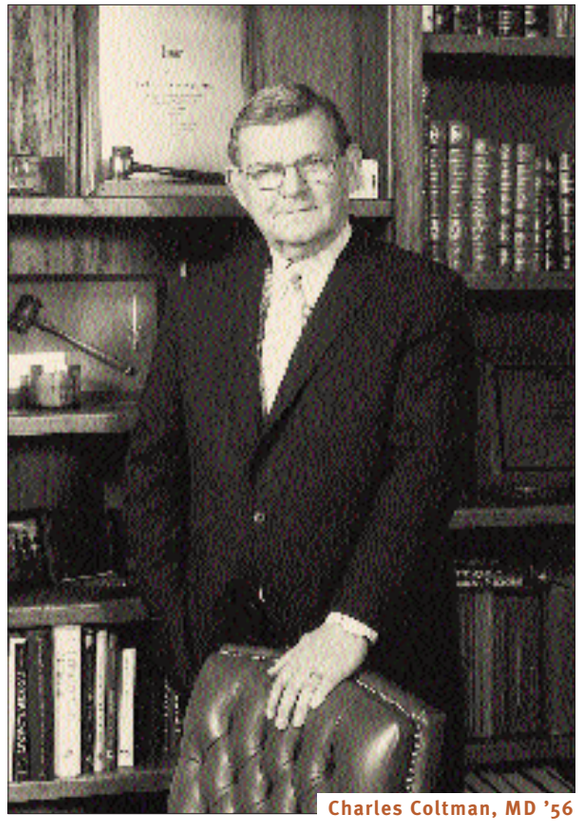
JAMES R. WATSON (MD FACULTY)
OCTOBER 31, 1999

THOMAS M. WATSON (MD '76)
NOVEMBER 6, 1999

JAMES A. WILSON (MD '66)
SEPTEMBER 12, 1999

CHARLES COLTMAN JR: HE LEARNED IMPORTANT LESSONS FROM THE CRIES OF CHILDREN.

BY E. DOUGLAS BANKS



Charles Coltman, MD '56

It's the early 1950s and Charles Coltman Jr., a student at the University of Pittsburgh School of Medicine, can't sleep at night. The cries of his infant son keep him up, and every time his wife, Eleanore, tries to put the boy into his crib, the cries start anew.

So Coltman, MD '56, consulted his freshman seminar professor—the pediatrician with the odd name, Dr. Benjamin Spock.

After hearing about the crying boy, Spock said he could fix the problem: You go home, Coltman recalls him saying, put him to bed and let him cry. Don't go near him. The first night, he'll cry for 45 minutes. Don't go near him. The second night, he'll cry 20 minutes. The third night, 10. The fourth night, he won't cry at all.

One problem: Coltman and his son were men among women, living in Coltman's boyhood home with his mother, three sisters, and his maternal grandmother.

"Well, I went home and announced this strategy to a roomful of women and they said, 'It's never going to happen,'" says Coltman. "I had to stand at the top of the stairs and block the women from consoling my son, Charlie. They kept trying to get past me, but I just stood there."

It was tough love, but Coltman believed in his teacher and, sure enough, it worked.

"I always say that Ben Spock saved my medical school career," says Coltman.

And Coltman's career certainly soared after graduation.

You can barely count his current appointments on one hand, let alone the positions he filled during more than 40 years of clinical research and administration. He is president and chief executive officer of the Cancer Therapy and Research Center in San Antonio, Texas, director of the San Antonio Cancer Institute, professor at the University of Texas Health Science Center, and chairman of the Southwest Oncology Group, the nation's largest multidisease, multidisciplinary organization devoted to clinical trials related to cancer. Under Coltman's direction, the group has made enormous research strides: seven FDA approved cancer therapies for treating leukemia, cancers of the prostate, ovary, bladder, and colon; a network of 4,000 investigators conducting cancer research at more than 375 institutions in 41 states as well as Canada and Korea; and the largest-ever prostate cancer prevention trial—in which 18,882 men have enrolled since 1993.

"He has, essentially, three or four full-time jobs," says Richard I. Fisher, chairman of the lymphoma committee for the group. "He probably has more responsibilities than any other oncology leader in the country."

"He probably has more responsibilities than any other oncology leader in the country."

But Coltman's research work didn't begin in Texas. Like much of his training, it began in Pittsburgh, surrounded by the cries of children.

During his second year of medical school, with his son finally sleeping through the night, Coltman drew blood from children in their elementary school gymnasium. These kids, standing in lines, some screaming, others crying, were the control group in a study that led to the polio vaccine.

He would go on to finish a residency in medicine and a fellowship in hematology, both at Ohio State University. Over the years, he has distinguished himself by contributing something like 350 articles and abstracts on leukemia, lymphoma, and Hodgkin's disease. Coltman also served as president of the American Society of Clinical Oncology and a director of the National American Cancer Society. Pitt's School of Medicine recognized him with the Hench Award in 1990; he also is a recipient of the Association of Cancer Centers' Outstanding Achievement in Clinical Research and the US Air Force's Harold Brown Award for significant contributions in chemotherapy research and development.

And he still finds time to sleep. ■

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Found in the 1989 *Hippocratean*: what appears to be an all-star team. Is this a fashion statement or can they slam dunk? We would love to know if you do. . . .