PENN Medicine

FEBRUARY 2006

Global Engagement: A New Office Sharpens the Focus on World Health

GOAL: A GOOD NIGHT'S SLEEP

TESTIFYING ON STEM CELL RESEARCH

GAMMA KNIFE BRINGS A NEW EDGE

Daniel Burke

Miss America's 30,000 Sticks

At a campus event that celebrated PENN Medicine's diabetes program, Mitchell A. Lazar, M.D., Ph.D., director of the recently created Institute for Diabetes, Obesity, and Metabolism, took the opportunity to articulate the institute's "big plans": to prevent diabetes, to cure diabetes, to improve diabetes treatment, to prevent complications from the disease, and to train the next generation of professionals to take on these ambitious roles. A tall order, but Lazar and the multidisciplinary team at the institute and the Penn Rodebaugh Diabetes Center exuded confidence. So did a special guest, Nicole Johnson Baker, who won the Miss America title in 1999. She competed in the pageant while wearing an insulin pump.

The event, scheduled during American Diabetes Month, was called "Translating Discoveries into Care." Several of the speakers made note of the alarming statistics related to diabetes and obesity. Lazar pointed out that an estimated one in three Americans born in 2000 would get diabetes. Nayyar Iqbal, M.D., assistant director of the institute's Type 2 Diabetes Unit, noted that as recently as 2001, 20 percent to 24 percent of Americans were obese; today, it is closer to 30 percent. And, as Iqbal emphasized, obesity leads to increased blood glucose, which leads to diabetes. In the question-and-answer segment that followed the program, Mark H. Schutta, M.D., medical director of the Rodebaugh Center, said bluntly that "diabetes will shave off six to seven years of your life."

But Schutta also made clear that there is hope. Type 2 diabetes, he asserted, "is a completely preventable disease." And a patient can have expert help. While acknowledging that "the patients have to do most of the work," he also said that "diabetes care is a team sport." As he spoke, he showed a slide of the personnel at the Rodebaugh Center, all of whom looked extremely fit! Lowering one's blood sugar through diet and exercise, Schutta said, is extremely important. Yet he also said that people on diets should be able to have "an occasional mimosa" or slice of cake.

Michael R. Rickels, M.D, assistant director of the Type 1 Diabetes Unit, spoke about the promise of pancreatic islet transplantation, which can help the body maintain the proper level of insulin. One major challenge is to keep the patient's immune system from rejecting the islet cells. Diabetes experts are also studying ways to make the processing of islet cells more efficient and to regenerate islet cells in the body. Schutta mentioned some new devices and therapies that the Rodebaugh Center is testing, such as the Continuous Glucose Monitoring System and the Insulin Pump Program (for patients who would normally take multiple insulin injections a day).

In her keynote speech, Nicole Johnson Baker began by describing the "grim" picture. By her estimate, some 21 million Americans have diabetes. Yet on the whole she offered a more positive view. After all, she noted, it has been only 85 years since the "miracle drug" insulin was introduced, and diabetics have had glucose meters for only about 30 years. (Johnson Baker remarked that it has been "so crucial and critical to know my numbers.") In addition, experts began studying "women-specific" aspects of diabetes only 10 to 15 years ago. Pregnant herself, Johnson Baker said that she has been a participant in research on how diabetes affects pregnant women. And something that she said happens to about 20 percent of pregnant women has happened to her: her body is now making about 30 percent of the insulin she needs. "The bad news," she added with some irony, is that "it will go away in about eight weeks" – after she delivers. But this change is a rich area for further study.

Living with diabetes (the name of her 2001 book) "has been a pain," said the former Miss America, estimating that she has had 30,000 insulin sticks in the last 12 years. "But I'm going to choose to live in a world of great hope." ■

Cover montage
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Globe: Comstock

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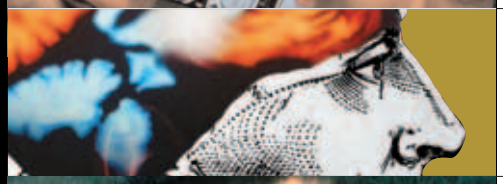
Neurosurgeons at the Penn Gamma Knife® Center have a new, 20-ton tool to accomplish the most delicate procedures. It uses 201 finely tuned beams of radiation to treat brain lesions and tumors.



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Morris Swartz, M.D., a pulmonologist, uses vacation time to photograph eye-catching landscapes across the country. Several of his prints were displayed at Penn's Faculty Club this past fall.

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DEPARTMENTS

Stuart Watson

Benefactors: Raymond and Ruth Perelman, left, share a moment with Dr. Denise Rubenstein and Dr. Arthur Rubenstein.

CAM: A Groundbreaking and a Gift

Only a month after the University of Pennsylvania Health System broke symbolic ground on the Center for Advanced Medicine, it announced a gift of $25 million from Raymond and Ruth Perelman to name the new state-of-the-art facility.

Scheduled to open in 2008, the $232 million center, now to be called The Raymond and Ruth Perelman Center for Advanced Medicine, will house Penn's Abramson Cancer Center, radiation oncology, cardiovascular medicine, and an outpatient surgical pavilion in its 300,000 square feet of clinical space. It will be located on the corner of 34th Street and Civic Center Boulevard, on the former site of the Convention Center. The Perelman Center for Advanced Medicine represents the largest capital project undertaken in the history of PENN Medicine.

As Arthur H. Rubenstein, M.B., B.Ch., executive vice president of the University of Pennsylvania for the Health System and dean of the School of Medicine, said at the groundbreaking on October 20, "We already have abundant talent and recognized national leadership at the Abramson Cancer Center. We already have exceptional programs in surgery and cardiovascular medicine. But what we haven't had until now is a building worthy of this level of excellence."

Among the several speakers at the groundbreaking was John H. Glick, M.D., director of the Abramson Cancer Center. "As a physician who has spent 35 years caring for cancer patients, it will be my privilege, and that of my colleagues, to deliver the most outstanding and humanistic care possible to our patients in this wonderful new facility," he said. "Our many physician leaders have worked with talented administrators to act as advocates for our patients and provide them with a world-class building that meets their needs today and well into the future."

While patients and their families have provided the motivation for the Center, many of them have made major contributions to its construction as well. Donors to the Center also include many of the School of Medicine's own faculty as well as trustees, patients, and alumni.

In her remarks at the groundbreaking, Amy Gutmann, Ph.D., president of the University of Pennsylvania, noted the political support for CAM. "This project has also enjoyed the enthusiastic backing of our city and Commonwealth officials." She went on to assert that the Center "will advance our boldest aspirations to redefine Penn as the eminent urban university. It will transform the delivery of cancer and cardiovascular care and outpatient surgery in Philadelphia and along the Northeast corridor; it will bring hundreds of new jobs to West Philadelphia, and we have also established local economic inclusion goals; and the Center will bring new luster and energy along the Schuylkill River, which is now in the early stages of a dramatic transformation."

The $25 million gift to help finance the construction and completion of the new facility continues a tradition of generosity to PENN Medicine by the Perelman family. Since 1992, Raymond Perelman has been president and chairman of the board of RGP Holdings, Inc., a privately held holding company that includes manufacturing, mining, and financial interests. A 1940 graduate of the Wharton School, he serves as a PENN Medicine Trustee. Mr. and Mrs. Perelman are trustees of the Raymond and Ruth Perelman Education Foundation, Inc., which supports Jewish cultural and welfare organizations, as well as arts and

With shovels in hand: (middle to right) President Amy Gutmann, Madlyn Abramson, Ralph W. Muller, Dr. John H. Glick, and Dr. Larry Kaiser.

history museums and other cultural institutions. In addition, the Perelmans are parents to Jeffrey E. Perelman and Ronald O. Perelman, both graduates of the University of Pennsylvania who have had distinguished careers in business and philanthropy while maintaining close ties to the city and the University.

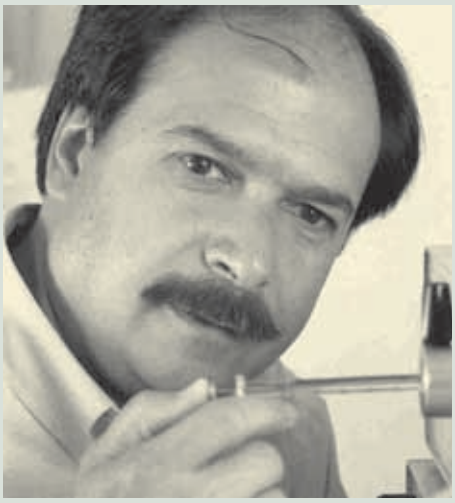
In announcing the Perelmans' "magnificent gift," Rubenstein said it would "transform the way medicine is practiced at Penn and world-wide."

"The Raymond and Ruth Perelman Center for Advanced Medicine will be a spectacular statement of where PENN Medicine is going in the 21st century," said Ralph W. Muller, chief executive officer of UPHS. "It will provide a place where our superb health-care professionals will practice the most advanced medicine available in a setting that is as patient-focused as it can possibly be."

Penn to Lead Search for New Mood-Disorder Drugs

In September, the National Institute of Mental Health (NIMH) awarded the School of Medicine $1.8 million to establish a National Cooperative Drug Discovery Group for the Treatment of Mood Disorders. The group comprises researchers from the Center for Neurobiology and Behavior at Penn and the Neuroscience Discovery Department at Wyeth Research Laboratories, Princeton, N.J.

The aim of this collaboration between academe and industry is to develop new antidepressant drug treatments based on the role of neurogenesis in regulating stress and depression. Advanced brain-imaging techniques show distinct shrinkage in the hippocampus and cortex, regions known to play a role in mediating mood and cognitive reasoning. Animal studies reveal that chronic stress leads to similar volume and cell loss in these brain regions, suggesting a link between depression and stress.



Irwin Lucki, Ph.D.

"Increasingly, we are learning that certain areas of the brain are responsible for generating new cells, and this renewal process is causing us to reexamine the way that stress affects the brain," said Irwin Lucki, Ph.D., professor of psychiatry and principal investigator of Penn's part of the cooperative. As Lucki explained, stress reduces the amount of neurogenesis, or cell growth, in these areas of renewal. At the same time, chronic administration of antidepressant drugs increases neurogenesis. The cooperative is seeking to identify compounds that facilitate neurogenesis in crucial areas of the brain as a basis for developing innovative therapies for depression.

Recently, researchers at Penn and Wyeth examined a hormone called insulin-like growth factor (IGF-1) that has been shown to promote neurogenesis. Brian Hoshaw, Ph.D., a research associate in Penn's Department of Psychiatry, and Jessica Malberg, Ph.D., a senior research scientist at Wyeth, discovered that IGF-1 produces behavioral effects similar to antidepressant treatments in animal models. By examining the way that IGF-1 and other neurotrophins increase neurogenesis, the research team may be able to develop better antidepressant drugs.

The Drug Discovery Group is also developing an animal model capable of detecting the effects of antidepressants on chronic stress using neurogenesis. With such a model, researchers could begin to better understand the delay in the efficacy of antidepressant drugs and how it may relate to changes in neurogenesis.

A New "Breast Cancer Center of Excellence"

The Department of Defense has named Penn's School of Medicine a Breast Cancer Center of Excellence. This designation, which comes with a five-year grant of $10 million to Lewis A. Chodosh, M.D., Ph.D., principal investigator and director of the center, establishes Penn as one of only 14 such sites in the United States. The center is part of a multidisciplinary approach to understanding the progression of breast cancer by using genetically engineered mouse models and state-of-the-art non-invasive imaging techniques.

"While tumor progression is a problem of unrivaled clinical importance, the mechanisms underlying it are poorly understood," said Chodosh, who leads the Breast Cancer Program at the Abramson Cancer Center and serves as director of cancer genetics at the Abramson Family Cancer Research Institute.

Researchers at Penn's center will employ an array of sophisticated technologies – including positron emission tomography (PET), magnetic resonance imaging (MRI), computed tomography (CT), magnetic resonance spectroscopy (MRS), single-photon emission computed tomography (SPECT), and ultrasound – to visualize and track tumor cells from their origins in living animals to their eventual progression to metastasis and recurrence. These animal models mimic crucial features that occur in humans with breast cancer. By identifying the critical molecular targets and pathways by which breast cancers progress, the researchers hope to develop more effective therapies against highly aggressive forms of this cancer.

Mitchell D. Schnall, M.D., Ph.D., associate professor of radiology at Penn, and Ruth J. Muschel, M.D., Ph.D., professor of pathology and laboratory medicine, are co-principal investigators of the grant. The Center of Excellence, which is based at Penn, includes two dozen investigators at Penn, the University of California at Davis, Albert Einstein College of Medicine, McGill University, and The Children's Hospital of Philadelphia.

Penn Named Part of a Site for National Children's Study

Together with The Children's Hospital of Philadelphia and Drexel University School of Public Health, the University of Pennsylvania has been named one of the six "Vanguard Centers," or study centers, that will implement the $2.7-billion National Children's Study (NCS). The study will examine the effects of environmental influences on the health and development of more than 100,000 children across the United States, following them from before birth until age 21. Teams from the Vanguard Centers will be the first to recruit participants and collect data as part of the decades-long research effort, and investigators anticipate that close to 1,200 families from Montgomery County will participate in the study. Penn was also awarded the contract to serve as the analysis center for the NCS as part of a joint proposal with Westat in Rockville, Md.

The National Children's Study uses a broad definition of "environment" that includes: natural and man-made environmental factors; biological and chemical factors; physical surroundings; social factors; behavioral influences and outcomes; genetics; cultural and family influences and differences; and geographic locations. Researchers will analyze how these elements interact with each other and what helpful and/or harmful effects they might have on children's health. By studying children through their different phases of growth and development, researchers expect to understand the role of these factors on health and disease better.

The study will also allow scientists to find the differences between groups of people, in terms of their health, access to health care, and other issues.

"Gathering this information not only advances the state of pediatric medicine but it will also provide possible cures and solutions to particularly troublesome childhood illnesses," said Donald F. Schwarz, M.D., M.P.H., M.B.A., associate professor of pediatrics at Penn and chief of adolescent medicine at Children's Hospital.

The Vanguard Centers will work within their communities to recruit participants (including women who are pregnant or likely to have a child in the near future and their families), collect and process data, and pilot new research methods for incorporation into the full study.

According to Jonas H. Ellenberg, Ph.D., professor of biostatistics at Penn and principal investigator for the analysis center, the NCS is unprecedented in its scope and complexity. The study has been in active planning for more than five years, and several national agencies and institutes have solicited extraordinary input from the scientific and lay communities on issues of design, community input, and ethical considerations.

Experts believe that the National Children's Study will be one of the richest resources of information available for answering questions related to children's health and development and will form the basis of child health guidance, interventions, and policy for generations to come.

How Effective Is That Treatment?

The Center for Clinical Epidemiology and Biostatistics (CCEB) is now part of the Effective Health Care Program, a new initiative within the federal Agency for Healthcare Research and Quality. The program is intended to help clinicians and patients determine which drugs and other medical treatments work best for certain health conditions.

CCEB becomes part of a new network of 13 Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) research centers that will conduct studies aimed at filling knowledge gaps about treatment effectiveness. It has been awarded $250,000 for its first study within the DEcIDE program. Operating under strict procedures to guarantee privacy and security, DEcIDE centers will use "de-identified" data available through insurers, health plans, and other organizations to answer questions about the use, benefits, and risks of medications and other therapies. To start, CCEB researchers will examine the association between antidepressant drugs and aspiration pneumonia in the aged. Brian L. Strom, M.D., M.P.H., the George S. Pepper Professor of Public Health and Preventive Medicine and director of the CCEB, is the principal investigator for the grant.

According to Sean Hennessy, Pharm.D., Ph.D., co-principal investigator of the Penn DEcIDE program, "Nearly all drugs are approved based on studies comparing the new drug to a placebo." Yet as Hennessy, assistant professor of epidemiology and of pharmacology, explains, "What patients and clinicians really need to know is not how well the new drug works compared with a placebo, but compared with what is already available. This lack of information on comparative effectiveness makes it very difficult to make evidence-based decisions. In the years to come, the DEcIDE Network will play a key role in addressing the need for information on comparative effectiveness."

Honors & Awards

This year's Jay N. Cohn New Investigator Award in Clinical/Integrative Physiology has gone to **Thomas Cappola, M.D.**, assistant professor of medicine and a cardiologist and heart-failure specialist at the PENN Cardiovascular Institute. The award is given at the annual meeting of the Heart Failure Society of America to recognize research excellence in young investigators. Cash prizes were awarded based on the investigators' abstract presentations. Cappola's was on a novel approach to analyze cardiac gene transcription in human subjects with advanced heart failure.

Julius Deren, M.D., professor of medicine in the gastroenterology division, was honored in September at the National Board of Trustees Dinner of the Crohn's and Colitis Foundation of America. Based at Penn Presbyterian Medical Center, he serves as medical director for the Inflammatory Bowel Disease Network for Penn's Health System.

Garret A. FitzGerald, M.D., the Elmer Bobst Professor of Pharmacology who serves as chair of the Department of Pharmacology and director of the Institute for Translational Medicine and Therapeutics, has won the Boyle Medal. The medal is awarded every other year by the Royal Dublin Society and *The Irish Times* to a distinguished Irish-born scientist working abroad; on alternate years, it is presented to a scientist working in Ireland. According to *The Irish Times*, research done by FitzGerald "has profoundly influenced the prescribing of low-dose aspirin used by millions of people around the world" to help against heart attacks. It also noted his early warnings on COX-2 inhibitors, such as Vioxx and Celebrex, which are used to alleviate arthritis pain.

Penn Faculty Members Garner National Honors

Four faculty members of the University of Pennsylvania School of Medicine were elected to the Institute of Medicine of the National Academies. Two other professors at the University of Pennsylvania were also elected, bringing Penn's total to six in this year's list of 64 new members and five foreign associates.

The Institute of Medicine was established in 1970 by the National Academy of Sciences to honor professional achievement in the health sciences and to serve as a national resource for independent analysis and recommendations on issues related to medicine, biomedical sciences, and health.

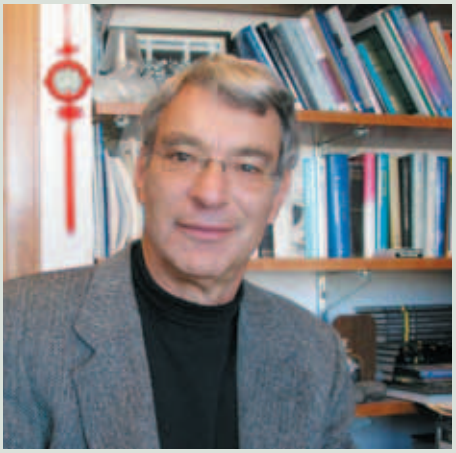
The new Penn IOM members are:

* Larry R. Kaiser, M.D., professor and chair, Department of Surgery, School of Medicine
* Virginia M.-Y. Lee, Ph.D., M.B.A., professor of pathology and laboratory medicine, Center for Neurodegenerative Disease Research, School of Medicine
* Stanley A. Plotkin, M.D., emeritus professor of pediatrics, School of Medicine
* Virginia A. Stallings, M.D., professor of pediatrics, School of Medicine
* Marjorie K. Jeffcoat, D.M.D., dean of the School of Dental Medicine
* Mary D. Naylor, Ph.D., professor of gerontology, School of Nursing

In addition, three faculty members of the School of Medicine were named Fellows of the American Association for the Advancement of Science. The new Fellows will be officially inducted February 18, 2006, during the Association's 2006 annual meeting in St. Louis.

The new Penn AAAS Fellows are:

* Ian A. Blair, professor of pharmacology, School of Medicine, and director of the Center for Cancer Pharmacology.
* Richard L. Doty, professor of otorhinolaryngology, School of Medicine, and director of Penn's Smell and Taste Center
* Irwin B. Levitan, professor and chair of the Department of Neuroscience in Penn's School of Medicine and director of the Mahoney Institute of Neurological Sciences.



Norman B. Hecht, Ph.D., the William Shippen Jr. Professor of Human Reproduction in the Department of Obstetrics and Gynecology, was named the recipient of the 2006 Distinguished Andrologist Award. He will receive the award next spring at the annual meeting of the American Society of Andrology.

Hecht has been one of the pioneers in the use of molecular biology to understand the pathways that control spermatogenesis. In addition to his prolific and groundbreaking research accomplishments, he has served the Society and the broader scientific community in a variety of capacities

and has trained many students who have gone on to successful independent careers. Hecht is serving as interim director of Penn's Center for Research on Reproduction and Women's Health.

The National Arthritis Foundation has presented the Sir John Charnley Award to **Craig Israelite M.D.**, an orthopaedic surgeon at Penn Presbyterian Medical Center. The award, given for excellence and achievement in the field of orthopaedics, is named for the English orthopaedic surgeon who invented the modern total hip replacement in 1962. Israelite has been an active volunteer with the National Arthritis Foundation. According to the Foundation, Israelite "graciously provides input on many of our programs and activities and has served on several committees. Dr. Israelite has been the driving force behind the Chapter's successful Medical Gala."

Leonard Jarett, M.D., Distinguished Professor of Pathology and Laboratory Medicine and former chair of the department, received a Distinguished Alumni Award from Washington University in St. Louis at its annual Founders Day celebrations. Jarett, who earned his medical degree at Washington University, was recognized as a leader in diabetes research whose work has led to advances in understanding how insulin is internalized in the cell nucleus. Before coming to Penn in 1980 as chair of the Department of Pathology and Laboratory Medicine, Jarett served as the first head of the Academic Division of Laboratory Medicine in Washington University's departments of Pathology and Medicine and as the first full-time director of Barnes Hospital Diagnostic Laboratories. At Penn, he has been chairman of the clinical practices and assistant dean of faculty affairs.

This fall, Jarett also received the Distinguished Scientist Award from the National Academy of Clinical Biochemistry. Recipients of the award have made noteworthy contributions to the understanding of the biochemistry of disease, the application of the principles of clinical biochemistry, or the important use of laboratory techniques. According to the Academy, Jarett's major research accomplishments included his observations that insulin caused occupied insulin receptors on adipocytes to behave differently from any other cells. He has had numerous publications on insulin's control of signal transduction.

Shiriki Kumanyika, Ph.D., M.P.H., professor of biostatistics and epidemiology, has won the first Population Research Prize of the American Heart Association. She was honored for her outstanding contributions to the advancement of cardiovascular science while serving as head of an outstanding laboratory studying cardiovascular population research. She has also received the 2005 Dr. Herbert W. Nickens Epidemiology Award from the Association of Black Cardiologists, Inc. (The award is named after the late Herbert Nickens, M.D. '73, G.M.E. '84, former director of the Office of Minority Health in the Department of Health and Human Services.) Kumanyika, who is also associate dean for health promotion and disease prevention in the School of Medicine and director of the Graduate Program in Public Health Studies, serves on the executive board of the American Public Health Association.

Sandra Norman, Ph.D., F.A.C.E., research associate professor of epidemiology in the Department of Biostatistics and Epidemiology, received two awards in October: the St. George Award of the National American Cancer Society and the Sword of Hope of the Pennsylvania Chapter of the American Cancer Society. Both are considered the highest service awards bestowed upon a member for distinguished, exemplary, and inspirational leadership. She is the first individual to have received these awards together at the annual ceremony. Norman is also a senior scholar in the Center for Clinical Epidemiology and Biostatistics.

Anil K. Rustgi, M.D., chief of the division of gastroenterology in the Department of Medicine, was recently appointed editor-in-chief of *Gastroenterology*. Published monthly by the American Gastroenterology Association, it is considered the specialty's leading peer-reviewed journal and is dedicated to publishing clinical and basic studies of all aspects of the digestive system. Rustgi, the T. Grier Miller Professor of Medicine and Genetics, also serves as director of Penn's Center for Molecular Studies in Digestive and Liver Diseases.

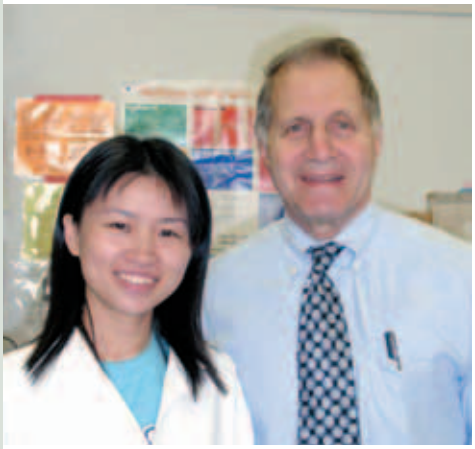
Several other members of Penn's medical faculty have been named to *Gastroenterology*'s editorial board as well.

Steven A. Thomas, M.D., Ph.D., associate professor of pharmacology at the University of Pennsylvania, received an honorable mention from NARSAD, a national organization that funds scientific research on brain and psychiatric disorders. He was praised for his research on the role of the neurotransmitter norepinephrine in the development of depression and in the action of antidepressant medications. Thomas received NARSAD Young Investigator grants in 1999 and 2001.

Two members of Penn's medical faculty were elected Fellows in the American Academy of Microbiology: **Craig B. Thompson, M.D.**, professor and chair of the Department of Cancer Biology, and **Jeffrey N. Weiser, M.D.**, professor of microbiology and of pediatrics. They were elected in recognition of their scientific achievements and original contributions that have advanced the field of microbiology.

Penn Student Wins Basic Genetics Research Award

Nuo Yang, a Ph.D. student in the laboratory of Haig H. Kazazian Jr., M.D., chair of the Department of Genetics, has received the Predoctoral Basic Research Award from the American Society of Human Genetics. She received the award at the society's annual meeting in Salt Lake City, where she delivered a talk entitled "Antisense transcript suppresses human LINE-1 retrotransposition via an RNAi mechanism." Yang was recognized for her research on transposable elements (transposons). Commonly known as jumping genes, transposons can move from one chromosome to another or within the same chromosome. One category of transposons is called LINE-1s (L1s), which make up 17 percent of the human genome. "My Ph.D. study is focused on the regulation of the jump, what makes L1s jump or not jump, and the effect on the genome," explains Yang. Transposons can trigger evolutionary changes in the human genome and are associated with several types of human diseases, including hemophilia A, beta thalassemia, and retinitis pigmentosa.



Yang and Kazazian

LETTERS

WOMEN IN ACADEMIC MEDICINE

My copy of *Penn Medicine* just arrived and I read your article on women in medicine ["A Matter of Potential," by Linda Bird Randolph, Summer 2005] with great interest. I am a graduate of the Class of 1951. Unexpectedly, I wound up in academic medicine when my husband of the same class decided to go into OB-GYN at U.N.C. By that time I already had two children and had to support the family. Gradually I worked up to an associate professor at the University of Texas Medical Branch in Galveston. I never made full professor because the demands of work and of home left me no extra time to do the research even to write up the material which I could have used to publish articles.

I do not regret my decision to give time to my family. I do know that others have reaped the benefit of my knowledge and observations. I am a pediatrician. I once told the Mead Johnson rep that we needed head circumference charts for children beyond the age of 3 years, the cut-off at that time. Eighteen months later I received a letter from the company thanking me for the input and several copies of the "new" head charts from 3 to 18 years of age. I also wrote a letter about two siblings who had had an unusual reaction to the pertussis portion of DPT immunizations, one of shock and weight loss, etc. It was nowhere in the literature. Now it is listed as a regular warning of such vaccine. I should have researched and published both of those ideas but no one mentored me or suggested such a thing or helped in any way. It was only in retrospect that I realized my errors.

I am delighted to know that you have such a program [FOCUS on Health & Leadership for Women] to help women academicians to get ahead. At least I know that my thoughts and observations have helped other children. Keep up the good work.

Ruth Abrams Dillard, M.D. '51
Boone, N.C.

REACHING POTENTIAL?

I was an NIH "Special Fellow" in Molecular Medicine, 1966-68, in [Penn's] Department of Medicine with Dr. George Ludwig.

Penn Medicine is "very well done" and it is a pleasure to read – very informative – regarding programs, research, and colleagues. Kudos.

The article "A Matter of Potential" was superb – I was one of the 9% of women who became a full professor, which is now about 12%.

Doris Bartuska, M.D., G.M.E. '68
Allegheny University of the Health Sciences

THE SCHOOL OF MEDICINE'S GLOBAL HEALTH PROGRAMS PROVIDES INTENSE, HANDS-ON, INTERNATIONAL EXPERIENCES THAT PARTICIPANTS WILL NEVER FORGET.

The immersion method

By Linda Bird Randolph

Something is fundamentally wrong with the traditional way American medical students are taught about international health, claims Neal Nathanson, M.D.

Attending lectures and viewing slide-show presentations that depict health-care challenges in other countries does have *some* educational benefit, says Nathanson. But he asserts that the best way to introduce students and trainees to a global health experience is to immerse them in a health-care environment far away from the ivy-covered walls of University City, Philadelphia.

"When you're in a classroom in Philadelphia, you don't know what is going on in Botswana, no matter how descriptive the lecture," says Nathanson, who serves as associate dean for Global Health Programs at the School of Medicine. "The only way to understand Botswana is to go there and immerse yourself in that situation."

That is exactly what GHP was able to help Adriana Izquierdo do in the spring of 2004. Izquierdo, who graduated this year, spent six years completing her medical degree while also earning a master's degree in epidemiology and biostatistics. What she witnessed in Botswana, she says, was "a sense of hope and optimism, in spite of really tough conditions. For example, the AIDS/HIV rate there is 40 percent, and very young adults are dying daily of disease and inadequate resources."

Nothing quite prepared Izquierdo for the culture shock she experienced in Botswana.

"I grew up speaking Spanish, learned English in school, as well as French and

Photographs of individuals by Addison Geary

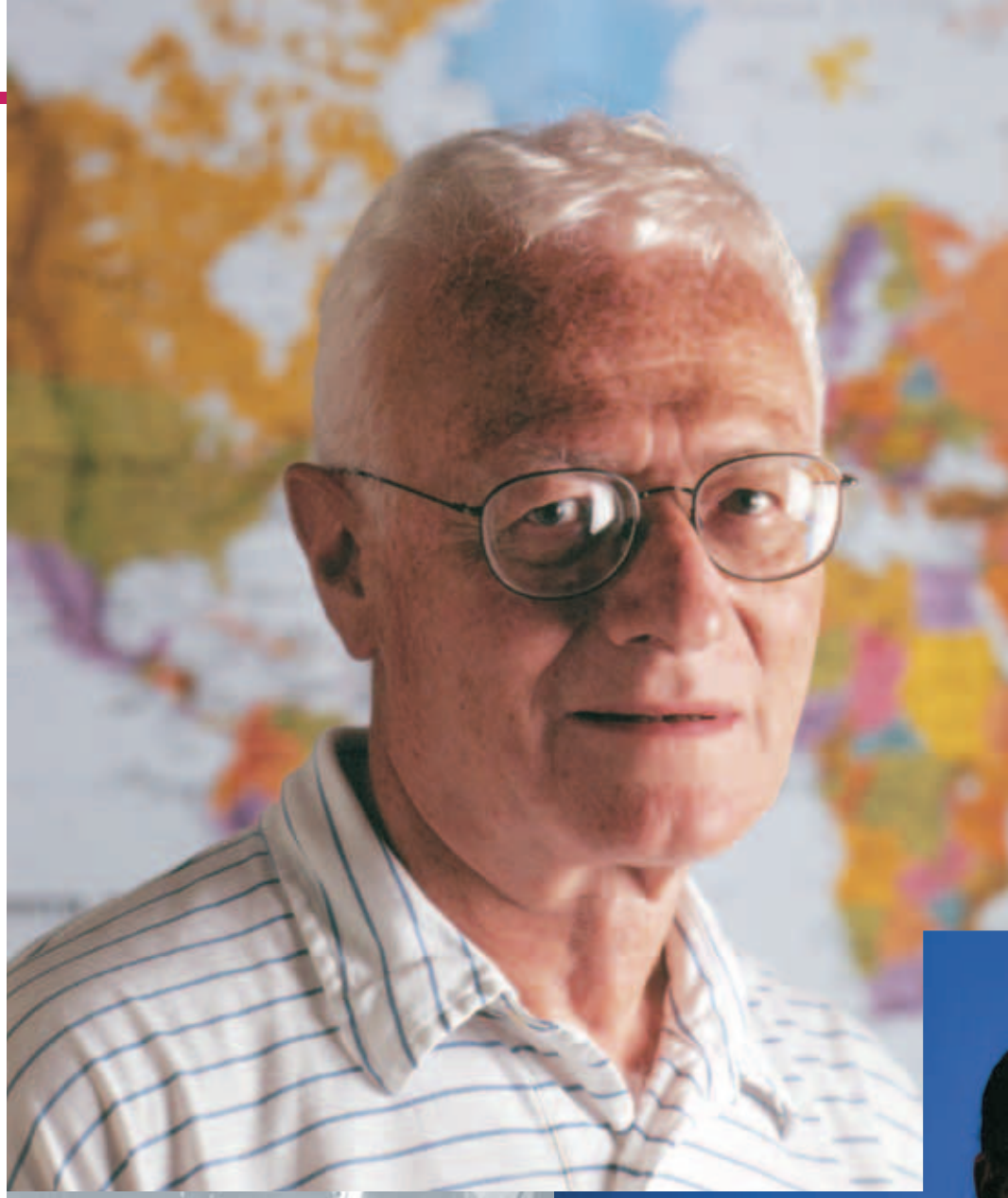
German, so it was the first time I was in a place where I couldn't communicate with the people in a fluent fashion. I think it was also tough working in a hospital that didn't count on the same technical, medical, and clinical resources as we are accustomed to having here at Penn, or anywhere in the United States for that matter. Talk about health disparities! So it was hard."

Under Nathanson's direction, Global Health Programs, started in July 2004, coordinates the school's global activities and supports the international aspects of Penn's research, educational, and service programs. Through the international rotations GHP arranges, medical and postdoctoral students can gain the direct exposure to international medicine they are seeking. At the same time, the program also hosts international medical students at Penn and recruits postdoctoral fellows who come from international institutions. Like Izquierdo, many of the Penn students experience the reality of health disparities when they take their rotations in poorer nations, but many of them are also inspired to try to do something about the matter.

"Today's students are into different types of things and quite a number of global health things," says Gail Morrison, M.D. '71, G.M.E. '77, vice dean for education for the School of Medicine. "We are all starting to truly realize that the world is much smaller than we anticipated. About five years ago, it became apparent that interest in global health issues was increasing. In fact, many students are now displaying an interest in international health issues as undergraduates."

A New Office but a Long Tradition

For Nathanson, associate dean of Global Health Programs is a new role for a longtime University citizen. From 1978 to 1994, he served as chair of the Department of Microbiology at Penn, then became vice dean for research and research train-



Top: Neal Nathanson, M.D., a long-time Penn faculty member, now serves as associate dean for Global Health Programs.

Bottom: Steven C. Larson, M.D., assistant dean, has long been a champion of global medicine.

ing for the School of Medicine. He left Penn to head the Office of AIDS Research at the National Institutes of Health. In 2000, he was drawn back to Penn as the University's vice provost for research. He assumed his current position last year.

In addition to Nathanson, the staff for the evolving operations of Global Health Programs includes Steven C. Larson, M.D. '88, assistant dean; Nancy Biller, M.A., M.P.H., administrative director; and administrative coordinator Valerie Sica. Larson comes to the post with a substantial amount of experience in global medicine. He helped establish Frontline Medicine, a program at the School of Medicine created to provide medical students, residents, and faculty members with the opportunities and resources to examine and study critical issues in the area of global health. He has also been a faculty advisor for students in the Global Health Interest Group.

"There is a national upturn in interest on the part of medical students on global health, whatever that means to them," says Nathanson, who added that the definition can vary from school to school and person to person.

More students request an elective in which they are sent to another country, and few schools across the country have formal set-ups to assist them in doing this. Things are likely to change.

In April, Nathanson gave a presentation at "Penn Preview" week, an event for medical-students-to-be who have been accepted at Penn but may not have made their minds up yet. In a one-hour presentation on global health, nearly all responded when he asked them to show their interest by a show of hands.

Throughout its history, Penn's School of Medicine has had an international bent. From its earliest days, graduates of the school often traveled to Edinburgh and elsewhere in Europe for the equivalent of graduate studies, according to Patrick B. Storey, M.D., emeritus professor of medicine. And until the 1940s, the school operated a medical school in Shanghai, known as the Pennsylvania Medical School at St. John's University, founded by Josiah McCracken, M.D. 1901.

Global Health Programs, in fact, was not the first international health program at the School of Medicine. The Office of International Programs was formally closed in July 2003. After a "transition year," during which Nathanson was recruited from his position as vice provost of research at the University and a new staff was put together, GHP was ready to open.

"We've never made any real attempt to figure out what wasn't working. We simply started from scratch," says Nathanson. "But what we are doing seems to be working."

The earlier office, set up about 15 years ago, had a number of highlights, opening channels with foreign medical schools in Latin America, the former Soviet Union, and the People's Republic of China. Dr. Storey, who had directed the Office of International Programs and who speaks Russian, was particularly accomplished at bringing physicians and medical students from Russia to Penn for training they would not get in their own country.

In Larson's mind, the major difference between the two similarly oriented programs is "philosophical." The Office of International Programs, he feels, put less emphasis on a "hands-on, in the field" experience. Global Health Programs, he continues, has sought "to provide all students the opportunity to explore global health through an 'in country' experience that highlights the realities of work within the confines of limited monies and resources."

The Timing of Non-Traditional Electives

"Medical students have limited opportunities to enhance their exposure to international health issues," says Nathanson.

"Penn's current curriculum is designed so that there are two windows of opportunity to take on independent electives that are not part of their required curriculum." These opportunities take place over the summer between the first and second year, and then again during the last 18 months of the medical school curriculum, when a student may be able to carve out three months or more to add on an elective that is not required for graduation.

Considering the current situation, says Nathanson, "students don't have enough time to get deeply into something of interest. Medical students are overwhelmed by intensive curriculum."

To address this problem, Nathanson and his staff have carefully constructed a Global Health Programs elective that is non-traditional in every sense.

"Participation in Global Health Programs is *not* for credit, there are *no* exams, there is *no* required reading," says Nathanson. "There are no papers, no lectures to sit through, and so forth. Our goal is to immerse students in an international setting." At the same time, there is no formal credit for those GHP rotations.

Another challenge for international initiatives is the limited funding. Students who take part in a Global Health Programs elective receive assistance with their out-of-pocket expenses. The money to subsidize their efforts is raised through private foundations, not through the School of Medicine. A primary provider of support is the Measey Foundation.

As Larson puts it, "The greatest challenge that I see facing GHP at Penn is funding. Interest in global health is a nationwide phenomenon that many of my colleagues at other institutions such as Harvard, Hopkins, Yale, etc., have observed. Unfortunately, we all struggle for the same 'piece of the pie' with respect to grants and available dollars from programs like the Fogarty, the Gates Foundation, and others. The simple fact that Global Health has become such an important issue with respect to medical education means that we need to heighten institutional awareness and prioritize fund-raising efforts to support the mission."

Through Global Health Programs, Neil Gupta has worked in clinical, laboratory, and community settings in Brazil, South Africa, and Senegal.

A Rotation, Not a Vacation

At first glance, taking a summer off to travel to an international setting to learn about foreign health-care sounds almost like a vacation. But students who have finished Global Health rotations report that the work they did while traveling in the program was the toughest they have ever done.

"No one site can take more than two or three students at any given summer," says Nathanson. "But demand and interest in rotations is up." In 2004, GHP sent 50 students abroad; last summer it was 75.

Opportunities for the program's participants abound, including those in about 30 different countries, including Botswana, Ghana, South Africa, India, Central America, Guatemala, and Peru, and in industrialized countries such as Austria, Belgium, England, France, Ireland, Japan, Netherlands, and Scotland.

Through Global Health Programs, Neil Gupta, now a second-year medical student, worked in clinical, laboratory, and community settings in Brazil, South Africa, and Senegal. "The most significant challenges that I faced," he says, "were in creating and defining my role in each of the

Julian Harris conducted research in the Dominican Republic on how HIV patients were adhering to anti-retroviral medicines.

communities I have worked in, professionally as well as socially, and then maintaining the energy and enthusiasm to execute that role effectively."

"I have learned to keep a proper perspective on challenges that I might face in the future," he adds. "The people I have worked with are chronically underserved and under-resourced in health care, education, housing, and economic opportunities. I have learned not only to make the very most of what is available, but to always continue to struggle for basic human and civil rights. The people I met had a profound appreciation for what is already around them, what they love and enjoy."

Like Gupta, Julian Harris, another second-year student, was taken aback by the social and economic conditions he encountered while conducting research in the Dominican Republic. He was there to study how HIV patients were adhering to anti-retroviral medicines.

"I learned that in countries where HIV is still highly stigmatized, providing people with access to medications is one of the best ways to decrease the stigma and to promote HIV testing and prevention," says Harris.

In addition, the disparity in income in the Dominican Republic "is much more stark than in the U.S," Harris notes. "The wealthiest Dominicans live as well as the wealthiest Americans, but poor people in the Dominican Republic – many of them Haitian immigrants – often lack the structural safety nets that are available to most poor people in this country."

In the Botswana hospital where she spent her rotation, reports Adriana Izquierdo, "There were beds on the floor and scant supplies." She found it emotionally challenging to deal with so much advanced disease and death. "Morning report always started with the death count," she says. "Two to 10 people had usually died the evening before. It was sobering." One of the main things Izquierdo learned was to "draw boundaries" and protect her own self and health, "or else you could easily go crazy."

"But somehow people managed," says Izquierdo, "and the nurses were an inspiration and a source of strength and encouragement."

Gupta, Harris, and Izquierdo are among many students who, through GHP, have a strong taste of what health care in other countries can involve. And that's exactly what Nathanson would like to see. "The vision behind Global Health Programs – or at least *my* vision – is that we become successful at giving the student some interest in seeing life in other countries, particularly developing countries, with the idea that this might be something they would want to do on a career basis."

According to Larson, interest in global health both at Penn and in institutions across the nation "has risen off the charts" in the last three or four years. "Students are arriving in their first year with a very sophisticated understanding of global health and, at the very least, a working knowledge of the vocabulary – sustainability, non-governmental organization, etc." As a board member of the Global Health Education Consortium, a national group, Larson feels safe in saying that Global Health Programs at Penn "is one of the most organized and sophisticated in existence at a U.S. medical school."

Nancy Biller, M.A., M.P.H., is GPH's administrative director.

Other Global Health Features

In collaboration with the School of Nursing, the School of Social Work, and the Wharton School, the School of Medicine has introduced a number of other elective courses in order to create a Global Health educational track for those with specific career interests in this area.

Not only does Global Health Programs "outsource" medical talents to other countries for rotations, it also works to attract postdoctoral students from other countries and bring them to Penn.

As Nathanson puts it, Global Health Programs is trying to send the message that, although other medical institutions offer mentoring, there are very few that have Penn's comprehensive training program for postdocs in global health. "I feel that Penn has maybe the best postdoc program in the country," he says. It is not just the individual experience in the laboratory, he explains, "which would be similar to those in other institutions, but this is a program that helps people make the transition from being a graduate student to being an independent researcher, which is what is supposed to happen."

He cites a real shortage of commensurate opportunities for people who earn their Ph.D. degrees in European counties. "Many do not have anywhere near enough opportunities once they get their Ph.D., and they are ending up as taxi-drivers. That's going to be a disaster for European science." Penn, he asserts, can help in that area, "because we have an abundance of opportunities."

Global Health Programs has also teamed with Penn's Bridging the Gaps program to create a Global Health Scholar Track. Bridging the Gaps provides interdisciplinary health-related service in underserved communities while training health and social-service professionals who are responsive to community needs. For medical students, explains Lucy Wolf Tuton, Ph.D., executive director of Bridging the Gaps, the collaboration "will offer students a menu of opportunities that make it possible to combine experiences abroad with experiences locally. As a result, students can gain greater insight into the reality that poverty, lack of access, and health disparities do impact the health of those in our local communities and throughout the rest of the world." The goal, she adds, is "to give students tools to be future leaders committed to improving the health of populations here or abroad."

This kind of initiative seems very much in tune with two of the three components of the Penn Compact, articulated by Amy Gutmann, Ph.D., the University's president, at her inauguration in October 2004. One principle is the better integration of knowledge. As she put it, "The most challenging problems cannot be addressed by one discipline or profession. We cannot understand the AIDS epidemic, for example, without joining the perspectives of medicine, nursing, and finance with those of biochemistry, psychology, sociology, politics, history, and literature."

Another principle of the Penn Compact is "to engage locally and globally. . . . Through our collaborative engagement with communities all over the world, Penn is poised to advance the central values of democracy: life, liberty, opportunity, and mutual respect."

According to Nathanson, "We are not trying to train anyone in public or global health." Instead, he says, "We are trying to give them a flavor of what is out there with the idea that if they are interested, they would go get additional training later on."

"I felt strongly – and I think the students also agreed – that simply giving students formal lectures about global health is not enough," Nathanson says. "Through our programs, we're trying to give them an experience that will show them what it's about. A small portion of them might make international health a career goal, but the experience is valuable to every medical student." ●

GIVING TESTIMONY

Two faculty members urged Pennsylvania lawmakers to support stem cell research.

By John Shea

Nicole Gaddis

In September, about a dozen members of the Commonwealth's House Democratic Policy Committee came to the School of Medicine to hold a public hearing on one of the most controversial matters in biomedicine: stem cell research. They were there to hear from experts and advocates from a variety of institutions and organizations. Given the range of those who testified – from a senior fellow at the conservative Family Research Council to the chairperson of domestic affairs for Hadassah to a Penn oncologist who has worked with stem cells – it was not surprising that they heard different views.

The meeting was held in the auditorium of Biomedical Research Building II/III, itself a monument to Penn's commitment to innovative research like the topic of the day. Television cameras from the Pennsylvania Cable Network (PCN) were positioned near the stage to film the proceedings, and large screens were available to show slides. First to speak was Arthur H. Rubenstein, M.B., B.Ch., executive vice president of the University of Pennsylvania for the Health System and dean of the School of Medicine. After welcoming the committee, he asserted that stem cell research is "an extraordinarily important area" that intersects medical practice and science. He cited the "vast constituency" at PENN Medicine that has a stake in the issue.

The first expert to testify was Arthur L. Caplan, Ph.D., chair of the Department of Medical Ethics and director of the Center for Bioethics. Having chaired a panel on cloning and stem cell research for the United Nations, Caplan was eager to provide a global context. There are, he said, "a lot of countries that have committed to do this work" – among them Singapore, India, the U.K., and Australia. Such nations have what Caplan called "a permissive or flexible policy" on embryonic stem cell research, yet all have continued to ban human cloning. According to a slide Caplan showed, the world as a whole believes in the value and importance of embryonic stem cell research "and rejects adult stem cell research" as an alternative or finds it inadequate.

The policy of the Bush administration is that federal funds would be available only for 60 existing stem cell lines. Caplan argued that there are at most 20 viable cell lines out of those 60, an insufficient amount for scientific research. California, he said, has indicated that it will fund stem cell research ($3 billion over ten years). Caplan asked, is the Commonwealth ready to tell its scientists that they will not be able to do the necessary clinical trials in Pennsylvania? Or that its citizens will have to go overseas for such trials?

Caplan also sought to address another crucial question: What is an embryo? "Some people sincerely believe that an embryo is a person," he said. On the other hand, he likened it to an acorn, with the potential to become an oak. Many embryos are "miswired or misprogrammed" and thus do not fully develop. Using a more elaborate metaphor, Caplan suggested that if there were a fire at a Home Depot, "we have lost the *ingredients*" for houses, not the houses themselves. What Pennsylvanians have to do, he said, is balance the loss of potential with "real needs" of "real persons," such as those in wheelchairs, those with damaged hearts, those with Parkinson's disease.

During the question-and-answer period that followed Caplan's remarks, Rep. Richard Grucela (Northampton), said, "with all due respect," that he hoped Caplan would find a better metaphor for human life than Home Depot. Rep. Dan B. Frankel (Allegheny) appeared more sympathetic to Caplan's argument. While noting that "I would assign some value to an embryo," he emphasized that he would choose

saving the life of "a productive human being" over a "potential" life.

The issue of adult stem cell research was pursued by several of the state representatives, who appeared sensitive to the notion that no embryos would have to be destroyed to produce adult stem cells. In fact, Rep. Thomas A. Tangretti (Westmoreland) claimed that the stem cell research program at the University of Pittsburgh, where the committee had visited in August, was focused entirely on adult stem cells. "From an ethical standpoint," asked Tangretti, shouldn't Pennsylvania explore the promise in adult stem cells? In response, Caplan noted adult stem cell research may not work, and it would be better "to see the chips put on all the numbers."

"So the question that faces us in the Commonwealth is not *whether* embryonic stem cell research is going to be done, it is *where* it's going to be done. . . . Are we prepared to fall behind? . . . Are we prepared to say that if people make breakthroughs in other countries for diabetes or Parkinsonism or cancer, that they can't bring them here? . . . Are we prepared to tell Pennsylvanians to go overseas or to California if they want to get into clinical trials?"
– Arthur L. Caplan, Ph.D.

Penn's second expert, Stephen Emerson, M.D., Ph.D., had a more forceful response. He has found that adult stem cells lack the regenerative power of embryonic stem cells. "There is a one in a million chance that [adult stem cells] can contribute at all," he said, adding: "It is true in a dish, you can see some cells grow," but outside a dish, adult stem cells have not worked.

Emerson, who is a professor of medicine, chief of hematology-oncology at HUP, and

EMERSONIAN VIEWS

Following are excerpts from the statement prepared by Stephen G. Emerson, M.D., Ph.D., for the House Democratic Policy Committee during its hearing on stem cell research. Emerson is a professor of medicine, chief of the division of hematology-oncology, and associate director of clinical research for Penn's Abramson Cancer Center.

Stem cell biology – that is, the study of how stems cells are produced, grow, and work in both animals and humans – is now moving to become the central paradigm in American biomedicine, influencing the way we think about injury and healing, disease and healing, prevention, diagnosis, and healing. The impact of stem cell biology is being felt in every area of medicine, research, and biotechnology, from spinal cord injury and repair to diabetes, from heart disease to breast cancer. On behalf of our patients and our citizens, we here in Pennsylvania have the opportunity to contribute to, lead, and take advantage of the next generation of discoveries and advances in stem cell research. It is therefore essential that we make every effort to create the legal, political, and economic climate that will foster stem cell research in our Commonwealth.

As a young medical student 30 years ago, I was fascinated by the miracle of human development, in which a fertilized egg divides thousands of times, each time sending signals to the daughter cells to form perfectly functioning tissues and organs in just the right pattern. We now know that this process is based on the creation, expansion, and tightly controlled growth and education of master cells called stem cells. Moreover, the medical research community is now coming to realize that this process of stem cell recruitment and development continues throughout life and is responsible for every aspect of human health and disease. When brain tissues are crippled by suddenly blocked cerebral arteries, they call out to the bone marrow to create and mobilize neural stem cells, in an attempt to repair the damaged brain tissue by actually recreating its intricate pattern of neural networks. And when oncologists diagnose breast cancer or leukemia, they are detecting the tip of the lethal iceberg, the core of which is a tiny population of cancerous stem cells. To cure the patient, we now know that we must find, hunt down, and selectively remove or kill this nest of malignant stem cells.

Discovering the language of stem cells, and the secrets of its translation, will make clear much that has previously been un-

decipherable. How do you repair heart muscle damaged by heart attacks? Deliver the right stem cell population to the damaged tissue, at the right time, with the right hormones to instruct the cells to form heart muscle. How do we prevent the crippling blindness of diabetes? Prevent blood vessel stem cells from rushing headlong into the diabetic eye, forming new, chaotic blood vessels that bleed and clog. . . .

We must support embryonic stem cell research as well as studies of adult stem cells, because it is embryonic stem cells that we know have the ability to create all tissues. Having studied adult stem cells for over 20 years, it is clear that adult stem cells do not normally regenerate tissues as do embryonic stem cells, and diseases like cancer have distinctive embryonic stem cell features that we need to solve. Unless we can unlock and harness the secrets of embryonic stem cells, trying to achieve our health goals with adult stem cells only will be severely hampered. These diseases are powerful villains, and we cannot fight them without the coordinated use of our best weapons. . . .

I do want to underscore the impact of stem cell research on the economy of our Commonwealth. Not only will current hospitals, schools, and industries be supported, but, in addition, new biotechnology companies targeted to develop new stem cell based diagnoses and treatments will follow. I had the opportunity to develop one of the first stem cell biotechnology companies, Aastrom Biosciences, and I think the lessons are useful. Aastrom was based on science discovered at the University of Michigan, out of a collaboration between the schools of Engineering and Medicine. . . . Several years later, Aastrom now is fully independent, employs 70+ scientists and other employees, and conducts clinical trials in bone repair and cancer therapy around the world. The State of Michigan has already reaped substantial rewards from their support of this venture, and the company is still very young.

Needless to say, not supporting stem cell research puts our biomedical enterprise at great risk. We will not sustain, let alone expand, the biomedical economy so vital to our Commonwealth's interests. We will not retain, let alone attract, the best researchers and physicians who want to study stem cells, develop and utilize new stem cell technologies and treatments, and the obvious economic benefits that will follow. And most of all, we will not be providing the citizens of Pennsylvania with access to the best medical research and the best care which they deserve. ●

associate director of clinical research for Penn's Abramson Cancer Center, described himself as a stem cell biologist who has worked with adult stem cells and embryonic stem cells "all my life." He also noted his knowledge of what has been published and reviewed in the field, explaining that he has a sense of "what is done and what can be done." Emerson emphasized that medicine is in the midst of a paradigm shift – "*everything* will be recast in the stem cell mode." For example, without understanding stem cell biology, "we won't cure cancer." In the future, doctors may be able to give a stroke victim a drug that will regenerate his brain cells. Furthermore, said Emerson, scientists need to work with *embryonic* stem cells to understand *adult* stem cells. Emerson's figures on the stem cell lines that are currently available for research were even lower – and bleaker – than Caplan's: "17 non-infected lines that are aging."

Like Caplan, Emerson also spoke to the matter of economics. "In Philadelphia, biomedicine is our main engine for the economy," he said, adding, "it would be an enormous, enormous mistake" not to support embryonic stem cell research. If the state did not, there would be a negative impact on the next generations of local scientists as well. He referred to Penn's achievements in research, but argued that it would be difficult to recruit young scientists who could go to institutions in states or nations that supported stem cell research. And when Rep. Babette Josephs (Philadelphia) raised concerns about the role of corporations that might be interested only in "the profit line," Emerson replied that the nation needs "open research" on stem cells – in *universities*.

Rep. Josephs has introduced a bill in the Pennsylvania House that would authorize research in the state on "human embryonic stem cells, human embryonic germ cells, and human adult stem cells from any source." ●

Unquiet SLUMBERS

By Martha Ledger

As they treat thousands of troubled sleepers a year, clinicians and scientists at Penn are learning more about the mysteries of sleep.

Sometimes you just get lucky. In 1995, reporter George Beschen was assigned to write a story for HUPdate *that saved his life. The piece was about the Penn Sleep Center and focused on obstructive sleep apnea, because the disorder accounted for 70 percent of patient visits. Beschen witnessed an overnight sleep study and also interviewed, among others, Richard J. Schwab, M.D. '83, G.M.E. '88, now associate professor of medicine, who ticked off a list of risk factors for sleep apnea that included a neck size of 17 inches or greater. Beschen, who is as fascinated by numbers as by words, was struck that the figure was so specific.*

Five years later, when he was 30, Beschen started to feel really tired. "I'd been tired before," he said, "but this was something entirely different. I couldn't keep my eyes open at meetings, and I started thinking this is what it must feel like to be old." He fell asleep once sitting at his desk at work; another time, when he was driving his sister home from the Jersey shore, his eyes started to close and his car momentarily swerved off the road.

Beschen had put on 30 pounds since 1995 and now weighed 230 pounds. He snored heavily, and his neck size grew to 17 1/2, then 18. The numbers triggered recollections of his sleep apnea article, and, thinking he might have the disorder, he tape-recorded his sleep.

"It was like learning I was a werewolf at night," Beschen says. "I was making sounds I didn't know I was capable of. I was very clearly gasping and wheezing. Hearing myself choke was bad enough, but then not hearing anything at all was even scarier." He arranged for a sleep study and, on a Tuesday night in March 2000, checked into the Penn Sleep Center.

Dr. Allan I. Pack, director of the Center for Sleep and Respiratory Neurobiology

* * *

Sleep apnea remains the most prevalent disorder treated at PENN Medicine's sleep clinics, still accounting for 70 percent of all patient visits. According to Charles R. Cantor, M.D., clinical assistant professor of neurology and medical director of the center, the clinics' total number of patients has risen 30 to 40 percent annually since 2001, and this year they will see close to 3,500 people with sleep apnea. Given the current obesity epidemic and given that obesity is a risk factor for sleep apnea, this figure should continue to climb. Almost everyone currently diagnosed with this disorder, as well as those in the foreseeable future, will receive a mechanical treatment invented 25 years ago. It successfully controls the disorder but does not seem particularly on the cutting edge when compared to the new surgical techniques and breakthrough drugs used to treat disorders in other specialties.

Photographs by Maureen Helwig, except where noted.

Yet what has advanced in sleep medicine – and dramatically so – is an understanding not only of sleep apnea, but also of the related mechanisms of normal sleep and wakefulness. Pioneers in a specialty that was recognized only a decade ago by the American Medical Association and only two years ago by the Accreditation Council for Graduate Medical Education, Penn researchers have illuminated both the specific problem of sleep apnea and the fundamental questions about the nature and function of sleep. In just the past few years, their discoveries have opened up new areas for investigation that will likely lead to new and improved treatments.

The motor for this collaborative machine is a research entity called the Center for Sleep and Respiratory Neurobiology (CSRN). The first of its kind in the country, it was founded in 1991 when William N. Kelley, M.D., then the dean of the School of Medicine and CEO of the Health System, was actively promoting multidisciplinary centers. Its 45 or so current members include physicians who work at the Penn Sleep Center, clinical and basic science researchers in the Division of Sleep Medicine, and clinical investigators from associated medical specialties like cardiology, genetics, and neuroscience. In addition, the CSRN serves as an umbrella for basic science researchers from various University schools and departments who are studying sleep behaviors or sleep chemistry. The research unit also provides lecture series, seminars, retreats, compilations of abstracts for international dissemination, mentoring for students, trainees, and young faculty members, and opportunities for joint scientific projects. It is one of only three Specialized Centers of Research in Neurobiology of Sleep and Sleep Apnea funded by the National Institutes of Health..

In varying combinations, CSRN members have published the findings of hun-

Dr. Richard J. Schwab can predict sleep apnea as quick as a wink.

SCREENINGS

Richard J. Schwab, M.D. '83, G.M.E. '88, associate professor of medicine, can look in my mouth and pretty well predict whether I've got sleep apnea. He's not so sure other doctors can because, except perhaps for a single lecture, medical schools do not teach students how to screen for the disorder. He was never taught how, yet he believes it takes just a little practice. Of course, he has done such screenings for his whole clinical career and has carried out research that involved volumetric measures of the structures that form the upper airway.

Schwab can also make an accurate prediction without the peek inside — and in 30 seconds or less. "You use four features: two physical findings and two questions," he says. "The physical findings you can determine in an instant: Is the patient overweight? Does the patient have a receding chin -- retrognathia? As soon as they're inside the door, you have this information.

"And then you ask them two questions. Do they snore? And are they sleepy

during the day? If you have positives on a minimum of two of the four, you should ask more questions related to sleep apnea and potentially think about a sleep study."

A more comprehensive survey for determining who is likely to have sleep apnea was developed by Greg Maislin, M.S., M.A., adjunct assistant professor of statistics in the Division of Sleep Medicine. Called the Multi-Variable Apnea Prediction Index, it makes its calculations based on a combination of symptoms, body size, age, and gender, and it now in use worldwide.

Whatever the tool of choice, Schwab emphasizes that screening is important, because sleep apnea is widely underdiagnosed, especially in patients with diabetes, hypertension, coronary disease, and stroke.

"Often patients feel like they've had a brain transplant after they're treated for apnea," Schwab says. "It's one of the few diseases you can actually treat, one where you can actually make a big difference." ■

— Martha Ledger

dreds of successful studies and, in the area of sleep apnea, have developed instruments currently in use worldwide. These include the Functional Outcomes of Sleepiness Questionnaire, the Multi-Variable Apnea Prediction Index, and screening strategies that have been used on commercial drivers. Joan Hendricks, V.M.D., Ph.D., the Henry and Corinne R. Bower Professor of Small Animal Medicine and section chief of critical care in Penn's School of Veterinary Medicine, described the only natural animal model of obstructive sleep apnea — the English bulldog. She also showed that the rest state of the fruit fly (*Drosophila melanogaster*) is analogous to mammalian sleep, providing the entire field of sleep research with a model organism for molecular and genetic studies.

The director of this synergistic enterprise is Allan I. Pack, M.B., Ch.B., Ph.D., professor of medicine, chief of the Division of Sleep Medicine, and director of the Center for Sleep and Respiratory

Dr. Charles R. Cantor

A CPAP (continuous positive air pressure) device at work.

Neurobiology, whose own work reflects the diversity of the center: "I do basic research. I do molecular mechanism of sleepiness. I do patient-oriented research, and I see patients." The focus of his career, however, has been sleep apnea.

The disorder has been on the medical radar screen for a relatively short time. In fact, writers, not doctors or scientists, first took note of it. World literature has many examples of overweight characters who snore their heads off at night and are dead-tired during the day. Pack is fond of Skrymir, a giant from a 13th-century Icelandic saga, whose nighttime snoring wakes the whole forest and whose daytime sleep is so profound that he scarcely feels mallet blows to the head.

A better-known example is Joe, the red-faced fat boy who falls asleep chewing a mouthful of pie in Dickens's 1837 novel *The Pickwick Papers*. In fact, Pickwickian syndrome — described as the combination of obesity and daytime sleepiness — was the name originally given to sleep apnea. Dickens, however, did not portray its most medically significant attribute: the breathless silences that occur between the snores. C. S. Burnett, the researcher who named the syndrome in 1956, missed the mark even more. He studied patients only in the daytime and was unaware of both their snoring and breath stoppage. Burwell wrongly attributed their daytime drowsiness to high blood levels of carbon dioxide. Sleep apnea was clinically described, snoring and all, for the first time in 1965 in Europe. Even then, the medical community paid little attention to it because there wasn't much interest in sleep.

Snoring, which by itself is not a marker for sleep apnea, occurs when the passage of air causes the soft tissues surrounding the upper airway to vibrate. The silences in between snores signal that these structures have collapsed and that a passageway for air has temporarily closed. These stoppages of breath can last for a few seconds or more than a minute. The sleeper awakens, breathes, and falls asleep again, and the cycle repeats itself, potentially for hours. Sleep specialists estimate that people with sleep apnea can lose as much as a third of their nighttime sleep. Even if they spend a proper number of hours in bed at night, they're exhausted the next day.

No wonder, then, that sleep apnea can make daily life a struggle. "The sleepiness is so intense," Pack says, "it makes people do crazy things just to stay awake." One of his patients reported applying ice to himself while driving. Sleep apnea also increases a person's risk for hypertension, myocardial infarction, and stroke. If untreated, severe sleep apnea can be life-threatening.

It also represents a huge public health problem, because sleepy people are more prone to auto and occupational accidents. Canada, Sweden, Great Britain, Australia, and France attribute 10 to 30 percent of auto accidents in their countries to drowsiness resulting from sleep loss or sleep disorders. Sleepiness has also been implicated in notorious disasters, like the *Exxon Valdez* grounding and the Staten Island ferry crash.

Sleep apnea is a prevalent disorder as well, about as common in the total population as asthma. According to the National Sleep Foundation, roughly 5 percent of adults and 2 to 3 percent of children have it. It is often linked to obesity, but anatomical features such as a large tongue, oversized tonsils, or a recessed chin can be risk factors, too. It even afflicts people who seem in good condition, like athletes. In a study of 300 NFL players published in the *New England Journal of Medicine* in 2003, 14 percent were found to have sleep apnea; within that group, 34 percent of the linemen, who are generally the bulkiest players on the field, had the disorder. (Sleep apnea is thought to have played a role in the premature death of Reggie White, former defensive end for the Philadelphia Eagles.) In addition, sleep apnea is a progressive disorder, so neither physician nor patient knows exactly when non-harmful symptoms, like snoring, become clinically significant. An estimated 95 percent of sleep apnea cases are undiagnosed and untreated.

Yet it is treatable. In 1981, Colin Sullivan, M.D., an Australian pulmonologist, invented a device that uses a stream of air to keep the soft tissue structures open. It is called CPAP (pronounced SEE-pap), which stands for continuous positive air pressure. The device consists of a mask that covers the nose and is connected, via five feet of hose, to a machine that generates air pressure. "It sounds crude," Pack acknowledges, "but it is very effec-

tive, and it meant we had a treatment." Oral devices and surgeries are also sometimes prescribed if CPAP treatment fails, or if patients don't want to be chronically under treatment. (Virtually all CPAP users, with the exception of those who lose considerable weight, are lifelong users.) But according to Richard Schwab, the first line of treatment is definitely CPAP. "We have all these new CPAP masks that are much more comfortable than they've ever been," he says. "Most patients — all motivated ones — will be able to tolerate CPAP. In the past, I don't think that was true."

It certainly wasn't. Lots of patients didn't take to CPAP at all, and for good reasons. The machine generates a continuous flow of air, so patients must get used to exhaling against its pressure. (Many current CPAPs have bi-level control, which lessens the air flow during exhalation.) The hose connection restricts movement in bed. For example, patients could not keep turning rotisserie-style into more comfortable positions. In some patients, it causes claustrophobia.

Physicians suspected the masks were being used far less than patients reported. One of the earliest important studies to come out of the Center for Sleep and Respiratory Neurobiology confirmed their doubts. In 1993, the Pack team proved that CPAP was being used much less than patients claimed. Researchers had microprocessors built into about three dozen CPAP units so that machine use could be monitored covertly. It turned out that fewer than half the patients studied met the criteria for regular use.

That finding prompted an awareness campaign to publicize the importance of "adherence," or faithful use. Says Pack, "We developed the adherence monitor, showed what the determinants for adherence were, and made adherence an important part of medical management." As a result, today's CPAP machines have built-in monitoring devices. Patients mail in smart cards or connect the machine's computer chip to a port for downloads by phone modem, or they upload information to a Web site that the physician checks. CPAP fittings also continue to improve. The Penn Sleep Center offers 20 different models, which represent just a fraction of what's on the market.

* * *

It took about 25 minutes for a technician to attach electrodes to Beschen's temples, chin, shins, and behind his ears. He placed two straps around Beschen's torso, taped a monitor to his pointer finger and placed a tube just under his nostrils. While being hooked up, Beschen watched the election returns from Super Tuesday.

At 11:30 p.m., he turned out the lights, and despite all the attached wires and what he recalls was an uncomfortable bed, he quickly fell asleep. The next thing he remembers is the technician saying, "You're not doing too well."

Beschen recalls thinking, he means this is a waste of time, you don't have sleep apnea, get up and go. "Do you mean I don't have it?" Beschen asked.

"No," the technician said, "you have it very bad." He helped Beschen put on a CPAP mask.

* * *

According to Pack, the biggest obstacle to CPAP use is attitudinal. "Patients just don't think this is a major condition." And here's where the research at the Center really kicks in. Study after study — from basic science to clinical — is showing just how potentially serious sleep apnea is.

For example, sleep apnea might irreversibly damage the brain. In experiments on mice, Sigrid C. Veasey, M.D., G.M.E. '91, assistant professor of medicine, has looked at what happens when a normal organism is intermittently deprived of oxygen, as happens to people with sleep apnea during nighttime breathing stoppages. It is already known that when a person's oxygen level goes down-up-down-up, enzyme levels change. The "up" part of the cycle produces a burst of harmful free radicals, those nasty things our high-antioxidant diets are supposed to neutralize. Veasey's mice, which were normal, showed a significant increase in total sleep time in the weeks following the experiment, as well as an increase in REM sleep. She finds this abnormal behavior consistent with damage to the brain's arousal systems that produce neurotransmitters and to other forebrain neurons important in wakefulness. In other experiments with normal mice,


Dr. Sigrid C. Veasey

Veasey has shown that intermittent reduction of oxygen also causes damage to upper airway motor neurons. The upper airway is already compromised in sleep apnea — the tissues already collapsing — and oxidative damage here would suggest that, without treatment, the disorder is going to get progressively worse.

Sleep apnea might also be contribute to Type-2 diabetes and coronary disease. Gary Foster, Ph.D., associate professor of psychiatry, is looking at the role of sleep apnea in "metabolic syndrome" — the combination of Type-2 diabetes, hypertension, and obesity. In a national, multi-year study of 4,500 people who have this syndrome, researchers are trying to determine if weight loss improves their cardiovascular outcomes. In a supplemental

Tommy Leonardi

Dr. David F. Dinges

study, Foster had the group tested for sleep apnea. The prevalence was staggering: 92 percent. It was actually hard to find anyone who didn't have it. And 40 percent had sleep apnea that was considered severe. The questions to answer now: How much of the cardiovascular risk from obesity is related to sleep apnea? And does sleep apnea contribute in some way to diabetes or to glucose control in patients with Type-2 diabetes?

Basic science research, much of it now focused on molecular mechanisms, has shown some of the chemical effects caused by the absence of sleep. Essential substances are not produced; others build up and are not neutralized or degraded. The person with sleep apnea is absorbing all these bodily insults.

* * *

When Beschen woke up in the morning, the technician showed him a printout of his sleep. Before CPAP, it was filled with jagged peaks. "It looked like a seismographic reading of an earthquake," Beschen recalls. From the point where he put on the mask, it read almost as a straight line.

"I took to it immediately," Beschen says. "I adapted to it so well that eventually I could even sleep on my stomach and wear very little of the actual harness. I didn't wear the headpiece, just the strap that went around the back of my neck. I grew to accept the sound of the machine and the restriction as part of going to sleep. It actually helped me separate from wakefulness."

* * *

Clinicians who treat sleep apnea have long noticed that some patients on CPAP have no daytime sleepiness while others continue to suffer from it. They noticed, too, that even when patients had equally severe cases — which they determined by measuring the number of breathing stoppages during sleep — some were sleepy during the day, and some were not. About two years ago, Penn researchers were able to explain these differences. More important, their work opened up a whole new line of investigation. It was as if a form inside the block of wood the scientists had been carving suddenly became visible.

The experiments were done by Hans P. A. Van Dongen, Ph.D., research associate professor of sleep and chronobiology, and David F. Dinges, Ph.D., professor of psychology in psychiatry, chief of the Division of Sleep and Chronobiology, and director of the Unit for Experimental Psychiatry (all within the Department of Psychiatry). They showed that healthy people differed greatly in the magnitude of their response to a night without sleep, and that they differed in exactly the same way on each occasion that they were deprived of sleep and retested.

In carefully controlled experiments, Van Dongen and Dinges kept subjects awake and tested the degree of their impairment, using, among other indicators, the highly sensitive psychomotor vigilance test that Dinges developed in 1985. The researchers kept bringing the subjects back for testing while varying the amount of sleep they gave them the week before the test. What they discovered is that an individual's response to sleep deprivation is extremely consistent. If you had almost no response to the deprivation the first time, you would have the same lack of response the next time, regardless of how much sleep you lost the week before. And if your response was an order of magnitude worse, you had *that* response every time. "In other words," Dinges says, "it was trait-like – which makes it look like it's genetic."

As he puts it, "This is one of the most exciting, also provocative, things we've ever uncovered."

They also found that lack of sleep exaggerated inherent differences. "The more you keep people awake," Dinges says,

Elena Nikonova, M.D., a postdoctoral fellow

"the more different they become from each other in their functioning. When they're alert, they're different, but the difference is only units. If you keep them awake, the differences keep getting bigger and bigger."

Dinges explains: If they were to keep people awake for more than 40 consecutive hours — a day, a night, and a day — everybody would become impaired. But within the range of "normal" sleep deprivation — a student pulling an all-nighter, a truck driver adding miles to make his trip more profitable, a pilot on a long-distance flight, a soldier during combat

operations — individual differences become clear.

Their experiments also showed that vulnerability to impairment differs depending on what skill is being tested. People were not crashing across the board, but doing so selectively. "It may mean that different parts of the brain in different people are differentially vulnerable," says Dinges. "So some people are very vulnerable in their memory when they don't get sleep. Others have trouble sustaining attention and vigilance, and others feel exhausted. And all combinations are possible, too.

Van Dongen and Dinges's findings on "inter-individuality" quickly prompted other researchers to confirm whether the response to sleep deprivation is in fact genetic. The customary route is to test a trait in both identical and fraternal twins. If sleep-deprivation vulnerability is genetic, the identical twins, who have the same set of genes, should test more like each other than do the fraternal twins. Pack and Samuel T. Kuna, M.D., G.M.E. '79, chief of pulmonary, allergy and critical care at the Philadelphia Veterans Affairs Medical Center and director of its Regional Sleep Center, have launched just such a study of 80 twin sets. They are depriving sets of identical and fraternal twins of sleep and comparing their scores on the psychomotor vigilance test, as well as their brain-wave patterns during recovery sleep. After testing 40 twin sets, Kuna reports that the preliminary results "seem to indicate that performance on the reaction time test is more similar in identical twins than in fraternal twins, suggesting that this may indeed be a heritable trait."


Dr. Samuel T. Kuna

Pack has designed another study that seeks to identify the genes related to sleep apnea. This work is being done in Iceland, where the population has extraordinarily favorable characteristics for genetic studies. First of all, the people are largely homogeneous: almost everyone living there now has been bred from an original mix of Viking men and Gaelic women. Little immigration has occurred since the island was settled between the 9th and 12th centuries. Second, the Icelanders created and have maintained detailed genealogical records. A company called DeCode Genetics has set up a vast data base through which Pack can identify who is related to whom. A colleague of Pack in Iceland has compiled a list of 1,650 people there using CPAPs. Pack can enter the name of a person with sleep apnea (kept confidential through protective identifiers) and have the program put together a list of all relatives (second cousins or closer, for example) who also have the disorder. The other critical aspect of the design is that 60 percent of the Icelandic population has given DNA to be genotyped. As Pack explains: "You have the sequences across the genome. You have basic information on the DNA. The idea is that if you and I are related and if we have the same medical condition, there's going to be some part of that genome that you and I are going to share much more in common than we do with the rest of the population."

Richard Schwab, who for many years has done magnetic resonance imaging and electronic beam computed tomography of upper airway structures, is also taking part in the genetic study in Iceland. Previously he showed that people with sleep apnea have smaller upper airways because their upper airway structures — tongue, uvula, lateral muscles — are generally larger. This finding suggests anatomic risk factors for sleep apnea.

He plans to do 600 MRIs of Icelandic patients with sleep apnea. Then, combining the information from these studies with the genealogical data base and DNA profiles, he hopes to uncover genes for intermediate traits, such as a large tongue. He expects multiple genes to be involved. The findings, he says, will "solidify the case for anatomic risk factors and lead to new screening strategies for patients with sleep-disordered breathing."

As Pack sees it, such screening would be valuable for high-risk groups in general, such as commercial drivers or individuals with new-onset coronary artery disease. "Through this investigation, we also hope to identify new targets for therapeutic intervention," says Pack. "Whether this will be achieved easily or not will depend on the nature of the genes."

* * *

Beschen used his CPAP device faithfully from March 2000 to August 2004. There were only one or two nights that he didn't use it.

He continued to gain weight, though, eventually reaching 245."I ignored my food allergies," he says. "The CPAP allowed me to indulge. It was like a crutch. It will give me sound sleep, I thought, no matter what I do."

In November 2003, Beschen started a diet he designed for himself, mostly based on what he had read about white flour and sugar, but also with some input from his sister, who is a nutritionist and herbalist. By September 2004, he had lost 65 pounds. He was able to go off medications he was taking for high blood pressure and for an allergy.

His nighttime breathing had become normal – and he put his CPAP unit away. ●

How Do Otters Remain Sleek and Warm? Or, What One Cell Biologist Does Away From the Bench

By Karen Kreeger

Micrograph of river otter underhairs.

John W. Weisel, Chandrasekaran Nagaswami, Rolf O. Peterson; NRC Research Press

Otters spend a considerable amount of time cavorting in water. But unlike polar bears, seals, dolphins, and whales, river otters do not have a thick layer of body fat to keep them warm. They are, in fact, remarkably sleek. How do the otters manage this apparent contradiction? Some recent research by a Penn scientist and his team has demonstrated that otters rely on a few unique adaptations — namely, their fur and the densely packed layer of specially adapted underhairs.

Using scanning electron microscopy and polarizing light microscopy, John W. Weisel, Ph.D., professor of cell and developmental biology at the School of Medicine, examined the structure of these hairs for clues to their exceptional insulation qualities. What he and his colleagues found is that the cuticle surface structure of the underhairs and the base of the less-abundant guard hairs are distinctively shaped to interlock: the wedge-shaped fins or petals fit into the wedge-shaped grooves between fins of adjacent hairs. Weisel's team reported its findings in the May 1, 2005 issue of the *Canadian Journal of Zoology.*

Weisel and Chandrasekaran Nagaswami, M.D., a research specialist in Penn's Department of Cell and Developmental Biology, usually work on defining the physical properties of blood clots. They apply this knowledge to find better treatments for heart disease. But two years ago, Weisel, who has long been an avid hiker, climber, and white-water kayaker, took a month of his sabbatical year to study wolves – a life-long interest of his – on Isle Royale National Park in Lake Superior, Michigan. While he was there, he also collected hair samples from the island's mammals, including wolves, moose, and otters.

Isle Royale has been a training ground for many ecologists, and lessons learned there were useful for re-introducing wolves

to Yellowstone National Park. But Weisel's scientific background was different. "While we have engaged molecular biologists in studies of animal genetics and isotope dynamics, John is the first structural molecular biologist that we have worked with," says Rolf Peterson, a wildlife biologist from Michigan Technological University, who has spent the last three decades doing field research on Isle Royale.

Once back in his lab at Penn, Weisel made use of his extremely powerful tools to examine the hair of wolf prey. His plan was to identify the diet of wolves by studying wolf scat. When he began, he had no inkling that he would find anything unusual about otter hair.

"Most hair from animals has a distinctive pattern, which is how we can distinguish one species from another," says Weisel. "But otter hair is so different that it caught my attention." The fins of one hair loosely insert into the grooves between fins of an adjacent hair, thus permitting the hairs to form a web-like pattern that keeps water from the otter's skin and decreases heat loss. The researchers also found that the grooves between fins trap air bubbles, which help increase the thermal insulation of the otter's coat. Indeed, biologists have observed otters actively blowing air bubbles into their fur while grooming, and their energetic rolling catches air in their fur. As Weisel puts it, "The air insulates like a down jacket."

Besides their playfulness, otters are also known for their constant grooming. This behavior is another important aspect of an otter's heat-conserving abilities. In addition to the interlocking structure of the underhairs, these hairs are coated with a thin layer of body oil from the otter's sebaceous glands. That layer provides another barrier to water. The fins of the underhairs are also aligned away from the body, which is consistent with the direction in which otters run their paws through their hair during this process of self-grooming. That way, their claws do not get caught on the fin-like projections.

Weisel is continuing these studies of mammal hair in his spare time. Already, he has returned to Isle Royale once since his sabbatical, doing radio telemetry of radio-collared wolves and collecting samples of their scat for DNA analysis.

"I discovered that it can be very enjoyable and stimulating to expand your scientific horizons beyond the familiar, and even get to take a 'busman's holiday' in a beautiful place with wonderful people," says Weisel of his experiences away from the bench. "There are still a great many new things to learn, but some approaches and ideas from one field can be useful in another." ●

Meanwhile, Back at the Lab . . .

In June, a team of Penn scientists led by John W. Weisel, Ph.D., published a paper describing the microscopic mechanical properties of blood clots. They used "laser tweezers" to measure the elasticity of individual fibrin fibers in clots. The "tweezers" is essentially a laser beam, which they focused on a microscopic bead "handle" that is attached to the fibers. Then they were able to pull on the fiber in different directions.

Clotting is the body's first defense against damage to the blood vessels. Clots are a three-dimensional network of fibrin fibers, stabilized by another protein called factor XIIIa. A blood clot needs to have the right degree of stiffness and plasticity to stem the flow of blood when tissue is damaged. Yet it must also be digestible enough by enzymes in the blood so that it does not block blood flow and cause heart attacks and strokes.

As reported in the online edition of the *Proceedings of the National Academy of Sciences* (28 May 2005), the investigators found that the fibers, which are long and very thin, bend much more easily than they stretch. That finding suggests that clots deform in flowing blood or under other stresses primarily by the bending of their fibers.

Weisel likens the structure of a clot composed of fibrin fibers to a microscopic version of a bridge and its many struts. "Knowing the mechanical properties of each strut, an engineer can extrapolate the properties of the entire bridge," he explains. "To measure the stiffness of a fiber, we used light to apply a tiny force to it and observed it bend in a light microscope, just as an engineer would measure the stiffness of a beam on a macroscopic scale."

According to Weisel, by understanding the microscopic mechanical properties of a clot, researchers may be able to make predictions about clot physiology. For example, when clots are not stiff enough, problems with bleeding arise, and when clots are too stiff, there may be problems with thrombosis, which results when clots block the flow of blood.

"If we can change a certain parameter, perhaps we can make a clot that's more or less stiff," says Weisel. For example, various peptides or proteins (such as antibodies) bind specifically to fibrin, affecting clot structure. The idea would be to use such compounds in people to alter the properties of the clot, so it can be less obstructive and more easily dissolved.
— K. K. ●

The Knife That Isn't a Knife

By Nicole Gaddis

Addison Geary 2005

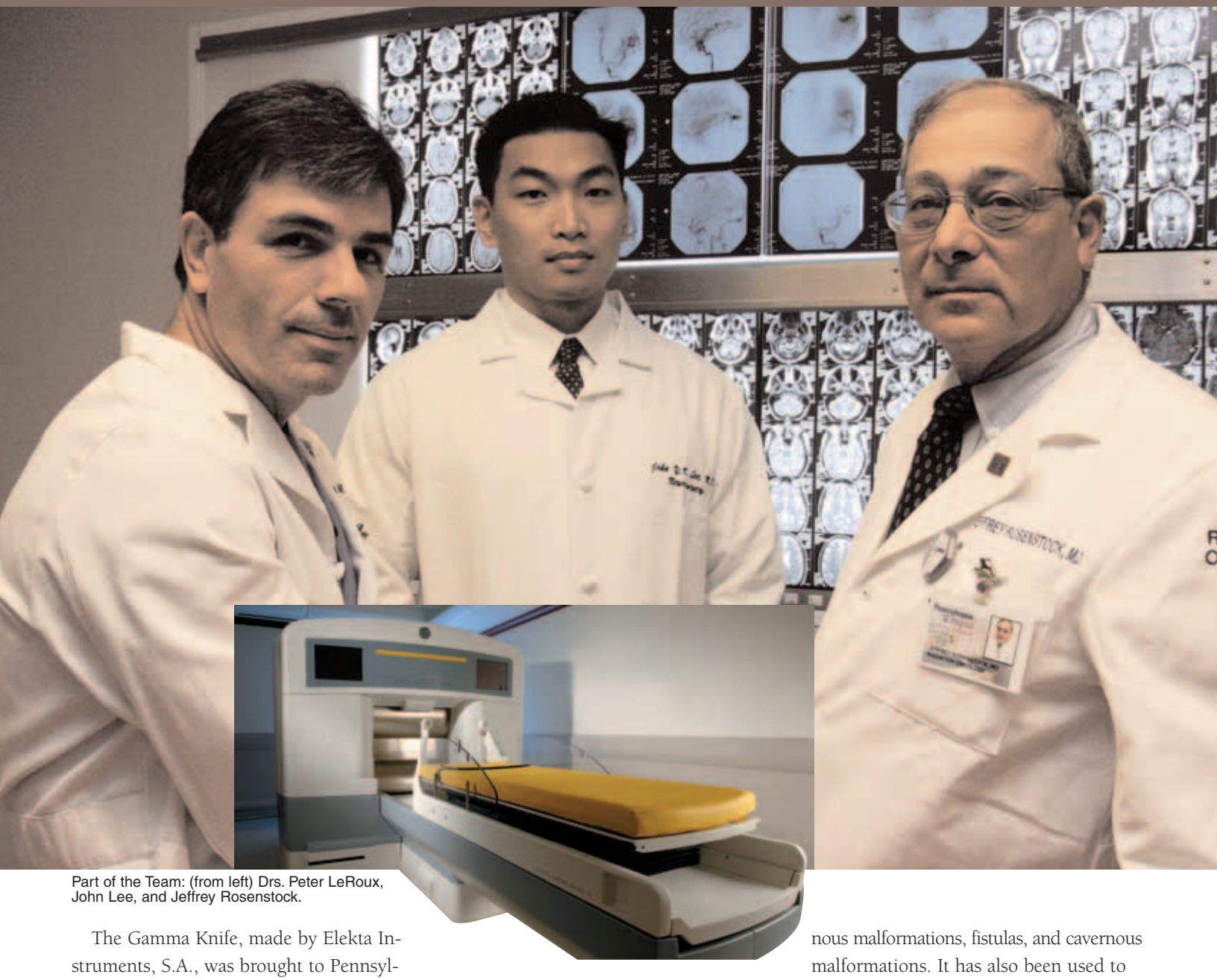
Delivery in Progress: The Gamma Knife arrives at Pennsylvania Hospital.

At first glance, it looks deceptively like your garden-variety CT scanner. It's only the collection of 350-pound "helmets" lined up against the wall and the black "safety line" running across the floor that tells you that this is quite a different beast. Welcome to the Penn Gamma Knife Center at Pennsylvania Hospital, where an expert, multidisciplinary team uses 201 finely tuned beams of radiation to treat brain lesions, tumors, and venous malformations.

Developed by Lars Leksell, a Swedish physician and neurosurgeon, in 1968, the Gamma Knife is a stereotactic device that uses multiple radioactive cobalt sources to destroy discrete anatomical regions in the brain while minimizing the effect in surrounding tissues. The device that was installed at Penn's Center is one of only ten of the latest-generation models in the country. It uses a robotic attachment to accurately position the patient within the device based on coordinates developed by the treatment team. In addition, the model Penn is using is faster, allowing surgeons to cut treatment times in half. Patients generally require only local anesthetic and mild sedation for a procedure, and many can go home an hour or so after treatment is completed. It's outpatient brain surgery, with no pain and no incision. And because there are no incisions, there is no risk of infection, bleeding, or other possible complications that come with cutting into the skull and exposing the brain.

"The Gamma Knife is a powerful and versatile complement to our existing neurosurgery services," explains Peter LeRoux, M.D., vice chair of neurosurgery for Penn's Health System. "This will give patients a much wider range of treatment options and will make many inoperable tumors and lesions quite treatable."

Weighing in at 20 tons, a powerful and versatile tool will help neurosurgeons accomplish the most delicate procedures.

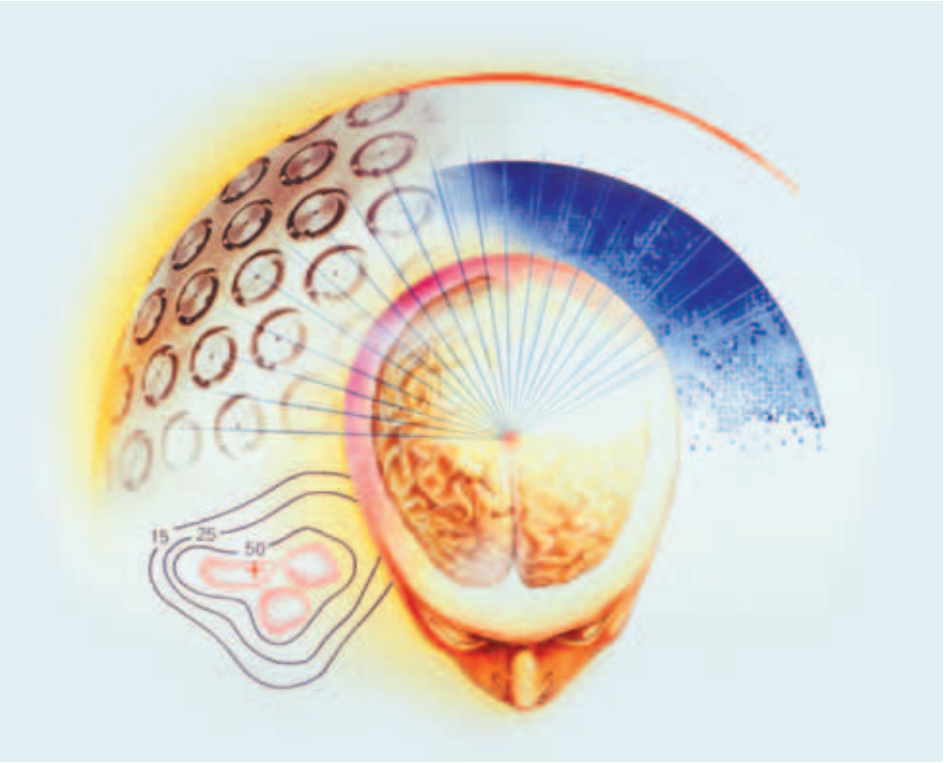


Part of the Team: (from left) Drs. Peter LeRoux, John Lee, and Jeffrey Rosenstock.

The Gamma Knife, made by Elekta Instruments, S.A., was brought to Pennsylvania Hospital in rather spectacular fashion in the early morning hours in September 2005. Spruce Street was closed as specialists brought the 20-ton unit through an 8 feet by 10 feet section of the exterior wall of the hospital's Spruce Building and carefully nestled it into a concrete-encased vault, 19 feet by 24 feet, that took three months to build. Because of the Gamma Knife's tremendous weight, the vault is supported by 14 pilings that plunge 80 feet down into solid bedrock. Penn's is the only Gamma Knife center in the U.S. that is located not in a basement but in an attractive, patient-friendly center on the ground floor. The location is not only convenient for patients and physicians, but also makes it much easier to replace the cobalt source once it has reached its half-life.

Besides being able to treat a range of malignant and benign brain and skull base tumors, the Gamma Knife can also treat vascular disorders such as arteriovenous malformations, fistulas, and cavernous malformations. It has also been used to treat facial pain (such as trigeminal neuralgia), epilepsy, and severe, disabling tremor caused by essential tremor or Parkinson's disease. Symptoms often resolve in a few weeks after treatment.

"Precision is paramount," notes John Lee, M.D., medical director for the Gamma Knife Center. Lee came to Penn after being part of the Gamma Knife team at the University of Pittsburgh Medical Center, where the device made its U.S. debut. "If we damage brain tissue, it stays damaged," he says. "Aiming customized doses of ra-



diation is safer – and more effective – than using open-brain surgery or whole-brain radiation. There's also a much lower risk of side effects such as paralysis and cognitive problems."

"Precision is paramount," says John Lee, M.D., medical director for the Gamma Knife Center. "Aiming customized doses of radiation is safer – and more effective – than using open-brain surgery or whole-brain radiation."

This precision comes not only from the technology of the Gamma Knife itself, but also the expertise of the neurosurgeons, otorhinolarygnologists, radiation oncologists, specialized nurses, and physicists who work together to develop the patient's treatment plan. A patient who comes to the Center is fitted with a lightweight stereotactic head frame that allows the physicians to pinpoint the area to be targeted by radiation while keeping the patient stationary. Detailed images of the target site in the brain are created using magnetic resonance imaging (MRI), computed tomography (CT), or angiography.

"Since we're sending individual beams of radiation to the target site, we essentially superimpose a series of overlapping 'soap bubbles' approximately the size of the site," says LeRoux. "We have a choice of four helmets that can surround a patient's head and are attached to the stereotactic frame." According to LeRoux, the helmets allow individual beams of radiation either 4mm, 8mm, 14mm, or 18mm in diameter to pass through. "We may use more than one helmet during a treatment period in order to best target the tumor or lesion while preserving healthy tissue."

Unlike other neurosurgical procedures, Gamma Knife radiosurgery does not require cutting or shaving the patient's hair. Once the patient is reclined comfortably on the device's couch and the helmet is in place, he is moved into the dome section of the Gamma Knife. The physicians administer the radiation from the control room, and this is where the complexity of the Gamma Knife system also becomes elegant: beneath two screens, which allow the physicians to monitor the patient in the treatment room, lies a single gray control panel that has a microphone and three simple buttons. Only one button needs to be pushed to begin treatment, and only one button is required to stop treatment. The system's software takes care of the rest.

One of the advanced features of the Gamma Knife used in Penn's health system is the built-in audio and video system, which allows physicians to see and talk to patients throughout the procedure. Just as important from the patients' perspective, the system allows them to speak to the physicians.

"The radiation does not actually remove diseased tissue," Lee explains. "It damages individual abnormal cells: brain tumor cells lose their ability to multiply, blood vessel malformations close off. The cells eventually stop growing and then begin to shrink. And these effects continue over time."

The treatment itself usually lasts an hour, and patients typically can go home the same day. "The most amazing thing about the surgery is its minimally invasive nature," says LeRoux. "Patients can have complex brain surgery during the day and then enjoy dinner that same night." The center's team monitors progress over the next year through regular imaging procedures (MRI, CT, angiography).

"Gamma Knife stereotactic radiosurgery is a successful, powerful technology with a proven 30-year track record," says Lee. "It offers new hope to patients with neurological conditions, ranging from tumors to epilepsy and movement disorders, that were once considered hopeless."

Startling that a behemoth can be such an elegant solution as well. ●

Treating THE DEADLIEST Brain Tumors

Researchers at the Hospital of the University of Pennsylvania are studying the effectiveness of a novel way to deliver drugs to extend the lives of people with Glioblastoma Multiforme (GBM), the most common and aggressive form of primary brain tumors. In this approach, the drugs attack only cancerous cells in the brain. "It is one of the largest and most comprehensive clinical trials ever conducted to identify new and more effective treatments for recurrent GBM," says Kevin D. Judy, M.D., associate professor of neurosurgery at Penn and the study's principal investigator of the Penn component of the trial. There are approximately 50 hospitals across the nation participating in what is called the PRECISE trial. Penn's Health System is the only study center in the region.

Treatment options to prevent the rapid recurrence or progression of the Glioblastoma Multiforme tumor are very limited. GBMs have a tendency to intermingle with the normal brain tissue that surrounds the main tumor, and some cancer cells can remain undetected and scattered throughout the brain tissue that surrounds the tumor site. In addition, most tumors grow back close to the cavity that is left after the removal of the main tumor; the cancerous cells may also invade membranes that cover the brain or may spread to the spinal fluid surrounding the brain.

Radiation has been the most effective therapy for these tumors, but the inherent resistance to radiation therapy and the risk of damaging the adjacent normal brain tissue limits its overall efficacy. GBMs are intrinsically resistant to most chemotherapy, and very few drugs cross the natural barrier present in the blood vessels of the brain (the blood-brain barrier). Even drugs that work in the laboratory and in animals cannot reach the tumor cells within the brain. These factors mean that only one form of chemotherapy for this type of tumor has been approved by the Food and Drug Administration. There are two forms of delivery, by vein or by local biodegradable wafers. The impact of these approved therapies, although statistically significant, increases survival in patients with this deadly tumor by only a few weeks.

On the other hand, preliminary results from the PRECISE trial show great promise. The study drug, IL13-PE38QQR (or cintredekin besudotox), is a combination protein that consists of two parts: a tumor-targeting molecule made from a human protein (Interleukin 13, or IL13) and a cytokine (a kind of "chemical messenger" protein), which allows the drug to bind to tumor cells that contain the IL13 receptor. Like a key to a lock, the cytokine binds to the receptor and allows the study drug to enter and potentially kill the tumor cells. Normal brain cells do not have an IL13 receptor, so the study drug does not bind to them.

The drug is administered using convection-enhanced delivery. A surgeon places from two to four small catheters in the patient's brain. Then a pump slowly pushes the drug solution through the catheters. Once in the brain, the drug attaches to the remaining tumor cells, but not to normal brain cells. "The way the drug is distributed is a very important component of this study," says Judy. "The placement of the catheters is the key to get the drug distributed in the right areas to kill those stray cells."

Patients in the study are randomly assigned to one of two groups: two-thirds receive the study drug and one-third receives FDA-approved chemotherapeutic "wafers" after the tumor is removed. The GLIADEL Wafer contains BCNU (carmustine), an approved chemotherapy drug used to treat brain tumors. During treatment, the surgeon places up to eight of the dime-sized wafers soaked in BCNU in the cavity created after removal of the tumor. The wafers slowly dissolve (over two to three weeks), releasing BCNU to the brain surrounding the cavity. GLIADEL typically extends the patients' median survival by eight weeks.

The median survival rate for 97 patients on the study drug almost doubled from 26 weeks to 44 weeks. Several patients have survived for more than three years, and the FDA has granted the drug the rare fast-track designation to accelerate its approval. NeoPharm, Inc., based in Lake Forest, Ill., is funding the PRECISE trial and supplies the cintredekin besudotox, which was developed in the FDA's Laboratory of Molecular Tumor Biology. ●

— Kate Olderman, with Nicole Gaddis

AN EYE

Crimson Aspen

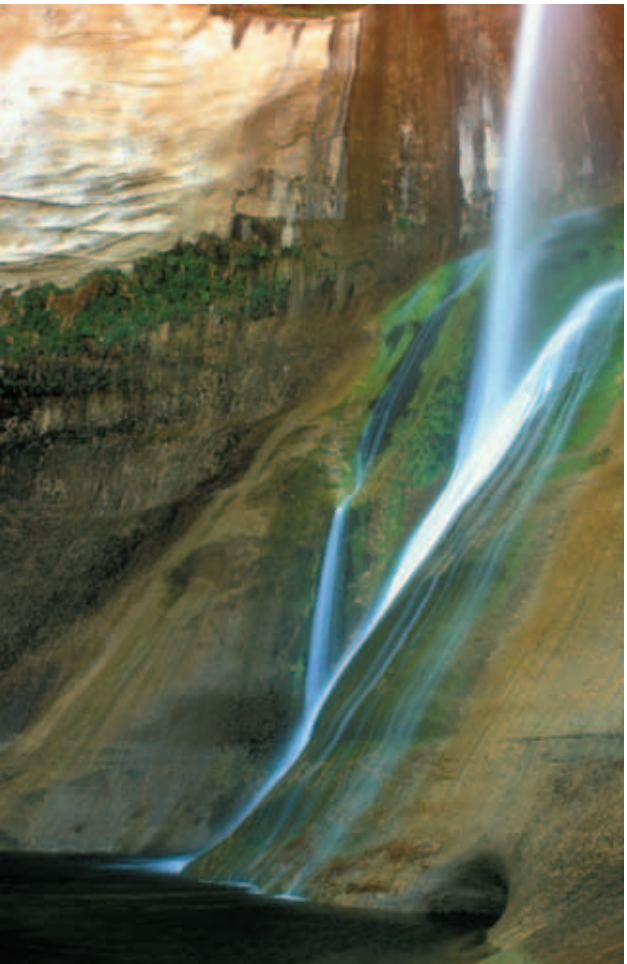
North Lake

Mist Meadow

FOR NATURE

"In the field I'm in, there's a lot of radiology, which is really a form of photography, in which we're analyzing images and looking for forms and shapes."

Cascade



As a specialist in pulmonary problems who is often called in for difficult cases, Morris Swartz, M.D., spends a good part of his day on alert. A clinical associate professor of medicine at the School of Medicine, he is director of pulmonary diagnostic services and respiratory services at Penn Presbyterian Medical Center. He frequently provides evaluations for shortness of breath, asthma, chronic obstructive pulmonary disease, lung nodules, sacroidosis, and other interstitial lung diseases. So when does he find time to pursue his love of photography?

"It's very hard," he says. "The only time I can really do this is when I disappear, when I go away. My job takes so many hours, and weekends are spent with family."

In this case, disappearing for Swartz means using vacation time for a photography trip into what he calls "beautiful, unspoiled nature." His usual equipment for the trip has been a Canon EOS 35 mm camera, Fuji Velvia slide film, and a Gitzo tripod. The sites he has visited include the Great Smokey Mountains National Park in Tennessee, Yosemite National Park, northern Arizona and southern Utah, as well as New Hampshire. And despite the relaxing surroundings, he remains on alert – for a landscape that inspires him. The fruits of Swartz's trips into the natural world were shown in "Earth Tones – Landscape Photography," an exhibition this fall at the Burrison Gallery of the University's Faculty Club.

Although the surroundings are very different, Swartz can find some similarities between photographing nature and working as a pulmonologist. "In the field I'm in, there's a lot of radiology, which is really a form of photography, in which we're analyzing images and looking for forms and shapes. But the real creative part of photography — the part where I use the right side of my brain – I don't get to use a lot while at work." Still, he points out, there are many "technical aspects in photography similar to the detail work that I do as a doctor."

But the technical aspects, for Swartz, are not the primary ones: "My photography is a real form of relaxation." And, he reports, his patients enjoy the photos that he displays in his practice. •

FOCUS ON FOUNDATIONS

The current group of RWJ Clinical Scholars at Penn gathered in November to present their findings on "young men in wheelchairs." Front row, from left to right: Joanna Starrels; Aliya Esmail; Peter Ehrenkranz; and Kristen Feemster. Back row: J. Sanford Schwartz, co-director of the program; Lucy Wolf Tuton, one of the program's faculty members; Melissa Times; Patrick Conway; Reena Duseja; Tara Lagu; and Eunice Franklin-Becker, managing director of Penn's program.

Foundations play an important role in advancing medical knowledge, by establishing endowed professorships, underwriting research, and creating new education programs. They range from national organizations with missions as broad as "improving health care" to small family foundations focused on a single disease or purpose. At PENN Medicine, foundations contributed $27.6 million in gifts and grants in Fiscal Year '05. Here we share with you the impact that three foundations – one national and two local – have had recently on the School of Medicine.

RWJ Clinical Scholars Learn to Translate Research into Results

The School of Medicine is one of only four sites in the country chosen to host the Clinical Scholars Program of the Robert Wood Johnson Foundation (RWJF), which helps young physicians learn to conduct health-services research. The highly prestigious two-year program, entering its fourth decade, has been hosted at different groups of universities over the years, including Penn from 1974 through 1996. Now, as the program has become more focused, the number of host universities has been limited to four – and Penn is again among them.

"In 2002, RWJF reformed the program, establishing the goal of producing individuals who could conduct meaningful, multidisciplinary research in collaboration with community organizations, and translate that research into real world results," explains Harold I. Feldman, M.D., M.S.C.E. '86, G.M.E. '91, professor of medicine and of epidemiology and director of the Division of Epidemiology, who serves as co-director of the program.

The Foundation, whose mission is to improve the health care of all Americans, was started by Robert Wood Johnson, founder of Johnson & Johnson. RWJF has awarded close to $4 billion to health care-related projects and programs since 1995. Its current president and CEO, Risa Lavizzo-Mourey, M.D., M.B.A. '86, was a Clinical Scholar at Penn in the mid 1980s.

Real World Results, Right Away

As one of their first assignments, the class of eight Clinical Scholars devoted much of last summer to a group project that was defined as broadly as possible: Look at young men in Philadelphia who are confined to wheelchairs and come up

with a recommendation to improve their quality of life.

"There were many lessons in this exercise," notes Feldman. "There's a lot of paradigm shifting going on as the Scholars transition from their residency – they were guided immediately away from the medical arena to a community context, setting the stage for them to look at health care through lenses outside of medicine."

After meeting with both representatives of community organizations and individuals in wheelchairs, the Scholars identified crucial issues and developed a concept to address several of them: affordable, accessible housing; meaningful employment; mentoring; and a sense of community. They presented the strategy to the Mayor's Commission on People with Disabilities under the name "Wheelworks." The program would employ and train young people in wheelchairs to design and perform home modifications, drawing on the skills of wheelchair-bound tradespeople who would train and serve as mentors.

One of the organizations the Scholars consulted was Magee Rehabilitation, which serves people in Philadelphia disabled by spinal cord injury, brain injury, stroke, orthopaedic injury, or amputation. Pat Thieringer, director of Magee's community programs, says that Magee is already acting on one of the Scholars' recommendations. They called attention to the lack of a single centralized source of information on resources for the wheelchair-bound, and Magee is now redesigning its website to address that need.

Thieringer is also interested in exploring the feasibility of launching Wheelworks or a similar program at Magee.

In addition to providing training for the Clinical Scholars, the group project was also intended to help them bond as a cohort. Peter Ehrenkranz, M.D., M.P.H., G.M.E. '05, one of the Scholars, says, "I was impressed by how quickly everyone jumped in and contributed their particular expertise – we come from different specialties, have worked with different populations, and have varied ways of looking at problems."

The Scholars, Present and Past

This year's class of Clinical Scholars, trained in the nation's top medical programs, comprises Ehrenkranz, Patrick Conway, Reena Duseja, Aliya Esmail, Kristen A. Feemster, Tara Lagu, Joanna Starrels, and Melissa Times. Like Ehrenkranz, Feemster and Lagu hold master's degrees in public health in addition to their M.D. degrees. The Scholars' specialties include internal medicine, pediatrics, surgery, and emergency medicine, and their diverse research interests include:

- Policy-driven research around emergency departments
- The impact of media on nutritional choices and the prevalence of obesity in children
- Barriers to HIV education and treatment services experienced by immigrants
- The effects of homelessness and neighborhood environments on children's health and access to health services
- The impact of existing pharmacy policy on disadvantaged communities.

The Scholars are joining an impressive club. For more than 30 years, some 900 physicians have participated in the Clinical Scholars program. Many of the 93 alumni of Penn's program have risen to leadership positions in academic medicine, government, health-care systems, foundations, and the

Penn and the Clinical Scholars Program: "A Real Congruence"

What made Penn such a strong competitor this time? J. Sanford Schwartz, M.D. '74, G.M.E. '78, co-director of the program, cites several factors. (A professor of medicine and of health management and economics, he participated in the program in the late 1970s.) "By any measure, we are one of the top institutions in health-services research and clinical epidemiology – and that is a direct outgrowth of having the CS program here for 20 years – and we were able to put together a remarkable set of committed community partners." Penn is also particularly strong in multidisciplinary education and collaboration. That strength, notes Schwartz, was vividly illustrated during the Foundation's site visit.

"All of our schools are represented in the Clinical Scholars faculty," says Schwartz. "At the site visit presentation, it was obvious that we all knew each other well, that we truly are collaborative; you can't fake that. I think the visitors sensed an extraordinary commitment to the program and everything it stands for throughout the university. There's a real congruence between what the Clinical Scholars program is about and what Penn is about."

The program's associate directors illustrate its collaborative nature. Joshua P. Metlay, M.D., Ph.D., a research associate in health-services research and staff physician at the Philadelphia Veterans Affairs Medical Center, serves as the program's associate director for veterans' affairs. Donald F. Schwarz, M.D., M.P.H., M.B.A. '87, also a former Clinical Scholar, will lead the program's community partnership advocacy activities. Schwarz is vice chair of Penn's Department of Pediatrics, as well as chief of the Craig-Dalsimer Division of Adolescent Medicine and deputy physician-in-chief at The Children's Hospital of Philadelphia.

FOCUS ON FOUNDATIONS

private sector. Among them are:

- David J. Brailer, M.D., G.M.E. '91, Ph.D. '92, National Coordinator for Health Information Technology, U.S. Department of Health and Human Services
- Raynard S. Kington, M.D., G.M.E. '88, Ph.D. '91, deputy director, National Institutes of Health (NIH)
- James L. Mills, M.D., M.S.C.E. '79, chief, Pediatric Epidemiology Section, NIH
- Risa Lavizzo-Mourey, M.D., M.B.A. '86, president and CEO, The Robert Wood Johnson Foundation; former Director of Penn's Institute on Aging and former Sylvan Eisman Professor of Medicine
- Gary Gottlieb, M.D., M.B.A. '85, president, Brigham and Women's Hospital
- Elliot J. Sussman, M.D., G.M.E. '80, M.B.A. '81, president and CEO, Lehigh Valley Hospital and Health Network
- Neil R. Powe, M.D., M.P.H., M.B.A. '86, director, Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins Medical Institutions
- Sankey V. Williams, M.D., G.M.E. '77, chief, Division of General Internal Medicine, University of Pennsylvania; Sol Katz Professor of General Internal Medicine; former director of Penn's RWJ Clinical Scholars Program
- Mitchell J. Blutt, M.D. '82, M.B.A. '87, president, Beta Advisors (an investment firm focused on health care); former executive partner, J. P. Morgan Partners LLC; PENN Medicine trustee.

"When you look at the graduates of this program at Penn, what's surprising is that the preponderance of them have made — are making — substantive contributions to improving the health of the public in some way," says Schwartz. "It would be hard to find another program that has had that kind of impact."

Jonathan A. Epstein, M.D.

The W.W. Smith Charitable Trust Supports Medical Research

For nearly 30 years, until his death in 1976, William Wikoff Smith led the Kewanee Oil Company, which was founded by his great grandfather, Joseph D. Potts, in 1871. Potts was one of the most prominent figures in Philadelphia in the 1880s and was asked to join Penn's board of trustees in 1886; both of his sons attended the College. Smith's will created The W. W. Smith Charitable Trust, which focuses its contributions, primarily locally, on meeting essential human needs, providing scholarships, and supporting medical research.

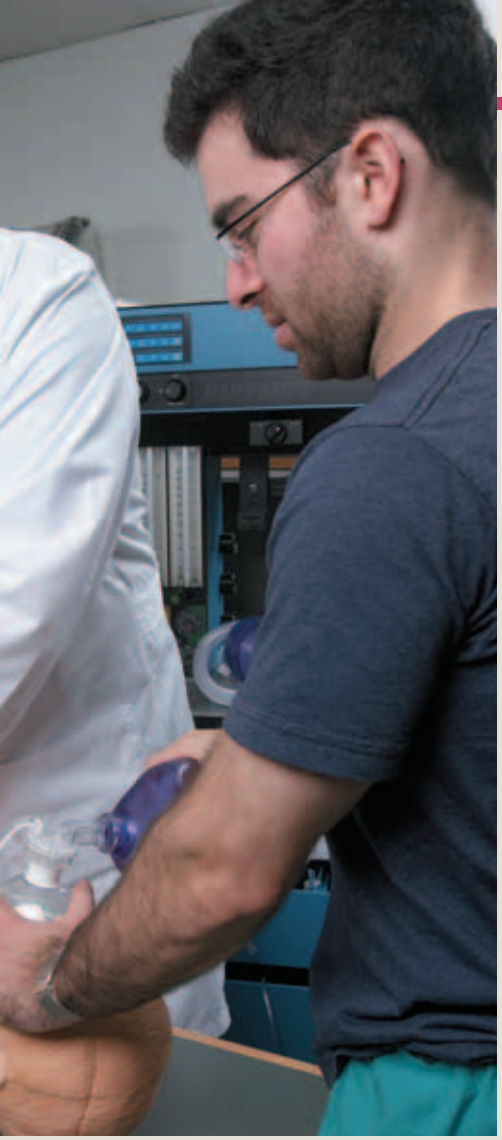
Over the past 25 years, the Trust has supported many Penn undergraduates and helped PENN Medicine scientists conduct research in cancer, AIDS, and heart disease. One of its grants was awarded to Jonathan A. Epstein, M.D., for his early research into the causes of congenital heart disease. Now one of the world's premier investigators in the field of molecular cardiology, Epstein is professor of cardiovascular medicine and director of the Penn Molecular Cardiology Research Center. When the Trust generously decided to establish the William Wikoff Smith Chair in Cardiovascular Research at Penn, the University provost recognized Epstein's outstanding research by appointing him the first holder of the professorship.

Andrew Kofke, M.D., M.B.A., left, tries out a simulation
Kofke, director of neuroanesthesia, also directs the

Benjamin and Mary Siddons Measey Foundation Funds Simulation Center

In 1958, as a memorial to his parents, William Maul Measey established the Benjamin and Mary Siddons Measey Foundation, whose purpose is to fund medical education initiatives in the Philadelphia area. Over the past few years alone, the Measey Foundation has funded several million dollars' worth of scholarships, fellowships, and professorships in the School of Medicine and supported its M.D./Ph.D. program, the FOCUS program for women in medicine, and programs in global and community medicine.

Two recent contributions are particularly noteworthy. With a $1 million gift, the Foundation established the Measey Medical Simulation Center, whose high-



model with Brian Ash, a fourth-year medical student. Measey Medical Simulation Center.

fidelity simulation models (nicknamed "Ben") and task simulators will allow medical students to practice many common medical procedures before they treat actual patients. The Measey Center also makes it possible to simulate and rehearse multi-faceted scenarios, including emergencies, that involve teams of health professionals.

A second million-dollar gift provided funding for the Clyde F. Barker – William Maul Measey Professorship in Surgery, which honors the Foundation's founder and Clyde Barker, M.D., chair of Penn's Department of Surgery from 1983 to 2001. Barker did pioneering work at Penn in transplantation, surgical oncology, laparoscopic surgery, surgical immunology, and gene therapy. He also directed the Harrison Department of Surgical Research for many years.

RECENT GIFTS

PENN Medicine trustee **Raymond Perelman, WEv '40**, and his wife, **Ruth Caplan Perelman**, have contributed $25 million to name "The Raymond and Ruth Perelman Center for Advanced Medicine." (See Vital Signs, page 2)

The Abramson Family Foundation continues to support research into the causes of and cures for cancer, contributing $10 million as part of its $100 million pledge for the Abramson Family Cancer Research Institute. **Madlyn Abramson** is a trustee of PENN Medicine.

With their leadership gift to the Perelman Center for Advanced Medicine, **Dr. Henry A. (M.D. '62) and Barbara McNeil Jordan** have created the Jordan Center for Gynecology in the Abramson Cancer Center. Dr. Jordan is a PENN Medicine trustee.

Jack and Rebecca Benaroya have committed $2.5 million for The Benaroya Parkinson's Program Fund, which will support research by John Q. Trojanowski, M.D., Ph.D., and Howard Hurtig, M.D., to discover new drug therapies and identify biomarkers for earlier diagnosis of Parkinson's Disease.

Dr. Sankey and Senator Connie Williams have contributed $2 million to create the Leon Hess Professorship in Internal Medicine in honor of Senator Williams's father. Dr. Williams is chief of Penn's Division of General Internal Medicine and the Sol Katz Professor of General Internal Medicine.

The Bingham Trust has made a $1 million grant to the Institute on Aging, which will fund pilot research initiatives in the field of aging and support new faculty entering the field.

With a $1 million gift to the Perelman Center for Advanced Medicine, **Stanley and Janet Zolot** have dedicated the Yetta Dietch Novotny Mammography Center within the Abramson Cancer Center.

To make a gift to PENN Medicine, or for more information, please contact the Office of Development and Alumni Relations, 3535 Market Street, Suite 750, Philadelphia, PA 19104-3309, 215-898-8094.

ALUMNI EVENTS

You can find out more about these and other upcoming events at http://www.med.upenn.edu/alumni

March

- Sunday, March 5, 2006, Academy of Dermatology Reception, San Francisco
- Tuesday, March 7, 2006, PENN Medicine on the Road, Palm Beach, Fla.
- Friday, March 10, 2006, Orthopaedic Surgery Annual Alumni Cocktail Reception, Chicago (at American Academy of Orthopaedic Surgery Meeting) – RSVP to Barbara.Weintraub@uphs.upenn.edu
- Saturday, March 11, 2006, The Orthopaedic Rehabilitation Association Specialty Day, Chicago – Register at www.aaos.org

April

- Tuesday, April 4, 2006, Elizabeth Kirk Rose Women in Medicine Dinner, Philadelphia
- TBA, Helen O. Dickens Dinner, Philadelphia
- Tuesday, April 25, 2006, PENN Medicine on the Road, Dallas
- Wednesday, April 26, 2006, PENN Medicine on the Road, Houston

May

- **Save the Date! May 12-14, 2006 is Medical Alumni Weekend.**
- TBA, Academy of Obstetrics and Gynecology Reception, Washington, D.C.
- TBA, American Urological Association Reception, Atlanta

Progress Notes

Send your progress notes to:
Jason B. Bozzone
Associate Director of Alumni Outreach and Reunions
PENN Medicine
Development and Alumni Relations
3533 Market Street, Suite 750
Philadelphia, PA 19104-3309

'50s

Rody P. Cox, M.D. '52, G.M.E. '56, Dallas, Texas, was recently nominated as a laureate of the Texas Academy of Internal Medicine, the Texas Chapter of the American College of Physicians. He is now a teaching attending physician and an active member of the faculty of internal medicine at University of Texas Southwestern (UTSW) and recently received the Aesculapius Award from the UTSW-St. Paul house staff for his teaching. He is recognized as a leading expert in maple syrup urine disease.

Ronald B. Berggren, M.D. '57, G.M.E. '61, Galena, Ohio, emeritus professor of surgery at Ohio State University, received the John C. Gienapp Award from the Accreditation Council for Graduate Medical Education (ACGME) for lifetime contributions to the Council and to graduate medical education. He has served on Council for more than 20 years and has been chair of its Institutional Review Committee, its Residency Review Committee for Plastic Surgery, and its Monitoring Committee. He has also been chair of the Council's board of directors.

Billy W. Long, M.D., G.M.E. '57, a member of Gastrointestinal Associates in Jackson, Miss., since 1981, was cited in the most recent "Best Doctors in America" survey. When Long is not performing more than 2,000 procedures annually, he makes medical mission trips to Guatemala, Belize, and Honduras. He was part of a team that built a hospital in Guatemala about six years ago. A former assistant professor of medicine at Penn, Long has also worked at the National Institutes of Health.

'60s

Doris G. Bartuska, M.D., G.M.E. '68, emeritus professor of medicine at Allegheny University of the Health Sciences, was one of five honorees at the First Health Sciences "Distinguished Service Awards" presented this fall by Wilkes University, where she earned her undergraduate degree. She served as a Special Fellow in Molecular Medicine for the National Institutes of Health and is a former president of the American Medical Women's Association and of the Philadelphia County Medical Society. In 1988, she was one of seven women honored by the Commonwealth of Pennsylvania for outstanding contributions to the state and the nation. Bartuska is also featured in a traveling exhibition titled "Changing the Face of Medicine," which examines the achievements of women in medicine. The exhibition can be accessed at the web site of the National Library of Medicine.

Frederick S. Keller, M.D. '68, the Cook Professor of Interventional Radiology and director of the Dotter Institute at Oregon Health & Science University, became the only practicing physician at OHSU to have an endowed chair established in his name. In August, the Cook Group Inc., manufacturers of medical devices, donated $2.5 million to create the Frederick S. Keller Chair of Interventional Radiology Endowment Fund. Keller received another recent honor when he was only the second American to be named a distinguished fellow at the Cardiovascular and Interventional Radiological Society of Europe. The honor, which he received at the organization's annual meeting in September in Nice, France, is given each year to individuals who have shown leadership in the field of interventional radiology. "Many medical devices used in interventional radiology are developed in the U.S.," says Keller, "but clinical trials on these devices are often first conducted in Europe, so the sharing of information is paramount." Keller also received the Gold Medal of the Society of Interventional Radiology in April 2005. He has been chairman of the Department of Diagnostic Radiology in the OHSU School of Medicine since 1992.

Andrew C. Von Eschenbach, M.D., G.M.E., '68, director of the National Cancer Institute, was appointed interim director of the Food and Drug Administration by President Bush. He is a former chair of urology at the University of Texas M. D. Anderson Cancer Center.

'70s

Jeffrey C. Oram-Smith, M.D. '71, G.M.E. '78, Colorado Springs, Colo., was named chief medical officer for Penrose-St. Francis Health Services. A general, vascular and trauma surgeon, he has been active in the Penrose system since 1980 and has been a partner with the Colorado Springs Surgical Associates since 1981.

Frederick P. Rivara, M.D. '74, M.P.H., the George Adkins Professor of Pediatrics at the University of Washington, has been elected to Institute of Medicine of the National Academies. He is the only new member from the State of Washington. Rivara has studied methods to control injuries, specifically in such areas as bicycle and pedestrian injuries, motor vehicle injuries, and alcohol-related trauma injuries. His current interests include examining the cost-effectiveness of trauma care, the impact of domestic violence on women and children, and the effectiveness of interventions in childhood and adolescence on later health outcomes. His goal is to focus public policy attention on implementing programs that can have a long-term impact on the health of children and adults. Rivara is head of the Division of General Pediatrics at the University of Washington, a faculty member of its Child Health Institute, an attending physician at Children's Hospital and Regional Medical Center and Harborview Medical Center, and a faculty member at the Harborview Injury Prevention and Research Center.

Richard H. Goodman, M.D.'76, Ph.D., director of the Vollum Institute at Oregon Health & Science University, has been elected to the Institute of Medicine of the National Academies. Goodman is also professor of cell and developmental biology and of biochemistry and molecular biology at the Oregon Health & Science University School of Medicine. His laboratory focuses on determining how extracellular and intracellular signals are integrated to control the onset and level of gene expression. Last December, Goodman's lab published a technique, developed in collaboration with scientists at Brookhaven National Laboratory in Upton, N.Y., and State University of New York, Stony Brook, for characterizing a family of genes regulated by the "cAMP response element binding" protein, or CREB. The molecule is among a group of proteins called transcription factors that interact with regulatory elements in DNA that are responsible for increasing or decreasing the level of gene expression in cells. In 2002, Goodman was elected to the National Academy of Science.

'80s

Stephen L. Comite, M.D. '82, is the co-author of three papers published earlier this year in a peer-reviewed dermatology journal, *Dermatology Online Journal*. The initial paper discussed a new non-invasive technique that uses massagers to produce vibration as a way to lessen the pain associated with certain dermatology procedures such as Botox injections for which local anesthesia may not be sufficient. The paper is the first in peer-reviewed dermatology literature, and one of the first papers in all of the medical literature, that contains movies showing the techniques involved. The second paper was an editorial discussing this innovative method of presenting medical information in a refereed Internet journal. The third paper discussed the use of a new filler, Radiance (recently renamed Radiesse), to cosmetically restore the faces of certain patients with HIV who suffer from a condition known as facial wasting or lipoatrophy. Comite is affiliated with

the Department of Dermatology at Mount Sinai Medical Center and has a private dermatology practice in midtown Manhattan.

David D. Lo, M.D. '86, Ph.D., is a member of the Department of Developmental Immunology at the La Jolla Institute for Allergy and Immunology. His research focuses on the development of the mucosal immune system and on the regulation of CD4 T cell responses. Director of Neurome's Vaccine Technology Division, he has served on numerous NIH review committees. He is editor-in-chief of *Current Immunology Reviews*. Author of more than 120 scientific articles, he was a featured speaker in November the University of California at Riverside's Health Sciences Initiative, where his topic was "Dual-use Weapons: Genes Regulating Both Tissue Development and Immunity."

Obituaries

Ralph W. Stevens, M.D. '33, Walla Walla, Wash., a retired ophthalmologist; May 27, 2004.

Gerald C. O'Neil, M.D., G.M.E. '39, Littleton, Colo.; April 17, 2005. O'Neil obtained both his B.S. and M.D. degrees from Creighton University, then received his Master of Medical Science degree from the University of Pennsylvania in 1938. He served his residency at Penn and performed medical research toward the measles vaccine. His pediatric practice spanned from 1940 to 1983. He served two terms as president of the staff of Children's Memorial Hospital in Omaha, Nebraska, and was on the teaching staff at Creighton School of Medicine and the University of Nebraska Medical Center.

Seymour F. Ochsner, M.D. '40, Metairie, La., former chairman of radiology and radiation oncology at the Ochsner Clinic in New Orleans; May 28, 2005. During his senior year at Penn, he contracted pulmonary tuberculosis. With limited treatment options at the time, he "endured 39 months of strict bed rest, read a few hundred books," as he once put it, and earned his medical degree several years later. He took his radiology residency at the Alton Ochsner Medical Foundation (named after a cousin) in New Orleans. He taught at the Tulane University School of Medicine for 32 years. A former president of the American College of Radiology, he received the College's Gold Medal in 1981. Ochsner also served as president of the American Roentgen Ray Society. The Seymour F. Ochsner Radiology Lectureship was established in his honor at Ochsner in 1999.

Sidney O. Krasnoff, M.D. '42, Philadelphia, a cardiologist and pioneer in the use of computers in medicine; August 15, 2005. In 1943, then an intern, he was called to active duty. He served in Europe, where he set up a mobile army surgical hospital on D-Day and went on to become a captain. He began his medical practice at Einstein Medical Center, where he later served as chairman of the medical staff. He taught at the Graduate School of Medicine of the University of Pennsylvania and at Temple University School of Medicine. He did volunteer medical work in Afghanistan in 1968. A member of dozens of professional organizations, he served as president of the Pennsylvania Society of Internal Medicine in 1960 and of the Philadelphia County Medical Society in 1980. In 1967, he published a pioneering textbook, *Computers in Medicine: A Primer for the Practicing Physician*, which was translated into several languages. Krasnoff retired in 1985 and pursued his love of writing. In 1998, he published *Truman and Noyes: Story of a President's Alter Ego*, a collection of letters between Harry S. Truman and advertising executive David Noyes.

D. Franklin Milam, M.D. '44, G.M.E. '48, Morgantown, West Va.; May 10, 2002. He was former chair of urology at West Virginia Medical Center.

Frederick E. Zimmer, M.D. '45, G.M.E. '49, Fort Myers, Fla., a retired physician; April 27, 2004. After interning at HUP, he was a fellow at the Mayo Clinic from 1949 until 1952. From 1952 until 1985, he was on the staff of the Geisinger Medical Center, where he eventually founded the Department of Endocrinology. He is survived by Cynthia Swartley Zimmer, M.D. '45, G.M.E. '49.

Charles Long II, M.D. '48, a physician who practiced at Cleveland's Highland View Hospital for 26 years; August 8, 2005. He was former chief of physical medicine and rehabilitation at Highland View and held a similar position at the Veterans Hospital in Tampa, Fla., where he retired in 1991. An expert in the treatment of hand injuries, he was an early developer of ways to employ mechanical and electronic devices to allow patients to regain use of their limbs. He was credited with inventing a fiber-optic hypodermic microscope. After serving as an Army medical officer, he moved to Cleveland Heights in 1956 and joined Highland View. In 1962, he traveled to Europe, Africa and India to do research and attend medical forums and work at the Christian Leprosy Mission in Vellore, South India. He also helped develop a clinical engineering laboratory at Highland View, where equipment was built to measure the electrical potential of muscles and custom devices were created to help patients use those muscles. He had been a clinical professor at Case Western Reserve University and at the University of South Florida.

William K. Runyeon, M.D. '48, Wyomissing, Pa., surgeon; June 8, 2005.

Robert L. Tornello, M.D., G.M. '49, Youngstown, Ohio; April 5, 2003.

Harry F. Zinsser Jr., M.D., G.M.E. '49, Bryn Mawr, Pa., emeritus professor of medicine and former chief of staff at Graduate Hospital; August 30, 2005. He earned his medical degree from the University of Pittsburgh in 1939, where he was president of the Alpha Omega Alpha Honorary Medical Society. He enlisted in the U.S. Army Reserves in January 1941. As part of the Surgeon General's Office, he inspected medical bases during the final months of the war in preparation for the invasion of Japan. Upon the Japanese surrender, Major Zinsser was assigned to Gen. Douglas MacArthur's Surgeon General's Staff in Tokyo. After the war, Zinsser was the Chief of Medicine at the Army's 361st General Hospital. In 1947, he moved to Philadelphia to take a research fellowship in the U.S. Public Health Service of the University of Pennsylvania. He was a member of the Penn medical faculty from 1947 to 1982. He also served as chief of cardiology at the University of Pennsylvania's Presbyterian Hospital and chief of cardiology and chairman of medicine at its Graduate Hospital. He is credited with performing the first heart catheterization and first angiocardiography at the University of Pennsylvania, and he designed and donated the first catheterization laboratories at both the Graduate Hospital and the Presbyterian Hospital. A former president of the Pennsylvania Heart Association, he had also served as vice president of the American Heart Association and as vice president of the College of Cardiology. He was an elected member of the American Society for Clinical Investigation.

Fausto M. Prezioso, M.D., G.M. '53, Towson, Md.; November 9, 2004.

Jerry W. Draheim, M.D. '53, Sylvania, Ohio; November 3, 2004. He was the former head of ophthalmology at Toledo Hospital.

Irwin J. Polk, M.D. '53, Mill Valley, Calif.; December 5, 2003. During World War II, he served in the U.S. Army. After completing his medical degree, he practiced pediatrics, then allergy, in New Jersey. He also earned a master's degree in public health from Columbia University. He ended his career in clinical medicine with the pharmaceutical company Hoffmann-La Roche Inc. The author of two books – one on asthma and the other on figure skating – he was once a nationally syndicated medical columnist.

William K. Buchanan, M.D. '54, Hudson, Ohio, anesthesiologist; May 29, 2005.

William E. Riemer, M.D. '54, Miami, Fla., pathologist; October 23, 2003.

Lindley Murray Winston, M.D. '54, Malvern, Pa; August 14, 2005. An advocate of community mental health, he served as a psychiatrist for numerous hospitals and smaller clinics and organizations. These included the Institute of Pennsylvania Hospital, Community Services for Human Growth in Paoli, and Family Service of Chester County in West Chester. He also had a private practice in Philadelphia, West Chester, and Malvern. He was a founding member of the American Association of Community Psychiatrists and received awards from the American Medical Association, the American Psychiatric Association, and the Eastern Pennsylvania Alliance for the Mentally Ill.

William L. Hamilton, M.D. '54, G.M.E. '58, a Philadelphia dermatologist; October 28, 1999.

Herman D. Colomb, M.D. '59, a psychiatrist and medical director of the post-traumatic stress syndrome team at Veterans Affairs Medical Center in New Orleans; October 28, 2004. He took his internship at Lankenau Hospital in Philadelphia and his residency at Pennsylvania Hospital. He served as a lieutenant commander in the U.S. Navy and was director of the Navy psychiatric clinic of Treasure Island, San Francisco. Colomb had been president of the medical staff of Coliseum Medical Center; former vice president of the medical staff of DePaul Hospital; president of the New Orleans Area Psychiatric Association; vice chairman of the Host Committee of the American Psychiatric Association; and former president of the Louisiana Psychiatric Association. A Maitre of the New Orleans Chapter of the Commanderie de Bordeaux, Colomb was elected Mr. Gourmet in 1991 by the Society of Bacchus America.

Joseph Nelson Vizzard, M.D., G.M. '59, Scotts Valley, Calif.; May 19, 2005. After serving as an officer in the U.S. Navy, he practiced medicine in Lafayette and San José for 40 years.

Arthur E. Reinhard, G.M.E. '62, Brooklyn, New York; July 6, 2003. He had been deputy director of medicine at Kingsbrook Jewish Medical Center.

Manuel H. Espinosa, G.M. '69, Easton, Pa.; October 17, 2004.

FACULTY DEATHS

Thomas W. Langfitt, M.D., former vice president of health affairs at the University of Pennsylvania and former president of The Pew Charitable Trusts; August 7, 2005. After earning his medical degree from Johns Hopkins School of Medicine in 1953, he served a second stint in the Armed Forces before completing his residency in neurosurgery at Johns Hopkins. In 1961, he became head of neurosurgery at Pennsylvania Hospital. He moved to the University of Pennsylvania in 1968 and served as chair of its neurosurgery program until 1987. Recognized for his research on the central nervous system, he was credited with advancing the treatment of traumatic brain injury. In 1974, Langfitt became Penn's vice president of health affairs, overseeing the hospital as well as all the health-related schools. He first became involved with the Pew Charitable Trusts as an adviser on their health-related grants. In 1980, he was elected to the board of the Glenmede Trust Company, which handles the assets of the Pew trusts, and advanced to president of both in 1987.Under his leadership, Pew grew into one of the largest charitable foundations in the nation while becoming less secretive and more engaged with its community. Langfitt stepped down as president of Pew in 1994, then served for two years as president of the College of Physicians of Philadelphia. While there, he led the development of an Internet-based medical information system that was designed to improve access to medical data among the poorer communities. Author of more than 200 professional publications, he sat on several medical advisory and editorial boards. He had also been a trustee of New York Life Insurance Co. and what is now GlaxoSmithKline, the pharmaceutical firm.

Harry F. Zinsser Jr., M.D. See the Class of 1949.

A Shining Example

When Arthur Peck, M.D. '52, applied to medical schools in 1948, he received 39 rejections and one acceptance. Initially, Peck was puzzled – his academic record was "unimpeachable," and he was active in many extracurricular activities. Peck suspected that the rejections were based not on his career as a student but on the fact that he was a Jew. In that era, he explains, most American medical schools limited their student bodies to 10 percent racial or religious minorities. Penn was the rare exception.

"I was considered a minority and I was not judged in the same way as other students," says Peck. "Penn gave me an opportunity that changed my life. They judged me on merit, not my religion."

The School of Medicine's dean, Isaac Starr, M.D. '20, eliminated the quota system at Penn, which had required applicants to provide photo identification and answer an extensive questionnaire about their family history. The purpose was to weed out prospective students who might fib about their heritage.

"Penn was a shining example of ethics and morals," says Peck. "The School had a moral compass, and I will always be grateful for that."

A retired psychiatrist who now resides in Tenafly, N.J., Peck has transformed his gratitude into philanthropy. He has established four charitable gift annuities and has allotted a percentage of his IRA to the School of Medicine.

His philanthropic tendencies are a family trait. Peck grew up during the Great Depression with parents who always made it a point to give to their favorite charities, including the Red Cross and the March of Dimes.

"My parents showed me that philanthropy was important by what they said and what they did. They could only give small amounts, but to me, the lesson was clear: philanthropy enriches your life."

Today, Peck's life is enriched by his various civic activities. He serves on Tenafly's library board, and in his spare time, he loves "horsing around" with his five grandchildren.

Dr. Peck's charitable gift annuities helped him find a way to make a significant gift, while obtaining a current income tax deduction and the security of guaranteed, partially tax-free, lifetime payments. His IRA gift will help him avoid its potential 80% reduction by taxes. These are just two of a multitude of creative gift opportunities that benefit both the School of Medicine and its donors. As you chart your financial future, the Planned Giving Office is ready to assist in developing an appropriate strategy. ***Contact Marcie Merz, J.D., Director of Planned Giving, PENN Medicine, 3535 Market Street, Suite 750, Philadelphia, PA 19104-3309, or e-mail: mmerz@ben.dev.upenn.edu.***

Professionalism and Humanism


Robert Clink

As I have told each entering class since becoming dean of this wonderful institution, I firmly believe there is no nobler and more satisfying profession than being a physician. All of us who become physicians have the opportunity to help others, often during their times of greatest need. For all the hard work and the years of education and training involved, being a doctor is among the highest of all callings. Whether we are in a clinic helping an elderly patient during a regular checkup or are on the Gulf Coast helping survivors of a disaster, our efforts are never in vain.

So we must ask ourselves why the popular press and even some of our professional journals seem ready to highlight those instances when doctors perform badly or treat a patient coldly and unprofessionally. Part of the answer, I believe, lies in that last word: *unprofessionally*. Being a physician is a profession. Like all professions, it has a long history and a set of standards that practitioners should embrace. We do not serve our patients or ourselves well when we depart from those standards.

Last summer, a series of articles that appeared in *The New York Times* offered a sobering look at the practice of medicine from the patient's point of view. The titles of the articles gave the gist of the series: for example, "In the Hospital, a Degrading Shift from Person to Patient" (August 16, 2005) and "Sick and Scared, and Waiting, Waiting, Waiting" (August 20, 2005). In the many examples and testimonies in the articles, the focus was not on the *quality* of the treatment but on the *manner* of the treatment, the interaction between patient and physician. Patient after patient spoke of being treated like an inanimate object or a helpless child, whose legitimate questions and pleas for more information were treated cavalierly.

What these news reports tell us is that, despite the efforts of our medical schools, some of our graduates continue to overlook one of the most important aspects of being a physician. Indeed, some may call it the single most important aspect: establishing a genuine relationship with the patient.

At Penn, we are not coasting on our reputation and tradition. During the White Coat Ceremony, which is held for our incoming students at the very beginning of the academic year, our speakers emphasize humanism and professionalism. In addition, one of the very first courses our new students attend is "The Doctor-Patient Relationship: Culture and Communication." As the course description puts it, "Regardless of your mastery of pathophysiology, you will not be able to take a good history from your patients if they do not feel they have established a therapeutic relationship with you." This matter is so important that I have made a commitment to address our new students during this course, and our curriculum emphasizes the doctor-patient relationship throughout all four years. Students must pass "The Doctor-Patient Relationship" in order to continue into the next module of the curriculum.

In this course, one of the things students learn is how to interview patients – which also means how to listen. They also learn that patients don't necessarily mention their most important concerns at first; the practitioner must be able to probe delicately to get a sounder sense of the patient's problems. All in all, the course emphasizes the importance of establishing *trust*.

In recent years, Penn has made increasing use of standardized patients. Taking the role of patient, actors help our students learn the craft – and art – of dealing with the human beings who come to them in need. Because the actors are not actually ill, the students feel less pressure during the interactions. The students deal with fictitious, yet credible, circumstances before they face them in real life. We also believe that the commentary they receive from the standardized patients can be extremely valuable.

Another important step our school has taken in recent years is establishing the Office of the Vice Dean for Humanism and Professionalism. We are one of the very few schools schools to have such a position. Our choice for the first dean was Paul Lanken, M.D., G.M.E. '77, who has long been a champion of those very values. In fact, he was a finalist for the 2001 Humanism in Medicine Award of the Association of American Medical Colleges.

Dr. Lanken has also been our chief liaison with STEP, Strategies for Teaching and Evaluating Professionalism. STEP is a partnership between the American Medical Association and 10 leading medical schools that is working to design innovative methods for educating the next generation of physicians in the competencies that constitute professionalism. The partnership has been an opportunity to share what our School has developed as well as to learn about successful initiatives by our peers.

We sometimes hear that we cannot teach values. Professionalism and humanism are certainly values, but they are also part of our professional code. At Penn, we are committed to providing a well-rounded medical education. ▪

Arthur H. Rubenstein, M.B., B.Ch.
Executive Vice President of the University of Pennsylvania for the Health System
Dean, School of Medicine

"We are all starting to truly realize that the world is much smaller than we anticipated," says Gail Morrison, M.D., vice dean for education. Student interest in international health has been rising steadily. In 2004, the School of Medicine opened its Global Health Programs office. Part of its mission is to go far beyond classroom lectures by offering students the opportunity to immerse themselves in another nation and culture.

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