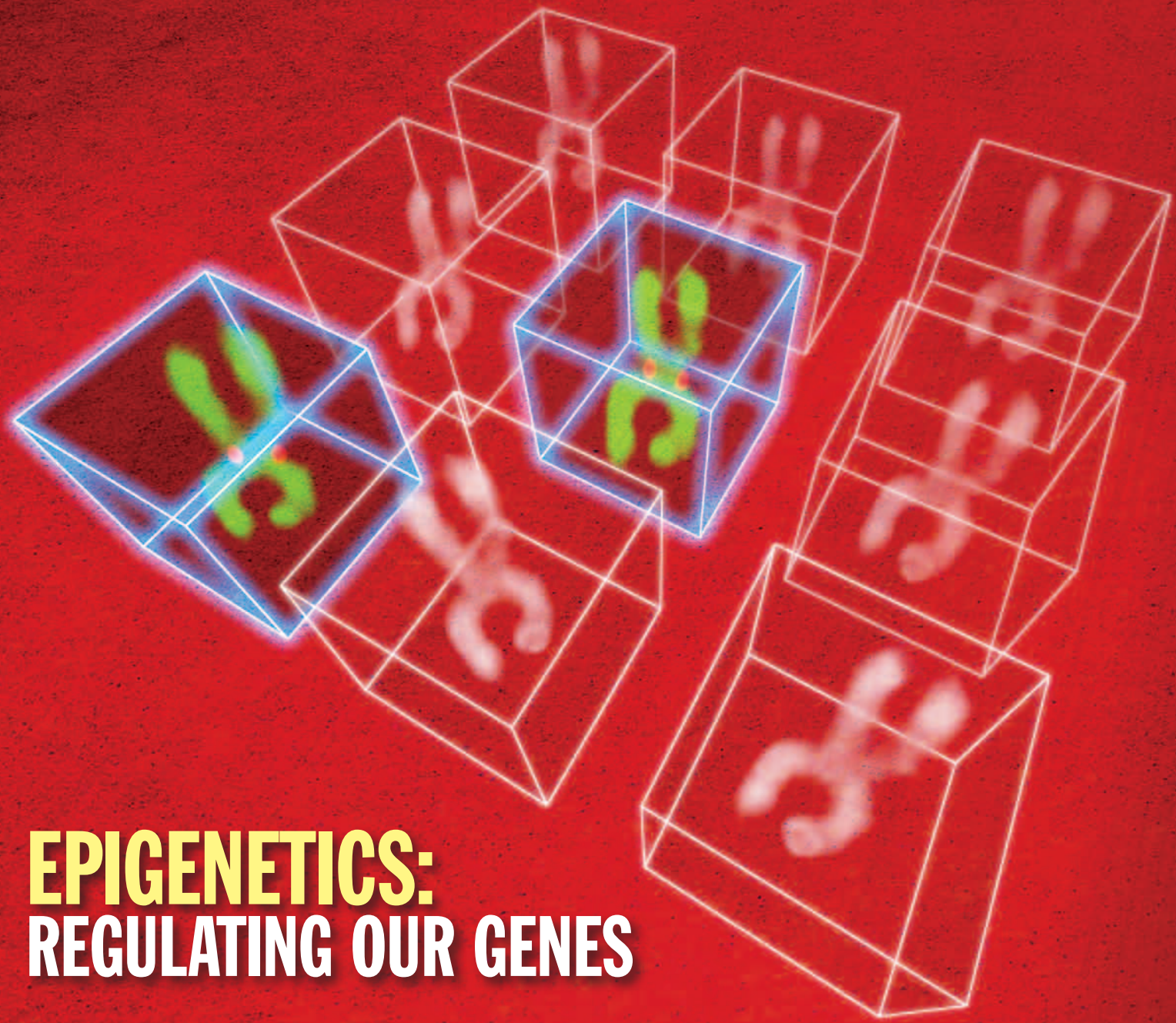
PENN Medicine

SPRING 2012



EPIGENETICS:
REGULATING OUR GENES

HUP's Surgical Team Performs
Its First Bilateral Hand Transplant

Looking Back at "The Doctors' Trial"

The TDP-43 Protein:
When It's Misfolded, Watch Out

Interprofessionalism

Patient care has always depended upon teams. Whether in the outpatient setting, operating room, or the intensive care unit, effective delivery of clinical care requires doctors, nurses, and pharmacists, along with many other members of the health care team (e.g., physical therapists, social workers, respiratory therapists), depending on the needs of a patient. The skills of these team members are distinct and complementary. Few would disagree that teamwork is essential for high-quality outcomes, coordination of care, cost-effective health care delivery, and patient satisfaction. Despite this, we have a tradition of training in silos, making the assumption that teamwork can be learned later – on the job.

For decades, there have been reports and recommendations concerning interprofessional teams as a means to improved patient care. While there has been progress in some clinical environments (e.g., geriatrics, ICUs, and others), it has been challenging to develop models that connect the professions during their formative educational experiences.

This year, the Perelman School of Medicine and the School of Nursing sponsored two symposia on the topic of interprofessionalism. The first symposium, in November, featured Dr. Richard Horton, editor in chief of *The Lancet*, as guest speaker. As Dean Afaf Meleis and I agreed, Dr. Horton was an ideal person to launch the series because *The Lancet* had published one of the most important and most wide-ranging documents in the field: "Health Professionals for a New Century: Transforming Education to Strengthen Health Systems in an Interdependent World" (2010). During his talk, Dr. Horton emphasized the need to do away with the barriers and silos among the health professions, in order to provide better care for our patients. He also argued that increased interprofessionalism was the only way to bring better care to the many areas of the world that have little health care of any sort.

The report in *The Lancet* was based on the work of a committee that included, among others, Dean Meleis; Dr. Harvey Fineberg, president of the Institute of Medicine; and Dr. Jordan Cohen, former president of the Association of American Medical Colleges. While the report acknowledged the significant advances in medicine and health care delivery in the 20th century, the authors noted that those advances have not been shared equitably and that fresh challenges have arisen. According to the executive summary: "Professional education has not kept pace with these challenges, largely because of fragmented, outdated, and static curricula that produce ill-equipped graduates."

In his address, Dr. Horton asserted that "we're on the edge of another revolution" in health care, based not on individual professions (or "tribes," as he put it) but on *need*. "What is it that the patient needs from a health system?" Part of his answer is that collaborative and non-hierarchical teams can best provide what the patient needs.

In Dr. Horton's view, we at the University of Pennsylvania are moving in the right direction. "You have a remarkable institution at Penn," he said, adding that he's never seen "the collaborative spirit" among professions so visible. One of the examples he cited is LIFE (Living Independently for Elders), a service of the Penn Nursing Network. The care team at LIFE is made up of primary care physicians, nurse practitioners, registered nurses, social workers, therapists, personal care workers, and other dedicated staff.

Among the speakers at this year's second event was Dr. Steven A. Wartman, president and CEO of the Association of Academic Health Centers. He pointed out that interprofessional education and practice (IPEP) was conventionally seen as leading to a decreased demand for acute-care services and thus less revenue. But he proposed that the collegiality and efficiency of IPEP would lead to higher quality, if not greater quantity. So far, he said, we don't really know the impact of interprofessional education on our graduates, but he added that there already are highly efficient practice teams working today. What our schools should do, then, is study such teams and "reverse-engineer" more of them.

Dr. Jordan Cohen was the symposium's keynote speaker. Although he said he was excited about the prospects of IPEP, serious obstacles remain and its advocates must gather more evidence of its effectiveness. He also argued that classroom settings were not the best sites for teaching interprofessionalism. Instead, he suggested using simulation centers and standardized patients. Presentations later in the afternoon appeared to support that view.

Even if some of the logistical obstacles can be overcome, there remain long-entrenched attitudes. Or, as Dr. Cohen summed it up, "It's the culture, stupid!" In traditional medicine, he continued, the emphasis was not on "group accomplishments." To promote interprofessionalism in education and practice, leaders must articulate its principles, encourage role models, and visibly award team success.

I agree with Dr. Cohen that furthering IPEP must not happen at the expense of the traditional in-depth education that our different schools have provided for many years. We will certainly continue to need specialists in all fields. The range of caregivers is very broad, and all of them have a place in the total care we give our patients.

Penn Medicine has several recent success stories of its own in the area of interprofessionalism. I was proud that the multi-specialty acute-care unit at HUP was one of the case studies presented during the symposium. It demonstrates how our Unit Based Clinical Leadership initiative has made a significant difference. The UBCLs, established a few years ago, are three-way partnerships that manage quality in our hospital units. Each unit has a physician leader, a nurse leader, and a project manager for quality. Particularly in reducing blood-stream infections, the impact of UBCLs has been remarkable. At the symposium, the three partners were represented by Dr. P. J. Brennan, chief medical officer of our Health System; Dr. Victoria Rich, chief nurse executive of our medical center; and Dr. Patricia Sullivan, vice president of quality and patient safety.

As Dr. Rich explained, these partnerships were created to build greater trust among practitioners, have them learn each other's expertise, and improve communication. "We role-model what we believe in."

Discovering, rewarding, and imitating best practices is essential. So is making sure we have the best structures and the right people in place. Along with Dean Meleis, I am committed to exploring interprofessionalism, to determine whether it can live up to the promise of better outcomes at lower costs. ●

J. Larry Jameson, M.D., Ph.D.
Executive Vice President of the University of Pennsylvania for the Health System
Dean, Perelman School of Medicine

Cover: The images are borrowed from work done by the lab of Ben E. Black, illuminating the epigenetic control of cell division. The green area shows the conventional nucleosomes of the human chromosome, containing the major form of the spool-like histones. The red shows the location of a molecule that plays a key role in how cells and their DNA correctly duplicate.

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Making the Grade – Again

For the third year in a row, the Perelman School of Medicine at the University of Pennsylvania has been ranked #2 in the nation by *U.S. News & World Report* in its annual survey of research-oriented medical schools. This is also the 15th consecutive year that the Perelman School was ranked among the top five medical schools. It was also ranked #11 among schools with a focus on primary care.

According to the *U.S. News* survey, the top five medical schools for research, in order, are: Harvard University; the Perelman School of Medicine and the Johns Hopkins University, tied at #2; Stanford University; and the University of California at San Francisco. The Perelman School also ranked among the nation's top medical schools in five areas of specialty training, including pediatrics (#2), women's health (#4), internal medicine (#5), drug and alcohol abuse (#5), and AIDS (#9).

U.S. News surveyed 126 medical schools and 23 schools of osteopathic medicine. The indicators used include student selectivity admission statistics (MCAT, GPA, and acceptance rate), faculty-to-student ratio, and research activity.

Photograph by Candace diCarlo

Mitchell Schnall has been a leader in imaging and characterizing tumors.

Two Magnets and More

The Hospital of the University of Pennsylvania has been accredited as a Magnet® organization for the second time by the American Nurses Credentialing Center. Magnet recognition, which has become the gold standard for nursing excellence, is bestowed upon less than seven percent of hospitals in the nation.

One month later, Penn Presbyterian Medical Center officially received Magnet status as well. It is the center's first such designation. In an e-mail message, officials of the Health System and PPMC noted: "We are proud of all the accomplishments and changes we've implemented during our journey to providing top-quality patient care and a culture of excellence."

Calling HUP's Magnet recognition "a tremendous honor," Victoria Rich, Ph.D., R.N., chief nurse executive of the University of Pennsylvania Medical Center, said, "We're committed to delivering the highest standard of nursing excellence to our community, and achieving this status for another four years highlights our dedication to providing supreme patient-centered care."

To be re-designated as a Magnet organization, HUP's leadership and staff went through a rigorous and lengthy review process that involved an electronic application and written documentation demonstrating qualitative and quantitative evidence regarding patient care and outcomes. Following approval of the application and documentation, appraisers from the credentialing center also conducted an on-site visit.

Penn Presbyterian also was named one of the nation's top 100 hospitals in the annual 100 Top Hospitals study conducted by Thomson Reuters, a first for Penn Medicine. The study evaluates performances over five years in quality, safety, patient experience, and fiscal operations. There are five separate peer comparison groups, and PPMC was listed among major teaching hospitals.

NCI Grant Funds New Center for Screening Breast Cancer

Penn Medicine researchers have received a five-year, $7.5 million grant from the National Cancer Institute to create the Penn Center for Innovation in Personalized Breast Cancer Screening. The center's team will use clinical, genomic, and imaging information to guide the use of new personalized strategies for breast cancer screening. The goal is to reduce false positive rates and improve outcomes. The research, which also involves experts from medical oncology and psychiatry, as well as colleagues in the Annenberg School for Communication and the Wharton School, will be conducted through August 2016. The team leaders are Katrina Armstrong, M.D., M.S.C.E., professor of medicine, chief of the Division of Internal Medicine, and associate

director of outcomes and delivery in the Abramson Cancer Center, and Mitchell Schnall, M.D. '86, Ph.D., the Matthew J. Wilson Professor of Radiology.

There are three parts to the center's research. First, the researchers seek to improve breast cancer screening by creating a new "breast complexity index" to predict the outcomes of individual screening. Second, the team will also compare the effectiveness of new imaging technology – for example, digital breast tomosynthesis compared to conventional mammography. Third, the researchers will create new strategies for communicating individual estimates of benefits and risks of alternative screening methods to better inform patients and health care providers.

Along with these three projects, the center will study outcome data from a diverse group of 74,000 women who undergo screening for breast cancer at six sites in Penn Medicine's integrated health network.

Sleep Problems May Increase Health Risks

According to a study by Penn's Center for Sleep and Circadian Neurobiology, people who suffer from sleep disturbances are at major risk for obesity, diabetes, and coronary artery disease. Based on a large and diverse sample involving the data of more than 130,000 people, the new research also indicates that general sleep disturbance (difficulty falling asleep, staying asleep, and/or sleeping too much) may play a role in the development of cardiovascular and metabolic disorders. The study was published in the *Journal of Sleep Research*.

"Previous studies have demonstrated that those who get less sleep are more likely to also be obese, have diabetes or cardiovascular disease, and are more likely to die sooner, but this new analysis has revealed that other sleep problems, such as difficulty falling asleep, staying asleep, or even too much sleep, are also associated with cardiovascular and metabolic health issues," said Michael A. Grandner, Ph.D., research associate at the Center and lead author of the study.

The researchers examined associations between sleep disturbances and other health conditions, focusing on the perceived quality of the sleep, rather than just the duration of the sleep. After adjusting for demographic, socioeconomic, and health-risk factors, the researchers found that patients with sleep disturbances at least three nights per week on average were 35 percent more likely to be obese, 54 percent more likely to have diabetes, 98 percent more likely to have coronary artery disease, 80 percent more likely to have had a heart attack, and 102 percent more likely to have had a stroke.

"Now we can clearly show that those who have chronic sleep problems are also much more likely to have chronic health problems as well," said Philip R. Gehrman, Ph.D., assistant professor of psychology in the Department of Psychiatry, clinical director of the Penn Medicine Behavioral Sleep Medicine Program, and the study's senior author. "As a society, we need to make healthy sleep a priority."

The research was funded, in part, by a grant from the National Heart, Lung, and Blood Institute.

Another Step in Treating Inherited Blindness

In February, scientists at the Perelman School of Medicine and The Children's Hospital of Philadelphia published their most recent study on treating Leber's congenital amaurosis (LCA), a retinal disease that progresses to total blindness in adults. Previously, the research team treated only one eye each of the 12 patients in the trial – the one with the worse vision. As described in *Science Translational Research*, the team has now treated three of the adult patients in the eyes that had not been treated. As a result, the patients were able to see better in dim light, and two were able to navigate obstacles in low-light situations. Because the treatment for LCA involves inserting a vector with genes into the eyes, the scientists monitored whether the treatment triggered an immune response that would have cancelled the benefits of the inserted genes. But there were no adverse effects.

"Patients have told us how their lives have changed since receiving gene therapy," said Jean Bennett, M.D., Ph.D., the F. M. Kirby professor of Ophthalmology at Penn, co-leader of the study. "They are able to walk around at night, go shopping for groceries, and recognize people's faces – all things they couldn't do before. At the same time, we were able to objectively measure improvements in light sensitivity, side vision, and other visual functions."

The Center for Cellular and Molecular Therapeutics at Children's Hospital sponsored both the initial clinical trial and the current study and also manufactured the vector used to carry the corrective gene. Katherine A. High, M.D., is director of the center. The William H. Bennett Professor of Pediatrics in the Perelman School of Medicine, she is a co-author of both studies.

There was even an unexpected benefit to the treatment. Testing showed improved brain responses not only in the

newly injected eye, but in the first one as well, possibly because the eyes were better able to coordinate with each other in fixating on objects.

The researchers caution that follow-up studies must be done over a longer period and with additional subjects before they can definitively state that readministering gene therapy for retinal disease is safe in humans. But according to Bennett, the findings bode well for treating the second eye in the remaining patients from the first trial — including children, who may have better results because their retinas have not degenerated as much as those of the adults.

A Possible Target for Treating Hair Loss

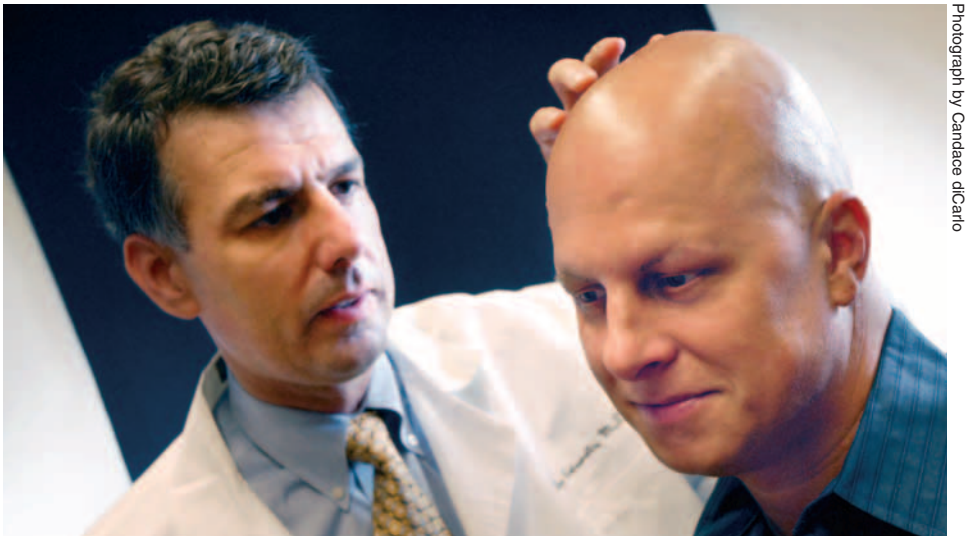
The bald scalps of men with male pattern baldness contain an abnormal amount of a lipid called prostaglandin D2. This discovery by researchers at the Perelman School of Medicine may lead directly to new treatments for the most common cause of hair loss in men. In both human and animal models, the research team found that PGD2 and its derivative, 15-dPGJ2, inhibit hair growth. The inhibiting process related to PGD2 occurred through a protein receptor called GPR44, which is a promising therapeutic target for androgenetic alopecia in both men and women with hair loss and thinning hair. The study was published in *Science Translational Medicine*.

Male pattern baldness strikes 8 of 10 men under 70 years old, and causes hair follicles to shrink and produce microscopic hairs, which grow for a shorter duration of time than normal follicles. The Penn researchers found that levels of PGD2 were elevated in bald scalp tissue at levels three times greater than what was found in comparative haired scalp of men with androgenetic alopecia. When PGD2 was added to cultured hair follicles, the hair treated with PGD2 was significantly shortened, while PGD2's derivative, 15-dPGJ2, completely inhibited hair growth.

As George Cotsarelis, M.D., chair of the Department of Dermatology and senior author on the study, told *Science News*, "Prostaglandins often have a yin and a yang." One may stimulate hair growth, but another might stop it.

Future studies may involve testing topical treatments to block the GPR44 receptor – potentially blocking PGD2 and halting the balding process.

The lead author of the new study is Luis Garza, M.D., Ph.D., a former postdoctoral fellow at Penn who is now at Johns Hopkins. Cotsarelis and Garza are co-inventors on a patent owned by the University of Pennsylvania that describes the PGD2 pathway as a target for inhibiting hair loss.



Photograph by Candace diCarlo

George Cotsarelis examines the scalp of Steve Wlodarczyk.

Funding Renewed for Musculoskeletal Disorders Center

Researchers at the Perelman School of Medicine at have been awarded another five-year, $3.2 million grant from the National Institutes of Health to continue the programs of the Penn Center for Musculoskeletal Disorders. Penn is one of five institutions in the nation with this Center award and the only one of the three up for renewal in the cycle to be re-funded. NIH reviewers gave Penn's center a perfect "ten."

The center, based in Penn's Department of Orthopaedic Surgery, aims to enhance and advance the research productivity of investigators in the broad topic of musculoskeletal tissue injury and repair. It also provides a pilot and feasibility internal grant program, seminars, and other educational programs for researchers.

An estimated 28,000,000 Americans report musculoskeletal injuries each year. "Carpal tunnel syndrome, rotator cuff injuries, osteoarthritis, osteoporosis, and low back pain are just a few of the injuries and disorders that affect a large portion of the population," said Louis J. Soslowsky, Ph.D., the Fairhill Professor, vice chair for research in the Department of Orthopaedic Surgery, and director of the Penn Center for Musculoskeletal Disorders. "Musculoskeletal disorders dictate whether, and for how long, a person can continue working at their job and/or when it's necessary to begin home health care or nursing home care when these disorders prevent individuals from taking care of themselves in their own homes."

In addition to the significant participation of faculty within the School of Medicine, investigators from Penn's schools of

Four Fellows

Four faculty members at the University of Pennsylvania have been named Fellows of the American Association for the Advancement of Science, three of them from the Perelman School of Medicine. This year 539 members have been awarded this honor because of their scientifically or socially distinguished efforts to advance science or its applications. The Perelman School's newest Fellows are:

David Boettiger, Ph.D., emeritus professor of microbiology, for distinguished contributions to tumor virology and to integrin-mediated cell adhesion, particularly for the identification of adhesion signaling and its regulation by mechanical forces.

Nigel Fraser, Ph.D., professor of microbiology, for outstanding discoveries about the mechanisms of herpes virus biology, particularly in the area of herpes simplex virus latency and reactivation.

David Weiner, Ph.D., professor of pathology and laboratory medicine, for pioneering and enabling discoveries in the area of DNA vaccines and promoting that field of research.

The fourth Fellow is **Nancy Bonini, Ph.D.**, professor of biology in the School of Arts and Sciences, who often works with researchers in the Perelman School of Medicine. An investigator of the Howard Hughes Medical Institute, she was recognized for distinguished contributions in the fields of basic and translational neuroscience, particularly as applied to understanding neurodegenerative disorders.

Veterinary Medicine, Dental Medicine, Engineering and Applied Sciences, and Arts and Sciences will participate as well.

Honors & Awards

Aaron T. Beck, M.D., emeritus professor of psychiatry, was named a recipient of the Prince Mahidol Award in Medicine, presented by the Royal Thai Government. The other recipient was David T. Wong, from Indiana University. Beck was recognized for his outstanding contributions in the development of cognitive behavioral therapy (CBT). He was the first person to successfully develop CBT and use it on patients suffering from depression. The therapy is now widely used by psychiatrists and psychotherapists.

Beck also received the 2011-2012 Edward J. Sachar Award from the Department of Psychiatry at Columbia University. Beck was honored for facing the challenge of treating low-functioning patients with schizophrenia. At the award ceremony, Beck was introduced by Nobelist Eric R. Kandel, Ph.D., who described Beck as "the most original and important contributor to psychotherapy and psychiatry of the last 50 years and the most important psychoanalyst since Freud."

James Eberwine, Ph.D., professor of pharmacology, has received a Senior Scholar Award from the Ellison Medical Foundation. The $600,000 award, disbursed over the next four years, supports basic biological research in aging. Eberwine is one of 20 investigators to receive this award. According to Eberwine, the grant will enable his research team to use cutting-edge technologies to assess how protein synthesis contributes to modulating the aging cell phenotype. This line of work will try to answer whether the decrease in neural connections seen in aging can be modulated by regulating dendritic protein synthesis.

Harold I. Feldman, M.D., M.S.C.E., a professor of epidemiology and a professor of medicine in the Renal Electrolyte and Hypertension Division, was elected to the board of the American College of Epidemiology. He is also a senior scholar in the Center for Clinical Epidemiology and Biostatistics His term will run through 2014.

Clara Franzini-Armstrong, Ph.D., emeritus professor of cell and developmental biology, was named a foreign member of the Accademia dei Lincei. Founded in 1603, this Italian academy of science has a rich history, including counting Galileo Galilei as a member. Franzini-Armstrong graduated from the University of Pisa. Her main field of interest, she has said, has been the disposition of membranes and macromolecular complexes that are responsible for excitation-contraction coupling in skeletal and cardiac muscles.

Prabodh Gupta, M.B.,B.S, M.D., professor of pathology and laboratory medicine, received the 2012 L. C. Tao Educator of the Year Award from the Papanicolaou Society of Cytopathology. The award recognizes meritorious service and contributions to the field of cytopathology education. Gupta's clinical expertise is in cytopathology with a particular interest in the development of cervical and lung cancer. Director of cytopathology and the cytometry laboratory at Penn, he is the author of nearly 250 scientific articles and chapters as well as a book, *The Fundamentals and*

Prabodh Gupta

Four Penn Researchers Awarded Sloan Fellowships

Four University of Pennsylvania faculty members, including two from the Perelman School of Medicine, are among this year's Sloan Fellowship recipients. Since 1955, the Alfred P. Sloan Foundation has granted yearly fellowships to scientists and scholars early in their careers, whose achievements and potential identify them as the next generation of scientific leaders. Each Fellow receives a two-year, $50,000 award to further his or her research.

In the Perelman School of Medicine, the new Fellows are:

Christopher Fang-Yen, Ph.D., assistant professor of neuroscience and assistant professor of bioengineering in the School of Engineering and Applied Science. His laboratory uses optical and genetic tools to study the neurobiology of a millimeter-long worm known as *C. elegans*. With only a few hundred neurons and a transparent body, this worm is an ideal model for researching how neural circuitry generates behavior.

Benjamin F. Voight, Ph.D., assistant professor of pharmacology. As a geneticist and computational biologist, Voight conducts research that involves constructing and applying statistical methods to genomics data collected across thousands of human genomes. The aim is to uncover how genetic variation contributes to the diverse set of traits evolved during recent human history and to the range of diseases present today. His work has identified risk-related alleles for type-2 diabetes and heart attack.

Fellows in the School of Arts and Sciences include **E. James Petersson, Ph.D.**, assistant professor of chemistry, who takes a multidisciplinary approach to studying how proteins change shape; and **Joseph Subotnik, Ph.D.**, assistant professor of physical and theoretical chemistry, who is seeking to understand how energy is transferred in a chemical reaction, how long that energy lasts before it is lost to friction, and how scientists can best control and manipulate that energy for future energy production.

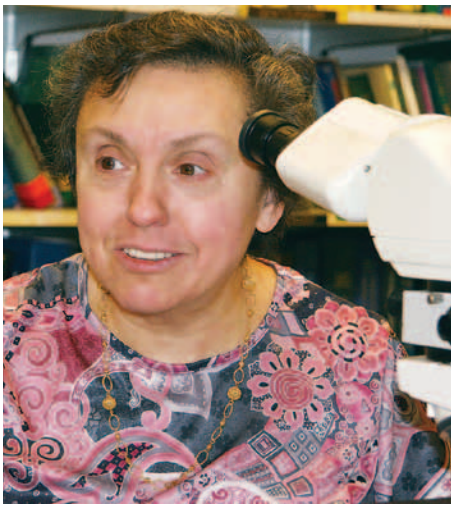
Basic Concepts of Cytopathology. Gupta received the 2011 Excellence in Education Award from the American Society of Cytopathology.

Rahul M. Kohli, M.D., Ph.D., assistant professor of medicine and of biochemistry and biophysics, has received a $500,000 grant for five years as a 2011 Rita Allen Foundation Scholar. The foundation's mission includes supporting "transformative ideas in their earliest stages to leverage their growth and promote breakthrough solutions to significant problems." Kohli and his laboratory group integrate chemical biology and enzymology approaches to study the action of enzymes that modify DNA. They are exploring the idea that such enzymes can be used to introduce an added layer of complexity by muffling, amplifying, or even rewriting parts of the genome. Understanding the dynamic genome has implications for advances in understanding infectious diseases, stem cell biology, and oncology, among other fields.

Shiriki Kumanyika, Ph.D., M.P.H., professor of epidemiology in the Department of Biostatistics and Epidemiology, received the Wade Hampton Frost Lecture Award from the Epidemiology Section of the American Public Health Association. The award recognizes a person who has made a significant contribution to addressing a public health issue of major importance by applying epidemiologic methods. Kumanyika's research focuses on nutritional factors in the primary and secondary prevention of chronic diseases, with a particular focus on obesity. Kumanyika is also senior advisor to the Center for Public Health Initiatives and associate dean for Health Promotion and Disease Prevention.

Mitchell Lazar, M.D., Ph.D., the Sylvan Eisman Professor of Medicine, and **Zheng Sun, Ph.D.**, a postdoctoral fellow in Lazar's laboratory, were senior author and lead author of "Diet-induced Lethality Due to Deletion of the Hdac3 Gene in Heart and Skeletal Muscle," published in September in *The Journal of Biological Chemistry*. The journal, which published more than 4,000 papers in 2011, has designated the article as its "Best Paper of 2011 in Metabolism." (See pp. 12-13 for more details about the article and the link between diet and epigenetics.)

Virginia A. LiVolsi, M.D., professor of pathology and laboratory medicine, was honored with the 2012 Harvey Goldman Master Teacher Award of the United States and Canadian Academy of Pathology. LiVolsi's clinical expertise is in thyroid and parathyroid pathology, gynecological pathology, and head and neck pathology/salivary glands. Her research interests include the pathogenesis of thy-



Virginia LiVolsi: A Master Teacher.

roid neoplasms. She has served as chair of the pathology panel of the Chernobyl Tumor Bank, an international group that examines and categorizes the thyroid tumors that have occurred in children and teenagers exposed to the nuclear disaster in Ukraine in 1986.

Peter D. Quinn, D.M.D., M.D., professor of oral and maxillofacial surgery in the Perelman School of Medicine, received the 2011 Donald B. Osbon Award for an Outstanding Educator, presented by the American Association of Oral and Maxillofacial Surgeons. Under his leadership, the University's School of Dental Medicine established its six-year residency program in oral and maxillofacial surgery, in which students complete the requirements for their M.D. degree at the Perelman School and finish with a two-year certificate in general surgery and a certificate at Penn Dental Medicine in oral and maxillofacial surgery. Quinn, who is also the Louis Schoenleber Professor of Oral and Maxillofacial Surgery in the School of Dental Medicine, serves as vice dean for professional services at the Perelman School and is senior vice president of the Clinical Practices of the University of Pennsylvania.

Kathy Shaw, M.D., M.S.C.E., professor of pediatrics, associate chair for quality and patient safety for the Department of Pediatrics, and division chief of emergency medicine at The Children's Hospital of Philadelphia, was named the recipient of the 2011 FOCUS Award for the Advancement of Women in Medicine. The award, presented by FOCUS on Health & Leadership for Women, honors Shaw's "extraordinary advocacy on behalf of women faculty and trainees at Penn Medicine."

Since her appointment as chief 15 years ago, Shaw has increased the number of women faculty in her division from 17 percent to 55 percent, with a notable increase in the number of women at the rank of associate or full professors. Over the past decade, Shaw has championed many initiatives to promote an atmosphere of community and flexibility that has allowed both men and women to juggle the many needs of family and life outside of medicine with the demands of an academic career. One example: she played a leading role in the creation of a maternity policy in the Department of Pediatrics.

Daniel Sterman, M.D., associate professor of medicine and director of interventional pulmonology, received the Pasquale Ciaglia Memorial Lecture in Interventional Medicine award, presented by the American College of Chest Physicians. Sterman is also the co-director of the Penn Medicine Mesothelioma and Pleural Program. His research interests are conducting human clinical trials of gene therapy and vaccine therapy for lung cancer, mesothelioma, and other pleural malignancies.

Transitions

Brian L. Strom, M.D., M.P.H., has been appointed to the new position of executive vice dean for institutional affairs at Penn Medicine. In this role, Strom is responsible for coordinating the institution's efforts in comparative effectiveness research, as well as the recently established Neuroscience of Behavior Initiative, which seeks to strengthen Penn's programs in basic, translational, clinical, and population research in the areas of addiction, depressive disorders, and neurodegenerative disease. (See p. 41) He will also provide administrative leadership in recruiting department chairs, directors of centers and institutes, and other senior faculty members. In addition, Strom will assist in implementing recommendations that emerge from the school's current strategic planning process.

In 2007, Strom was named vice dean for institutional affairs. As the George S. Pepper Professor of Public Health and Preventive Medicine, Strom has served as the founding chair of the Department of Biostatistics and Epidemiology and the founding director of the Center for Clinical Epidemiology and Biostatistics. The Perelman School will soon begin a search for a permanent chair and director.

Letters

Einstein's Brain

I am enjoying the Fall 2011 edition of *Penn Medicine*. Very nicely done. Portions of Einstein's brain are/were also held at the Armed Forces Institute of Pathology – which became the National Museum of Heath and Medicine – during my tenure as director there with U.S. Surgeon General C. Everett Koop, M.D., formerly professor at Penn. The AFIP-NMHM since 1966 was formerly located at Walter Reed Army Medical Center (which was just closed down).

Marc Micozzi, M.D. '78, Ph.D. '84

Remembering Anatomy Lab

It's been 65 years since I was a first-year medical student in the gross anatomy lab. I have always felt that above all other experiences in medical school, it was the one of prime importance in converting me into a physician from a layperson.

Professor Roy Williams is a very clear memory, especially the day when he asked me to show him the *pes anserinus*. The incident finished with him shouting, "Good God, girl, don't you know what a *pes anserinus* is?" I didn't then but I still do now.

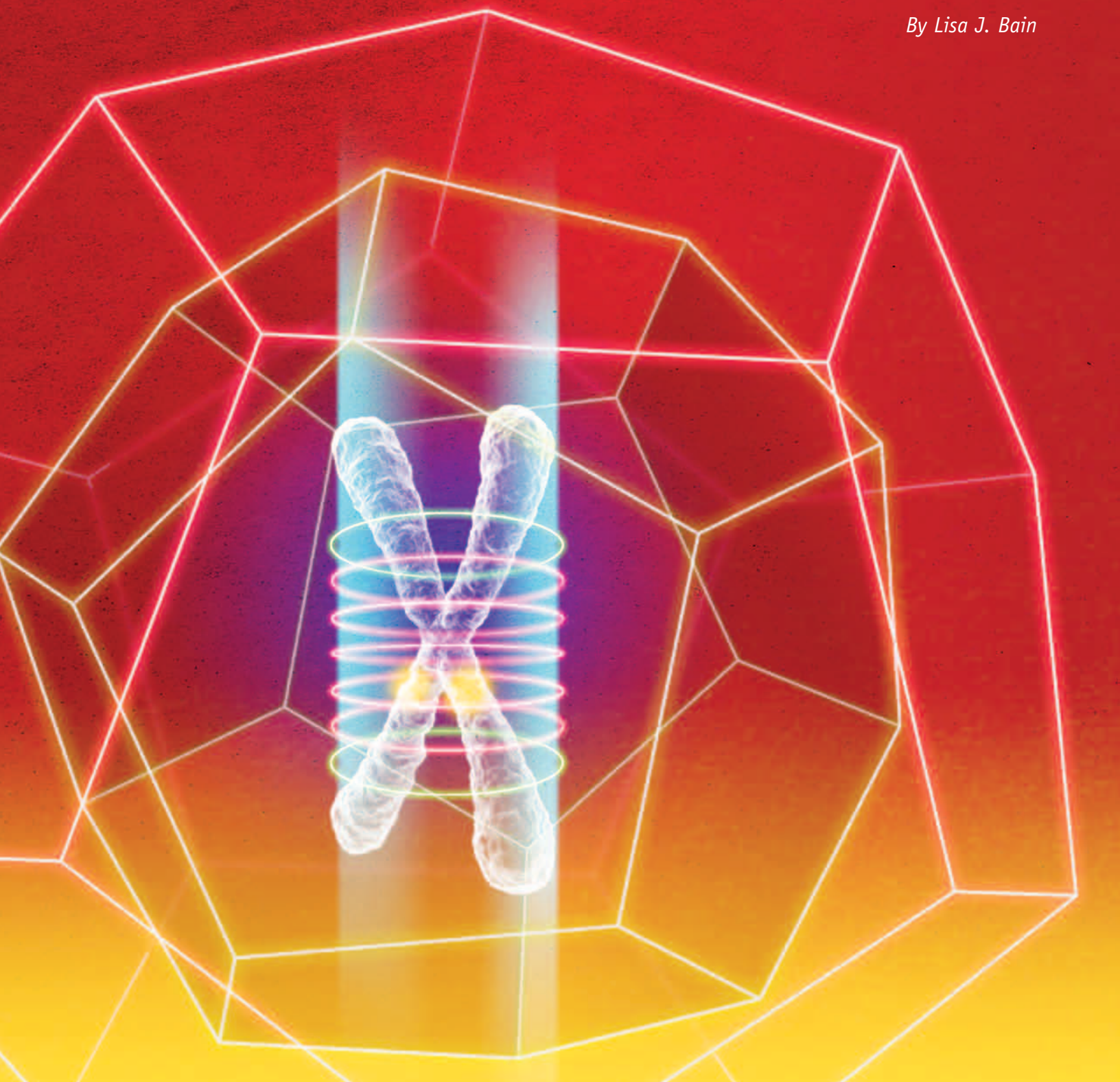
Thank you for Ledger's and Attiah's articles in the Fall issue.

Bernadine Z. Paulshock, M.D. '51, G.M.E. '53

EPIGENETICS: ABOVE AND BEYOND DNA

Shelley Berger, Ph.D., leads Penn Medicine's wholehearted venture into a rapidly expanding field of science.

By Lisa J. Bain



"Shelley, what the heck is epigenetics?"

The question was posed by Glen Gaulton, Ph.D., executive vice dean and chief scientific officer of the Perelman School of Medicine. All eyes turned to Shelley Berger, Ph.D., sitting among other faculty panelists at the official opening of the Translational Research Center last May. Colleagues, administrators, students, and other interested parties in the center's large and modern auditorium waited for her answer. "Frankly," Gaulton continued, "I don't think there's an area that epigenetics does not touch nowadays."

But he was not putting Berger on the spot. After all, he knew she was director of the Penn Epigenetics Program, established only a couple of years ago to make sure the school did not lag behind in what the popular press had begun calling "the new science."

Taking Gaulton's bait, Berger explained that, until recently, scientists believed that gene mutations were the only source of human diseases – but it turns out to be more complicated. "Epigenetics is a layer of regulation over our genes that is key to how genes are turned on and off." Identical twins, Berger noted, have identical genomes – but as they age, they become different because of epigenetic changes. "One of the areas that's fascinating to study with respect to epigenetics," she continued, "is aging." Currently, her laboratory is using a single-cell organism to try to understand how changes in the epigenome underlie aging – and are relevant even to human aging. As another example, Berger cited the work of Ted Abel, Ph.D., the Brush Family Professor of Biology in Penn's School of Arts & Sciences, who is studying how "a single change in the epigenome" can impair memory function in mice.

It's clear, then, that this "new science" has a tremendous reach. It's also clear that Penn Medicine was determined not to be left behind. And that is where Shelley Berger comes in.

On the Trail of Gene Regulation

Weekends are a good time to get work done with few distractions. So it was not surprising that even though it was the Saturday after Christmas in 1995, Berger was working as usual in her office at The Wistar Institute when she got a call from Jerry Workman, Ph.D., a scientist and collaborator from Penn State University. Berger and Workman had been trying to understand the biochemistry of Gcn5, a yeast protein that Berger had found to play a role in the process of activating genes. "We figured this gene was going to be doing something interesting, we just didn't know what," said Berger.

"Are you sitting down?" asked Workman.

"No," replied Berger.

"Well, sit down," he said and then proceeded to tell her that another scientist, David Allis, Ph.D., then at the University of Rochester, had discovered a mechanism by which the Gcn5 protein regulates gene activity. Gcn5, it turns out, is a histone acetyltransferase (HAT), which means it's an enzyme that adds chemical tags called acetyl groups to histone proteins that package DNA, relaxing the tightly compacted structure so it can be more easily copied.

"I was depressed all weekend," recalled Berger. "I thought, 'oh man, the biggest thing that happened about this gene I was studying – and I didn't discover it!' But by Monday I thought, 'Wow, this is amazing.' I could just understand how important this was going to be." More-

Photographs by Tommy Leonardi, except where noted.

"Epigenetics is a layer of regulation over our genes that is key to how genes are turned on and off." It has implications for almost every area of both basic and translational science.

Shelley Berger

over, she realized that she was in a great position to ask important questions about whether the enzymatic activity Allis had discovered was really essential for gene regulation. "So we immediately set out to do that. We started collaborating with David Allis, and within six months or less my group had some very nice papers on the subject."

Today, the study of how the inherent DNA structure can be modified by adding acetyl groups and numerous other chemical groups that influence how genes are expressed has coalesced into one of the hottest areas of biomedical science – epigenetics.

"Shelley and her colleagues have played a seminal role," said Allis. "It started with her postdoctoral work with the genetics of these proteins. . . . And now 15 years removed, it's really a huge enterprise of people."

In January, 2010, *Time* magazine brought epigenetics to the mainstream by featuring the topic as its cover story, "When Your DNA Isn't Your Destiny." A few years earlier, at the urging of Arthur H. Rubenstein, M.B., B.Ch., then the dean, Penn's medical school had begun to build an epigenetics program. Looking around for someone to lead the program, Rubenstein said that he and his Penn colleagues found that "the very best person in the country was actually at The Wistar Institute, and that was Shelley Berger. She had done extremely innovative and creative work in a variety of areas of epigenetics and was already viewed as an international leader in this area." A program was crafted with Berger as the leader, and she was recruited as director of the Penn Epigenetics Program and the Daniel S. Och University Professor in the departments of Cell & Developmental Biology and of Genetics. She was also named the 10th Penn Integrates Knowledge (PIK) University Professor, a University-wide initiative that recruits faculty whose research and teaching cross multiple disciplines and at least two schools at Penn. Berger's other appointment is in the Department of Biology of the School of Arts & Sciences (SAS).

Shelley Berger, left, and Jessica Bryant, a graduate student in Cell & Molecular Biology.

Shortly after her arrival at Penn, Kenneth Zaret, Ph.D., was recruited from the Fox Chase Cancer Center to serve as co-director of the Penn Epigenetics Program as well as associate director of the Penn Institute of Regenerative Medicine. Scientists on the program's executive board come from departments ranging from Biochemistry and Biophysics to Pediatrics, and members of the program are drawn from Penn as well as The Children's Hospital of Philadelphia, Wistar, Fox Chase, Drexel University, Thomas Jefferson University, and Temple University. According to Rubenstein, Berger and Zaret have built a program that "has become among the leading epigenetics programs in the country in a very short time."

Beyond DNA

The sequencing of the human genome was announced with much fanfare in 2003, but the Human Genome Project raised as many questions as it answered, if not more. Scientists were hoping that by mapping all the genes, they would be able to identify mutations in those genes that caused disease. But what they found was that simple disease-causing mutations, such as the mutations in the BRCA 1 or 2 genes that cause breast cancer, are relatively rare. Most diseases, even those that run in families and thus are thought to be inherited, arise through much more complicated mechanisms. What had become apparent, even before the Human Genome Project started, is that gene activity depends not just on the sequence of the gene but on whether and when that gene is expressed. And gene expression is a complicated process controlled

by proteins that package, spool, and compact the DNA in the nucleus of cells; and by chemical groups that sit on top of the package like switches, turning the genes on and off. The spool (chromatin) comprises proteins called histones, and the switches are called epigenetic marks. The prefix "epi-" means "above."

Epigenetics can help explain some of the perplexing biomedical questions that simple Mendelian genetics cannot. Why, for example, might one child have autism while his identical twin is unaffected? Or what could explain the observation that pregnant women who experienced starvation during the Dutch famine of 1944, when the Nazis blockaded food and fuel shipments to the Netherlands, gave birth to children who were more susceptible to a variety of health problems, including diabetes? The answer, it seems, lies in the fact that environmental conditions can alter the epigenome, resulting in heritable changes that can be passed to offspring, with DNA. Epigenetics alter the readout of the genetic code, in some cases ramping a gene's expression up or down. In the case of the centromere, it marks the site where spindle fibers attach, independently of the underlying DNA sequence. Researchers have suspected that CENP-A is the crucial epigenetic marker protein.

At the Crossroads of Chromosomes: Revealing More of the Epigenetic Structure of Cell Division

On average, one hundred billion cells in the human body divide over the course of a day. Most of the time, the body gets it right but sometimes problems in cell replication can lead to abnormalities in chromosomes. Many types of disorders, from cancer to Down syndrome, can result.

In 2010, researchers at the Perelman School of Medicine defined the structure of a molecule that plays a central role in how DNA is duplicated and then moved correctly and equally into two daughter cells to produce two exact copies of the mother cell.

Nikolina Sekulic and Ben E. Black

Ben E. Black, Ph.D., assistant professor of biochemistry and biophysics, and Nikolina Sekulic, Ph.D., a postdoctoral fellow in the Black lab, described the structure of the CENP-A molecule, which defines a part of the chromosome called the centromere. The centromere is a constricted area to which specialized molecules called spindle fibers attach and help pull daughter cells apart during cell division.

"Our work gives us the first high-resolution view of the molecules that control genetic inheritance at cell division," said Black. "This is a big step forward in a puzzle that biologists have been chipping away at for over 150 years."

Investigators have known for more than 15 years that part of cell division is controlled by epigenetic processes rather than encoded in the DNA sequence itself. The tightly bound DNA spools are built of histone proteins, and chemical changes to these spool proteins can either loosen or tighten their interaction

What hasn't been known, however, is how CENP-A epigenetically marks the centromere to direct inheritance. The Black team found the structural features that confer CENP-A the ability to mark centromere location on each chromosome. Without CENP-A or the centromere mark it creates, the entire chromosome – and all of the genes it houses – are lost when the cell divides.

The work by Black and Sekulic is a major advance in the understanding of the molecules that drive human inheritance. But it also raised the exciting prospect that the crucial epigenetic components are now in hand to engineer clinically useful artificial chromosomes that will be inherited alongside our own natural chromosomes – and, says Black, with the same high fidelity.

– Karen Kreeger

even though there has been no change in the genes themselves.

Epigenetics is also thought to play a critical role in the development of cancer, for example, by turning off a tumor-suppressor gene. "Cancer is one disease that is unequivocally linked to epigenetic dysfunction," said Allis. Last fall, Mariusz A. Wasik, M.D., professor of pathology and laboratory medicine, Qian Zhang, M.D., Ph.D., research assistant professor, and colleagues in the Perelman School of Medicine found that a cancer-causing fusion protein works by silencing the tumor suppressor gene IL-2R common gamma-chain (IL-2Rγ). In *Proceedings of the National Academy of Sciences*, they reported that the IL-2Rγ gene promoter is silenced by a chemical change to the DNA itself – in this case, the adding of a methyl group to DNA's molecular backbone. Describing his study, Wasik wondered whether this form of epigenetic silencing could be made more generally applicable. "Can we overcome the tumor-suppressor gene silencing using inhibitors of DNA methylation – which are already approved to treat some forms of blood cancer – to inhibit the expression of NPM-ALK and possibly other cancer-causing proteins in patients?"

Epigenetic dysfunction has also been linked to problems in the brain affecting learning and memory, addiction, alcoholism, and complex psychiatric disorders, and to chronic inflammation and other immunologic disorders.

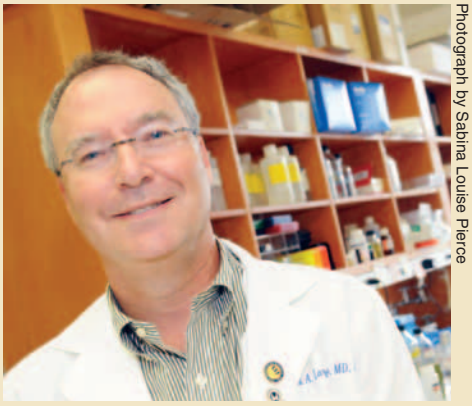
At a more basic level, epigenetic changes underlie many aspects of cell differentiation and cellular memory. How, for example, does a single fertilized egg that contains all the DNA for an organism give rise to separate populations of liver cells and brain cells with distinctly different patterns of gene expression? And how does a liver cell, when it divides, remember that it is a liver cell and not a brain cell? The answers to these questions are not known, but the study of epigenetics is likely to provide some clarity.

Epigenetics on the rise

The publication of Allis's landmark paper resulted in a sea change in scientists' understanding of gene regulation. Almost immediately, Berger converted her entire research focus to the study of chromatin mechanisms, particularly how modifications to histone proteins regulate not just gene transcription, but also replication and DNA damage. "Everything that has to be done on the genome is regulated by these enzymes that add and take off these little chemical groups," she said. "It was lucky for me that I was in the beginning of this change, because I had been studying this gene and we had all the reagents in hand."

Moreover, the excitement about epigenetics extends into almost every area of

A Recipe for Heart Disease: High-Fat Diet and Lack of an Epigenetic Enzyme



Photograph by Sabina Louise Pierce

Mitchell Lazar

It's no secret that a high-fat diet is not healthy. Now Penn Medicine researchers have discovered a molecular clue as to precisely why that is.

Writing last fall in the *Journal of Biological Chemistry*, Mitchell Lazar, M.D., Ph.D., Zheng Sun, Ph.D., a postdoctoral fellow in Lazar's laboratory, and their colleagues revealed that when mice lacking a particular enzyme that controls gene expression are fed a high-fat diet, they experience rapid thickening of the heart muscle and heart failure. This molecular link between fat intake and an enzyme tasked with regulating gene expression – at least in mice – has implications for people on so-called Western diets and for combating heart disease. Modulating the enzyme's activity could be a new pharmaceutical target.

The team found that the mice engineered to lack the enzyme HDAC3 tended to underexpress genes important in metabolizing fat and producing energy. Essentially, when fed a high-fat diet, the hearts of these animals cannot generate enough energy and thus cannot pump blood efficiently.

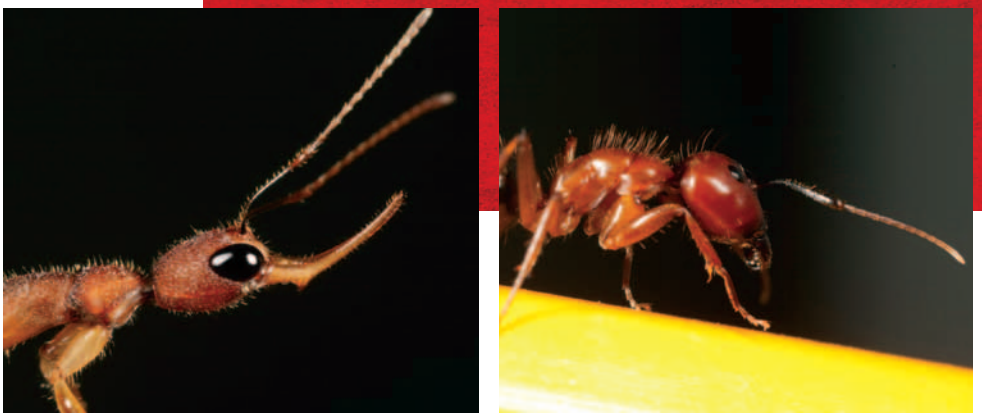
These same mice tolerate a normal diet as well as non-mutant, normal animals. "HDAC3 is an intermediary that normally protects mice from the ravages of a high-fat diet," says Lazar, the Sylvan Eisman Professor of Medicine and director of the Institute for Diabetes, Obesity, and Metabolism.

HDAC enzymes control gene expression by regulating the accessibility of chromatin – the DNA and protein structure in which genes reside. Within chromatin, DNA is wound around proteins called histones.

When an animal eats, its metabolism changes, but food doesn't change a cell's genome. Instead, food modulates the "epigenome," the molecular markers on the chromatin that influence gene expression by affecting how tightly DNA is wrapped around its protein scaffolding.

Previously, researchers at the University of Texas Southwestern Medical Center showed that if HDAC3 were deleted in heart tissue in the middle of embry-

both basic and translational science. In Berger's lab alone, research projects include studies related to aging, infertility, immunological memory, cellular metabolism, and the response to stress, and even a study on how epigenetic differences between different castes of female ants (queens vs. workers) might explain the extreme differences in both physical and behavioral characteristics. The ant study was published in *Science* (August 2010) with colleagues Danny Reinberg, Ph.D., of New York University, and Juergen Liebig, Ph.D., of Arizona State University. Despite the extreme differences, all females within the ant colony appear to be genetically identical. The researchers believe that epigenetic mechanisms are critical in establishing the variations. "Think of the workers and the queen as different tissues in our bodies," said Berger. "It's an epigenetic marking system on the scale of a whole organism."



Epigenetics can explain how female ants become queens or workers.

Indeed, epigenetics is the link that ties these different research programs as well as different organisms together. Berger said that after studying chromatin mechanisms in yeast for many years, she wanted to place it into the context of physiological pathways, so she started to cast around for some pathways in yeast that could be used as models for what is going on in mammalian cells. She chose spermatogenesis, the making of sperm, which is very similar to the process of sporulation (the making of spores) in yeast. Since then, her lab has found a number of important modifications in chromatin histone that occur during sporulation that are relevant to spermatogenesis.

Now, funded with a grant from the National Institutes of Health, Penn recently launched the Penn Center for the Study of Epigenetics in Reproduction. Marisa Bartolomei, Ph.D., professor of cell and developmental biology, is the principal investigator. The center also includes the Berger lab as well as Ralph Meyer, Ph.D., assistant professor of developmental biology at the School of Veterinary Medicine, and Richard M. Schultz, Ph.D., the Charles and William L. Day Distinguished Professor of Biology in SAS. "The really cool part in my opinion is that we reach all the way to a human *in vitro* fertilization clinic," said Berger. Collaborators Christos Coutifaris, M.D., Ph.D., the Nancy and Richard Wolfson Professor of Obstetrics and Gynecology professor of obstetrics, and Carmen Sapienza, Ph.D., at Temple University, will be collecting samples from humans who are having fertility problems. They will try to determine whether epigenetics plays a role in increasing the risk of complications among babies conceived through *in vitro* fertilization.

Other scientists in the Epigenetics Program are going in equally diverse direc-

onic development, the animals developed severe thickening of the heart walls (hypertrophic cardiomyopathy) that reduces the organ's pumping efficiency. These animals usually died within months of birth.

Lazar and his team wanted to know what would happen if the gene was inactivated in heart tissue *after* birth. To their surprise, they found that these animals were essentially normal.

On a diet of regular chow, the engineered mice lived as long as their normal littermates, although they did tend to accumulate fat in their heart tissue. On a high-fat diet, however, these animals deteriorated rapidly and died within a few months of hypertrophic cardiomyopathy and heart failure.

To understand why, Lazar's team compared the gene expression patterns of the young mutant mice to their normal siblings. They found that the mutant mice tended to underexpress genes important in fat metabolism and energy production.

According to Lazar, this study identifies an "interesting and dramatic example" of the link between diet and epigenetics. At present, his team is working to identify the molecular nature of that link. They are also investigating whether the same pathway and interaction occurs in humans because it may contribute to the increased heart disease associated with Western diets.

Whatever the outcome of those studies, says Lazar, there is one sure-fire intervention people can always use to stave off the ravages of over-nutrition: changing your diet.

– Jeffrey Perkel and Karen Kreeger

tions, across departments and schools. Cancer is a major area of epigenetics research, and many cancer researchers have hopped on the epigenetics bandwagon. For example, Roger Greenberg, M.D., Ph.D., assistant professor of cancer biology, is studying how, in cancer, epigenetic changes in proteins affect the ability of cells to repair damaged DNA. Meanwhile, Ted Abel at the School of Arts & Sciences is trying to understand learning and memory in terms of epigenetic marking. Indeed, a whole field is emerging that tries to understand how neurons become differentiated based on epigenetic changes.

Penn has tremendous strength in the area of neuroscience and neurodegenerative disease, and combining that with epigenetics has given rise to a new project recently funded by the N.I.H. (with scores almost unheard of in the peer-review process). Berger is a co-principal, along with Nancy Bonini, Ph.D., in the Department of Biology at SAS and an investigator of the Howard Hughes Medical Institute, and Brad Johnson, M.D., Ph.D., a physician at the Hospital of the University of Pennsylvania and associate professor of pathology and laboratory medicine, on a study aimed at understanding epigenetic changes that may underlie neurodegenerative diseases such as Alzheimer's disease, Parkinson's dementia, frontotemporal lobar degeneration (FTLD), and amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease).

The project takes advantage of brain tissue collected by Penn's Center for Neurodegenerative Disease Research under the supervision of collaborator John Trojanowski, M.D., Ph.D., director of Penn's Institute on Aging, as well as Bonini's fruit fly model of neurodegeneration; a cultured human astrocyte model developed by Claudio Torres at Drexel; second-generation sequencing technologies; and bioinformatics expertise available at Penn.

Using Epigenetics to Predict the Fate of Personalized Cells

Discovering the step-by-step details of the path embryonic cells take to develop into their final tissue type is the clinical goal of many stem cell biologists.

To that end, Kenneth S. Zaret, Ph.D., the Joseph Leidy Professor of Cell and Developmental Biology, and Cheng-Ran Xu, Ph.D., a postdoctoral research associate in the Zaret laboratory, looked at immature cells called progenitors and found a potential way to predict their fate. The study appeared last spring in *Science*.

Cheng-Ran Xu and Kenneth Zaret

In the past, researchers grew progenitor cells and waited to see what they differentiated into. Now, they aim to use this epigenetic marker system, outside of a cell's DNA and genes, to predict the cell's eventual fate.

"We were surprised that there's a difference in the epigenetic marks in the process for liver versus pancreas before the cell-fate 'decision' is made," said Zaret, who also serves as co-director of the Penn Epigenetics Program and associate director of the Penn Institute for Regenerative Medicine. "This suggests that we could manipulate the marks to influence fate or look at marks to better guess the fate of cells early in the differentiation process."

How the developing embryo starts to apportion different functions to different cell types is a fundamental question for developmental biology and regenerative medicine. Guidance along the correct path is provided by regulatory proteins that attach to chromosomes, marking part of the genome to be turned on or off.

Chemical signals from neighboring cells in the embryo tell early progenitor cells to activate genes encoding proteins. These proteins, in turn, guide the cells to become liver or pancreas cells, which have been found to originate from a common progenitor cell. Over several years, Zaret's lab has unveiled a network of the common signals in the mouse embryo that govern development of these specific cell types.

"By better understanding how a cell is normally programmed we will eventually be able to properly reprogram other cells," noted Zaret. In the near term, the team also aims to generate liver and pancreas cells for research and to screen drugs that repair defects or facilitate cell growth.

With regenerated cells, researchers hope to one day fill the acute shortage in pancreatic and liver tissue that is available for transplantation in cases of type I diabetes and acute liver failure.

– Karen Kreeger

Brad Johnson

"There have been broad hints in the scientific community that epigenetics plays an important role in aging," said Johnson, "but neurodegeneration is kind of an unexplored area."

Modifying the epigenome: a promising translational path

One of the aspects of epigenetics that has the biomedical community so excited is that translating it to the clinic appears to be the next logical step. In fact, there are already cancer drugs on the market that act by inhibiting the chemical groups that are epigenetic marks. As Johnson puts it, "It's druggable. These aren't necessarily irreversible changes. If you get a mutation in the DNA or a deletion in the DNA, it's hard to change that. But if it's just the chromatin state, you might be able to reset it – and that's exciting."

Epigenetics also holds great promise in the area of personalized medicine, according to Garret FitzGerald, M.D., the Robert L. McNeil Jr. Professor in Translational Medicine and Therapeutics and director of Penn's Institute for Translational Medicine and Therapeutics. "There is a remarkable variability in how people respond to drugs, and obviously getting an understanding of that leads us progressively to a more personalized approach to medicine. So clearly one of the marks of environmental influences on the genome is on the epigenome, and that's where Shelley's expertise and the group of people she's built around her is so vital."

Another area in which epigenetics offers great translational potential is in regeneration. Understanding how worker ants and queens, or liver cells and pancreas cells, can develop along different pathways despite having the same DNA could eventually lead to techniques that would enable the regeneration of damaged or diseased organs. For example, Kenneth Zaret's laboratory studies how stem cells, which have the potential to develop into multiple cell types, make the choice for one cell fate or another.

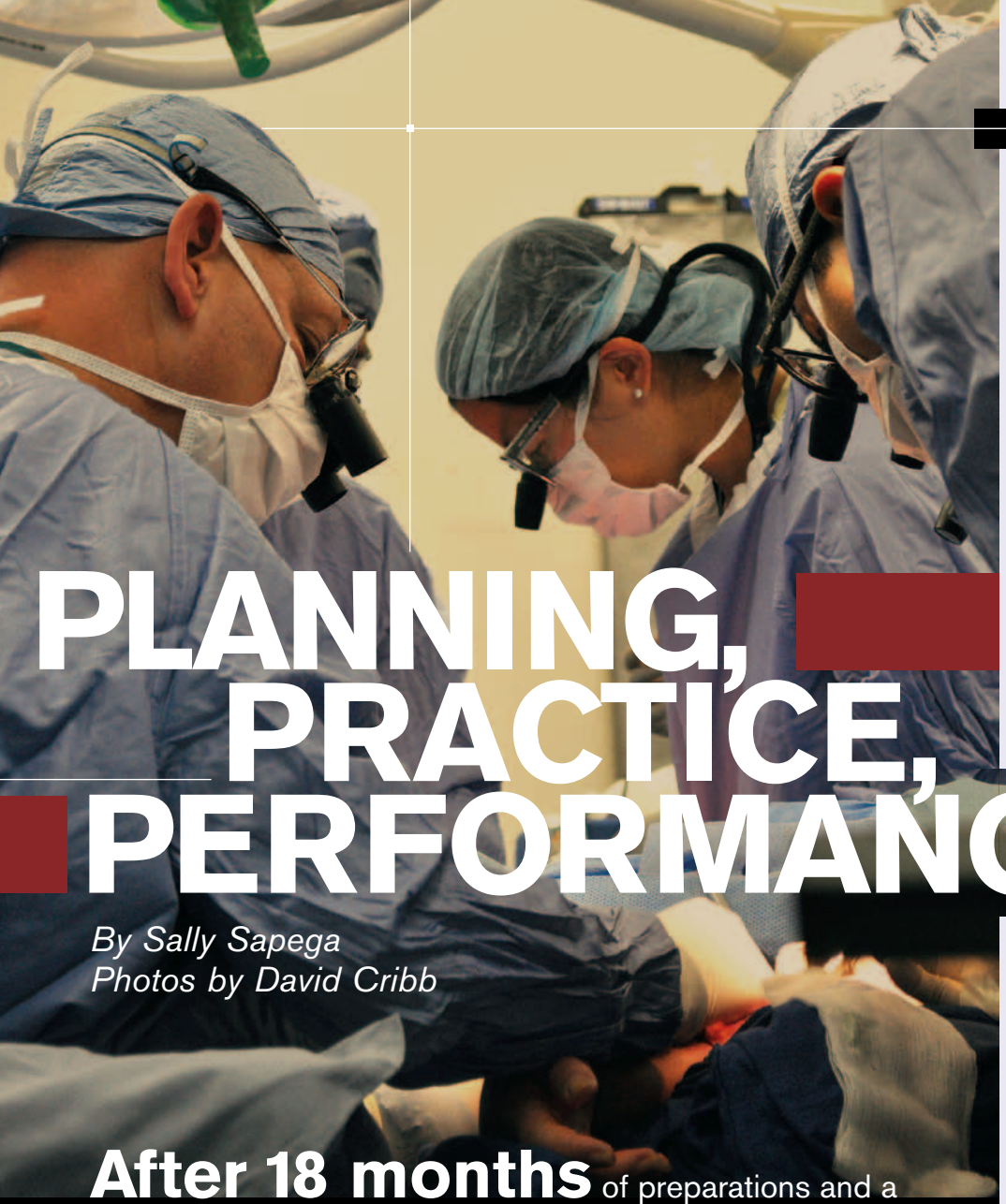
> "We think if we understand how cells get programmed, then we can understand how they can get reprogrammed as well."

"We're asking very basic questions about how cell fate choices are made in a mammalian embryo," said Zaret, who is also the Joseph Leidy Professor of Cell and Developmental Biology. "We think if we understand how cells get programmed, then we can understand how they can get reprogrammed as well." His lab has already deciphered much of the wiring that leads a precursor cell to become a liver cell or pancreas cell. "Now we are interested in using the same approaches to understand the wiring of how a pancreas progenitor would make the choice to become a beta cell, which is important for diabetes." Reprogramming pancreas cells to become insulin-producing beta cells could potentially lead to a treatment for diabetes.

Diabetes, infertility, neurodegenerative disease, cancer. As Glen Gaulton remarked, epigenetics touches just about every area of medicine. In similar fashion, FitzGerald said, "I think it's fundamental to everything. But our understanding of the biology is still very much at an evolutionary stage, and particularly our understanding of the implications of blocking changes in the epigenome are at an extraordinarily early stage." At a recent symposium, Berger showed graphically the correlation between aging and changes in the epigenome. "That's very provocative," said FitzGerald, while noting that Berger was careful to ask, "are these a consequence or a cause of aging?" As FitzGerald sees it, "There are huge questions that we haven't even begun to ask, never mind answer."

Berger faces these daunting questions with seemingly limitless energy and enthusiasm – and, as noted by Arthur Rubenstein, with charisma. Said Allis: "She's smart and high energy. There's no moss growing on Shelley. She's a go-getter. She can synthesize the big picture."

The big picture, that is, as it pertains all the way to the smallest units in human biology. •



PLANNING, PRACTICE, PERFORMANCE

By Sally Sapega
Photos by David Cribb

After 18 months of preparations and a thorough examination of the ethical issues, a multidisciplinary team at HUP completed its first bilateral hand transplant. And after the surgery came rehabilitation.

In September, a surgical team at the Hospital of the University of Pennsylvania successfully completed the first bilateral hand transplant in the Delaware Valley region. The complex procedure required 30 specialists in organ transplantation, orthopaedic surgery, reconstructive micro-surgery, plastic surgery, and anesthesia. Even with two teams working simultaneously, the operation lasted more than 11 hours.

While the procedure itself was clearly an achievement, the planning for it was no less impressive. In addition, because this kind of operation has been performed very few times anywhere, there were ethical issues that had to be considered first. Customarily, organ transplants are performed only to save lives. That fact balances the risks of both the surgery and the lifelong dependence on powerful drugs to prevent rejection. A bilateral hand transplant would not be life-saving – was it worth these risks?

Those were the initial concerns of Abraham Shaked, M.D., director of the Penn Transplant Institute, when, in 2009, he was first approached by L. Scott Levin, M.D., chair of the Department of Orthopaedic Surgery, professor of surgery, and director of Penn Hand Transplant. Levin raised the possibility of doing such a procedure at HUP. "I thought he was a little crazy!" said Shaked. But that was before he had met the patient, a young woman who had lost all of her limbs due to a severe post-surgical infection. When he did, his feelings changed: "The first time we met, she gave me a hug, with no hands or arms." Immediately, he continued, "you start to think about life in a different way. For us to give a productive life to these types of individuals – that's the meaning of life for them."

Levin also spoke early on with Arthur L. Caplan, Ph.D., director of the University's Center for Bioethics and professor of medical ethics. "We wanted to do things the right way," said Levin.

At first Caplan was, he said, "a little critical" of the plan. Transplanting the hands would require powerful immunosuppressive drugs, and Caplan did not believe there was an acceptable risk-benefit ratio. But, he came to think, if there was a patient who was emotionally and psychologically prepared and "who would truly benefit" from the operation, he was willing to change his mind. "I came to understand that this transplant is not cosmetic; it is truly functional, allowing a patient to carry out activities of daily living. Prosthetics don't give the kind of function you need for a good quality of life if you are a double amputee. . . . Morally, this takes us to a different place."

PRACTICE, PRACTICE, PRACTICE

The surgical techniques used to perform the hand transplant were not new, said Benjamin Chang, M.D., associate chief of plastic surgery, associate professor

of clinical surgery, and co-director of Penn Hand Transplant. "We've all fixed bones, re-attached muscles, repaired nerves, and sewn skin." The major difference was that this would be vascularized composite allotransplantation (VCA). Unlike working with solid organs, the surgeon performing a hand transplant must deal with multiple tissues, including blood vessels, bone, nerves, muscles, tendons, and skin.

Preparations started 18 months before the actual surgery. Using the patient's measurements and x-rays, the transplantation team created a step-by-step procedure specifically tailored to her needs. Chang said they divided the surgery into multiple parts. One team procured the donor limbs, while two other teams opened and prepared the patient's stumps to receive them. Two teams then prepared the donor arms and, finally, two teams attached the donor limbs to the patient's stumps. Chang led one of the latter teams while Levin, who is board certified in both orthopaedic and plastic surgery, led the other team as well as the procurement team. According to Chang, Levin "was the driving force that made all this possible."

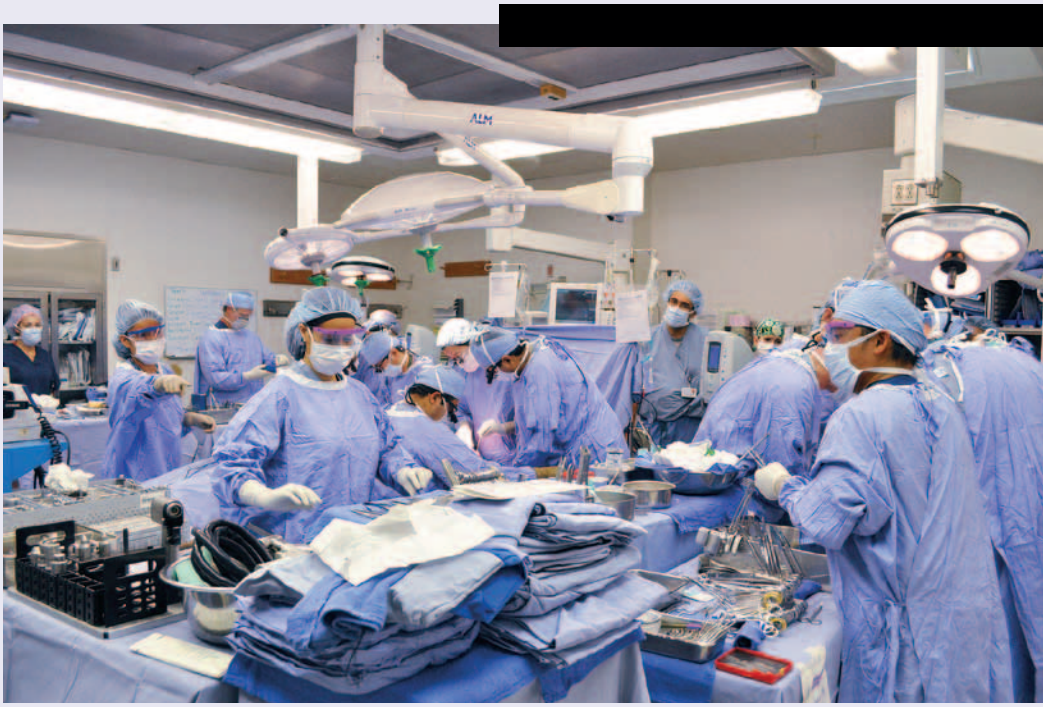
Pilots review checklists before their flights, and the surgical team decided to follow their example. "We created and printed out a checklist of each step and taped it on the OR wall," Chang explained. As each team completed a step, Stacey Doll, director of quality and regulatory compliance – solid organ transplant, checked it off. "This ensured that we didn't miss anything and also guided us in the right order," said Chang. They also had sterile engraved tags made so they could identify and then clearly mark each of the many muscles, tendons, nerves, and blood vessels that needed reattachment. Doll worked with the hand transplant team from the start to help organize the process and assemble all the available resources in Penn's solid organ transplant program. As Shaked put it, "She should be credited as conductor."

The team had several rehearsals. After each one, they'd debrief and further tweak the procedure to improve it. "We prepared as a team for patient safety and for a predictable outcome," Levin said. "There were no surprises to speak of."

Chang summed it up: "Our extensive planning – and practice, practice, practice – paid off."

A VITAL PARTNER: GIFT OF LIFE

According to Levin, "our most important partner" in the elaborate process was Gift of Life, the nonprofit organ and tissue donor program that serves the region. It was a unique transplant, "presenting challenges on many levels," said Richard Hasz, vice president of clinical services for the program.

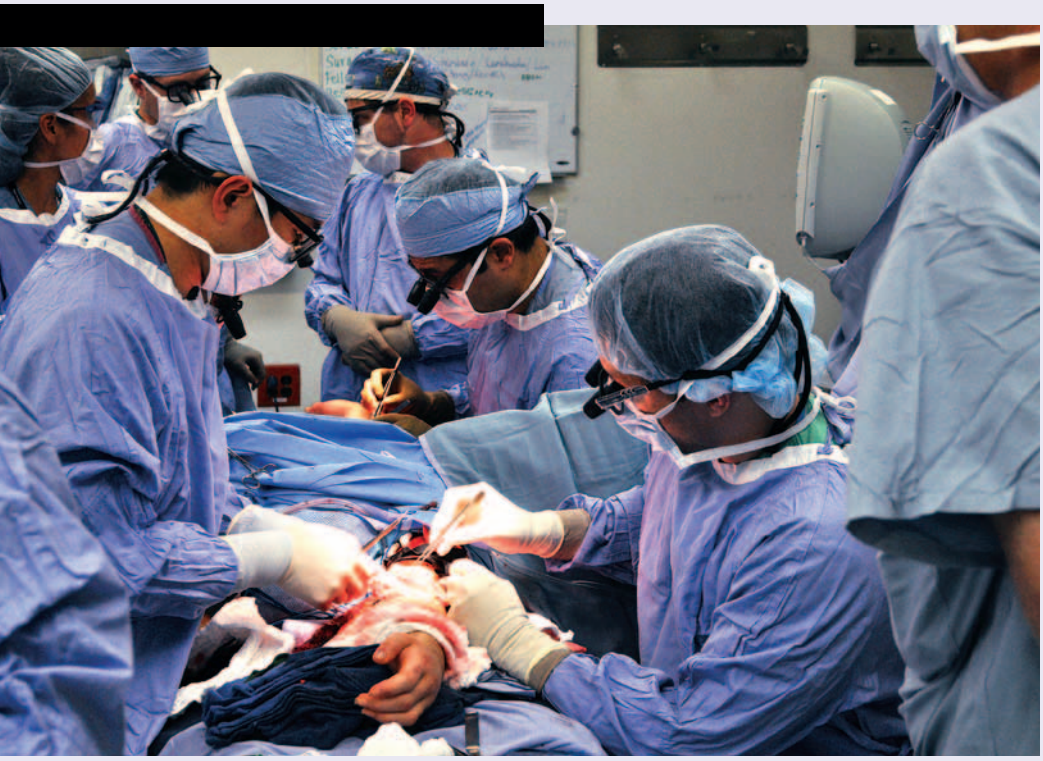


The first challenge centered on the donor family. Unlike most transplanted organs, a person's hands are recognizable. "We needed to understand both the critical medical and emotional aspects of this particular donation process," Hasz said. Finding a good match was another challenge. As visible transplants, the hands had to be the right size, gender, skin type, and age, with no obvious trauma, tattoos, or other visible marks.

Gift of Life also created a new protocol for the procurement process, "to establish the timing and sequence of the organ and hand removal," Hasz said. In addition to the donation of limbs, "five individuals received organs from that donor and at least 50 received tissue." The protocol placed hands first, but, as Hasz noted, "the surgeons knew up front that the solid organs were a priority. We would stop the hand procurement if we were in danger of losing any of the organs." Despite these challenges, it took Gift of Life only a couple of weeks to identify the donor. "Families in this area are very giving, especially if you explain the compelling need," he said. "This family had amazing strength."

RELEARNING HOW TO MOVE

The preparation for the hand transplant went beyond the surgery; it also presented new challenges to the rehabilitation team. Levin chose Laura Walsh, M.S.,



team leader of hand therapy, and Gayle Severance, M.S., both occupational therapists and certified hand therapists, to do post-surgical therapy.

Walsh and Severance created customized protective splints to protect the transplanted limbs – especially the point at which they are attached to the patient's own arms – and also to allow her to use her arms for basic tasks, such as eating and using a computer. While the patient was still in the hospital, they began a rigorous workout schedule of 4 to 6 hours a day, working to strengthen the patient's shoulder and arm muscles to move the new limbs.

Once the patient could again feel hot and cold (protective sensation) on her new limbs, sensory re-education began to help her recover the brain-hand sensory connection. As Walsh explained, when sensation initially returns, the brain is only getting "very global signals. For example, the brain can process that the hand is holding a round object but cannot distinguish a baseball from an orange."

In sensory re-education, the patient touches an object first with eyes closed – to allow the brain to process what is felt – and then with eyes open to "fully educate the brain on what the body is really feeling," continued Walsh. "We'll do this type of exercise over and over with varying shapes and textures."

> It takes a diverse team to perform such complex surgery and to work with the patient afterwards: among them, specialists in organ transplantation, orthopaedic surgery, reconstructive micro-surgery, plastic surgery, anesthesia, quality and regulatory compliance, hand therapy, and occupational therapy.

WHAT'S STILL AHEAD

Through the months following the operation, Levin said the patient was doing "superbly," but she has much rehabilitation ahead. Levin originally estimated that it would be at least a year before the nerves grow far enough into her arms to have independent motion of her fingers and possibly longer to regain feeling in her fingers. As Levin told *O&P Business News* in February, the patient now "can wipe away a tear and scratch her nose. We have also adapted some utensils to her splints so she can eat by herself."

In January, the patient was filmed picking up a plastic cup from a table with her new hands. The following month, she left Penn to return to her home in Virginia, where she will continue rehabilitation. But she will return to Penn periodically for progress checks and updates with the team. In February, as she left the hospital, she did a very simple but meaningful thing – she waved.

Six months following the transplant surgery, the patient has regained finger and thumb function, which allows her to eat by herself. Reports Levin, "The rate and degree of reinnervation of her muscles has been remarkable."

The multidisciplinary team at Penn expects to continue performing bilateral transplants, following the same basic principles but customizing their preparation – as they did with their first transplant – to assure optimal outcomes. Levin's ambition, he said, was "to move to the next level," not only for civilians but for "our wounded warriors."

"We prepared, we studied, we listened to each other, and then we came together to make it happen," he said. "It's our goal to work seamlessly together in the field of VCA so we can successfully treat these patients and give them their lives back." ●

FROM COMA TO CONSCIOUSNESS

By Brian L. Edlow, M.D. '07

AN ALUMNUS RELATES HOW A PATIENT'S JOURNEY BACK FROM BRAIN INJURY INSPIRED HIM

Fourteen days after being hit by a car while riding his bike, Doug Markgraf was able for the first time to listen to a verbal command, process this information, and respond by squeezing his right hand. This was the moment, made possible in part by a dedicated team of neurocritical care physicians at the Hospital of the University of Pennsylvania, that marked Doug's transition from coma to consciousness. What followed for Doug was one and a half months of inpatient rehabilitation, a year of outpatient rehabilitation, and a difficult road to functional recovery that continues to this day, more than five years after his severe traumatic brain injury. Last summer, in an inspiring feat of physical fitness, will, and determination, Doug got back on his bike and rode 3,200 miles across the country to raise awareness for traumatic brain injury. Along the way, he stopped at rehabilitation centers to encourage other survivors.

At the time of Doug's accident, I was a Penn medical student rotating in the neurological intensive care unit. My mentors were Joshua Levine, M.D., assistant professor of neurology, and Andrew Kofke, M.D., professor of anesthesiology and critical care. I had the opportunity to care for Doug while he was in a traumatic coma. Being present at the moment when Doug recovered consciousness and bearing witness over the past several years to his improbable recovery has been a singular source of inspiration for me as a clinician and researcher. I am now a fellow in neurocritical care at Massachusetts General and Brigham and Women's hospitals, and my research focuses on developing new magnetic resonance imaging (MRI) techniques to predict outcomes in patients like Doug who are in a traumatic coma. Over the past five years, through each stage of my training, I have continued to follow Doug's recovery by reading his blog and exchanging e-mails with him and his parents. I am always humbled to remember that we as clinicians had no prognostic tools that could have predicted this outcome.

> "BEING PRESENT AT THE MOMENT WHEN DOUG RECOVERED CONSCIOUSNESS HAS BEEN A SINGULAR SOURCE OF INSPIRATION FOR ME AS A CLINICIAN AND RESEARCHER."

Brian Edlow, left, presents Doug Markgraf with a Certificate of Appreciation.

At the time of Doug's coma, an outcome of vegetative state – or even death – seemed significantly more likely than a near-com-

plete recovery and a bike ride across the United States. I recently invited Doug to Boston to share his story with residents and medical students. In anticipation of this trip, Doug and I reviewed the MRI scan that was performed during his coma, and I shared my astonishment with Doug that the severity of "diffuse axonal injury" on his MRI scan made his recovery seem unlikely. We discussed that there has been only one report in the medical literature of another patient with such severe injury seen on MRI, with lesions on both sides of the brainstem, who attained Doug's level of functional independence.

Yet, what is most compelling to me about Doug's story is not the rarity of his recovery but the eloquence with which he describes the cognitive and emotional challenges that he faced after emerging from the coma. When he describes his experience to residents and medical students, Doug recalls the confusional state that often follows traumatic coma and explains that he felt as if his life were a dream. He refused to accept that he had spent two weeks in a coma. Instead, he constantly yearned to return to sleep so that he would have another opportunity "to wake up from this nightmare." When asked to reflect on how his life has changed since the coma, Doug thoughtfully explains that all of his achievements – graduating from college, becoming a middle-school teacher, and dedicating himself to a mission of advocacy – have made him feel prouder of who he is today than he ever did before the coma. The reason is all that he has overcome.

As I reflect on Doug's story and how it has influenced my career path, I am struck by how many questions about traumatic brain injury, and traumatic coma in particular, remain unanswered. Significant advances in functional brain imaging – many of which have occurred in the laboratory of John Detre, professor of neurology and

A Cross-Country Bike Trip to Raise Awareness

A survivor of traumatic brain injury makes a return visit to HUP

By Gregory Richter

More than five years ago, Doug Markgraf was struck by a pickup truck as he rode his bicycle in a bike lane in West Philadelphia. The impact threw him to the pavement. Although Markgraf was wearing a helmet, he suffered a traumatic brain injury (TBI) and broke his arm in several places. His racing bike and helmet were destroyed.

Markgraf spent two weeks in a medically induced coma at the Hospital of the University of Pennsylvania as his caregivers tried to prevent a secondary brain trauma. No one knew if he would ever walk or even talk again.

After being transferred to a rehabilitation facility, Markgraf spent much of the next year undergoing inpatient and outpatient rehabilitation. As he grew stronger, he set a new personal goal: to bike across the continental United States as a way to raise awareness and funding for TBI research. Equipped with a tent, food, a smart phone (to update his blog, take photos, and more), and a phone charger that generates electricity as he pedals, Markgraf began his journey in San Francisco

Doug Markgraf on his arrival at HUP.

on June 27, 2011. His overall mission was to talk to people about traumatic brain injury in at least one hospital in every state.

It wasn't always easy. Each night, he struggled to find a place to sleep – in his tent under the stars, on a new friend's couch, and so on – and to keep the bike stocked with essential items. As he explains, "When the tread on my back tire fell off, I thought, 'This is such a waste of

money.' Then I realized I'd been riding for 1,500 miles!"

Stops along the way included TBI treatment and rehabilitation centers. There he talked to doctors, patients, and others about preventing and treating traumatic brain injury and the need for stronger policies supporting insurance coverage for TBI rehabilitation. Nearly two months after beginning his journey, Markgraf arrived on his bike at HUP. He was welcomed to the Neurointensive Care Unit, where he visited some of the staff members who saved his life five years earlier.

"At treatment and rehabilitation centers along the way, Markgraf talked to doctors, patients, and others about preventing and treating traumatic brain injury and the need for stronger policies supporting insurance coverage for TBI rehabilitation."

James M. Schuster, M.D., Ph.D., associate professor of neurosurgery and an avid cyclist as well, was among those welcoming Markgraf back. "You're a testament to why we do this," said Schuster. "It's great, it's awesome."

"I don't think that people realize how great this makes us feel," said Eileen Maloney-Wilensky, M.S.N., director of the Neurosurgery Clinical Research Division.

Although Markgraf's memory is still fairly limited (he does not remember the actual accident) and he commonly experiences mental fatigue, he is experiencing a remarkable recovery. After completing his college education, he's back at school – teaching robotics at a local high school – and he ran in the Philadelphia Marathon in November. Currently, he is also working on a documentary that tells his story.

He sums up his message this way: "We all can do amazing things." ●

To read more about Markgraf's recovery and mission, go to http://dougtrails.wordpress.com/.

radiology, at Penn's Center for Functional Neuroimaging – have provided valuable new insights into how widely distributed neural networks are recruited to compensate for injured pathways. Advances in structural brain imaging, which is the focus on my current research, have provided unprecedented information about the neuroanatomic connectivity of these networks.

But the reality is that prognostic models that integrate these functional and structural data are still lacking. There are few clinically available tools to help physicians predict which patients in traumatic coma will make a recovery like Doug's, and which will be like Doug's next-door neighbor in the neurocritical care unit. This patient had the same type and severity of traumatic brain injury but died one month later, never having regained consciousness. I have two goals that are guiding my career as a young physician-scientist. One is to be able to predict which patients will transition from coma to consciousness. The other is to develop new therapies to facilitate this transition. Doug's advocacy mission and his dedication to continuing his recovery on a day-to-day basis continue to inspire me to seek answers. ●

"AT THE TIME OF DOUG'S COMA, AN OUTCOME OF VEGETATIVE STATE – OR EVEN DEATH – SEEMED SIGNIFICANTLY MORE LIKELY THAN A NEAR-COMPLETE RECOVERY AND A BIKE RIDE ACROSS THE UNITED STATES."

Saga of a Disease Protein

When normally folded, TDP-43 plays an important role in the body. Now, scientists are finding that when it is misfolded, the protein can wreak havoc.

By Karen Kreeger

Photographs by Addison Geary

If it is anything, science is incremental. It's a slow accumulation of knowledge punctuated by "eureka" moments. As the years go by, one of my favorite aspects of working in science communications is watching how discoveries unfold – and in the case of TDP-43, I mean that both literally and figuratively. TDP-43 is a normal protein that undergoes pathologic misfolding in its disease state.

As with all proteins, it is the shape of TDP-43 – the way the linear sequence of amino acids is ultimately folded into a three-dimensional protein – that is crucial in how it works or doesn't work. Normally folded, the TDP-43 protein is active mainly in the nucleus of cells throughout the body. It aids in editing the transcription of the genetic code.

A misfolded form of TDP-43 first became a major suspect in neurodegenerative diseases in late 2006, when Virginia M.-Y. Lee, Ph.D., M.B.A., and John Q. Trojanowski, M.D., Ph.D., at Penn's Center for Neurodegenerative Disease Research and the Institute on Aging, made an important discovery. The husband-and-wife team found mutated TDP-43 accumulated in post-mortem brain tissue from individuals who had been diagnosed with certain types of frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS, commonly known as Lou Gehrig's disease). The misfolded disease protein was recovered only from affected central nervous system regions, including the hippocampus, neocortex, and spinal cord. The approach that led to this discovery was an exploratory study of proteins that behaved abnormally, in studies of FTLD cases first. What Lee and Trojanowski did not expect was to find a form of TDP-43 in all the ALS cases they subsequently studied.

John Trojanowski and Virginia Lee

To identify the protein, the research team first made antibodies to the presumptive misfolded disease protein they believed was responsible, whose identity they didn't know at this stage of their studies. Next, they took brain extracts containing the mystery protein and injected them into mice. The mice then developed the monoclonal antibodies that recognize TDP-43. All 72 cases of FTLD or

ALS the researchers examined contained misfolded TDP-43.

"Since many cases were studied, the data became very compelling," recalls Lee, the John H. Ware 3rd Professor in Alzheimer's Research, professor of pathology and laboratory medicine, and director of the Center for Neurodegenerative Disease Research. Still, in the discussions at the time, other scientists were skeptical that TDP-43 was to blame for the pathology of ALS.

Two years later, however, further proof emerged that TDP-43 is the misfolded protein in ALS and FTLD, through findings that TDP-43 mutations track with the disease. A flurry of reports, including one from Penn, showed that DNA isolated from brain tissue of ALS and FTLD patients harbored mutations in the gene that encodes TDP-43. Penn researchers surveyed 259 individuals either with ALS or with both ALS and FTD, where misfolded TDP-43 protein was present. The team was also able to determine the DNA sequence of the TDP-43 gene. In addition, the investigators found two families in which a mutation was present. Within the same family, all members who have the disease carry the mutated form of TDP-43. Unaffected individuals lacked the mutation. Other groups made similar findings around the same time, strengthening the evidence.

"When all the mutations began to appear in 2008, investigators who expressed some doubts about our finding were won over," says Trojanowski, the William Maul Measey-Truman G. Schnabel Jr., M.D., Professor of Geriatric Medicine and Gerontology, professor of pathology and laboratory medicine, and director of the Institute on Aging.

"A paradigm shift"

The emerging field of TDP-43 biology soon underwent a change in understanding how and where the diseases manifested themselves in the brain. Trojanowski and Lee showed that misfolded TDP-43 accumulates throughout the brain as well as the spinal cord of ALS patients. What that suggests is that ALS has broader neurological effects than scientists previously appreciated.

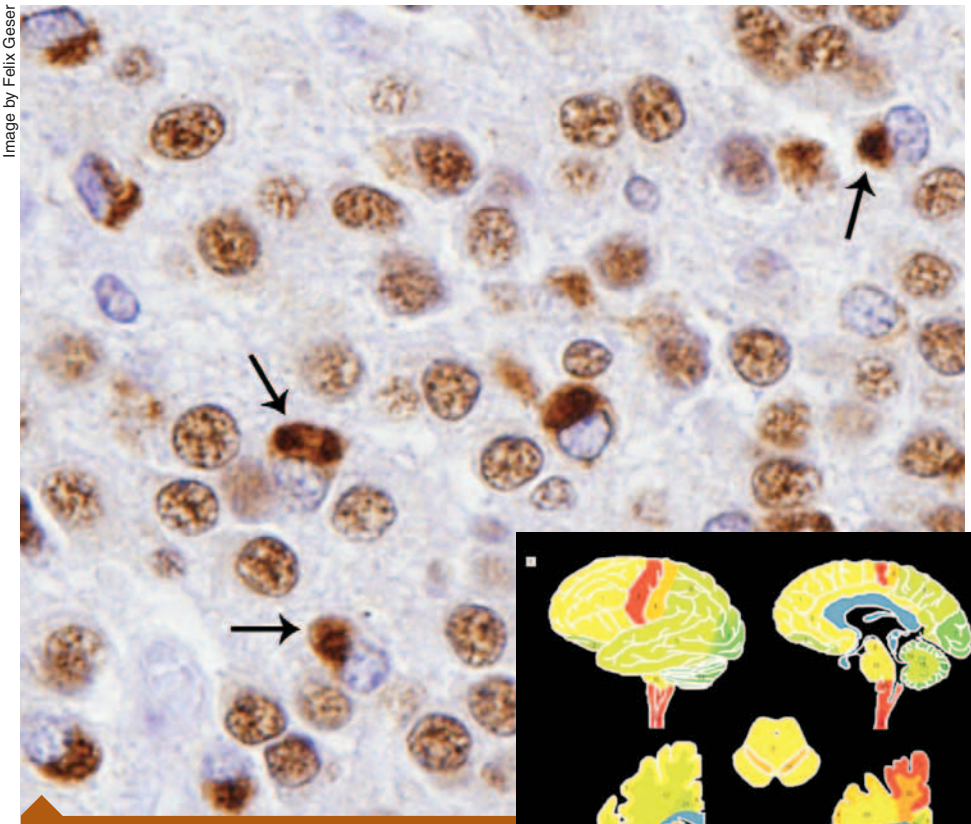
By again using TDP-43-specific antibodies to examine post-mortem brain tissue of ALS patients, Lee and Trojanowski observed effects in the areas of the brain and spinal cord that control voluntary movements. That was expected, based on the disease's symptoms. What they did not expect, however, was to see the effects in regions of the brain that involve cognition, executive functioning, memory, and involuntary muscle control.

As initially proposed in 2006, the new evidence supported the idea that ALS, as ALS-PLUS (ALS with cognitive impairments), and FTLD all had the same underlying molecular pathology involving abnormal TDP-43.

As Trojanowski puts it, "This constituted a paradigm shift in the way we think about these diseases."

At this point, researchers had firmly established that TDP-43 was the culprit in some cases of ALS and FTLD. They did not yet know how mutated TDP-43 might cause disease or what other genes and proteins played a role. This deepening of inquiry would take research to several different labs at Penn (and elsewhere) and at least three animal models.

Image by Felix Geser



The arrows indicate misfolded disease proteins in neurons in the hippocampus.

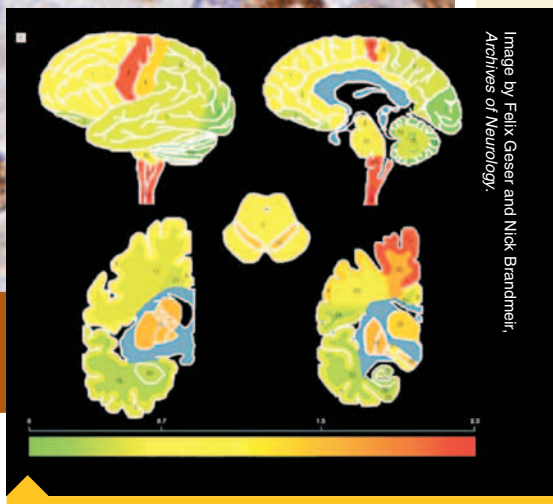


Image by Felix Geser and Nick Brandmeir, *Archives of Neurology*.

Red, orange, and yellow depict areas of highest density of TDP-43 pathology.

More genetic factors that affect TDP-43

During his days as a postdoctoral student at Massachusetts Institute of Technology, Aaron Gitler, Ph.D. '04, used a novel approach to screen for neurodegenerative disease genes. Although the approach was novel, the material was not: yeast cells, the same cells that bakers and brewers have used for centuries to make bread and beer. In the simple yeast cells, misfolded TDP-43 forms clumps just as it does in human nerve cells. The clumping process takes decades to show up in humans but the researchers could model the process within a matter of hours in yeast cells. This advance allows for rapid genetic screening to identify proteins or even drugs that potentially could reverse harmful effects. The next step would be to test the "hits" they found in animal models.

Using a combination of the yeast TDP-43 system and fruit flies, Gitler, then an assistant professor of cell and developmental biology at Penn, and Nancy Bonini, Ph.D., professor of biology in Penn's School of Arts & Sciences and an investigator of the Howard Hughes Medical Institute, found evidence that mutations in the ataxin 2 gene were a genetic contributor to ALS cases associated with TDP-43 abnormalities. More specifically, the study showed that repeats of a bit of DNA that encodes the amino acid glutamine in the ataxin 2 gene – a genetic stutter, as it were – are associated with an increased risk for ALS. The research began with Gitler's yeast screens in which genes that could suppress or enhance TDP-43 toxicity were identified. The team transferred 5,500 yeast genes into a strain of yeast they had engineered to express misfolded human TDP-43. Among the genes that modified toxicity was the yeast counterpart of ataxin 2.

Photograph by Candace diCarlo

Nancy Bonini

Gitler and Bonini transferred the genes to fruit flies to assess the effects of the genes and their interactions in the nervous system. When the researchers directed expression of misfolded TDP-43 to the eye of the fruit fly, a progressive, age-dependent degeneration began. When directed to motor neurons, the flies progressively lost the power to move spontaneously. Gitler, Bonini, and researchers at the Center for Neurodegenerative Disease Research then went on to show that people with the same genetic stutter in their ataxin 2 gene had an increased risk for developing ALS. (Gitler has now joined the Stanford School of Medicine.)

But ataxin 2 was not the only gene affecting misfolded TDP-43. Vivianna Van Deerlin, M.D., Ph.D., associate professor of pathology and laboratory medicine at Penn, led an international study using post-mortem brain tissue from 515 patients with frontotemporal lobar degeneration that was associated with TDP-43. The researchers found that these patients had many genetic variations called SNPs in common in a region on chromosome 7 containing the protein TMEM106B. In contrast, in the control group of more than 2,500 disease-free patients, there were no such genetic variations. Based on this finding, the team concluded that the TMEM106B gene variants confer a higher genetic risk for all FTLD-TDP patients, as well as in the subset of FTLD patients with disease-causing mutations in another protein called progranulin.

James Shorter

Virginia Lee consults with Todd Cohen.

Beginning to understand how mutated TDP-43 causes disease

At the same time that some researchers were delving into the genetic evidence linking TDP-43 and disease, James Shorter, Ph.D., assistant professor of biochemistry and biophysics, was studying how TDP-43 misfolds at the protein level. He found that, in the absence of other molecular components, pure normal TDP-43 rapidly assembles into short soluble polymers called oligomers and aggregates. These bear remarkable outward structural resemblance to the aggregates observed in the degenerating motor neurons of ALS patients. As Shorter notes, both normal and mutated TDP-43 form aggregates in his system, and some TDP-43 mutants accelerate aggregation.

In particular, Shorter's laboratory found that a section at one end of TDP-43's amino acid sequence starts the misfolding and aggregation of pure TDP-43. This finding corroborated observations made about yeast by Aaron Gitler.

According to Shorter, it was a chance conversation among Shorter, Gitler, and Oliver King at the Boston Biomedical Research Institute that led to an unexpected twist in the investigation of TDP-43. Using a sophisticated bioinformatics approach, King recognized that the misfolding-initiating section of TDP-43 is remarkably similar to the type of section that enables some proteins to form prions in yeast. Prions are misfolded proteins that are implicated in mad cow disease in cattle and in Creutzfeldt–Jakob disease in humans. The unexpected conclusion was that virtually all of the mutations in TDP-43 that are linked to ALS lie in the prion-like section of TDP-43.

Shorter's lab then went on to establish that, in the context of the pure protein, some ALS-TDP-43 mutations can accelerate aggregation, whereas other mutations do not. These findings meshed with other observations made by Gitler's group in yeast, in which some ALS-linked TDP-43 mutations promote aggregation and toxicity, whereas others do not and result in proteins that are very similar to normal TDP-43. These data suggested that there is more than one way by which mutations promote ALS.

Shorter's team is now investigating methods to prevent or reverse the misfolding of TDP-43. Shorter notes, "The powerful combination of our pure protein biochemistry and Aaron Gitler's approaches in yeast is likely to yield many new and profound insights into ALS, which will undoubtedly change the way we think about this disease."

A later chapter in the TDP-43 story added yet another wrinkle: Virginia Lee

In the Center for Neurodegenerative Disease Research, slides of brain tissue.

showed in a mouse model the first direct evidence of how mutated TDP-43 can cause neurons to die. When human mutated-TDP-43 genes are put into mice, the mouse nerve cells die because they stop producing enough normal mouse TDP-43. Because cells regulate the exact amount of TDP-43, over-expression of the human TDP-43 protein prevents the mouse TDP-43 from functioning normally.

In Lee's view, this effect leads to neuron death in this model rather than clumps of TDP-43 because these clumps were rare in the mouse cells observed in this study. She says that it is not yet clear why clumps were rare in these mice but so prevalent in human post-mortem brain tissue of ALS and FTLD patients.

The researchers are now back to looking for more genetic partners for TDP-43-specific genes that are regulated by TDP-43 and trying to discover how messenger RNA (mRNA) is involved. In addition to other functions, TDP-43 stabilizes the structure of mRNA.

Knowing the genes involved in the normal function of TDP-43 will help researchers identify what goes awry when normal TDP-43 is missing or nonfunctional or when clumps of misfolded TDP-43 crowd a cell's interior.

The continuing work on animal models is about to bear fruit as well: Five years after the publication of the original paper on TDP-43, Lee notes that the center she directs will soon launch studies of strategies to prevent TDP-43-mediated degeneration of the nervous system using this mouse model of TDP-associated amyotrophic lateral sclerosis and frontotemporal lobar degeneration.

An epilogue – but not the last word

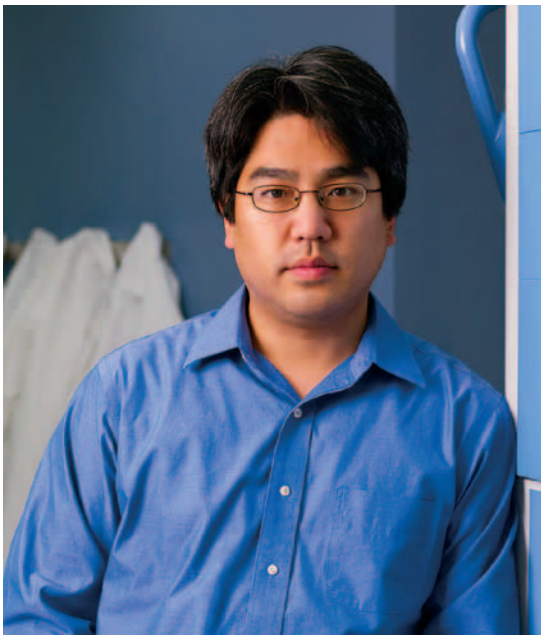
A major hurdle in understanding neurodegenerative diseases is establishing a clear picture of what leads up to neuron death. In recent years, much data have been published indicating that increased oxidative stress plays a role in the degeneration and death of neurons. Oxidative stress is an imbalance between the production of reactive oxygen molecules and the body's ability to get rid of them. Disturbances in the normal oxygen state of tissues can damage all components of the cell, including proteins and DNA.

Most recently, Todd Cohen, Ph.D., a postdoctoral fellow in the Lee lab, studied how TDP-43 reacts to oxidative stress. His work was published in the *EMBO Journal* in December. Stress induces the protein to move from the nucleus to the cell cytoplasm; its ability to fold properly is altered as well. Then, in January, Lee, Trojanowski, and Edward B. Lee, assistant professor of pathology and laboratory medicine, published a related review of TDP-43-mediated neurodegeneration in *Nature Reviews Neuroscience*. There, they suggest two reasons for the neurodegeneration. It could result from the protein's loss of function as it misfolds and is no longer available to regulate gene expression; or it could result from a gain of toxic properties as it forms clumps in the cell cytoplasm, disrupting normal day-to-day functions.

In the *EMBO Journal*, Cohen explained how TDP-43 reacts to stress chemically and showed that it is reversible. His team found that oxidizing chemicals caused cross-linking between sulfur molecules of the amino acid cysteine in the TDP-43 proteins in culture. This linking caused the protein to misfold. In addition, the researchers also saw sulfur-sulfur bonding between two or more proteins, which was the start of debilitating TDP-43 clumps.

What was more surprising was that they were able to break up the TDP-43 clumps in the cultured cells and in post-mortem human brain tissue samples from FTLD-TDP patients. They also showed that these disaggregated proteins became functional again.

The "big take-home message," says Cohen, is that antioxidant therapy – particularly a well-known one called NAC – could prevent the sulfur cross-linking in the first place. That would prevent the protein misfolding and the multi-protein clumps seen in many neurodegenerative diseases. According to Cohen, future studies – first in animal models and eventually in humans – could evaluate whether taking NAC or related antioxidant supplements could be an effective treatment strategy to prevent amyotrophic lateral sclerosis or frontotemporal lobar degeneration.


Edward Lee

There appears to be more and more to this saga of TDP-43, a single protein that plays some very important roles. The way scientists are producing data around TDP-43 and many neurodegenerative diseases suggests that the collective research effort is beginning to gain momentum. ■

Matches Made, Futures Glimpsed

Photographs by Daniel Burke

On March 16, at the Perelman School of Medicine as around the nation, anxious medical students finally learned where they would be going in the next phase of their training. At Penn, 140 students gathered in Dunlop Auditorium, along with cheering squads of relatives, Dean Larry Jameson, faculty members, and staffers. Gail Morrison, M.D. '71, G.M.E. '76, the senior vice dean for education, called Match Day "one of our most exciting days in medical school." Jon B. Morris, M.D., associate dean for student affairs, displayed his own matching letter from some years back. One of his first thoughts at the time was how to tell his wife that "we were to spend the next five years of our lives in Cleveland." Dean Jameson was reassuring, asserting that the students would be successful wherever they went: "Penn has prepared you very well."

Sharing the excitement are Jessica Spivey and Brian Levins. Spivey will be staying here at HUP for anesthesiology, and Levins will be going to New York University for radiology.

Joy Wan shows her letter from the National Resident Matching Program. She will do a dermatology residency at HUP.

Among those well-prepared students are Kathryn Hall and Michael Hall, shown here with their 10-month-old son. Kathryn will start a three-year residency in pediatrics at The Children's Hospital of Philadelphia. Michael will spend the next four years at HUP, training in anesthesiology. Kathryn started Power Up Gambia, a non-profit organization that has brought life-saving solar energy to a hospital in Gambia. (See *Penn Medicine*, Summer 2010). To concentrate on her residency, she intends to step down from her role in the organization for the next three years.

Medicine in the Third Reich:

THE 65TH ANNIVERSARY OF THE DOCTORS' TRIAL AT NUREMBERG

By Harry Reicher, L.L.M.

Top: Dr. Carl Clauberg, far left, with an experimental subject.

Bottom: Defendants in the Doctors' Trial in the dock.

Recent discoveries about United States medical experiments in Guatemala remind us that we can never take ethics for granted and that researchers sometimes can become blind to the humanity of their research subjects. The worst documented example was Nazi medicine.

Facts have a disquieting tendency to surface, sometimes despite efforts to overlook them or conceal them. A full 65 years after United States physicians began an ethically horrendous medical experiment in Guatemala, a vivid picture of what they did has finally been provided. Last September, the Presidential Commission for the Study of Bioethical Issues publicly released *Ethically Impossible: STD Research in Guatemala from 1946-1953*. The commission, chaired by Amy Gutmann, Ph.D., president of the University of Pennsylvania, recounts how American medical researchers in the United States Public Health Service intentionally left more than 1,300 Guatemalan prison inmates, psychiatric patients, commercial sex workers, and soldiers exposed to sexually transmitted diseases. Guatemalan officials also took part.

The purpose of the study was to test the effectiveness of antibiotic penicillin. The study was approved by the Syphilis Study Section of the Public Health Service, which included physicians from Johns Hopkins University, Harvard University, and the University of Pennsylvania, among others; and the study grant was approved by the Surgeon General. STDs, as the commission report states, "were long a concern of the U.S. government," particularly as the diseases affected soldiers.

Writing about what she called "this shameful chapter in American medical history" in *The Huffington Post*, Gutmann noted that the experiments, done completely without obtaining consents, "resulted in a living hell for many of their subjects." Even more so, having conducted a similar experiment with Terre Haute, Indiana, prisoners where they received informed consent, the same doctors deliberately did not inform the Guatemalans. As the commission report states, "Obtaining informed consent of subjects is a cornerstone ethical requirement." In the view of the commission, the participating medical researchers "were morally culpable and blameworthy. . . ." The good news, however, is that the commission also concluded that such experiments "could not be approved under the current system for protecting human subjects in U.S.-funded research."

In December, the commission released a related report called *Moral Science: Protecting Participants in Human Subjects Research*. It found that the current system, although sound, is not perfect. The commission recommended 14 changes to current policies to better protect human subjects. "The Guatemala experiments remind us never to take ethics for granted," Gutmann noted at the time of the second report. "Good science requires good ethics, and vice versa." (For more on the Presidential Commission and its findings, go to http://bioethics.gov/)

But what happens when such experiments are in fact supported by the state? Or conform to a prevailing ideology? In this context, *Penn Medicine* presents an article by Harry Reicher, LL.M., an adjunct professor of law at the Penn Law School. A specialist in global human rights and international law, Reicher has served on the United States Holocaust Memorial Council. What follows is an edited version of a lecture Reicher delivered under the auspices of the Midwest Center for Holocaust Education, in conjunction with *Deadly Medicine: Creating the Master Race*, a travelling exhibition prepared by the United States Holocaust Memorial Museum.

2012 marks six and a half decades since the conclusion of the historic Doctors' Trial at Nuremberg, Germany, which brought to the bar of justice leading figures in the Nazi medical establishment. These were doctors who committed major atrocities in the name of medicine and in the name of science, and in the process inflicted horrific pain, suffering, and death on their victims. The trial, which resulted in convictions and sentences, including the death sentence, sent a powerful message, particularly to the medical profession: Doctors, like political and military leaders, as well as others, live, simultaneously, in two legal systems, the national and the international. And it is not enough for individuals to look to the national legal system to determine what is permissible, and even required, under national law. Rather, the inquiry must always encompass the requirements of international law.

When we talk about the Nuremberg trials, we are really referring to a monumental precedent in the history of international law, international criminal law, and international human rights. There were differences of opinion about how World War II and Holocaust-era perpetrators should be dealt with. The view of the United States, presented particularly through President Harry S. Truman and Justice Robert Jackson of the U.S. Supreme Court – who stepped down from the Court temporarily in order to lead the U.S. prose-

Photographs: United States Holocaust Memorial Museum

cution team at the Nuremberg trials – was that there must be orderly trials. That sounds trite today, so many years later, but it was far from obvious to everyone in 1945. Respectable voices, including the British War Cabinet meeting in solemn session in London, insisted that trials were really unnecessary. Their view, essentially, was: We know who these people are; we know what they did; we know who was responsible; all we need to do is to take them out, put guns to their heads, and shoot them. The United States' view prevailed, with the result that abiding precedents, of both a substantive and a procedural nature, were established.

MAJOR RATIONALES FOR ORDERLY TRIALS

There were three major rationales for insisting upon having orderly trials, and all of them resonate down into the 21st century. First, it was important to set international law precedents. Lawyers and judges look to the past in order to determine how cases should be decided, now and in the future. The idea was to create precedents that would send a loud and unequivocal message to future would-be Hitlers.

A second rationale was to set a high moral plane. To paraphrase Justice Jackson: We are a civilized society. We do not act like *them*. If people are guilty, let them be found guilty, after fair and orderly trials, with all notions of due process applied, giving the defendants every chance to defend themselves. If, after that, they are found guilty, let them be treated accordingly.

And the third important rationale was to collect the historical record. The Nazi regime was unparalleled in history in its obsession with recording everything that was done, down to the minutest detail. People such as Truman and Jackson took the view that international society was obligated to assemble the massive collection of documents, place it in one major repository, and make it available to future generations of historians, scholars, and anyone else interested in studying the Nazi regime of evil.

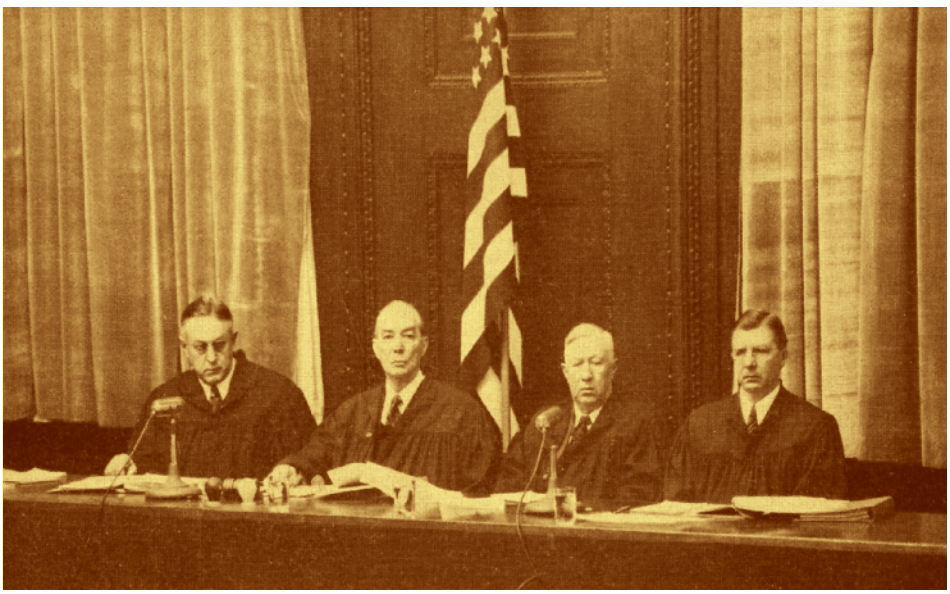
The rationale for the Nuremberg trials was to create precedents that would send a loud and unequivocal message to future would-be Hitlers.

THE NUREMBERG TRIALS

The term "Nuremberg Trials" is really a compendious reference to 13 trials, the first of which is most well known in the public domain. That was the trial of the leading figures in the Nazi political and military establishments, who were both alive and in captivity. Hitler, Himmler, and Goebbels had committed suicide. Whoever was left from the main leadership, and was in captivity, was put on trial. After that, however, the United States, acting in accordance with international law, and by agreement with the other allied victors, mounted a series of twelve trials in the American zone of occupation. They took place, broadly, according to the occupations of those on trial.

In addition to the trial of the doctors, there was a trial of the lawyers who had perverted the German legal system and converted it into a weapon to be used against the victims. Another trial was of industrial leaders, in particular the leaders of I. G. Farben, the massive conglomerate that put its technological and corporate know-how and its facilities at the disposal of the Nazi regime, effectively becoming a full partner in both the Second World War and the Holocaust. And so on.

It was important that the lessons of Nuremberg be applied beyond the political and military circles of the country's leadership and that the principles be related to, and the lessons be imprinted on, every single profession and occupation. If doctors were capable of committing atrocities, then what does it say about the latent capacities within every single one of us? And what would it take to bring out those latent capacities?



Tribunal judges, from left to right: Harold L. Sebring, Walter B. Beals, Johnson Tal Crawford, and Victor C. Swearingen.

THE TRIAL OF THE DOCTORS

As far as the Doctors' Trial was concerned, all three of the rationales for trials at Nuremberg were important. For a start, it was important to establish standards. One of the defenses proffered by the doctors was that there were no clear-cut standards in the field of medicine, particularly when it came to experiments on human beings. One of the major outcomes of the Doctors' Trial, in fact, was the Nuremberg Code of medical ethics, which articulated firm standards for the practice of medicine, insofar as it comes to experiments on human beings.

The second rationale – setting a high moral plane – was very important in the context of doctors. Those on trial were charged with extreme viciousness, callousness, and utter brutality.

The third rationale – to create a historical record – was also important, because what was involved in the trial was counter-intuitive. The medical profession, in the public consciousness, has always connoted healing and sustaining life. By contrast, in Germany, exactly the opposite took place.

There were 23 defendants in the trial, leading figures in the Nazi medical establishment. Twenty of them were actually doctors; the other three were important administrators in the country's medical hierarchy. They were implicated in various capacities. Some actually performed the experiments, as well as other atrocities. Some supervised experiments, took notes, and wrote them up. Others observed them and reported back to Berlin, to people such as Himmler. Yet others provided the "human subject matter," and some assisted generally.

The lead defendant was Dr. Karl Brandt. He was, among other things, Hitler's personal physician. He was responsible to Hitler and reported directly to him. Brandt had the dubious distinction of being personally and centrally involved in the first official act of state-sanctioned euthanasia under the Nazi regime, which took place in 1938 in Leipzig. A child was born severely handicapped, to parents who were both members of the paramilitary SS. The parents were racially committed Nazis and, in keeping with their ideological inclinations, they took the view that it was in order for their child to be put to death. Brandt went there, surveyed the case himself, and gave the order. Subsequently, a letter dated September 1, 1939, gave Dr. Karl Brandt and another doctor the authority to launch a euthanasia program. The letter, signed by Adolf Hitler himself on his personal stationary, had the force of law.

Dr. Karl Brandt (back row, far right) is seen accompanying Adolf Hitler (front row, center) in November 1941.

Of particular significance was the phrase that said that patients who, on the basis of human judgment, were considered incurable "can be granted mercy death." The implication was that putting them to death was actually doing them a favor. They were being released from being trapped in a terrible physical or mental situation. (At the same time, in terms of the underlying racial ideology of the Nazi Party, it was also a release and a relief for the state as a whole, which was no longer obliged to support them.) Eight years later, when Brandt was being sentenced to death at Nuremberg, he did not renounce this view.

The euthanasia program gave rise to the chilling phrase "life unworthy of life," which carried with it two deeply disturbing implications. First, certain people, because of physical and mental ailments, and perhaps other conditions as well (for instance, their race), were not worthy of living. The second implication was that there were people (other than the patients themselves) who were entitled to form the judgment that these lives should not be maintained – and to make the judgment to extinguish them.

THE CHARGES AGAINST THE DOCTORS

The main charge in the Doctors' Trial was crimes against humanity. The first time it was articulated as a crime in international law was in the main trial in Nuremberg, which began in 1945. For purposes of the Nuremberg trials, the term meant major atrocities: murder, enslavement, torture, inhumane treatment, and so on. Today, it is a main pillar of all the courts and tribunals dealing with major human rights atrocities, whether in the

Dr. Sigmund Rascher

former Yugoslavia or Sierra Leone or Cambodia or elsewhere. And it is also a major pillar of the jurisdiction of the permanent International Criminal Court.

The other major pillar of all these courts and tribunals is the crime of genocide, which was not yet fully developed as a crime in 1946, when the Doctors' Trial started, although the term "genocide" itself was already known. It subsequently became an important staple of all the tribunals mentioned above. The key element in the crime of genocide is the taking of actions intended to wipe out a group, in whole or in part: a racial, ethnic, religious, or national group. Sterilization is therefore capable of being an act of genocide, because the line stops there. If it is done to enough people, in a short enough period of time, it is possible to wipe out a whole group in one generation.

The charge of crimes against humanity arose out of a variety of circumstances. Euthanasia was a key element. In addition, many different experiments were performed on human beings without their consent, without anesthesia, no matter how agonizing those experiments were, and with no regard to human pain and suffering, and even death. Brandt himself was involved fully in a range of those terrible experiments.

THE EXPERIMENTS

Let us now examine briefly two of the important experiments and highlight two other personalities who were very involved in different aspects of Nazi medicine.

The first example is the high-altitude experiments that were conducted in 1942, at Dachau concentration camp. A low-pressure chamber simulated the loss of pressure that a pilot in the Luftwaffe would experience if he were flying at a height of 68,000 feet. These excruciating experiments were the idea of Dr. Sigmund Rascher, a captain in the air force.

After attending an important course on aviation medicine, he wrote a letter to Himmler saying that, during the course, "considerable regret was expressed that no tests with human material had yet been possible for us, as such experiments are very dangerous and nobody volunteers for them." He asked Himmler to put human subjects at his disposal. He did not disguise the fact that the experiments might result in death. The point was, he felt, that experiments on monkeys were unsatisfactory, because they did not properly replicate the conditions experienced by human beings. Himmler's answer: "Prisoners will, of course, gladly be made available."

This exchange sounds callous; it sounds coldblooded; it sounds inhuman. But at the same time, it was also logical, in a perverse way. What they were saying was a corollary of the underlying racial ideology of the Nazi regime. In his infamous tract *Mein Kampf*, Hitler began by laying down what he called an immutable law of nature, namely, that nature abhorred interbreeding between higher and lower species. The result was that the level of the higher species would be dragged down. These starting propositions were the prelude to Hitler's whole theory about the importance of preventing intermingling and interbreeding between Jews and Aryans.

The premise underlying all this was critical: Humans were seen as species, akin to animals and plants. Species could be experimented on to improve them; it was possible to experiment to develop a better rose, with a new color. Plants could also be used as guinea pigs; likewise with animals. And the same applied to human beings. The ultimate corollary of such thinking was that, if plants had weeds, it was acceptable to exterminate them. That logic was extended to Jews, who were seen as racial vermin.

Against this background, Rascher's suggestion, and Himmler's response, make perfect sense. And so, the high-altitude experiments were conducted.

Another type of experiment involved sterilization. This does not mean sterilizations carried out under the 1933 *Law for the Protection of Heredity Health*, which provided for sterilization of those with hereditary physical and mental disabilities. Rather, this was experimental sterilization. Here, the key figure was Dr. Carl Clauberg, a man who looked for all the world like the friendly uncle who had come for a weekend visit.

In many ways, Clauberg was the epitome of the Nazi doctor. Before the war, he was a noted gynecologist, involved in

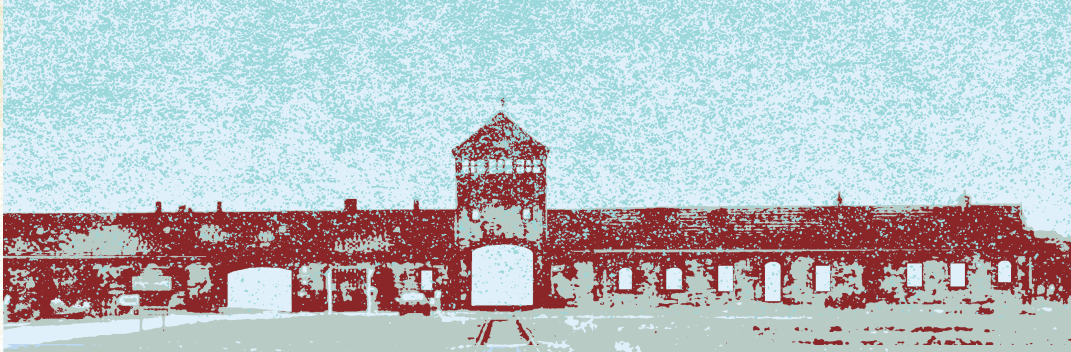
Dr. Carl Clauberg

important and meaningful research. He was seeking to develop techniques to unblock blocked fallopian tubes, giving women who were incapable of having children the ability to bear them. Then came Auschwitz, and Clauberg had an idea. He thought he could reverse the process and actually block fallopian tubes, thereby sterilizing women. He asked for Himmler's help, and Himmler readily agreed. Clauberg took charge of Block 10 of Auschwitz concentration camp. That was his laboratory, where he practiced his experiments, sterilizing women. He inflicted considerable suffering on them: the humiliation of being constantly undressed, poked, and measured by men; having acids and other concoctions injected into the reproductive organs, without anesthetic; the odors that emanated from the body. The ultimate result was many women left sterile, incapable of having children.

At first, Clauberg's stated goal was to sterilize 1,000 women per day. As more teams of doctors and assistants were trained, and as techniques were improved, how long would it have taken to sterilize enough women in order to wipe out the whole of the Jewish people in Germany, and then in Europe as well? Not so long, if one extrapolates the figures, and if he had been successful.

CONSEQUENCES – AND DEFENSES

Countless people died during, or as a result of, such experiments. Untold numbers suffered terrible pain, degradation, humiliation, and dehumanization. Clauberg taunted his victims and made nasty jokes, such as telling them that they had just been injected with sperm from animals. All of this was premeditated, fully conscious and fully intended. Which leads to the question: what defenses could these people – people such as Brandt and Rascher and Clauberg – offer to justify



Learning from the Past, Looking to the Future

AN INTENSE PROGRAM AT AUSCHWITZ AND ELSEWHERE UNDERSCORES THE NECESSITY OF MEDICAL ETHICS.

By Elliot Rabinowitz

This past summer I had the rare opportunity to participate in a program called the Fellowships at Auschwitz for the Study of Professional Ethics (FASPE). The program encourages graduate students from multiple disciplines to explore the ethical failures of their professional predecessors during the Holocaust as a way of setting the stage to discuss contemporary ethical issues. As part of the medical program of FASPE, I spent twelve days with a cohort of fourteen medical students and a few faculty members traveling from New York City to Berlin, Krakow, and Oświęcim (Auschwitz). In that historic environment, we learned from the past and took part in many thoughtful and intense discussions. The FASPE experience will live with me for the rest of my life, and the numerous lessons taught implicitly and explicitly throughout our discussions will undoubtedly serve to guide my clinical practice as a physician.

Physicians were not simply bystanders of the atrocities committed in Nazi Germany. Rather, they were active participants in the Nazi political party and even worked in the concentration and extermination camps. When we explore the social, economic, cultural, and occupational pressures that led to their willing participation, it quickly becomes clear that many of the same pressures exist today within the medical profession. FASPE not only provided an opportunity to explore these pressures but also allowed me to see what horrible situations can come about if we do not take the time to understand and appropriately address these pressures.

FASPE challenged me to ask many difficult questions: Why is it important to study history, specifically the participation of physicians during the Holocaust, when we address contemporary issues in medical ethics? How am I like the Nazi doctors? How can I be sure that I, as a future physician, do what is right by my patients? What does it truly mean to "do no harm"? These were only a few of the questions addressed during our incredible journey.

Physicians are often viewed as leaders of their societies. As medical professionals, we must critically assess the successes and failures of those who have come before us in an effort to remedy their mistakes and avoid similar failures in the future. To do so, I must not distance myself from the Nazi doctors, but rather accept that we have similarities as well as differences. My instinct, of course, is to state that I could never do anything like those physicians. But we know that no single doctor was responsible for the murder of millions. Instead, many doctors participated in the Nazi movement, some more fully than others. Individual decisions by hundreds, if

not thousands, of medical professionals contributed to what became mass murder. Learning how those doctors were educated, becoming aware of the cultural norms that affected their decisions, and understanding how they justified their actions can only benefit me in my own future practice with patients.

How will I know what I do as a doctor is right by my patients? And how can I ensure that I will uphold the ethical principle of nonmaleficence when interacting with my future patients? My experience with FASPE reminds me that patients' best interests are of primary importance; the wishes of families and societies are only secondary and tertiary. My peers on the program taught me that we must support each other and believe that we truly have the power to make positive change in our patients' lives.

While these explanations begin to address these complex questions, I simply do not have absolute answers. It is this uncertainty that will remind me to constantly reevaluate my clinical decisions and actions. It is what will encourage me to talk with my peers and explore as a team what will be best for each and every patient. The ultimate goal of asking these questions is not to come up with concrete answers, but to continue to discuss these questions to further my growth and awareness as a physician. Having correct interpretations of our ethical principles in all possible clinical situations would certainly simplify the task of practicing medicine. But in medical practice we must maintain flexibility and judgment if we are to avoid the mistakes of our predecessors. Only then, as caring, thoughtful, and loving physicians, will we truly serve our patients to the best of our ability.

Now that I have had the rare opportunity to walk out of that crematorium where so many innocent people had been barred within, I hope to use my increased knowledge and improved emotional awareness to guide my future relationships with patients. Let me never forget the immense responsibility of the medical position I hope to assume, and how the grave decisions I will make with and for my patients will shape both the quality of their lives and, importantly, the quality of their deaths.

Elliot Rabinowitz, soon to be M.D. '12, looks forward to his training in pediatrics at the Boston Combined Residency Program.

and to rationalize what they had done? Of the 23 defendants in the Doctors' Trial, none pleaded guilty.

Broadly speaking, the defenses could be divided into the legal and the ideological. First, the defense was that the defendants were acting under superior orders. The charters of the Nuremberg tribunals recognized the potential legitimacy of this defense, but not as an exculpatory defense that would obtain an acquittal. It could only be used as a plea in mitigation of sentence.

The International Military Tribunal, which tried the main case, developed a very thoughtful analysis, based on the notion of a moral choice, with a spectrum. At one end, there was the poor, hapless private on the battlefield, whose commanding officer put a gun to his head and told him, "Either you shoot that person there, or I shoot you." In that sort of situation, there was no real moral choice. At the other end of the spectrum were people like highly qualified, experienced, senior medical practitioners. They had devised what had to be done and advised how it was to be carried out. They were not simply taking orders. These people were directing things; they were giving the orders. The defense of "superior orders" was totally inappropriate, even in mitigation of sentence.

A second legal defense: What was done was lawful under German law. In the case of people who had been sterilized under the law for sterilization, there was an explicit law, and the doctors who had been involved could claim to have been acting under it. More generally, however, during the Nazi era Germany operated under the *Fuhrerprinzip*, the Fuhrer principle, by which all governmental power in Germany – legislative, executive, and judicial – was ultimately aggregated in one person, Hitler himself. His word was law. Thus, when he signed the letter dated September 1, 1939, to Karl Brandt, instructing him to proceed with the euthanasia program, Brandt could say he was acting under the law.

The fundamental fallacy here may be simply stated. Doctors were all part of the same regime, as were lawyers; they were *agents* of that regime. The regime set out to drive certain people out of society. The legal system was wildly successful in achieving its desired object. The doctors then turned around and claimed their acts were lawful under that system. This was the ultimate "bootstraps" argument and therefore had to fail at the threshold.

The third important defense was that there were no clear standards, especially when it came to experimentation on human beings. And if there were no clear standards, then doctors could not fairly be prosecuted criminally, because no one could say, with confidence, what was really illegal.

There is some force to that argument. It is inherent to any system of fairness, and to due process, that a person be able to know, in advance, what the consequences of his or her actions are. Underlying the defense is the principle that it is inherently unfair to take people by surprise. But could it really be said that senior medical practitioners, at the top of their country's military and civilian medical establishments, were taken by surprise by what they were being charged with at Nuremberg? Could it really be

Dr. Karl Brandt being sentenced to death.

said that people such as Karl Brandt and Sigmund Rascher and Carl Clauberg did not know that it was wrong to kill people; to torture them; to inflict massive pain and suffering on human beings; and to render them incapable of having children?

In one sense, the answer is "yes," and that brings us to the ideological defense: It was done to protect and preserve the German folk, the *volk*. It was the corollary of the underlying ideology of the Nazi party, that all humankind was viewed as divided into different racial groups, organized in hierarchical formation, with Aryans at the top and Jews at the bottom. Others were in between. All of history was seen as a struggle by the higher racial groups to prevent pollution of their blood and the "dragging down" of their racial group by the lower racial groups. Jews were the worst polluters of good Aryan blood; Jews were racial vermin, and they could be treated as such.

From this perspective, the doctors were not violating the Hippocratic Oath; they were actually living up to the Hippocratic Oath. What they had done was to redefine the patient. The patient was not the person sitting across from the doctor. The patient was the *volk*, the racially homogeneous body politic or nation. And if there was a group such as Jews, deemed a malignant tumor on the *volk*, they had to be excised, just like a malignant tumor on an individual body. Karl Brandt, speaking just before he was sentenced to death, could therefore say, in all good conscience, that when he approved euthanasia, he did so with the deepest conviction that it was right. Performing euthanasia was not murdering these people; on an individual level, they were being released from bondage in a diseased body or a racially diseased body. But in the wider scheme of things, the Nazis were ridding the *volk* of a malignant tumor.

For the Nazis, if there was a group such as Jews, deemed a malignant tumor on the *volk* (the body politic), they had to be excised, just like a malignant tumor on an individual body.

THE VERDICTS

Of the 23 defendants who were tried in the Doctors' Trial, 16 were found guilty and seven were found not guilty. Of the 16, Brandt and six others were sentenced to death, and those death sentences were carried out. The rest had a term of imprisonment imposed, and in every single case, on appeal, the term of imprisonment was lowered, so that overall the sentences were very light.

Sigmund Rascher was actually killed near the end of the War by the Nazis themselves, because of a violation of the adoption laws.

Carl Clauberg ended up being captured by the Soviets and put on trial in the Soviet Union in 1948. He was found guilty and imprisoned for 25 years, but pardoned in 1955. He returned to Germany, where he was arrested. He was scheduled to go on trial in 1957, but shortly before his trial was to begin, he was found dead in his cell, in mysterious circumstances. One of the suggestions was that he had been killed, because it was feared he would reveal damaging information about the wartime activities of perpetrators of atrocities who had resumed their careers in Germany after the War, as respected medical practitioners.

On a personal note, after acknowledging the sheer horror of what took place, I am disappointed that so few of these Nazi doctors were punished. Other trials were conducted, and there were people who were found guilty and sentenced to death, and the death sentences were carried out. But, overall, the number of defendants

"Life Unworthy of Life":
Considering the Meaning of Auschwitz

HISTORY BECOMES VISCERAL – AND PERSONAL – FOR A MEDICAL STUDENT VISITING THE OLD NAZI DEATH CAMP.

By Noemi Spinazzi

Painting by Noemi Spinazzi

This year, I completed the Fellowship in Auschwitz for the Study of Professional Ethics (FASPE), an intensive two-week program that takes place in New York, Berlin, Krakow, and Auschwitz. For two months prior to the start of FASPE, I studied the role of physicians during the genocide, readings such accounts as *The Origins of Nazi Genocide: From Euthanasia to the Final Solution*, by Henry Friedlander, and *The Nazi Doctors: Medical Killing and the Psychology of Genocide*, by Robert Jay Lifton. I also read autobiographies such as Primo Levi's *Survival in Auschwitz*.

I learned about "life unworthy of life," a phrase used by Nazis to describe targeted populations whose societal value they deemed too low to allow their survival. When I reached the Museum of Jewish Heritage in Manhattan, I felt knowledgeable about the complex sociopolitical and economic forces that facilitated the rise to power of the Nazi regime, as well as the psychological factors that may have helped the perpetrators silence their consciences. The phrase "life unworthy of life" was in my mind a suggestive historical document of sorts, a window into the thought process of all the physicians who endorsed the plan for the Final Solution.

Over the course of my trip, however, the phrase became a central theme in my emotions. Listening to testimonies of Holocaust survivors, slowly pacing along the deportation plaques of Track 17 in Berlin, walking in the rain through Auschwitz I and II, I began pondering what defines a life worth living. At the platform in Auschwitz II/Birkenau, I imagined being there with my family, exhausted from a long trip but hopeful about the future. I pictured being separated from my father and little brother, watching family members walk through the gates to the left of the platform, only to learn later that they were walking to their deaths. Walking in mud, soaked from all the rain and looking forward to a warm shower and dry clothes, I attempted to picture what it would be like to have no dry clothes or warm meal to look forward to; to be starved and exhausted yet keep walking through that mud, struggling to survive. I wondered if I would fight as hard as the survivors did, if I would consider that life worth living.

In Auschwitz I saw a photograph that resonated with my ambiguous feelings about the heroic effort it took prisoners to survive the camp. It shows a young woman at the time of liberation. Her naked body is emaciated; she is looking over her shoulder. In her eyes, you can see her exhaustion, her disillusionment; if I had to describe it with one word, I would choose *indifference*, as though nothing could get beneath her thickened skin. When the photo was taken, did she feel glad to be alive, or did she just keep replaying those moments on the ramp when she saw her family and friends for the last time?

As I stared into her eyes, verses from Primo Levi's poem "If this is a man" resonated within me:

> Consider if this is a woman,
> Without hair and without name,
> With no more strength to remember,
> Her eyes empty and her womb cold,
> Like a frog in winter.

Looking at this woman without hair and without a name, I found that the poem that had always defined the Holocaust for me took on a new, visceral meaning. Levi's words describe more than the humiliation and dehumanization that prisoners suffered: they question whether men and women like the one in the picture are anything more than the biochemical reactions that keep them alive – if their "life" is actually life at all.

I could not get the young woman's eyes out of my head for that day and the following week. I tried to draw her in my travel journal, but nothing could convey the emptiness in her stare. One survivor's story, her sorrow in knowing she had survived all her beloved sisters, was reflected in the void of those eyes I couldn't capture. I decided to convey my unsettled feelings through a painting. In the process, I realized that the only way to truly express the vacuum in her eyes and in her life was to leave her face blank, much like her expression. I worked with bright but cold colors to portray the contrast between the hopes of liberation and the sorrow for the losses that overwhelmed the survivors once they started thinking again.

I have not come to a conclusion about whether I would find life worth fighting for if I were put in the position of the millions of concentration camp prisoners. Part of me thinks that if I knew my family had been exterminated, I would let myself die – I would refuse to hold on to a life so unworthy of effort. At the same time, when I think of the impact survivors and their progeny have had on society, on history, and on their communities, I wonder if what I see today is the realization of a dream that kept survivors from giving up, a small ray of hope that made their grim lives worth fighting for.

Noemi Spinazzi, soon to be M.D. '12, will take her residency in Pediatrics at the Children's Hospital of Oakland.

dealt with was very, very small. A huge number were not punished and were rehabilitated into the medical profession (as well as the legal profession, and so on). They resumed their careers, sometimes with mysterious gaps in their résumés. That is not to say that this diminished, in any way, the significance of the Nuremburg precedent. Its principles live to this day. But it is dismaying to see that so many people performed atrocities, yet escaped justice altogether.

In studying this era, I have reflected a great deal on the potential for evil in the art of medicine. For me, the Doctors' Trial reflects what I have seen in relation to the lawyers – namely that, if the art of medicine falls into the right hands and is administered and ministered by good, decent, and compassionate people, it can do the greatest good. It can be the noblest profession, practiced at the highest level of altruism. But if it falls into evil hands, it can become an instrument of so much brutality, so much evil, so much inhumanity.

In his ground-breaking book *The Nazi Doctors: Medical Killing and the Psychology of Genocide*, Robert J. Lifton ponders the question of how it was possible for doctors to come into Auschwitz concentration camp, climb up onto the selection ramp, and, with a flick of the wrist, consign people to almost instant death in the gas chambers. These were people who had studied medicine, the art of healing, the art of saving lives; who had taken the Hippocratic Oath.

Lifton suggests two important factors. One was the mentoring system. The older, "wiser" doctors took the younger ones under their wing and indoctrinated them with the Nazi ideology outlined above. Secondly, they were plied with liberal doses of alcohol, which can lower resistance, lower inhibitions, increase receptivity to suggestions, and so on. In accord with our understanding of human nature, if ordinary human beings are subjected to indoctrination, then over time they can be made to change their attitudes and views, even their whole way of thinking. But what is absolutely extraordinary to me, however, is Lifton's conclusion that, on average, this process took just two weeks.

At his sentencing, Karl Brandt showed no emotion, which I find very troubling. How could this horror have happened, especially in the Germany of Goethe and Schiller and Beethoven and Bach, the Germany in which culture and intellect ruled supreme? My own personal answer is that Germany was a society that for very long emphasized the importance of intellect and intellectual achievement; as a result, there was a commensurate downgrading of human emotions.

Someone who has largely surrendered emotion may come to look at a human being – but not *see* a human being.

In addition, there was the militaristic ethos that pervaded German society and suffused its school system and the home. It turned people into those who prided themselves on their intellect and prided themselves, in many ways, on lack of emotion. Someone who has largely surrendered emotion may come to look at a human being – but not *see* a human being. Brandt had just been sentenced to death, yet his first concern was to straighten his carefully brushed and combed hair.

Brandt's career and death can symbolize the Doctors' Trial and its judgment on the Nazi practice – and perversion – of medicine. ●

MARIE CURIE: EXAMPLE AND INSPIRATION

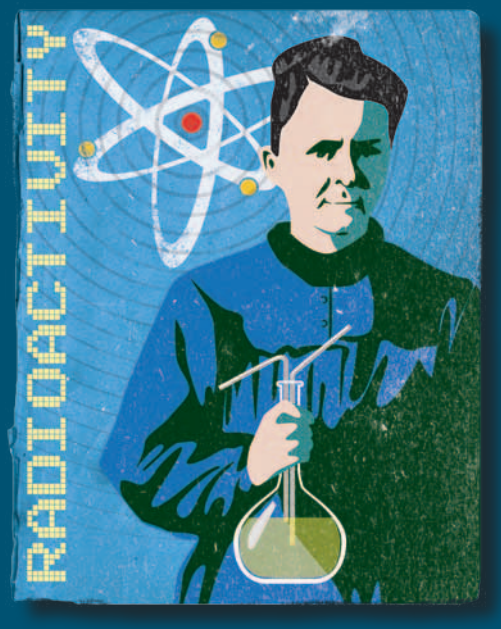
BY M. CELESTE SIMON, PH.D.

Marie Sklodowska-Curie was a truly phenomenal scientist and trail-blazing woman. She was the first woman to win a Nobel Prize and the first person to win two Nobel Prizes. She is also the only individual to win Nobel Prizes in two distinct scientific disciplines (physics and chemistry).

Born on November 7, 1867, Marie was the daughter of two well-known teachers in Warsaw. Under their guidance, she became passionate about physics, chemistry, and mathematics. Marie studied under Henri Becquerel in Paris and discovered that uranium salts emit rays that resembled X-rays in their penetrating power. In fact, she essentially discovered radioactivity. She showed that radiation was not the outcome of some interaction of molecules but actually came from the uranium atom itself. In her systematic search for other substances beside uranium that emit radiation, she identified thorium as a second radioactive element and discovered two other radioactive elements, "polonium" and "radium." For this seminal work, Marie shared the 1903 Nobel Prize in physics with her husband, Pierre Curie, and Becquerel.

In 1911, Marie received a second Nobel Prize, this time in chemistry, for the discovery of radium and polonium. That same year, however, the French Academy of Sciences did not elect her a member – she was shy two votes. The first woman to be elected to the Academy was her doctoral student, Marguerite Perey, elected in 1962.

In addition to being outstanding scientists, Marie and Pierre were devoted parents, raising two daughters. Their elder daughter, Irène Joliot-Curie, won the Nobel Prize in chemistry in 1935 for discovering that aluminum could be made radioactive and made to emit neutrons when bombarded with alpha rays. Apparently, both Pierre and Marie were significantly weakened by prolonged radiation exposure. Pierre died in an accident with a horse-drawn vehicle in 1906, while Marie survived until 1934, when she succumbed to aplastic anemia. Because of their levels of radioactivity, her papers from the 1890s are considered too dangerous to handle; even her cookbook is highly radioactive. Despite her tremendous fame, Marie realized early in life that a woman might not be considered capable of the original work she in fact conducted. Since that time, she has served as an enormous inspiration for all scientists – in particular, women scientists.



Progress: Perceptible but Slow

In the 100 years since Marie Curie won her second Nobel Prize, women have continued to have an influence in science. But progress in increasing the numbers of women in science, while perceptible, has been slow. In the 20th century, two other women were recognized for significant contributions to the biological sciences. One is Rosalind Franklin, who performed critical experiments that helped elucidate the nature of DNA. The other, Rosalyn Yalow, developed radio-immunoassays for serum insulin and won the Nobel Prize for this achievement in 1977.

On a personal note, my mother was the only woman in a decade to graduate from Louisiana State University with a degree in chemical engineering. She, in turn, raised six children, including some working in engineering, architecture, and the life sciences.

I first learned about Marie Curie as a student in grade school and high school. There I encountered my own inspirational science teachers, Sister Merici and Sister Eileen Freschet at Ursuline Academy in Cincinnati. Sister Eileen taught me chemistry; I fell in love with the subject in particular and with science in general. Since then, I have gone on to work in developmental biology and cancer biology. I've had the good fortune to interact with other outstanding women in science, including Lasker Award winner Janet Rowley, National Academy members Elaine Fuchs and Susan Lindquist, and many others who paved the way for current female scientists like myself. It should be noted that some scientific fields have recently been dominated by women; the 2009 Nobel Prize in Medicine was shared by Carolyn Greider (Johns Hopkins) and Elizabeth Blackburn (UCSF) for discovering the mechanisms that maintain telomeres.

I am delighted to work at the University of Pennsylvania, which includes a number of prominent women in the ranks of its faculty. And I find it intriguing that my current laboratory (run in conjunction with my husband, Brian Keith) has the address of 421 Curie Boulevard! ●

Dr. Simon is scientific director of the Abramson Family Cancer Research Institute; a professor of cell and developmental biology; and an investigator of the Howard Hughes Medical Institute. She made these remarks, slightly edited, at a campus event honoring the life and achievements of Marie Sklodowska-Curie.

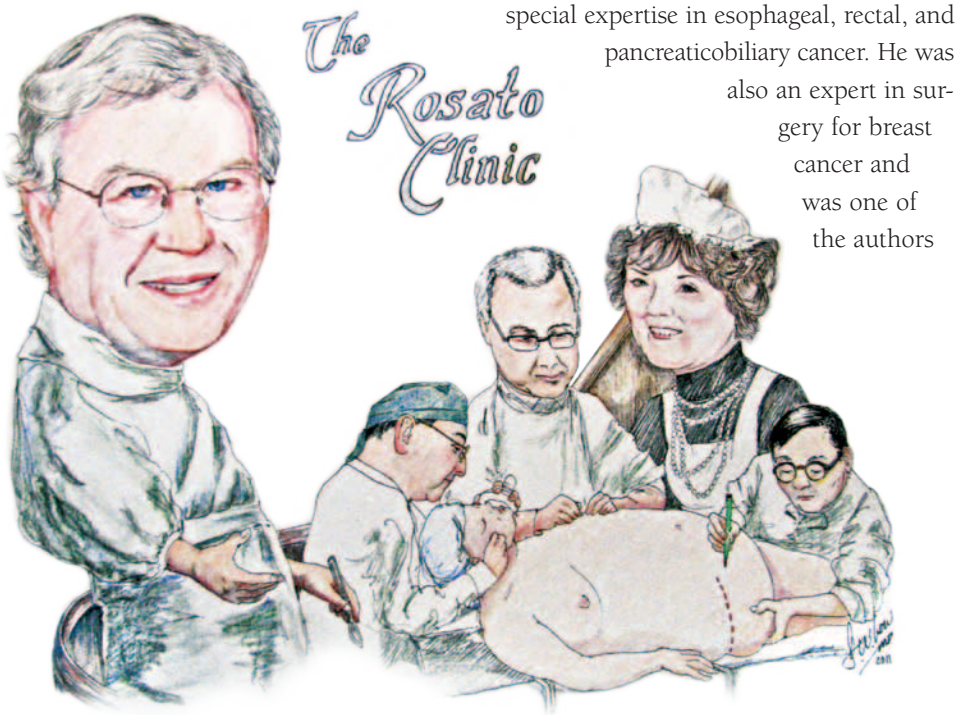
Ernest Rosato, Master Surgeon and Teacher

Penn Medicine recently lost one of its rare 50-year citizens, Ernest F. Rosato, M.D. '62, professor of surgery and former chief of the Division of Gastrointestinal Surgery. He died on January 6.

It was no surprise that Rosato was selected to be the speaker at the medical school's White Coat Ceremony in 2009. He was widely known for his surgical mastery, his teaching skills, and his readiness to be a mentor to medical students, residents, and junior members of the faculty. As Rosato made clear in his remarks, he was very proud to have entered his "second half-century" at the Perelman School of Medicine. He spoke about the importance of tradition and evoked a few of the towering figures in Penn's past who had influenced him and had made him a better surgeon and teacher. It's very likely that many people at the school today would single Rosato out in the same way.

Rosato graduated from St. Joseph's University in 1958. In 1995, his alma mater honored him with the Reverend Clarence E. Shaffrey, S.J., Award, presented in recognition of service and outstanding achievement in the medical profession. After earning his M.D. degree from Penn in 1962, Rosato completed his medical training at HUP in 1968. Beginning as an assistant instructor in surgery at HUP, he rose quickly through the faculty ranks. He was named associate professor of surgery in 1972; professor three years later; and chief of the Division of Gastrointestinal Surgery in 1988. He served as chief until 2004.

Widely known as "the master surgeon of last resort," Rosato was particularly interested in gastrointestinal cancer, with a special expertise in esophageal, rectal, and pancreaticobiliary cancer. He was also an expert in surgery for breast cancer and was one of the authors of *Breast Cancer Treatment: A Comprehensive Guide to Management* (1991).



David W. Low, M.D., G.M.E. '78, professor of surgery and a former chief resident under Dr. Rosato, drew this humorous tribute to his mentor. In addition to Rosato, the figures represent Stanley Muravchick, M.D., Ph.D., professor of anesthesiology; Jon B. Morris, M.D., professor of surgery; Dr. Rosato's wife, Geraldine; and the artist himself. Any resemblance to Thomas Eakins's *Agnew Clinic* is not coincidental.

Over the course of his career, he published some 200 articles and was a Fellow of the American College of Surgeons. Rosato was also honored by nonspecialists: he was frequently included among the "Top Docs" in *Philadelphia* Magazine and was recognized by Best Doctors in America and by America's Top Doctors, the latter as recently as 2010.

The feelings Rosato had for Penn Medicine were clearly mutual. In 1977, he received the Lindback Award for Distinguished Teaching, given by the University. In 2008, he was named the recipient of the I. S. Ravdin Master Clinician Award, one of the Perelman School's Awards of Excellence. That particular award recognizes "a skillful, compassionate practitioner with a long and consistent record of contributions" to the school. According to the selection committee: "Implementing innovative, non-traditional, and highly sophisticated approaches to the most complex surgical problems has become his trademark, and, as such, Dr. Rosato is frequently sought out by surgeons who have reached their clinical limit."

Rosato learned from and worked with Ravdin, the well-known former chair of Penn's Department of Surgery. In his White Coat remarks, Rosato noted that, despite some paternalism and brusqueness on Ravdin's part, "everybody loved Rav because he loved his students and believed in them." Rosato shared that same belief in his students – and they clearly recognized his commitment to making them better doctors.

As for the William Y. Inouye Faculty Award in Surgery, selected by the chief residents of the Department of Surgery, Rosato seemed to have a lock on it practically every year. Since 1985, he received the award an amazing 18 times. ▪

– John Shea

Development Matters

TO ALTER THE COURSE OF DISEASE, DONORS SEEK LARGE-SCALE SOLUTIONS

Recently, two families affected by very different, though equally devastating, diseases sought answers, and indeed hope, at Penn Medicine. One family wanted to spur research to discover the causes and potential cures for very rare "orphan" diseases. The other wished to help individuals at the opposite end of this spectrum – those who suffer from the most common and widespread behavioral conditions that afflict humanity.

Both families were knowledgeable in the practice of philanthropy and chose to make their impact through anonymous giving. Although their goals were ambitious, they were confident that Penn Medicine was the institution best positioned to bring success to their transformative endeavors. The result? Two game-changing, generous gifts that create programs to accelerate new scientific advances and their clinical applications for the benefit of all: The Penn Center for Orphan Disease Research and Therapy, and the Neuroscience of Behavior Initiative.

A NEW CENTER TO ADDRESS ORPHAN DISEASES

This story begins in a conversation about a child whose grandfather sought help from Penn Medicine. Glen N. Gaulton, Ph.D., executive vice dean and chief scientific officer of the Perelman School of Medicine, vividly recalls that first meeting. The grandfather explained that his beloved granddaughter had been diagnosed with a rare and currently incurable disease. Understandably, he and the family were devastated but also experienced what Gaulton refers to as "a feeling of total powerlessness" that was linked to the need to do something to "contribute in some way to improve his granddaughter's life." An experienced philanthropist who understood the power of investing in good ideas and good leaders, the donor was eager to learn more about the world of medicine and the impact of biomedical research.

Glen N. Gaulton, Ph.D., guided the conversations with the family who established the Penn Center for Orphan Disease Research and Therapy.

Deeply moved by the donor's feelings, Gaulton tried to put himself in the grandfather's shoes. He knew that Penn, through its history of innovation and collaboration, could help address the issues confronting this family. But how? What special role could Penn play?

Over the next few months, Gaulton and the donor examined the network for the child's particular illness within the landscape of orphan diseases as a whole. Each orphan disease (defined as affecting fewer than 200,000 U.S. patients) is unique, with specific causes, areas of research, and treatments. Each also has its own patchwork of investigators, clinical care providers, supporting foundations, and affected patients and families. Yet these diseases also have central elements in common, including the reliance on common research methodologies to determine the genetic basis and biochemical causes of disease and the need to rapidly advance research to clinical applications. Addressing these properties is essential for researchers to develop new therapies and cures. However, the vast majority of these disorders are under-funded by traditional government and pharmaceutical company sources because the potential benefits affect so few. These resources are also both expensive and technologically challenging, making it difficult for small research teams to progress on their own.

As the two men talked, the idea of creating a new kind of resource that could address not just one but simultaneously many orphan diseases began to take shape. Researchers could draw on the new program for state-of-the-art scientific support, including access to gene mapping and sequencing, drug screening, small and large animal models, as well as being able to conduct clinical trials and submit FDA applications. Foundation advocacy groups and families could draw on the program to organize scientific symposia and grant award programs, in essence cut-

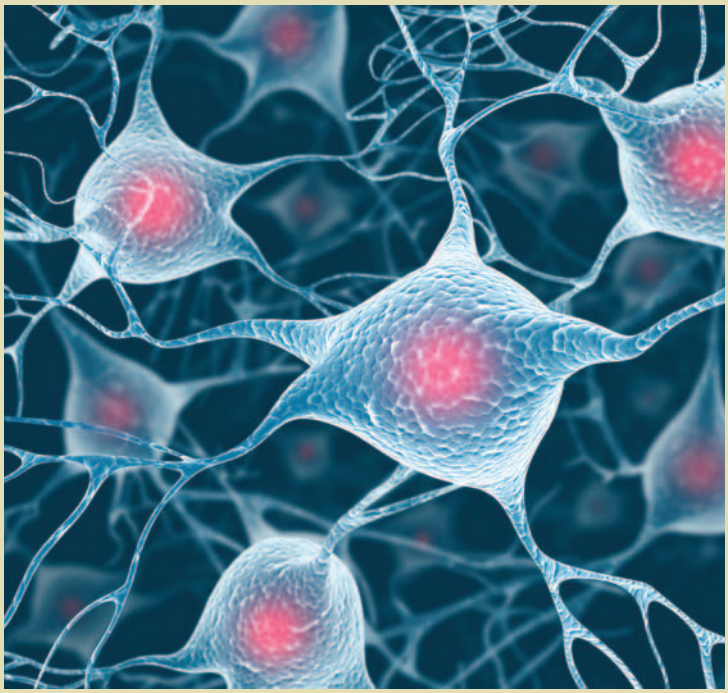
(continued on page 42)

A NEUROSCIENCE INITIATIVE TO COMBAT A VAST SOCIETAL PROBLEM

Every family and every community knows the losses caused by behavioral disorders. From the severely depressed parent, to the college freshman struggling with substance abuse, to the traumatized returning veteran – these conditions harm individuals and families across the social spectrum and cause suffering on a massive scale. Many of these disorders are especially heartbreaking because they tend to affect people in the prime of life and represent a huge loss of productive potential. And while neurodegenerative diseases like Alzheimer's generally occur toward the end of life, their effects on patients and families are no less tragic.

The members of one family made the decision to do all they could to combat this heavy personal and societal toll.

These donors were seeking nothing less than a transformation in the way we approach these areas – from research, to treatment, to outcome. They were long accustomed to turning to the best, and for them that meant Penn. Brian L. Strom, M.D., M.P.H., executive vice dean for institutional affairs and professor of biostatistics and epidemiology, became their guide on how a significant investment might make a real difference.



Brian L. Strom, M.D., M.P.H., heads the Neuroscience of Behavior Initiative.

The discussions with Strom reinforced the donors' view of Penn as the place for transformation. The presence of an already distinguished scientific and medical neuroscience community at Penn became the basis for their decision to create the Neuroscience of Behavior Initiative, which will focus on three areas: substance abuse, depressive disorders, and neurodegenerative diseases.

As a successful businessman, the head of the family had long believed that the best way to get results is to *invest in people*, so continuing discussions centered on creating a vehicle for bringing the very best minds in the field of behavioral neuroscience to Penn Medicine. It would be an initiative based on scientific stars – risk-takers who have the courage to face opposition when exploring bold new ideas.

"We want jaw-dropping names up front that will say to the world of neuroscience that something special is happening at

(continued on page 42)

A NEW CENTER TO ADDRESS ORPHAN DISEASES (CONTINUED)

ting through the mass of scientific data and approaches using a "Think Tank" concept. The impact of such a center would be huge – the donor's gift could help thousands of families. For a committed philanthropist, this became the "Aha!" moment.

And so the Penn Center for Orphan Disease Research and Therapy was born. The Center, the only one of its kind in the world, is dedicated to supporting research programs working on rare diseases with the specific technologies that they need to hasten scientific breakthroughs and to advance discoveries rapidly to the clinic. The Center will bring together scientists, provide administrative resources, create partnerships between academic institutions, foundations, and industry and government agencies, and serve as a resource for patients and families.

Jean Bennett, M.D., Ph.D., with members of families who support her work on gene therapy for Leber's congenital amaurosis (LCA). A rare genetic disorder that results in the progressive and finally complete loss of vision, LCA is one of the orphan diseases that Penn researchers have studied.

This is truly a global initiative, and Penn has made it clear that the Center will support the best work wherever it is occurring. As the search for the Center director is under way, the first round of grants has been funded; recipients are not only at Penn but also at such institutions as Weill Cornell Medical School, the University of California San Diego, and the University of Minnesota.

The Center for Orphan Disease Research and Therapy is a model for the far-reaching, collaborative, philanthropic endeavor Penn has the power to create. It provides every family with a chance to directly join in the fight against rare diseases. All this would not have happened without the strong philanthropic instinct of a concerned grandfather. For the donor, and now patients and families worldwide, this Center offers a fresh basis for hope.

A NEUROSCIENCE INITIATIVE TO COMBAT A VAST SOCIETAL PROBLEM (CONTINUED)

Penn," says Strom, who has been named to head the Neuroscience of Behavior Initiative. Great people attract more great people. Four search committees – one crosscutting and one for each area of investigation – are at work. Already the word is out, and premier scientists are approaching Penn leaders such as eminent Alzheimer's disease researchers John Q. Trojanowski, M.D., Ph.D., and Virginia M.-Y. Lee, Ph.D., M.B.A., about new possibilities. Drs. Trojanowski and Lee are the co-director and director of the Penn Center for Neurodegenerative Disease Research, respectively.

Highly visible meetings and symposia are also being designed to bring people to Penn and increase the reach of the work. With this gift, the donor and his family are confident that the brilliant minds at Penn will have the tools to generate meaningful changes in the fight against behavioral disorders.

Virginia M.-Y. Lee, Ph.D., M.B.A., and John Q. Trojanowski, M.D., Ph.D., leading researchers in neurodegenerative disease. Dr. Trojanowski chairs the Neurodegenerative Disease Search Committee and is also part of the Behavioral Neuroscience Initiative Internal Advisory Committee.

Recent Major Gifts

Abramson Family Foundation continues its distinguished tradition of philanthropy to Penn Medicine with a recent gift of $4.42 million to benefit cancer research at the Abramson Family Cancer Research Institute.

Canon, Inc. donated an Adaptive Optics Scanning Laser Ophthalmoscope to the Scheie Eye Institute. Valued at $3 million, this powerful microscope yields real-time views of the living human retina with unprecedented optical quality, helping to reveal retinal disease and improve diagnosis.

M. Thomas Grumbacher and Nancy T. Grumbacher have generously made a first-time pledge of $1 million to create the Nancy Grumbacher Ovarian Cancer Research Fund, which supports the research on ovarian cancer by Dr. George Coukos in the Department of Obstetrics and Gynecology at Penn Medicine.

Mr. James S. Riepe and Mrs. Gail Petty Riepe pledged $1 million to endow the Arthur H. Rubenstein Endowed Scholarship Fund, honoring the School's former dean. The fund will provide financial support to a medical student or students who would otherwise be unable to meet the cost of a medical education at the Perelman School.

Ralph and Brian Roberts pledged $1.5 million to establish the Roberts/Ende Department of Medicine Fund. This gift will support clinical, educational, administrative, and faculty development initiatives in the Department of Medicine at Penn Presbyterian Medical Center, including the creation of the Chief of Medicine Service, to be directed by Dr. Jack Ende.

Mr. Richard W. Vague, through a pledge of $5 million, funded the Richard W. Vague Endowed Professorship in Immunotherapy at the Perelman School of Medicine and established the Richard W. Vague Pancreatic Cancer Immunotherapy Research Fund to provide financial support for work in pancreatic cancer performed at the Abramson Cancer Center by the Associate Director for Translational Research, currently Dr. Robert Vonderheide.

Joseph R. Zebrowitz, M.D., and Lauren J. Wylonis, M.D., have pledged $1 million to establish a variety of funds that will benefit some key initiatives at the School, including medical student aid, child forensic psychology, enhanced patient care, and the new Medical Education Center.

*For more information, please contact the **Office of Development and Alumni Relations** at 215-898-0578.*

To make a gift, please mail your check made out to The Trustees of the University of Pennsylvania to:
Penn Medicine Development and Alumni Relations
3535 Market Street, Suite 750
Philadelphia, PA 19104-3309

To make your gift online, please visit:
www.med.upenn.edu/alumni/gifts

Calendar

American Urological Association Reception
Monday, May 21, 6:00 p.m.
Marriot Marquis, Atlanta, Ga.

Red Carpet Premiere of *Head Games*
Thursday, June 7, 6:00 p.m.
Translational Research Center, Rubenstein Auditorium

Head Games is a revealing documentary about the concussion crisis in sports, from the acclaimed director of *Hoop Dreams*, Steve James.

Penn Medicine in Bar Harbor
Wednesday, August 8, 9:30 a.m.
Asticou Inn, Bar Harbor, Maine

For more information on these events, please e-mail PennMedicine@alumni.med.upenn.edu

Progress Notes

Send your progress notes to:
Donor Relations
Penn Medicine Development and Alumni Relations
3535 Market Street, Suite 750
Philadelphia, PA 19104-3309

'60s

Robert H. Seller, M.D. '56, G.M.E. '60, is an emeritus professor of family medicine and medicine at the State University of New York at Buffalo School of Medicine and Biomedical Science, where he also served as chairman of the Department of Family Medicine. He recently established the David S. Seller, M.D. '22, and Robert H. Seller, M.D. '56 Prize. It will be awarded annually to a Penn Med graduating student who demonstrates excellence in diagnosis.

The sixth edition of Seller's textbook *Differential Diagnosis of Common Complaints* was published in December 2011. Since the first edition in 1986, it has been translated and published in Spanish, Indonesian, Polish, Lithuanian, Italian, and Chinese.

'70s

David L. Rosenfeld, M.D. '70, G.M.E. '76, chief of endocrinology and infertility at North Shore University Health Care System, received the Margaret Sanger Award from Planned Parenthood of Nassau County, N.Y.

Marie Savard, M.D. '76, G.M.E. '79, has joined the Philadelphia office of Diversified Search as a managing director in its Health Care Practice, the largest executive search firm in the United States that was founded and is owned by women. Savard is a member of the Board of Trustees of the University of Pennsylvania and earned her B.S. degree from Penn's School of Nursing. A former director of the Center for Women's Health and associate professor at the Medical College of Pennsylvania, Savard has been a health columnist for *Women's Day* magazine and is a part-time contributor to ABC News.

Marc S. Micozzi, M.D. '78, Ph.D. '84, is the editor, with Michael A. Jawer, of *Your Emotional Type* (Healing Arts Press), which examines the interplay of emotions and chronic illness and pain. They argue that certain chronic conditions (such as asthma, allergies, chronic fatigue, depression, fibromyalgia, and others) are intrinsically linked to certain emotional types and are best treated by choosing a healing therapy in line with an individual's type. A national leader in the field of complementary and alternative medicine, Micozzi is adjunct professor of physiology and biophysics at the Georgetown University School of Medicine. He organized and edited the first U.S. textbook in the field, *Fundamentals of Complementary & Alternative Medicine*, now in its fourth edition.

'80s

Eric G. Neilson, M.D., G.M.E. '80, became the Lewis Landsberg Dean and Vice President for Medical Affairs of Northwestern University Feinberg School of Medicine in September. He is also the chair of the board of the Northwestern Medical Faculty Foundation. From 1998 to 2010, he chaired the Department of Medicine at Vanderbilt University and was honored with the Robert H. Williams Award from the Association of Professors of Medicine for outstanding leadership as the chair of an academic department of internal medicine. Earlier, Neilson spent 23 years at the University of Pennsylvania School of Medicine, where he served as the C. Mahlon Kline Professor of Medicine and Pediatrics and director of the Penn Center for Kidney and Hypertensive Diseases.

James F. McLeod, M.D., G.M.E. '83, was appointed senior vice president of clinical research and development as well as chief medical officer of Galleon Pharmaceuticals, a leader in the pharmaceutical treatment of breathing-control disorders. Before joining Galleon, he managed the experimental medicine group at Merck Research Laboratories and the early clinical research and experimental medicine group at the Schering-Plough Research Institute. He is board-certified in internal medicine and endocrinology and metabolism.

'90s

Charles R. Bridges, M.D., Sc.D., G.M.E. '91, has been named chair the Department of Thoracic and Cardiovascular Surgery at Carolinas Medical Center. He joins CMC and the Sanger Heart & Vascular Institute from Penn Medicine, where he was professor of surgery and chief of cardiothoracic surgery at Pennsylvania Hospital. His expertise and experience allows patients to receive "bloodless" or "transfusion-free" cardiac surgery that historically has been performed on patients with certain religious beliefs that do not allow blood transfusions. Bridges's journal series on Jehovah's Witness patients will appear this year in the *Annals of Thoracic Surgery*. He is also the recipient of a $3 million grant for four years from the National Institutes of Health to investigate novel molecular and regenerative therapies as a means to improve heart function in patients with advanced heart failure.

Stephen B. Gruber, M.D. '92, Ph.D., M.P.H., a physician-scientist who has been at the University of Michigan, was appointed director of the Norris Comprehensive Cancer Center at the University of Southern California's Keck School of Medicine. He was also named the H. Leslie Hoffman and Elaine S. Hoffman Chair in Cancer Research and visiting professor of medicine at the Keck School. Gruber's research interests include the genetic epidemiology of cancer, with emphasis on colorectal cancer; the molecular pathogenesis of cancer, integrated with genetic epidemiology; and clinical cancer genetics and molecular epidemiology; and clinical cancer genetics and translational research in cancer prevention. Since 2005, he has been chair of the Colorectal Family Registries Advisory Panel for the National Cancer Institute. For the past three years, he chaired the Cancer Genetics Education Committee of the American Society of Clinical Oncology.

Charles F. Orellana, M.D. '92, G.M.E. '95, was named senior medical director at Clinical Care Associates, the primary-care network of the University of Pennsylvania Health System. He joined C.C.A. in 1995, practicing internal medicine at Bala Cynwyd Medical Associates. Orellana currently oversees physician recruitment, quality improvement, and the graduate and undergraduate education programs and research at the network. Over the last six years, he has been instrumental in developing an orientation and mentoring program for C.C.A. physicians.

K. Andrew Larson, M.D. '99, North Palm Beach, Fla., medical director for the Bariatric Wellness and Surgical Institute of JFK Medical Center, and his wife, Ivy Larson, a healthy lifestyle coach, have developed Clean Cuisine, a science-based nutrition plan. Created more than a decade ago by Andrew Larson when his wife was diagnosed with multiple sclerosis, the plan is based on anti-inflammatory unrefined whole foods. They are the authors of *Whole Foods Diet Cookbook, The Gold Coast Cure: The 5-Week Health and Body Makeover*, and others. Andrew is a Fellow of the American College of Surgeons and a Fellow of the American Society for Metabolic and Bariatric Surgery and is president-elect of the Palm Beach County Medical Society.

OBITUARIES

'30s

Maurice J. Blocklyn, M.D. '37, Darby, Pa., retired chief of radiology and chief of staff at Crozer-Chester Medical Center; March 28, 2011. The Medical Center's School of Radiologic Technology honored his work by creating the Maurice J. Blocklyn Academic Award, for the graduate with the highest grade-point average. Blocklyn was also a volunteer who tutored young people in reading, arithmetic, French, and mathematics.

Lloyd W. Stevens, M.D. '37, G.M.E. '44, Bryn Mawr, Pa., former director of surgery at Presbyterian Medical Center; September 25, 2011. From 1939 to 1979, he was on the medical faculty at the

University of Pennsylvania, from which he retired as a professor of clinical surgery. Stevens pioneered many surgical techniques and was the author of 35 papers in professional journals and numerous chapters in medical textbooks. At Presbyterian Hospital, he was twice president of the medical staff. He was also on the surgical staff of HUP, Graduate Hospital, Medical College of Pennsylvania, and Philadelphia General Hospital, where he served as visiting chief of surgery from 1950 to 1976. Stevens was surgeon to the Philadelphia Eagles from 1945 to 1949, during which the team won two national championships. He received a citation from the Dominican Republic Gastroenterological Society and was given the Roth Award for excellence in teaching and practice by the gastroenterology department at Presbyterian Hospital.

Jackson E. Kress, M.D. '39, G.M. '47, Green Valley, Ariz., a retired physician of internal medicine at the Western Montana Clinic in Missoula, and former clinical assistant professor of medicine at the University of Washington; May 8, 2011.

'40s

Benjamin Dickstein, M.D. '40, G.M.E. '46, Warminster, Pa, a retired pediatrician; June 30, 2011. He served as a flight surgeon in the Army Air Forces during World War II. Overseas, he served with the 441st Troop Carrier Group, which dropped paratroopers over Normandy on D-Day, and participated in the assault over the Rhine. He was awarded the Bronze Star for his service in Europe. After his discharge from active duty as a lieutenant colonel, he completed a residency in pediatrics at The Children's Hospital of Philadelphia and established a practice in Northeast Philadelphia.

Robert P. Sagerson, M.D. '40, Spokane, Wash., a retired radiologist and former president of the medical staff at Sacred Heart Hospital; May 4, 2011. He spent 47 months on active duty during World War II as a radiologist in the Army Medical Corp. He then served as an instructor in radiology at the Harvard Medical School.

John W. Isgreen, M.D. '41, G.M.E. '54, Montrose, Colo., a retired radiologist; August 29, 2011. During World War II, he was stationed in New Guinea and received two Bronze Stars. After his discharge, he worked as a radiologist at the Salt Lake City Veterans Administration Hospital for two years before continuing his practice as a radiologist in Woodland, Calif., until 1968.

Jerome Lehner, M.D., G.M. '41, Maitland, Fla., a retired ophthalmologist who specialized in facial-reconstruction surgery; March 15, 2011. During World War II, he served with the U.S. Army in a London, attaining the rank of major. He was 103 years old.

Harold G. Barker, M.D.'43, G.M.E. '49, Rye, N.Y.; March 9, 2011. He entered the U.S. Army Medical Corps in 1944 and served in England, Belgium, and Germany before being discharged as captain in 1946. He spent the rest of his career as a faculty member at Columbia University College of Physicians and Surgeons and an attending surgeon at Columbia Presbyterian Medical Center. He became professor of clinical surgery in 1968. From 1974 to 1982 he was also director of medical affairs at Columbia Presbyterian. His research in surgical nutrition and metabolism and gastrointestinal physiology was supported by grants from the National Institutes of Health for 22 consecutive years. He was also chairman of the Surgical Section of the Medical Society of New York (1961-62).

Robert O. Brandenburgh, M.D. '43, Bloomington, Minn., retired president of the American College of Cardiology and former chair of cardiology at the Mayo Clinic; June 5, 2009. During World War II he served in the U.S. Army Air Force.

John W. Manning III, M.D. '43, Saginaw, Mich., a retired professor of surgery at Michigan State University; June 8, 2011. As a lieutenant in the U.S. Navy during World War II, he served at Nagasaki, Japan. He was the youngest person ever admitted as a Fellow to the American College of Surgeons.

Hugh P. Smith, M.D. '43, G.M.E. '47, Santa Barbara, Calif.; March 5, 2011. He took his residency in internal medicine at Emory University. After a career in internal medicine and radiology, he became a professional photographer of birds, and his work appeared in books and calendars and in the Roger Tory Peterson Institute Museum in New York. During World War II, he served as a doctor with the U.S. Navy and was among the first U.S. troops to land in Nagasaki, weeks after the atom bomb was dropped on the city.

John M. Howard, M.D. '44, G.M. '51, Toledo, Ohio, a retired professor of surgery at the University of Toledo; March 17, 2011. During the Korean War he directed the U.S. Army Surgical Research Team that pioneered the MASH unit, for which he was awarded a Legion of Merit.

Samuel R. Moore Jr., M.D. '44, Warminster, Pa., retired medical director of Life Insurance Co. of North America and an amateur archaeologist; May 19, 2011. He served in the Navy at the Naval Hospital in Philadelphia during World War II. After his discharge from the military, he completed a residency in internal medicine at Philadelphia General Hospital. He had also been assistant medical director of Provident Mutual Life in Philadelphia. He established the medical department at the company, now a subsidiary of Cigna, and for 30 years conducted physicals for life-insurance applicants and examined claims.

Hugh H. Bennett Jr., M.D. '45, G.M. '49, Greensboro, N.C., a retired radiologist who also had operated a chain of independent cinemas; December 6, 2010. During World War II he served in the U.S. Army Medical Corps, attaining the rank of captain.

William A. Butcher, M.D. '45, Tucson, Ariz., a retired physician who had maintained a practice in internal medicine and cardiology; April 5, 2011. He interned at the University of Chicago and was a resident in internal medicine and cardiovascular disease at the Mayo Clinic in Rochester, Minn. He received his master's degree in medicine from the University of Minnesota. During World War II, he served in the U.S. Navy Medical Corps.

Robert G. Page, M.D. '45, G.M.E. '49, York Harbor, Me.; August 31, 2011. He practiced medicine in Londonderry, Vermont, both as a private physician and with the Mountain Valley Health Center. A lecturer at Yale University and adjunct professor at Dartmouth Medical School, he had held several positions at the Medical College of Ohio, including dean, provost, dean of faculty, and professor of medicine and pharmacology. He was also an associate dean at the University of Chicago. As part of the Marshall Plan from 1951 to 1953, Page was a professor of pharmacology at the University of Rangoon in Burma. He had been a lieutenant j.g. in the U.S. Navy and a senior surgeon for the U.S. Public Health Service.

Alan Rubin, M.D. '47, G.M.E. '52, Philadelphia, a retired clinical professor of obstetrics-gynecology at Penn; May 16, 2011. He was chief of gynecology at the former Graduate Hospital when he retired in 1989. Earlier, he was chairman of the obstetrics and gynecology department at Albert Einstein Medical Center. In 1964, he described the Rubin Maneuver, a technique he developed to free infants' shoulders during difficult deliveries, in *The Journal of the American Medical Association*. Also in the 1960s, he was one of the first physicians to demonstrate a link between diabetes in men and erectile dysfunction. He was one of the first to recognize a hereditary link in some women with breast cancer and was an early user of tissue cultures as a method of screening drugs for use as anticancer agents. He and his wife, the late Helen Metz Rubin, M.D., G.M. '48, an anesthesiologist, met as residents at Penn and married in 1947. In 1951, they teamed up to study how Dramamine, used for motion sickness, prevented nausea after anesthesia. He served on the executive committee of Penn's Medical Alumni Society for 49 years and was the society's president in 1962. He was a longtime member of the Planned Parenthood Physicians Advisory Committee in Philadel-

phia and for many years headed fund-raising for the Federation Allied Jewish Appeal at HUP.

Walter F. Ballinger II, M.D. '48, St. Louis, Mo., former chair of surgery at Washington University in St. Louis; April 29, 2011. After World War II, he served as a U.S. Army medical officer at Spandau Prison in Berlin. He wrote eight textbooks and more than 200 medical articles and was editor of the *Journal of Surgical Research* and co-editor of *Surgery. Archives of Surgery* named him one of 24 surgeons with "significant contributions to surgery in the areas of research, clinical care, and surgical education."

Thomas Morrison Birdsall, M.D. '48, Haverford, Pa.; September 27, 2011. During the Korean War, he served in the Navy in a military hospital in Japan. After his discharge in 1954, he joined the staff at Presbyterian Hospital. He eventually became chief of urology at Presbyterian and at Riddle Memorial Hospital in Media and was on the staff of Delaware County Memorial Hospital in Drexel Hill. Birdsall retired from his urological surgical practice in 1989. He remained on the staff of Delaware County Memorial Hospital until the mid-1990s, compiling medical histories of patients being admitted for surgery. After retiring from medicine, he was a volunteer for Main Line Meals on Wheels.

William A. Shaver, M.D. '48, G.M.E. '55, Aiken, S.C., a retired associate director of surgical education at Roanoke Memorial Hospital in Virginia; March 5, 2011. From 1966 to 1973, he was a clinical professor of surgery at Penn. During World War II, he served in the U.S. Navy.

Irwin R. Cohen, M.D. '49, Palm Beach Gardens, Fla., a retired cardiologist; March 16, 2011. He had worked for the ACGME, which reviews medicine and surgery specialties and accredits programs at teaching hospitals.

Walter L. Kester, M.D. '49, G.M. '53, West Chester, Pa., a former vice chief of medical services at Chester County Hospital; March 23, 2011. During the Korean War he served with the U.S. Marines.

Ray P. Landes, M.D. '49, G.M. '56, Harleysville, Pa.; June 14, 2011. He completed an internship at the Bryn Mawr Hospital before serving two years as a medical officer in the U.S. Navy, attending to troops being transported to and from Korea. He was an internist in private practice in Souderton and was on the staff at Grand View Hospital from 1956 to 1985. He later served as a staff physician at the Veterans' Administration Out-Patient Clinic in Allentown until retiring in 1992.

Antonio Martinez-Tapia, M.D., G.M. '49, Titusville, Fla.; May 26, 2011. A retired ophthalmologist, he was born in Santa Cruz del Sur, Cuba, and received his medical degree from the University of Havana.

'50s

Robert Bruce Bergmann, M.D., G.M. '50, Massapequa, N.Y.; September 21, 2011. He served as captain in the U.S. Air Force from 1952 to 1955. He had been president of the Nassau County Medical Society, the Nassau Academy of Medicine, and the Academy's Section of Ophthalmology. He also served on many committees of the Medical Society of the State of New York and was a member of the N.Y. State Board of Professional Medical Conduct. In 2004, he received a Hobie Award for lifetime service, presented by the New York State Ophthalmology Society. He also received the Sidney Mishkin, M.D., Lifetime Distinguished Service Award from Nassau County Medical Society in 2010.

Russell R. Hansen, M.D. '50, G.M.E. '54, Woodland, Calif.; August 29, 2011. He served in the Naval Medical Corps during World War II. After completing his residency in pediatrics at the University of California at San Francisco in 1955, he moved with his family to Woodland to begin his practice at the Woodland Clinic.

Robert W. Neilson Jr., M.D. '50, St. Augustine, Fla., a retired thoracic surgeon; September 7, 2009. During World War II he was a second lieutenant in the 98th Infantry Division of the U.S. Army. He spent three tours as a volunteer surgeon in the Vietnam War.

Charles R. Beittel Jr., M.D., G.M.'51, Royalton, Pa., a retired obstetrician-gynecologist; January 4, 2011. He was an Army Air Corps veteran, serving at the rank of captain.

Abol H. Fotouhi, M.D., G.M. '51, Binghamton, N.Y., a retired surgeon; August 18, 2010. Born in Iran, he earned his medical degree from Jefferson Medical College.

Rose Pully, M.D. '51, Kinston, N.C., a retired physician; April 8, 2011. After retiring from her private practice in family medicine, she became a clinical professor of family medicine at East Carolina School of Medicine in Greenville.

Sheldon D. Sax, M.D. '51, G.M.E '58, Flushing, N.Y., a retired physician and surgeon; August 6, 2011. He began his career as a staff surgeon at the Manhattan VA Hospital, where he later became the assistant chief of surgery, then entered private practice. He was on the staffs of Booth Memorial Hospital and Flushing Hospital and Medical Center. A clinical assistant professor of surgery at NYU School of Medicine, he later worked for the Department of Health for the State of New York. He was a Fellow of the American College of Surgeons.

Alice Wolferd Staub, M.D., G.M. '51, Roxborough, Pa., a retired family physician on the staff of Jeanes Hospital; June 23, 2011. To earn tuition for medical school, she worked as a secretary, technician, and chemist for the U.S. Department of Agriculture in Philadelphia.

John J. Sullivan, M.D., G.M. '51, Auburn, N.Y., a retired ophthalmologist; December 12, 2009.

Frank X. Hasselbacher, M.D., G.M. '52, Louisville, Ky., a retired psychiatrist who had maintained a practice in Camp Hill, Pa.; April 6, 2011. Born in Nurnberg, Germany, he received his M.D. degree from Columbia University College of Physicians and Surgeons in 1946. He had worked for the state mental hospital systems of Pennsylvania and Connecticut and served as director of State Mental Health Services of Pennsylvania.

Desiderius I. Zubritzky, M.D., G.M. '52, Mt. Vernon, Pa., former chief of medicine at McKeesport Hospital; April 11, 2009. He earned his medical degree in 1945 from the University of Pittsburgh. After leaving McKeesport Hospital, he became an internal medicine clinician at the Veterans Administration clinic in Pittsburgh. He was a Fellow of the America College of Physicians.

Royal T. Farrow, M.D. '54, Dalton, Ga., a retired chief of pediatrics and chief of infectious diseases at Hamilton Memorial Hospital; March 26, 2011. He was a president of the Whitfield-Murray County Medical Society and was named the Dalton Man of the Year in 1981.

John C. Grammer Jr., M.D., G.M. '54, Dallas; April 19, 2011. A Dallas cardiologist for 30 years, he was the founding director of the coronary-care unit at St. Paul Hospital, now part of the University of Texas Southwestern Medical Center. He served in the Navy Medical Corps during the Korean War, assigned to a Marine Corps unit.

David W. Kraemer, M.D. '54, G.M.E. '58, Mt. Lebanon, Pa., a retired obstetrician-gynecologist; June 11, 2011.

Cyrus Wolfman, M.D. '54, Vancouver, B.C., a retired psychiatrist; November 30, 2011. He had been with the Brookdale University Hospital and Medical Center for more than 19 years and had been director of its Department of Psychiatry. He received a lifetime-achievement medal from the American Psychiatric Association.

Tet H. Pang, M.D., G.M. '55, San Francisco; September 19, 2011. A graduate of National Sun Yat-Sen University in Taiwan, he was a thoracic and cardiovascular surgeon for 25 years at Fairview General Hospital (now Cleveland Clinic) in Cleveland.

William P. Gibbons, M.D. '56, Altoona, Pa., a retired plastic surgeon at Altoona Hospital; June 25, 2011.

Harrison McMichael, M.D. '56, G.M.E. '60, Paoli, Pa., emeritus professor of pathology and labo-

ratory medicine at Penn's School of Medicine; November 20, 2011. He was a pathologist for the United States Air Force before returning to Penn as a professor. He served as associate dean for curriculum with Penn's medical school 1976-1990. He had been a research fellow of the Heart Association of Southeastern Pennsylvania.

Pracha Pises, M.D., G.M. '56, Walnut Creek, Calif.; March 14, 2011. He was a Fulbright Scholar and a clinical professor of medicine at Northwestern University, U.C.L.A., Stanford, and U.C.S.F. While in private practice for 33 years in Oakland, he was also the chief of gastroenterology and director of the Motility Lab at Peralta Hospital.

Erwin R. Schmidt Jr., M.D., G.M.E. '56, Lafayette Hill, Pa., an orthopaedic surgeon at HUP for more than 45 years; June 12, 2011. He was also an associate professor of orthopaedics. During World War II, he served in Europe with the U.S. Army's 42nd "Rainbow" Infantry Division and was awarded a Bronze Star. From the late 1950s to the mid-1970s, he was a physician for Penn's football team. He later worked at the student health center and was an orthopaedic consultant to the student health center at Swarthmore College. For many years, he also cared for patients at the Children's Seashore House in Atlantic City. He retired in 1998.

Matthew A. Asbornsen, M.D. '57, Bangor, Me., August 21, 2011. He served two years in a research laboratory at the United States Army Chemical Center, then completed his residency in internal medicine at the University Hospitals of Cleveland. Board certified in internal medicine, he was a member of the American College of Physicians.

Lawrence M. Baker, M.D., G.M.E. '57, Chestertown, Md., a retired thoracic surgeon; May 25, 2011. After serving in the Army from 1943 to 1946 and completing his medical training, he practiced general and thoracic surgery at Kent General Hospital, now Bay Health, in Dover, Del. He was a Fellow of the American College of Surgeons and The American Board of Surgery and a diplomat of the National Board of Medical Examiners.

J. Thomas Murphy, M.D. '57, Wayne, Pa., January 29, 2010.

Theodore L. Donmoyer, M.D. '58, G.M.E. '62, Lehigh Valley, Pa., a retired cardiologist; July 28, 2011.

Michael T. Mahoney, M.D., G.M. '58, September 26, 2011, a retired urologist; West Orange, N.J. He was in the Army Air Force during World War II, including service in India, Burma, and China. In addition to his private practice, he had been chief of urology service at the Presbyterian Unit of United Hospitals and held senior attending positions at St. Mary's Hospital and St. Michael's Hospital. A Fellow of the American College of Surgeons, Mahoney served on the Roseland Board of Health.

Theodore Atherton Tristán, M.D., G.M. '58, Camp Hill, Pa.; February 28, 2011. He founded Tristán Associates, a private practice at the Polyclinic Medical Center that later opened an office on Union Deposit Road where patients could get X-rays done on an outpatient basis. He continued to teach radiology residents at the Harrisburg Breast Diagnostic Center until his retirement in 1989.

Percy H. Wood, M.D., G.M.E. '58, Bennington, Vt., retired clinical director of the Carrier Clinic (now the Carrier Foundation), a private psychiatric hospital in Belle Mead, N.J.; January 7, 2011.

Stanley Davis Fons, M.D. '59, Bedford, N.H.; September 21, 2011. During his many years at Elliot Hospital in Manchester, he served in several capacities, including chief of staff and head of the diagnostic radiology department. He was instrumental in securing the hospital's first CT scanner and also taught in the hospital's radiology technician school. He had been a major in the New Hampshire National Guard.

Joseph S. Harun, M.D., G.M.E. '59, Lower Gwynedd, Pa.; May 17, 2011. He left his own dermatology practice to joined Carter-Wallace, a pharmaceutical firm, where he helped develop penicillamine to treat severe arthritis. In the late 1960s, he joined Ciba-Geigy, where he was involved with the development of new uses for clofazimine. Ciba-Geigy researchers ultimately discovered that the drug, intended for the treatment of tuberculosis, could be used in combination with other drugs to treat leprosy and infections in AIDS patients. From the mid-1990s until he retired in 2000, he was a consultant to pharmaceutical companies and helped organize funding for AIDS research at academic medical centers.

Walter L. Norton, M.D. '59, New Smyrna Beach, Fla., a retired rheumatologist; March 15, 2011. He was a faculty member at the University of Texas Southwestern Medical School in Dallas from 1963 to 1967. In 1979 he traveled to Saudi Arabia, where he was a rheumatologist at the King Faisal Specialist Hospital, Riyadh.

'60s

Joseph C. Donnelly Jr., M.D., G.M.E. '61, West Chester, Pa.; May 14, 2011. He served in the U.S. Navy for two years as a medical officer aboard the aircraft carrier *Lexington* and as a staff surgeon in Navy hospitals in Rhode Island and Newfoundland. He was a thoracic and cardiovascular surgeon at Lankenau Hospital and was later on the staffs of St. Joseph Medical Center and Community General Hospital, both in Reading. For five years before retiring in 1997, he taught residents from Jefferson Medical College at the Veterans Affairs Medical Center in Wilmington. He had been president of the Pennsylvania Association for Thoracic Surgery and the Pennsylvania Chapter of the American College of Chest Physicians.

Richard W. Miller, M.D. '61, Marshfield, Wis., a retired physician who was instrumental in establishing the nuclear-medicine program at the Marshfield Clinic; March 9, 2011.

James P. Boland, M.D., G.M.E. '62, Charleston, W.Va., a retired professor of surgery at West Virginia University; April 5, 2011. During his fellowship in cardiothoracic surgery at Parkland Hospital in Dallas in 1963, he attended Texas Governor John Connally, who was shot during the assassination of President John F. Kennedy.

Brian M. Gottlieb, M.D. '62, Whitefield, Me., a retired psychiatrist who had served as the Minnesota state medical director; February 9, 2011.

Theodore N. Smith, M.D., G.M.E. '62, Syracuse, N.Y.; June 5, 2011. He met his wife of 52 years, Charleen Herrling, during his ophthalmology internship at Upstate Medical University. He was in clinical practice in ophthalmology for more than 45 years and taught medical students and residents at Upstate. As a volunteer, he provided free eye surgery for people in Central America and Kenya.

Eugene T. Tragus, M.D., G.M. '64, Phnom Penh, Vietnam, former director of the emergency medicine department at Angkor Hospital for Children; April 19, 2011.

Paul M. Hemler, M.D., G.M.E. '66, Camp Hill, Pa.; February 7, 2011. A retied anesthesiologist, he had a general practice in Lancaster for ten years before joining Holy Spirit Hospital. He later took a position with the Commonwealth of Pennsylvania, reviewing cases for hospital utilization.

Stuart H. Myster, M.D. '67, Corpus Christi, Tex., a retired pathologist; March 20, 2008. He served in the Navy Medical Corps for twenty years as a physician, retiring as captain in 1987. During his military career, he worked in California, Japan, and Washington. Myster was a civilian pathologist in Washington, Illinois, and Texas.

'70s

Joseph M. Farber, M.D., G.M.E. '70, Piedmont, Calif., ophthalmologist; September 3, 2011. He enlisted as a medical officer in the U.S. Navy and served in Vietnam.

'80s

Daniel Brookoff, M.D. '82, Ph.D. '85, G.M. '86, Memphis, Tenn., April 13, 2011. A physician who had specialized in treating bladder-pain syndrome or interstitial cystitis, he had established pain-management clinics for the disorder in Memphis and Colorado.

Ricardo Eng, M.D. '87, G.M.E. '91, Moorestown, N.J., a radiologist at Kennedy Memorial Hospital; March 9, 2011.

'90s

Jeffrey H. Ware, Ph.D. '94, Haddonfield, N.J., a senior research scientist in the Department of Radiation Oncology in Penn's Perelman School of Medicine; October 23, 2011. His dissertation fellowship at Penn was funded by the National Institutes of Health. Ware's work included the study of compounds that protect astronauts from space radiation and their possible application in preventing cancer in high-risk individuals. According to Stephen Hahn, M.D., chair of the Department of Radiation Oncology, Ware was "an exceptional researcher" who had dedicated his professional life to "one of our more important missions, which is trying to find better treatments for cancer patients."

'00s

Anthony L. Halperin, M.D. '10, April 7, 2011. As an undergraduate at Brown University, he spent a summer working as an emergency medical technician with the Spanish Red Cross. At Penn, he was involved in the Guatemala Health Initiative and was a 2009-2010 Fogarty International Clinical Research Scholar in Lima, Peru.

FACULTY DEATHS

Arthur I. Alterman, Ph.D., Broomall, Pa,, a research professor of psychology in psychiatry and a senior scientist and former scientific director at the Veterans Affairs Medical Center-University of Pennsylvania Center for Studies of Addiction; October 5, 2011. For 27 years, he studied substance-abuse treatments at the center, using funding from the National Institutes of Health and the Department of Veterans Affairs. His main interests included characterizing risk factors for substance abuse; defining antisocial behavior in substance abusers; studying relationship of personality disorders to treatment response; and studying the effectiveness of treatments for cocaine, alcohol, and nicotine dependence. He was the author of about 250 publications. From 1970 to 1980, he was director of alcoholism research at the Coatesville Veterans Affairs Medical Center, affiliated with Thomas Jefferson University. From 1981 to 1984, he held the same position at the Highland Drive Veterans Affairs Medical Center in Pittsburgh. According to John Cacciola, Ph.D., a former colleague, Alterman was a mentor to "numerous, now nationally and internationally recognized scientists, and his research itself opened new avenues that countless others have pursued."

Harrison McMichael. See Class of 1956.

Erwin R. Schmidt Jr. See Class of 1956.

William A. Shaver. See Class of 1948.

Thomas Ten Have, Ph.D., M.P.H., professor of biostatistics in the Center for Clinical Epidemiology and Biostatistics; May 1, 2011. After earning his degrees at the University of Michigan, he joined Penn's medical faculty in 1997. In addition to serving as director of the Biostatistics Data-Core and associate director of the Division of Biostatistics, he was also a senior fellow at the Institute on Aging. He studied the intersection of causal statistical methods and behavioral interventions on behavioral and medical outcomes. A Fellow of the American Statistical Association, he had received the Harvard Award for Lifetime Contributions to Psychiatric Epidemiology and Biostatistics.

Jeffrey H. Ware. See Class of 1994.

LEGACY GIVING

62 Years Later, Surgeon Still Gives – to Patients and to Penn

Dr. Principato (far right) with granddaughter Marie and her husband Robert at great granddaughter Camilla's baptism.

Throughout his career as a successful surgeon, Eugene Robert Principato, M.D., G.M. '50, always heeded the advice of his father, Dr. Robert Principato: "If you want to be a great doctor, treat the street cleaner as you would the president of a bank."

Even now, at the age of 90, he follows these words of wisdom when he meets patients. Dr. Principato still performs surgery once a month at Camden's Cooper University Hospital.

"I like to think of myself as a surgeon specializing in the human element.

A protégé of Penn legends I. S. Ravdin and Jonathan Rhoads, Dr. Principato trained at Penn for only one year. The experience stayed with him, and to this day he consistently honors his education with charitable gift annuities (CGAs). In fact, he holds the record for donating 14 CGAs, the most given by any Penn Medicine graduate.

"Why not give to the place I admire and love and who gave me the impetus for a great career?" he asked. "I am not wealthy enough to give a lot of money. With a CGA I give something, and I get income in return."

With a charitable gift annuity, the donor transfers cash or stock to Penn Medicine and receives a lifetime annuity payment and a current income tax deduction. Ultimately, the remaining funds go to the Penn program designated by the donor. It is a classic win-win arrangement, and one of the simplest ways to make a gift.

Dr. Principato has great respect the Perelman School of Medicine as a hub of learning and compassionate care. "The people who make up Penn are brilliant. They are there to help and care about patients, and the mark they have made on research is far reaching."

"I have a sixth sense when it comes to my patients, and I do my best to recognize their fear and put them at ease," he said. "Beyond all the innovation of today, this is what our students should be practicing. Caring for the mind should come first!"

Dr. Principato chose one of a multitude of creative gift opportunities that benefit both Penn Medicine and donors. The Office of Planned Giving is ready to assist in developing an appropriate strategy to incorporate your charitable objectives. Contact Christine S. Ewan, J.D., Senior Director of Planned Giving, at 215-898-9486 or e-mail her at cewan@upenn.edu. For more information, please visit the website at www.plannedgiving.med.upenn.edu.

A Starr's Take on Health Care Reform

Earlier this year, the Penn campus received a visit from one of the nation's most prominent sociologists of medicine and health care – Paul Starr, Ph.D. Author of a Pulitzer Prize-winning book, *The Social Transformation of American Medicine* (1982), Starr is a professor of sociology and public affairs at Princeton University. His book is often considered a starting point in discussions of health care's future and health care's reform. As the Republican presidential primaries have shown, that topic remains one of the most important issues in the nation.

The event, hosted by Penn's Leonard Davis Institute of Health Economics, drew a large audience of physicians, economists, students, and administrators. Starr's topic was the contentious history of health care reform in America. He noted that the fate of the Patient Protection and Affordable Care Act of 2010 "is completely open": it may survive, it may die, or it may be substantially revised. What has always surprised him, he continued, is "the rancor in our conflict," which is not found in other democracies, where instead the focus is on ensuring that costs are spread widely. Only in the United States, Starr asserted, is such an initiative equated with a loss of freedom – and the politics of health care has become *more* acrimonious over time.

For a period in the 1990s, Starr was not only a student of health care but an advisor as well, when he spent time in the Clinton White House. As Starr put it wryly, "I got into the middle of the crossfire."

In his talk, Starr presented the struggle for health care reform as "a historical drama in three acts." Each scene begins with optimistic reformers. In fact, early in the 20th century, New York State came close to much broader health care coverage. Franklin Roosevelt felt he did not have enough Congressional support to pass a health care bill, but Harry Truman did propose a program of universal health insurance. The proposal was defeated by the American Medical Association and insurance companies, who compared it to "socialized medicine," even Communism. Those against such programs, in Starr's words, "had developed a script of opposition," inspired by the Cold War. Universal coverage was depicted as inimical to American life, something foreign.

Bipartisan Support: Hard to Find

Act II ranged from the 1950s to the Nixon Presidency. In 1965, Lyndon Johnson signed Medicare and Medicaid into law. What Congress passed, however, greatly increased the costs of health care – to a great extent because of concessions to the A.M.A. But history took a couple of sharp turns. In the midst of the Watergate scandal, a weakened Nixon was looking to redeem himself and was in favor of a broad plan. Wilbur Mills was then the powerful Democratic chairman of the House Ways and Means Committee, and his backing was essential to Nixon's plan. But Mills's legislative power was undermined by scandal. According to Starr, the opportunity for bipartisan support disappeared.

Act III, as Starr presented it, began during the Clinton years, through the years of the Republican Congress, and into the Obama administration. In that period, health care insurance was "at the top of the agenda for Democrats." But there was also "a cacophony of different ideas," even within Clinton's own party. Despite some initial headway toward a bipartisan agreement, "it all came to ruin." The limits on expenditures and attempts at cost containment worried business groups. In 2006, universal coverage was enacted in Massachusetts through the efforts of Governor Mitt Romney, with advisors from, among other resources, the conservative Heritage Foundation. Both Romney and the Foundation reject such a system now.

Although President Obama could build on earlier plans, that did not make the bill's passage any easier. Starr noted "the wild ups and downs," with raucous town hall meetings, and getting enough Congressional votes was a "cliffhanger." Despite the passage of the Affordable Care Act, "we know that it isn't over" only two years later. A presidential election looms; the Supreme Court is scrutinizing the act; and many states have challenged its constitutionality. As Starr put it, "It's gonna take another miracle" for the Act to survive in an era when the political parties are much more ideological and swings in power could bring significant changes in policy.

In the question-and-answer period, Starr conceded the achievements of the last two years but expressed concern about "the slow timetable for implementation." Some parts of Obama's plan would not go into effect until 2014. If the act allowed for consolidation by 2013, Starr said, there would be a better chance it would survive, even with a change of political power. According to Starr, it would be very difficult to take health insurance away from the 30 million people who gained coverage through the act.

Even as someone in favor of health care reform, Starr believes that supporters must do a better job explaining it. Today, he said, many families are more opposed to the Obama plan, even if it would benefit them. As Starr said in conclusion, the historical drama of health care reform may actually be "a kind of tragedy." •

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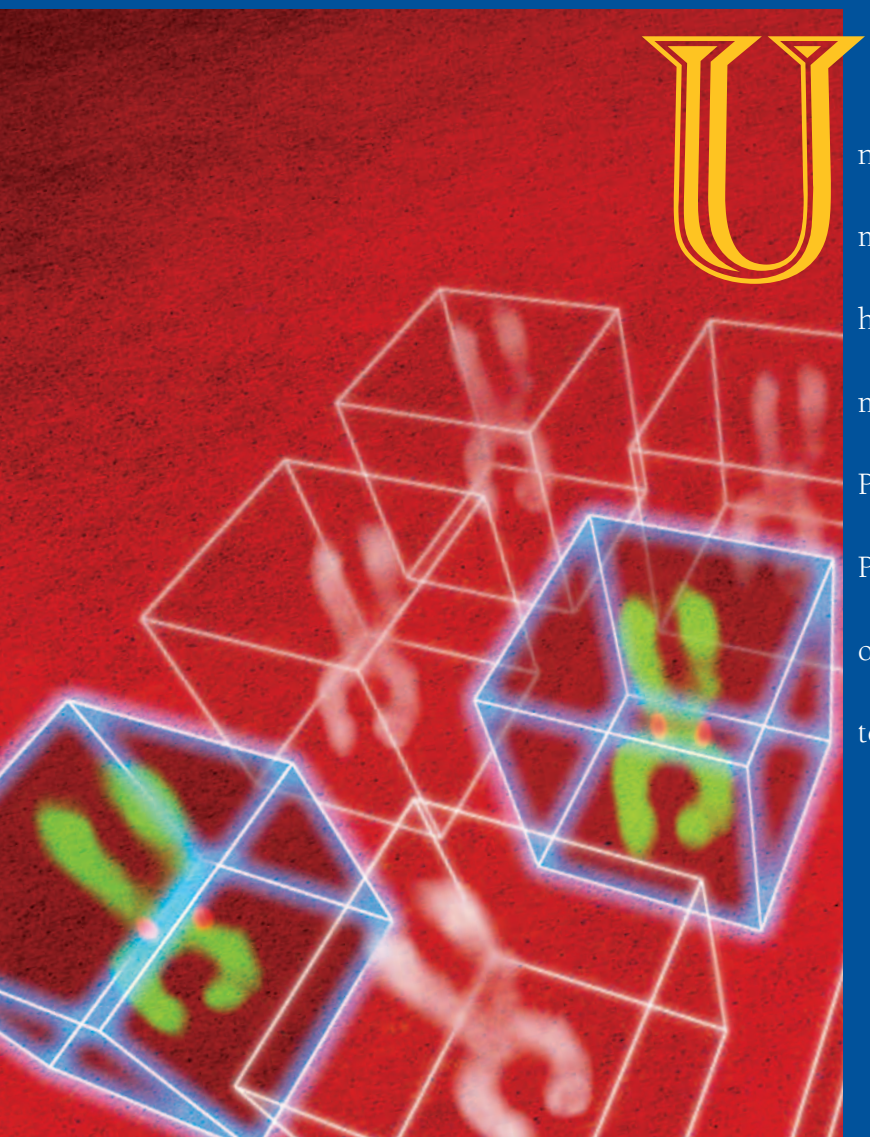

Until recently, scientists believed that gene mutations were the only source of human diseases – but it turns out to be more complicated. As Shelley Berger, Ph.D., director of the Penn Epigenetics Program, explains, “Epigenetics is a layer of regulation over our genes that is key to how genes are turned on and off.”