PENN Medicine

SUMMER 2008

FISHERS' $50 MILLION GIFT SUPPORTS NEW TRANSLATIONAL RESEARCH CENTER

GENE THERAPY RESTORES PARTIAL SIGHT

Help for Unhealthy Environments

Behind the Jannetta Procedure

Comparing Drugs:
When Cost and Science Collide

Going Public

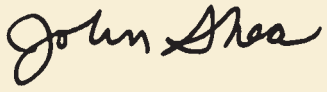
Faculty members and alumni of Penn's School of Medicine are no strangers to print, whether publishing study results or writing textbooks. But not everyone has the inclination to weigh in on controversial topics. For one thing, the authors may have to express themselves a little more forcefully and less subtly to be heard. For another, the responses to these ventures are often less genteel than might appear in the letters section of a professional journal. Not everyone, in other words, has the heart for lively public discourse.

Paul A. Offit, M.D., apparently does. A well-known advocate of vaccines, he is the Maurice Hilleman Professor of Vaccinology in Penn's Department of Pediatrics and chief of infectious diseases for The Children's Hospital of Philadelphia. This spring, he wrote an opinion piece for The New York *Times*, about as public a forum as one can imagine. His piece was a response to the news that the federal government had agreed to compensate the family of Hannah Poling. At 19 months, she received five vaccines; afterwards, she was diagnosed with encephalopathy. At an April press conference following the decision, her parents announced that the government had admitted that vaccines had contributed to her autism. As Offit puts it in his op-ed, "Health officials at the Centers for Disease Control and Prevention and at the American Academy of Pediatrics have steadfastly assured the public that vaccines do not cause autism. Now, in a special vaccine claims court, the federal government appeared to have said exactly the opposite. What happened?" (March 31, 2008). Readers are not kept in suspense about Offit's view: the op-ed's title is "Inoculated Against Facts."

In his piece, Offit argues that a few years ago, "vaccine court judges turned their back on science by dropping preponderance of evidence as a standard." He disputes the claim of an expert who testified on behalf of the Polings that the five vaccines had stressed Hannah's already weakened cells: "The Institute of Medicine has found that multiple vaccines do not overwhelm or weaken the immune system."

Within the day, readers had sent in 114 comments, arriving from all over the United States and several foreign countries. Many comments supported Offit's position, and because of the Times's policy, even those who disagreed had to express themselves civilly. Not so on the Internet, where one blog describes Offit as a "vaccine terrorist" and another wonders "what sort of deal with the devil" Offit has made. After the piece appeared, Offit received about 50 e-mails a day for several weeks – the largest response to anything he's written – "and 90 percent was incredibly favorable."

But on the day in June that we spoke, Robert F. Kennedy Jr., a lawyer who has argued for a connection between mercury in vaccines and autism, was at a rally in Washington, D.C., where he called Offit a "biostitute." (Apparently a combination of *biology* and *prostitute*.) Then there is the hate mail and the occasional death threats Offit receives. In the face of such attacks, why continue to speak up for vaccines? "Because it's the right thing to do." A moment later, Offit adds, "But it's sometimes not the easy thing to do." Ad hominem attacks, he says, are utilized "when you don't have data."



Offit makes no secret of his work on vaccines, and the *Times* op-ed piece included a note that he is a co-inventor and co-patent holder of a rotavirus vaccine. By an odd form of reasoning, some people on the other side of the issue believe that being an expert in the field automatically disqualifies a person as a trustworthy source. But Offit has seen enough to convince him of the benefits of vaccination, and he's concerned that parents are being misled – and children will suffer as a result.

His most recent book is *Vaccinated: One Man's Quest to Defeat the World's Deadliest Diseases* (Smithsonian Books, 2007). An account of the life of Maurice Hilleman, who created almost three dozen vaccines, the book was favorably reviewed in both *The New England Journal of Medicine* and *The Journal of the American Medical Association*. Offit's next book, scheduled to be published in the fall by Columbia University Press, promises to be more controversial: "Autism's False Prophets: Bad Science, Risky Medicine, and the Search for a Cure." In the prologue, Offit cites many of the threats he's received and describes how he came to specialize in infectious diseases. "Some people who believe vaccines cause autism hate me because they think I'm in the pocket of the pharmaceutical industry, that I say vaccines are safe because I am paid to do it. To them, it is logical that I would spend 25 years working on a rotavirus vaccine – a vaccine that has the chance of saving hundreds of thousands of lives every year – so that I could lie about vaccine safety and hurt children. But the reason I say vaccines don't cause autism is they don't."

Paul Offit is not backing down. ●

Cover:

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BEGINNING TO SEE THE LIGHT

Some 20 years after the idea first came to them, Jean Bennett, M.D., Ph.D., and Albert M. Maguire, M.D., have used gene therapy to restore partial sight to patients with Leber's congenital amaurosis (LCA). Until now, there has been no treatment for this retinal disease.

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Penn's translational research will have a new home in 2010. (Architectural rendering)

$50 Million Gift Supports New Translational Research Center

Anne and Jerome Fisher have made a $50 million gift to support the construction of a new biomedical-research center dedicated to the growing field of translational medicine. Scheduled to open in 2010, the 400,000-square-foot Anne and Jerome Fisher Translational Research Center will dramatically increase Penn's research space. It will also enhance PENN Medicine's ability to recruit top scientists in strategic areas, such as cancer, cardiovascular disease, and diabetes. The center will accommodate the research and office-based activities of 100 principal investigators and 900 additional staff.

"All of us at the University of Pennsylvania are enormously grateful to Anne and Jerome for this incredibly generous and transformational gift, which will further position Penn at the forefront of bench-to-bedside medicine," said Amy Gutmann, Ph.D., president of the University. She noted the Fishers' "long and steadfast commitment to Penn," which includes funding renovations to the fine arts library and helping establish the Fisher Program in Management and Technology.

"This new research center makes possible an unprecedented level of focused scientific exchange among researchers, clinicians, and educators from which will emerge important new medical knowledge and treatments," said Arthur H. Rubenstein, M.B., B.Ch., executive vice president of the University of Pennsylvania for the Health System and dean of the School of Medicine.

"Anne and I love Penn," said Jerome Fisher, "and we have long felt that investing in this world-class university is investing in the future of humankind itself. We are especially pleased to be able to make a contribution that will impact advances in health care."

Anne Fisher served on the Board of Overseers for the Graduate School of Fine Arts, now known as the School of Design, from 1992 to 2002, and in 1999 was awarded the Dean's Medal in Landscape and Architecture.

Jerome Fisher, a 1953 graduate of the Wharton School, is founder and emeritus chairman of the Nine West Group Inc. He has served on the Wharton School's Undergraduate Executive Board and was a University trustee from 1996 to 2000. He has been a member of PENN Medicine's Board of Trustees since 2006 and is an honorary emeritus trustee of the University.

The Anne and Jerome Fisher Translational Research Center will be adjacent to PENN Medicine's two new state-of-the-art outpatient facilities, the Ruth and Raymond Perelman Center for Advanced Medicine (opening this year) and the Roberts Proton Therapy Center (opening in 2009).

The international firm of Rafael Viñoly Architects PC is designing the center to incorporate innovative features that will support the collaboration of researchers across disciplines.

The Fishers' gift is part of "Making History: The Campaign for Penn," which has a goal of $3.5 billion to be raised by June 30, 2012. So far, more than half of that amount has been raised.

Stuart Watson

Celebrating the Fishers' gift are, from the left, Ralph Muller, Amy Gutmann, Jerome Fisher, Anne Fisher, and Arthur Rubenstein.

Glowing Showings

For the 11th consecutive year, the University of Pennsylvania School of Medicine was ranked among the top five medical schools in the United States in the annual survey by *U.S. News & World Report*. The school was ranked #4 among the research-oriented medical schools.

Penn was also listed in the top ten in four clinical specialty programs highlighted by the magazine: pediatrics (#2), women's health (#3), internal medicine (#4), and drug/alcohol abuse (#6). Penn's Ph.D. programs in biological sciences ranked 21st overall; immunology/infectious disease was ranked #7 and microbiology ranked #8. Among medical schools with a primary-care orientation, Penn was ranked 31st.

According to the *U.S. News* survey, the top five medical schools are: Harvard University, Johns Hopkins University, Washington University in St. Louis, Penn, and the University of California at San Francisco.

This year, *U.S. News* surveyed 126 medical schools, weighing peer assessments, assessments by residency program directors, research activity, student selectivity, and other factors.

The Hospital of the University of Pennsylvania (HUP) also fared very well in a *U.S. News* survey, landing on its "Honor Roll" of best hospitals in America. As featured in its July 23rd issue, HUP was ranked tenth among the approximately 5,400 facilities surveyed. Only 19 hospitals were honored with the "Honor Roll" designation, awarded for excellence in multiple specialties.

HUP also ranked in the top 20 in 11 of the 16 specialty categories that *U.S. News* surveys. Five HUP specialties were rated among the top 10 nationally: Digestive Disorders; Ear, Nose, and Throat; Endocrinology; Kidney Disease; and Respiratory Disorders. Other specialties in which HUP was ranked were: Cancer; Geriatric Care; Gynecology; Heart & Heart Surgery; Neurology & Neurosurgery; Orthopaedics; Psychiatry; Rehabilitation; Rheumatology; and Urology.

"We are especially pleased to note that 14 specialties at HUP improved in their rankings over last year," said Ralph W. Muller, chief executive officer of the Health System. "This achievement highlights the success of our commitment to quality of care. Together with our focus on biomedical research and medical education, this ongoing commitment enables our hospital to continue to grow and excel as one of the nation's best."

Pennsylvania Hospital, part of Penn's Health System, was listed among the top hospitals in Orthopaedics and Urology.

Johns Hopkins Hospital was ranked first this year, closely followed by the Mayo Clinic in Rochester, Minn.

Since 1990, *U.S. News & World Report* has provided a ranking of hospitals' quality of care on a nationwide basis, evaluating hospitals based on factors such as mortality rate, technology, staffing of nurses, factors related to the individual specialties, and reputation among a group of randomly selected, board-certified physicians. This year, only 170 hospitals scored high enough to rank in even a single specialty. To be on the "Honor Roll," hospitals must be ranked very highly in at least six of the 16 specialties.

Olivia Fermano

Double Treat

Joshua Udoetek had more than one reason to be happy on Match Day 2008. For a start, both he and his wife, Sade, matched to Baylor College of Medicine for their residencies. In addition, the Penn tradition is that students' names are randomly picked from a hat, and when called, the students go to the stage to receive the envelopes informing them of their match. As the last student called to the stage, Udoetek won the bag containing a dollar from each of his 139 fellow students. Cheering him on, from left, are Barbara Wagner, director of student affairs; Jon B. Morris, M.D., associate dean for student affairs; Gail Morrison, M.D., vice dean for education; Arthur H. Rubenstein, M.B.,B.Ch., dean of the School of Medicine; and Helene Weinberg, registrar.

Eight Glasses of Water? Not So Fast

Many of us "know" that we should be drinking eight glasses of water a day. All that water, we have been told, would bring benefits, such as helping flush toxins from the body; suppressing appetite; improving our skin; and reducing headaches. In popular lore, water seemed only slightly less effective than an apple a day in keeping the doctor away.

But Stanley Goldfarb, M.D., a professor of medicine in the renal, electrolyte, and hypertension division, and Dan Negoianu, M.D., a research fellow in the division, have done research that basically throws water on these beliefs. In a widely publicized editorial in *The Journal of the American Society of Nephrology*, they noted "multiple web sites warning health-conscious readers they must drink eight glasses of 8 oz/d to remove dangerous 'poisons'." While acknowledging that "individuals in hot, dry climates" have an increased need for water, they ask whether "average, healthy individuals living in a temperate climate" need the extra water. They conclude: there is no scientific evidence that they do. In most cases, the benefits are told in "wives' tales" or "urban myths."

In fact, as Goldfarb told NPR in April, "drinking large amounts of water surprisingly tends to reduce the kidney's ability to function as a filter. It's a subtle decline, but definite."

In most cases, Goldfarb and Negoianu argue, there is no evidence of a *lack* of benefit, either.

As an educator and associate dean for curriculum for the School of Medicine, Goldfarb may have a special interest in debunking unsubstantiated health beliefs. He recently received the Lindback Award for Outstanding Teaching from the University. According to the supporting material, students in his Nephrology and Introduction to Health Care Systems classes praise his ability to "make clear extremely complex material" and his "mastery of evidence-based clinical studies."

Transitions & Appointments

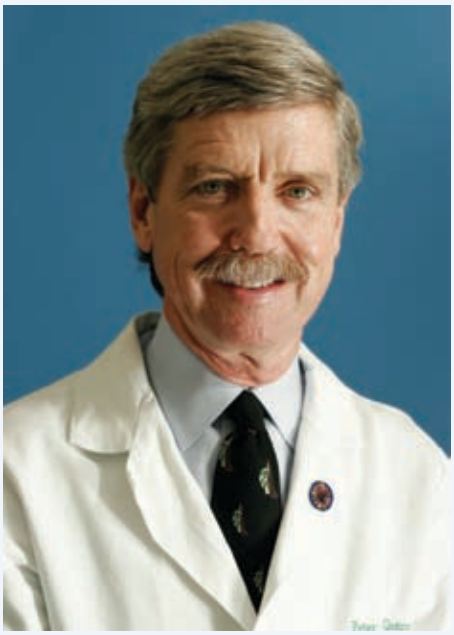
Larry Kaiser, M.D., the John Rhea Barton Professor and Chairman of the Department of Surgery, has been named the president of the University of Texas Health Science Center in Houston. Kaiser, who joined Penn in 1991 as associate professor and chief of general thoracic surgery, founded and directed Penn's Lung Transplantation Program. He was appointed chair of the department in 2001 and was named surgeon-in-chief of the Health System in 2006. A pioneer in the technique of video thoracoscopy, he is a fellow of the American College of Surgeons and a member of the Institute of Medicine of the National Academies.

The UT Health Science Center in Houston has an operating budget of $725 million. It employs more than 1,300 faculty and enrolls some 3,775 students.

A search committee has been formed to identify outstanding candidates for PENN Medicine's next chair of the Department of Surgery. Richard P. Shannon, M.D., chair of the Department of Medicine, is heading the committee.

David W. Kennedy, M.D., vice dean for professional services for the School of Medicine and senior vice president of the Health System, stepped down from those positions on June 30. He was elected president of the Academy of American Otolaryngology: Head and Neck Surgery and will assume office in the fall. A former chair of Penn's Department of Otorhinolaryngology – Head and Neck Surgery, Kennedy led the Clinical Practices of the University of Pennsylvania for seven years. He will continue as president of the International Rhinologic Society and as editor-in-chief of the *American Journal of Rhinology*.

Effective July 1, **Peter D. Quinn, M.D., D.M.D.**, chair of the Department of Oral and Maxillofacial Surgery, will become vice dean for professional services and senior vice president. He is also the Schoen-



leber Professor and Chair of Oral and Maxillofacial Surgery and Pharmacology in the School of Dental Medicine. He has been chair of HUP's Medical Board, chair of the Faculty Senate in the School of Dental Medicine, and chair of CPUP's finance subcommittee and billing oversight committee. He will take office as president of the American Society of Temporomandibular Joint Surgeons next year.

Honors & Awards

Abass Alavi, M.D., professor of radiology and neurology, received an honorary degree from University of the Sciences in Philadelphia. He was recognized as a pioneer in the field of molecular imaging. Alavi and his team introduced Fluorodeoxyglucose (FDG) Positron Emission Tomography.

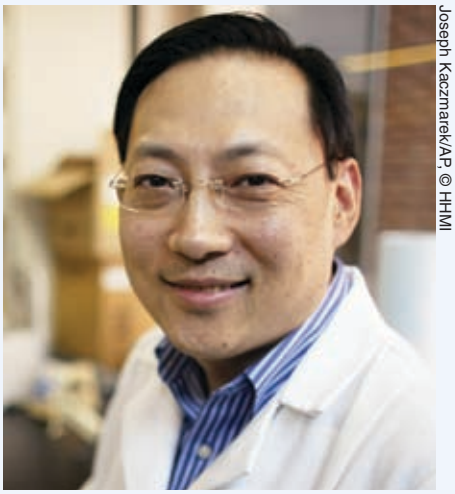

Alavi, left, receives his degree.

Lance B. Becker, M.D., professor of emergency medicine and founder/director of the Center for Resuscitation Science, was named a recipient of the American Heart Association's Award of Meritorious Achievement for helping to found the Resuscitation Science Symposium. He was recognized during an awards luncheon in April during *You're the Cure* on Capitol Hill in Washington, D.C.

Arthur L. Caplan, Ph.D., the Emanuel & Robert Hart Professor of Bioethics and Chair of the Department of Medical Ethics, was made an honorary fellow of the American College of Legal Medicine at the college's annual meeting in March. Caplan is director of Penn's Center for Bioethics. At the annual meeting, he also delivered the 2008 Sandy Sanbar Lecture.

Sean Hennessy, Pharm.D., G.M.E. '96, Ph.D. '02, assistant professor of epidemiology and pharmacology, received the 2008 Leon I. Goldberg Young Investigator Award from the American Society for Clinical Pharmacology and Therapeutics. The award recognizes and encourages young scientists who are active in clinical pharmacology. As recipient, Hennessy presented a lecture entitled "Unraveling Drug Effects Through Epidemiology." He is a former president of the International Society for Pharmacoepidemiology and currently serves as a member of the U.S. Food and Drug Administration's Drug Safety and Risk Management Advisory Committee.

Zhe Lu, M.D., Ph.D., professor of physiology, was selected to be a Howard Hughes Medical Institute (H.H.M.I.) investigator. The institute honors and supports some of the nation's most creative biomedical scientists by giving them the opportunity to tackle their most ambitious and risky research projects. Lu is one of the 56 biomedical scientists chosen this year, and H.H.M.I. has committed more than $600 million to support these newly selected investigators.


Joseph Kaczmarek/AP. © HHMI

Lu works on ion channels, tunnels in a cell's membrane that allow ions – such as potassium or chloride – to enter or exit. He has been exploring the inner workings of ion channels and how this knowledge sheds new light on the pathology of such diseases as cystic fibrosis and MRSA.

This is the first time that H.H.M.I. opened up a general competition to the direct application process. It chose the finalists from among 1,070 applications submitted in a nationwide competition, which was announced in 2007.

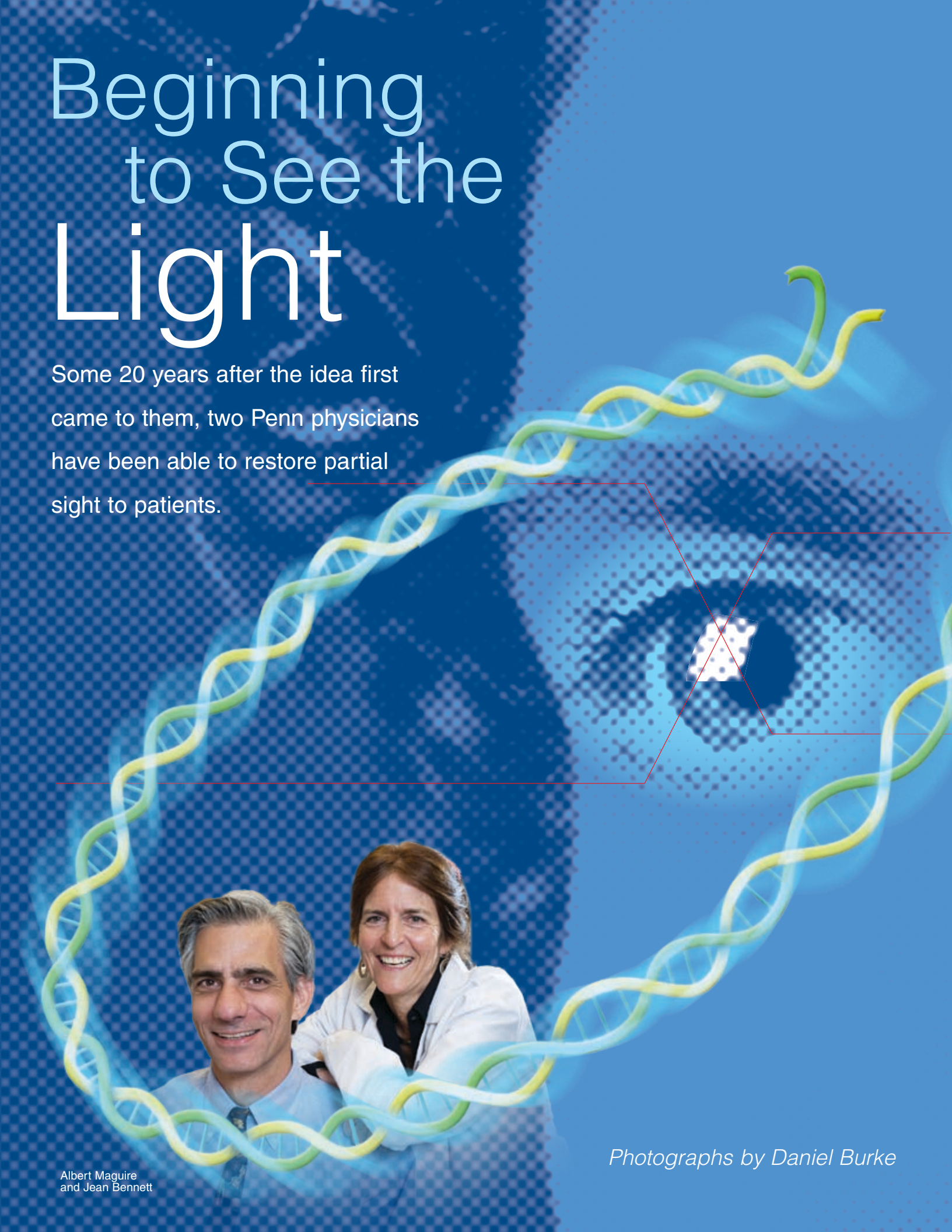
Terrence R. Malloy, M.D.'63, G.M.E '67, chief of urology at Pennsylvania Hospital, was honored in May at the national meeting of the American Urological Association. Malloy received the Gold Cane Award, presented to a senior urologist who has made outstanding contributions to the profession and to the association.

Barbara K. Schmidt, M.D., has won the first annual "Trial of the Year Award" from the Society for Clinical Trials for her study on the caffeine treatment for premature infants. It was published in *The New England Journal of Medicine* last year. The award was announced on International Clinical Trials Day, May 20, during the Society's annual meeting. Last year, Schmidt was appointed the Kristine Sandberg Knisely Professor in Neonatology for a term of ten years. She is a professor of pediatrics at the Children's Hospital of Philadelphia and a clinician-educator in the School of Medicine.

Brian L. Strom, M.D., M.P.H., chair of the Department of Biostatistics and Epidemiology and director of the Center for Clinical Epidemiology and Biostatistics, received the 2008 John Phillips Memorial Award for Outstanding Work in Clinical Medicine. The award, given by the American College of Physicians, was presented in May at the College's annual meeting. Previous recipients of the award include Arthur Rubenstein, M.B.,B.Ch., executive vice president of the University of Pennsylvania for the Health System and dean of the School of Medicine, and William N. Kelley, M.D., former CEO of the Health System and dean of the School of Medicine (now professor of medicine and of biochemistry and biophysics). Strom serves as vice dean for institutional affairs in the School of Medicine and senior advisor to the provost for global health.

Beginning to See the Light

Some 20 years after the idea first came to them, two Penn physicians have been able to restore partial sight to patients.



Albert Maguire and Jean Bennett

Photographs by Daniel Burke

Back in 2001, Jean Bennett, M.D., Ph.D., was eager to speak about her team's exciting success in restoring eyesight to dogs. Through gene therapy, researchers from Penn, Cornell University's College of Veterinary Medicine, and the University of Florida were able to reverse blindness in dogs afflicted with a variation of Leber's congenital amaurosis (LCA). A severe form of retinal degeneration, in humans LCA usually begins to steal sight in early childhood and causes total blindness during a patient's twenties or thirties. The disease damages light receptors in the retina. Being a scientist, however, Bennett expressed caution about the pace of future developments. As Bennett, then associate professor of ophthalmology at Penn, put it in 2001, "We are nowhere near the introduction of the missing protein in humans to restore sight."

Her caution was understandable. With her husband, Albert M. Maguire, M.D., associate professor of ophthalmology at Penn, Bennett had been researching inherited retinal degenerations such as LCA since the late 1980s. There was no treatment then available for LCA and none on the horizon. When Bennett and Maguire arrived at Penn in 1992, they had already thought long about the possibility of injecting a corrective gene into a patient's eye that would replace the faulty gene. But the molecular geneticist (she) and the surgeon (he) did not find the going easy. In fact, as Maguire recently told *The Philadelphia Inquirer*, very early in his career, he shared the idea he and Bennett had for treating LCA with a pioneer in retinal surgery. Bluntly, the expert told Maguire it would never work.

Seven years after their study about the dogs was published in *Nature Genetics*, Bennett, Maguire, and their multi-institutional team have taken another exciting and impressive step: In a clinical trial conducted at The Children's Hospital of Philadelphia, researchers from Penn have used gene therapy to safely restore vision in three young adults who have Leber's congenital amaurosis. Although the patients have not achieved normal eyesight, the preliminary results set the stage for further studies of an innovative treatment for LCA and possibly other retinal diseases.

The international team – led by Penn, Children's Hospital, the University of Naples Federico II, the Telethon Institute of Genetics and Medicine (both in Italy), and several other American institutions – reported their findings in April in an online article in *The New England Journal of Medicine*.

"This is the first gene therapy trial for a nonlethal pediatric condition," said Maguire, who injected the gene into the retina of one eye of each of the three patients. As the title of the study makes clear, the focus at this stage was "Safety and Efficacy of Gene Transfer" for LCA. But the investigators found more than they may have been expecting.

As Maguire pointed out, "Patients' vision improved from detecting hand movements to reading lines on an eye chart" – an improvement that encouraged both the research team and the three patients.

The improvements were noticed starting two weeks after the injections. All three patients reported improved vision in the eye that had received the injection. "Standard vision tests showed significantly improved vision in the patients," said Alberto Auricchio, M.D., a study leader from the Telethon Institute of Genetics and Medicine and the University of Naples Federico II. The researchers also reported that each injected eye became approximately three times more sensitive to light, which is essential for vision. Each injected eye improved compared to the uninjected eye, which had previously functioned better.

The patients were tested over a period of six months after Maguire administered the gene therapy. After treatment, one patient was able to navigate an obstacle course better than before the injection – a sign of the improved visual acuity that all three had to varying degrees. The patients also had less nystagmus, an involuntary movement of the eyes that is common in LCA. One patient experienced better vision in the uninjected eye as well, leading the researchers to suggest that the reduced nystagmus benefited both eyes.

The Penn/Children's Hospital study appeared in *The New England Journal* with a similar study conducted at University College London, where the results were also promising but somewhat more modest. Both studies made an immediate impact. Morton F. Goldberg, M.D., an ophthalmologist at the Wilmer Eye Institute of Johns Hopkins University, told the *Los Angeles Times*: "In the field of retinal dystrophies, this is, I believe, the most important therapeutic discovery" in four decades. "It's a landmark." Savio L. C. Woo, Ph.D., a gene-therapy specialist at the Mount Sinai School of Medicine and former president of the American Society of Gene Therapy, called the Philadelphia trial "exceptionally exciting. . . . It's absolutely remarkable."

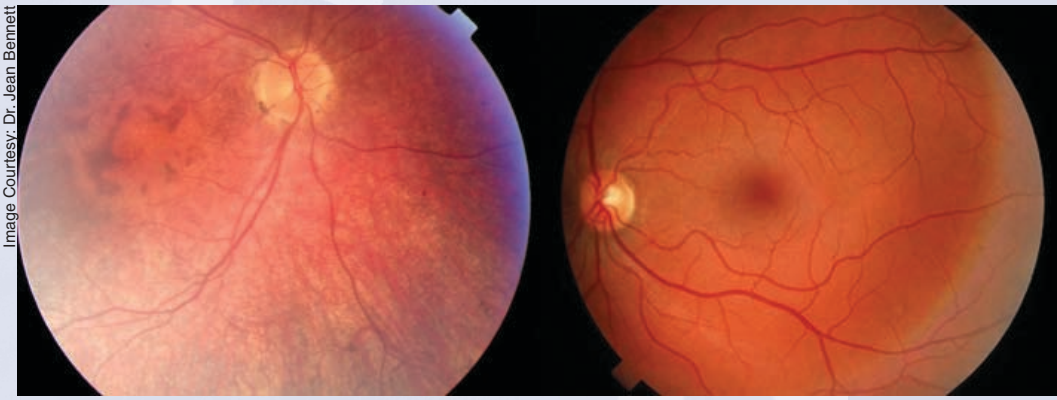


Image Courtesy: Dr. Jean Bennett

Left panel: Right eye of an LCA patient prior to injection. Note pigment epithelial atrophy in the macula, retinal thinning, mild pallor of the optic disc, and vascular attenuation. Right panel: A normal eye, by comparison.

Joan W. Miller, M.D., of the Massachusetts Eye and Ear Infirmary, was more cautious in her editorial in *NEJM*. She noted that the increased visual acuity reported by the patients in the Philadelphia study is "subjective," but also pointed out that the pupillary light reflex that Maguire tested was "an objective measure of retinal function," suggesting improvement in the treated eyes. In all, she wrote, the preliminary results suggest that the procedure is safe and efficacious.

An excellent start, and Bennett, Maguire, and their collaborators are moving straight ahead. "The current clinical trial will continue with more patients," said Bennett. "We expect improvements to be more pronounced if treatment occurs in childhood, before the disease progresses."

Who are the other principals in this very promising study? The original direction came from Bennett, who is also senior investigator at the F. M. Kirby Center for Molecular Ophthalmology at Penn's Scheie Eye Institute, and Maguire. Bennett and members of her laboratory had already cloned the human counterpart to the gene that was used in the initial dog studies – the gene that makes the protein needed by the retina to sense light and send images to the brain. The challenge facing them was to refine the human gene and optimize it for use in humans.

A major contributor to the effort was Jeannette Bennicelli, Ph.D., a senior research investigator who has worked with Bennett for six years. Bennett said the assistant professor of pathology and laboratory medicine "was a key force in helping with the cloning and testing."

Part of Bennicelli's responsibility was to take the human gene used in the dog and modify a few of what she called its "10,000 building blocks" to make the gene as efficient as it could be. She narrowed the search to specific areas of the gene that she knew were involved in governing how the correct protein was made. Bennicelli arranged – and re-arranged – the gene's building blocks and tested each version two to three times, hoping that each one would be the "perfect" gene. "I worked on one version for 18 months that I thought would work," she recalled, "but, in the end, I wasn't getting as much expression of the gene as I wanted." So she started over.

Finding the best combination is essential before going to the Food and Drug Administration, Bennett said. "Once you present your data to the FDA, you're locked into that reagent. We were looking for something that would last a lifetime, something that could treat many people with just one administration."

As part of her research, Bennicelli investigated the gene's ability to infect the cell, the amount of protein it made, and how well it was expressed. She was also involved in making sure the delivered gene was as small as possible, to avoid an immune response. By the end of 2006, she had filled three notebooks with results.

All testing was done on cultured retinal cells. Dan Chung, D.O., who is in training to be a pediatric retinal specialist, harvested tissue cells from the back of the retina in animal models and grew them in culture for testing. He also worked closely with Maguire on the surgical aspects of the study, helping to inject copies of the working gene into animal models and to measure the restoration of visual behavior.

Part of determining how well the gene therapy worked depended on – of all things – an obstacle course. It would test the patients' mobility. As Bennett explained, the obstacle course had to have a flexible design so her team could make quick changes to it. "Patients with LCA have incredible memory," she noted. "That's how they live – memorize how many steps from the front door to the street, how many steps to climb to the first-floor classroom."

Medical and undergraduate students in Bennett's lab set to work creating a course that would imitate obstacles in everyday life. Purchases were made at Home Depot, toy stores, a carpet warehouse, and furniture stores. To allow for easy re-arranging, the students put Velcro on the backs of the tiles that covered the floor. They painted arrows on them to guide the patient through the course. Built-in obstacles included a raised tile that mimicked a tree root and a black tile that represented a hole in the ground. Patients would also have to maneuver around a floor lamp and step over a toy.

Another crucial part of the LCA study, of course, was getting the right vehicle to deliver the normal version of RPE65 to the affected patients. What they used was a "vector" manufactured in the Center for Cellular and Molecular Therapeutics of nearby Children's Hospital. The center is directed by Katherine A. High, M.D., the William H. Bennett Professor of Pediatrics in Penn's School of Medicine and an investigator of the Howard Hughes Medical Institute. A pioneer in translational and clinical studies

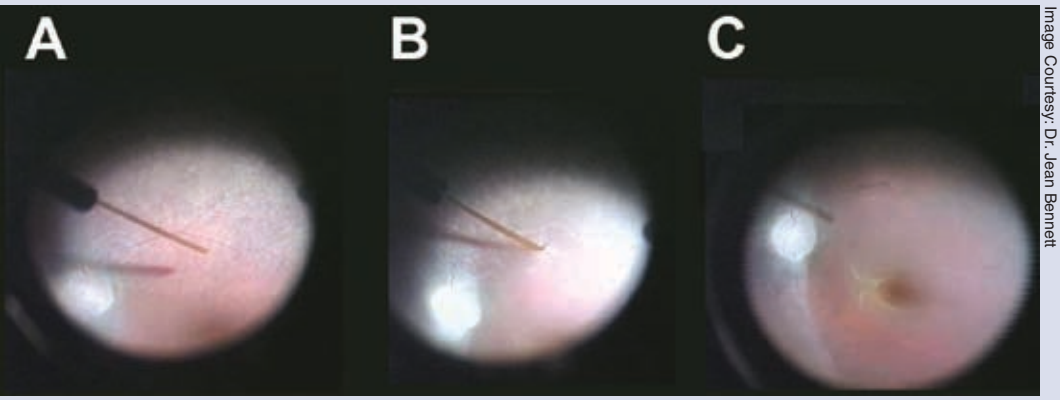


Image Courtesy: Dr. Jean Bennett

Images extracted from a video taken during the subretinal injection.
Panel A: pre-injection. The cannula is approaching the retina. Its shadow is seen near the optic disc.
Panel B: the injection has just begun. The cannula tip is in the subretinal space and the retina is rising.
Panel C: the injection has been completed and the cannula tip has been removed from the retina. The "bleb" covers the entire macula and is bordered on the left side by the optic disc. The raised fovea is visible.

Katherine A. High, M.D.

of gene therapy for genetic disease, she is a former president of the American Society of Gene Therapy who led studies that cured hemophilia in dogs. In 2005, High began a collaboration with Bennett and her group to translate their exciting animal findings into a clinical study.

The vector High and her team produced was a genetically engineered adeno-associated virus, intended to carry a normal version of the gene efficiently and without harmful effects. Three patients from Italy, ages 19, 26, and 26, received the gene therapy via surgical procedures performed by Maguire between October 2007 and January 2008 at The Children's Hospital.

The vector showed no signs of causing inflammation in the retina or other toxic side effects. One of the three patients did have an adverse event, a hole in the retina that did not affect eyesight and may have been related to the surgery rather than to any biological effects of the therapeutic gene or the vector used to carry it.

The patients enrolled in the study to date were identified at the Department of Ophthalmology at the University of Naples Federico II, an institution with extensive experience in collecting and studying patients with inherited retinal diseases. Supervising their enrollment was Francesca Simonelli, M.D.

According to High, "This result is important for the entire field of gene therapy." She noted that gene transfer has been in clinical trials for more than 15 years, "and although it has an excellent safety record, examples of therapeutic effect are still relatively few. The results in this study provide objective evidence of improvement in the ability to perceive light, and thus lay the groundwork for future studies in this and other retinal disorders."

The pace of moving from pre-clinical discoveries into clinical trials has typically been slow in the field of gene therapy. The main reason is the breadth of expertise required, ranging from in-depth knowledge of the disorder to detailed understanding of vector design, manufacture, and pre-clinical evaluation. In addition, the complexities of regulatory oversight at both the federal and local levels present challenges. Through its Center for Cellular and Molecular Therapeutics, The Children's Hospital has been able to gather the necessary experts and provide them with sufficient resources to make the "bench to bedside" translation of gene therapy more easily.

In 2007, the scientists at the center's Clinical Vector Core were awarded a National Institutes of Health contract to produce clinical-grade vectors for trials throughout the United States, which attests to the high quality of their manufacture. The center's staff for regulatory affairs has expertise in clinical gene therapy and coordinates trial approvals from multiple scientific and ethics review committees; manages the study activities at all clinical sites; and ensures compliance with international quality standards for conducting, monitoring, and reporting clinical trials.

Bennett and her team have already moved to the second phase of the published trial. She explained that they are increasing the dose and testing the reagent in younger individuals. Another member of Bennett's lab, Defne Amado, who is pursuing her M.D./Ph.D. degrees, is working on a different strategy that could be used to treat any form of retinal degeneration. If successful, it would be, in Bennett's words, "a magic bullet!"

They are also planning a second trial on other diseases that manifest in children, such as Stargardt Disease. An inherited form of macular degeneration, said Bennett, "it causes loss of central vision and often becomes symptomatic in the pre-teenage years."

As noted, experts in the field have recognized the enormous promise shown in the Philadelphia and London studies. Among them was Paul Sieving, director of the National Eye Institute, who told *Science*: "It is a marvelous thing for the field and for the future." ●

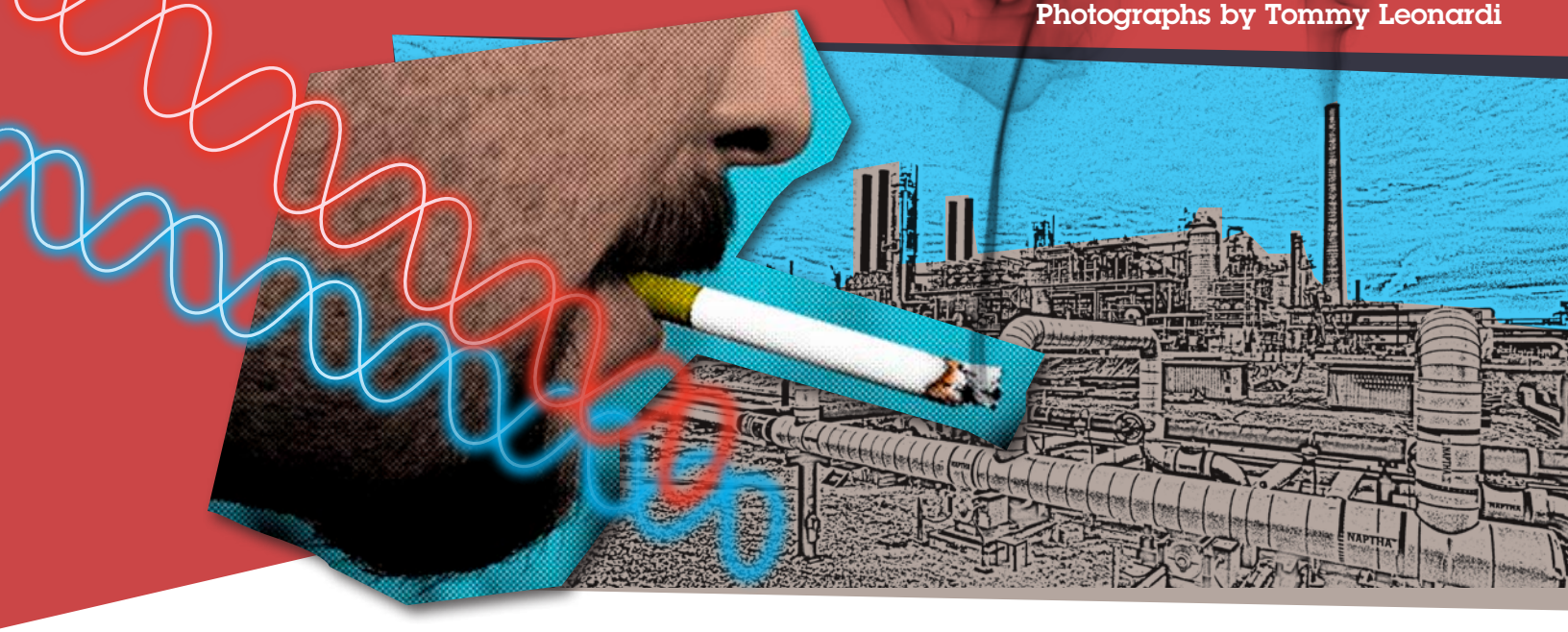
Contributing writers: Karen Kreeger, Joey Marie McCool (Children's Hospital), and Sally Sapega.

When Genes Meet Environment

Penn's Center of Excellence in Environmental Toxicology Tackles Some Stubborn Health Problems

By Thomas W. Durso

Photographs by Tommy Leonardi



Lung cancer is the leading cause of all cancer deaths among both men and women in the United States. Yet while 85 percent of lung cancer is found in people who smoke, only 10 percent of smokers get lung cancer. In addition, the incidence of lung cancer can vary based on geographical location. For example, the incidence of the disease is 50% higher in urban areas such as Philadelphia than in rural areas such as Dauphin County in central Pennsylvania.

Statistical and epidemiological data of this sort tell Penn scientists that there are significant interactions between genes and environment that determine a person's susceptibility to lung cancer. In trying to figure out why, they have developed several theories. One compelling theory is that carcinogens are likely to be higher in urban areas than in rural areas – and that may increase the incidence of lung cancer in smokers and nonsmokers alike.

Unraveling the interactions between genes and environment in diseases of complex genetic traits is one of the areas of research emphasized in Penn's recently established Center of Excellence in Environmental Toxicology (CEET).

Last August, CEET investigators presented studies at the national meeting of the American Chemical Society in Boston involving one class of chemical carcinogens (polycyclic aromatic hydrocarbons, or PAHs) that are found both in tobacco smoke and in air pollution. "PAHs are present in soot that is found at relatively high concentrations in the air we breathe in urban environments," says Trevor M. Penning, Ph.D., director of CEET and a professor of pharmacology, biochemistry and biophysics, and obstetrics and gynecology. The CEET team discovered that these carcinogens cause DNA damage not by binding to DNA themselves but by causing mutations to DNA by generating reactive forms of oxygen. These studies were recently published in the *Proceedings of the National Academy of Sciences* (May 2008). In parallel studies published the same month in *Chemical Research in Toxicology*, CEET researchers show that one of the major genes mutated in lung cancer (the tumor suppressor gene p53) is mutated by the reactive forms of oxygen. Reactive oxygen turns off the suppressor function of p53, which allows tumors to grow.

Penning

"The link between reactive oxygen and carcinogen exposure points to preventive measures that could involve using antioxidants," says Penning. "These studies speak to the power of environmental health science and its translation into medicine."

In late 2002, Edward A. Emmett, M.D., M.S., director of occupational and environmental medicine in the Department of Emergency Medicine, led a School of Medicine retreat focused on environmental health. At the same time, Penning was leading a retreat in molecular toxicology. The retreats had a similar goal – to create a center for environmental health sciences at Penn with a focus on environmental toxicology.

Emmett and Penning teamed up and, after hashing out their ideas a couple of years, wrote a grant proposal to the National Institute of Environmental Health Sciences. They were competitive but unsuccessful in their first try. The next year, 2006, they landed a four-year grant of $4.1 million from the institute to fund the new Center of Excellence in Environmental Toxicology.

Researchers affiliated with the center seek to understand the mechanistic link between environmental exposures and diseases of environmental etiology, with an eye toward early diagnosis, intervention, and prevention strategies. It is not housed in a single facility but instead draws on the expertise of 50 Penn faculty members from 16 departments and five schools, including the School of Law and the Wharton School. CEET is one of only 22 Environmental Health Science Centers in the country and the first in Pennsylvania.

"The N.I.E.H.S. grant provides us the means to be the coordinating unit for all environmental health science initiatives across the University, not just within the School of Medicine," says Penning. "Environmental health is actually much broader than just the School of Medicine."

Emmett

The center's leaders identified four research cores in which its scientists would work: oxidative stress and oxidative stress injury; endocrine/reproductive disruption; lung and airway disease; and genes and the environment. These are areas that affect Southeastern Pennsylvania's environmental and public health in substantial ways.

"When we put the center together, one of the things we realized is that it was going to be an urban center and that we were going to be dealing with environmental health issues that affect the urban environment," Penning says. "Moreover, those issues that we face and their solutions might be translatable to urban environments not just across the country but globally as well."

Penning and others dug through disease registries for the Philadelphia area and found two especially relevant problems. One was a high incidence of lung and airway disease, including ozone-exacerbated asthma, chronic obstructive pulmonary disease, and lung cancer. As Penning puts it, "It was very obvious to us that one of our research themes should be lung and airway disease."

The second major regional health issue was a high incidence of adverse pregnancy outcomes – pregnancies that fail to go to term, resulting in low birth weight and developmental defects. "What are these stresses that cause those adverse pregnancy outcomes to begin with?" Penning asks. "Those stresses can be socioeconomic, but that's part of the built environment, the man-made environment, and that is also an aspect of environmental health."

Those two areas of focus have led to numerous projects. For example, as described earlier, researchers are investigating genetic susceptibility to lung cancer and the development of biomarkers of exposure and response to tobacco smoke. Others are studying the genetics of folate and homocysteine metabolism as it relates to spina bifida; identifying exposures that alter genetic imprinting in embryos before they have been implanted; identifying biomarkers of pre-term birth; seeking genetic alterations that play a role in the development of melanoma; and conducting large, population-based epidemiologic studies of the etiology of autism spectrum disorders.

Ian Blair, Ph.D., professor and vice chair of the Department of Pharmacology, codirects CEET's research core in oxidative stress and oxidative stress injury and is the principal investigator on an N.I.H.-funded project to study biological indicators of exposure to cigarette smoke. He hopes that his and his colleagues' work will provide tangible evidence compelling enough to convince people to change the behaviors that harm them and persuade communities to mitigate the environmental factors that lead to poor public health.

"If you look at the literature, probably about 50 percent of deaths through known causes arise from some kind of environmental factor – cigarette smoking, poor diet, poor exercise – that you can actually do something about," says Blair. "One of the most exciting things that we have done is to show that we have a specific marker of how smoking damages DNA, and we very much hope that by conducting population screens, we will have a test that will tell people that they may belong to the subset of patients who

may have smoking-related illness. If you show people they have high cholesterol, they'll often modify their diet. If we could show smokers how they damage their DNA, in that particular individual it might catch their attention more than reading a box that says, 'Smoking will kill you.' "

Identifying and validating biomarkers of cigarette smoke exposure and response require sophisticated approaches. Changes induced by toxicants can occur at the genome, proteome, or small-molecule level. Blair's group has focused on biomarkers that could be detected by non-invasive techniques in the plasma and urine. They reasoned that smoking-induced DNA damage would be repaired to yield small-molecule adducts (changed DNA) in the urine.

The next challenge was to develop analytical methods that were sufficiently specific and sensitive. To this end they developed liquid chromatography-mass spectrometric methods to purify the changed DNA and detect its mass. By spiking the sample with a synthetic source of the adduct labeled with a heavy isotope, they are able to quantify the adduct relative to this internal standard. This method is being used to distinguish smokers from nonsmokers in a test and validation set of patients.

In addition to bringing scholars together on research projects, CEET presents an annual symposium on topics related to the center's initiatives. In 2006, for the first symposium, the theme was environmental health and disease. Last year's theme was genes and environmental health, chosen to highlight the Pennsylvania Department of Health's recent four-year, $4.2 million award to CEET to establish a Center for the Study of Gene-Environment Interaction in Lung Cancer. These symposia allow scientists to reflect on where the field has been and where they should direct their efforts.

Blair

"We have a lot still to learn," says Margaret R. Spitz, M.D., professor and chair of the Department of Epidemiology at the University of Texas M.D. Anderson Cancer Center. She delivered a keynote address to the 2007 symposium. "We know that smoking causes lung cancer, but that's not enough. Why do some smokers get cancer and others don't? What was the relevant environment or exposure? What is the role of second-hand smoke exposure and the role of other exposures such as dust and radon?"

According to Spitz, CEET's efforts could eventually lead to the development of individually tailored treatments to induce the patients at the highest risk to change unhealthy habits and seek early intervention.

Another keynote speaker, Thomas Kensler, Ph.D., a professor of environmental health sciences at the Johns Hopkins School of Public Health, notes that scientific progress has given researchers "phenomenal" tools to gain insight into pathways and processes of disease. Now they can go into the field and measure exposure levels in people. In effect, he says, they can do "real-time monitoring that provides us with much greater insight into what the true exposures are and therefore what the consequences are likely to be."

As Kensler suggests, moving from the lab to the community is essential, and that is a primary focus of CEET, although in atypical ways. N.I.E.H.S. recommends community outreach for its grant recipients, and most of them develop K-12 educational programming. CEET has taken a different approach.

Edward Emmett, who serves as CEET's deputy director, runs a residency program that places PENN Medicine residents in communities where there is a perceived environmental or occupational health hazard. The residents then work with local leaders to identify areas where CEET may wish to conduct community-based participatory research.

One highly successful example of this approach was the discovery by the residents of Little Hocking, Ohio, that they had highly elevated levels of C8 (perfluorooctanoic acid), a chemical used in the production of nonstick surfaces for cookware. The levels were 60 to 80 times higher in people living near a Teflon manufacturing facility along the Ohio River than those found in the general population. Emmett and his collaborators concluded that water was the major source of contamination. C8 is nondegradable and has a half-life of four to five years in humans; its accumulation has been associated with

birth defects and development defects as well as cancer in rodents.

The usual procedure would have been for the research team to write and publish a paper about its findings, then allow the media to disseminate the story to the communities where the testing was conducted.

"They said, 'We don't want that,'" says Emmett, recalling the responses of community leaders. "As soon as we were sure of the results – and we needed to be sure of the results – we decided the individual participants should get them first. The communication should maximize constructive responses and minimize pointless concern."

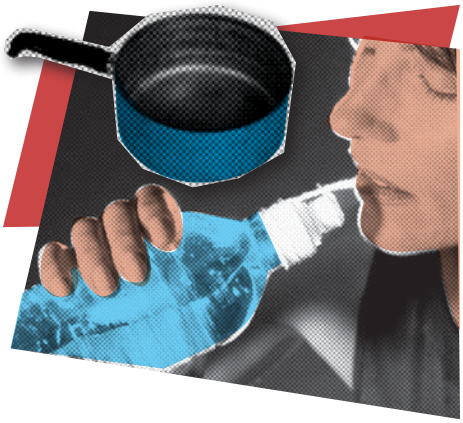
The Penn scientists presented their findings at a well-attended community meeting in Little Hocking, making recommendations on how residents should cope and answering their questions about the study. Only afterward did they publish their results in a pair of papers that appeared in the *Journal of Environmental and Occupational Medicine*.

The community-based research was publicized in *Environmental Health Perspectives* (an N.I.E.H.S. publication) and elsewhere. More recently, the project was named 2008 recipient of the Community-Campus Partnerships for Health Award, presented in May.

CEET also works with Penn's School of Arts and Sciences, conducting academically based community seminar courses in which researchers teach undergraduates studying environmental health sciences about such issues as exposure to lead and tobacco smoke, as well as exposure to and abatement of allergens. As Penning explains, "Once they've learned that material, they then go into, say, a middle school to translate that information to the children and their families. It's a train-a-trainer model."

The final part of CEET's three-pronged outreach approach is forming partnerships with certain communities to assist local leaders with risk assessment and communication. In this capacity, the center currently is working most closely with the city of Chester, Pa.

"That area is very environmentally challenged," says Penning. "It is the home of all the waste incineration for Delaware County." He also notes the presence of the I-95 interstate highway and the oil refineries on the Delaware River. "It's a city of lower socioeconomic status, so there are real issues of environmental justice there."



CEET is working with community groups in Chester to inform them of the environmental health impact of another trash incinerator in the city, and it is developing a pair of on-line tools for city residents. One, TOXOLINK, will allow them to ask questions about chemical exposure and health risks. The other will give them access to GIS (geographic information system) tools so they can enter their street addresses and view information about their air quality, water quality, and more.

"Once we have these two things put together," says Penning, "we will actually be in a very powerful situation to do both environmental epidemiology, from a research perspective, but also identify communities in real need."

Community leaders have been receptive to such efforts. They have found that working with an organization like CEET lends validity to their calls for help.

"When you do environmental issues and you are trying to get the support of local government and industry, it's important that they understand that there are outside interests that are monitoring and are concerned about the same things in your community," says Rev. Horace Strand, pastor of Faith Temple Church and president of the Chester Environmental Partnership. Penn's presence, he continues, grabs the attention of government and industry representatives. "Penn has credibility. With Penn at the table, we also have someone with some expertise who understands the scientific data and who can advise us on things that we as laymen are not experts in."

In Emmett's view, the prevalence of such public-health dangers as obesity and smoking even in the face of overwhelming evidence of their short- and long-term dangers points to the difficulty of convincing people to change their habits. Yet CEET, with its focus not on macro-level communication but on micro-level community partnerships, may be on to something.

In the wake of the announcement of Emmett's C8 findings, the company manufacturing the chemical almost immediately offered free bottled water to residents in the affected areas until it could install filters at its plant to prevent further release into the local water supply.

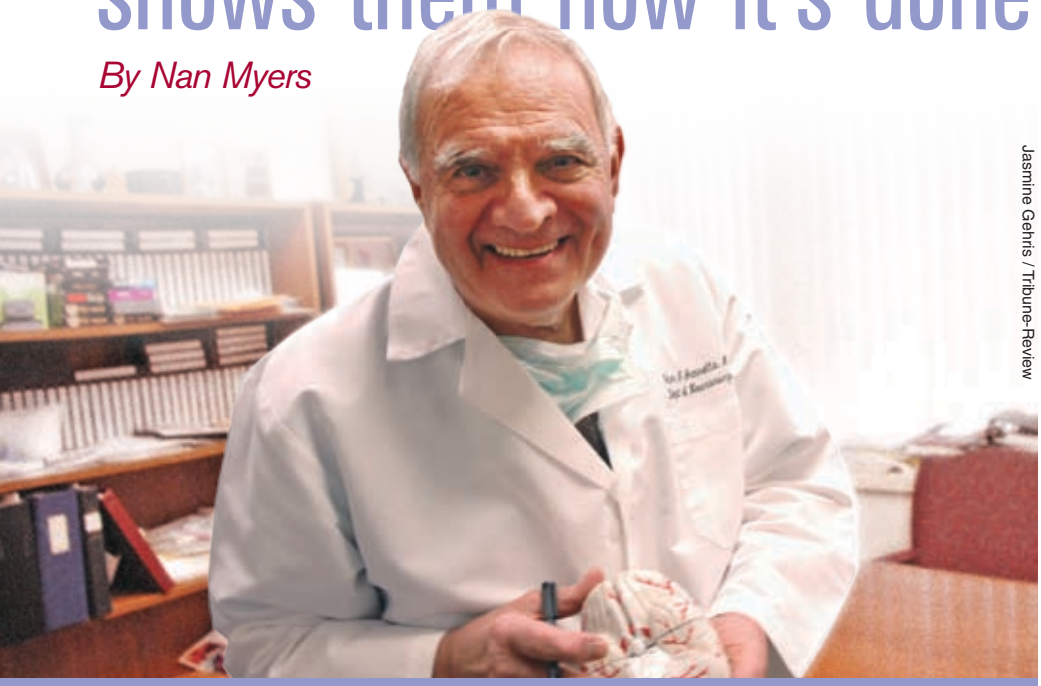
An astounding 78 percent of people took the company up on its offer.

"There was a feeling in the communities that they had become empowered," says Emmett. "We have gone back and have looked at the levels of C8, and they have fallen in people. The levels have gone down significantly. The message got through very effectively." ●

For more on the Center of Excellence for Environmental Toxicology, see www.med.upenn.edu/ceet.

Peter Jannetta shows them how it's done

By Nan Myers



Jasmine Gehris / Tribune-Review

Honored by a big bash last fall, the celebrated neurosurgeon continues his research and explores new applications of microvascular decompression.

Besides his skills as a neurosurgeon, Peter J. Jannetta, M.D. '57, G.M.E. '64, had something else that he would need in his profession: persistence in the face of skepticism.

In 1965, while serving a neurosurgery residency at the University of California at Los Angeles, Jannetta was asked to put together a dissection of the cranial nerves to present to a class of dental students. "I was working on the trigeminal nerve, which is the largest of the cranial nerves, and I noticed that something was different," he explains. This discovery was the genesis of what would become the radically new Jannetta Procedure. After drilling through the skull and viewing the area microscopically, the neurosurgeon locates a vein or artery pressing against the trigeminal nerve. This is a large nerve that carries sensation from the face to the brain, so the patient's pain can be excruciating. The surgeon then cuts the vein, or, if an artery is involved, moves it aside and inserts a tiny pad between the artery and the nerve to relieve the pressure.

The process, known as microvascular decompression, does not damage or destroy the nerve. Jannetta successfully performed his first procedure in 1966 and eliminated the facial pain of a 41-year-old man.

Jannetta is proud of this accomplishment, but it took a long time before the traditional medical community accepted it. "It was considered controversial for many years but finally he was proven right," says William C. Welch, M.D., chief of neurosurgery at Pennsylvania Hospital.

"He had some significant resistance," agrees Frederick Simeone, M.D., a former professor of neurosurgery at the University of Pennsylvania School of Medicine who recently retired. "But when enough surgeons began to do the procedure and saw that it worked, the procedure was slowly accepted."

And many of the neurosurgeons performing the procedure were in fact trained by Jannetta. "I was able to develop people so they could become the chairs of neurosurgery," he says. At last count, there are 17 neurosurgery chairpersons in the United States who were trained by Jannetta.

"He hired me at the University of Pittsburgh Medical Center in 1993," says Welch. "I went to Pittsburgh because of Peter Jannetta. In 1993, it was the best Department of Neurosurgery."

An internationally recognized expert in the treatment of cranial nerve disease, Jannetta credits much of his success to the training he received and the relationships he developed at Penn.

For example: He learned to use the microscope in surgery when he was a general surgery resident working with Dr. Solomon D. Erulkar in the pharmacology department. He credits the influence of Dr. Jonathan Evans Rhoads, then chair of the Department of Surgery, with convincing the Louisiana State University School of Medicine in New Orleans to hire him as associate professor and chief of the neurosurgery division after he left U.C.L.A. – but before he finished his neurosurgery residency. "I began there on December 1 and completed my residency on December 30," Jannetta recalls. And he remembers the words of Dean John McK. Mitchell, who told the incoming Class of 1957 how lucky they were to

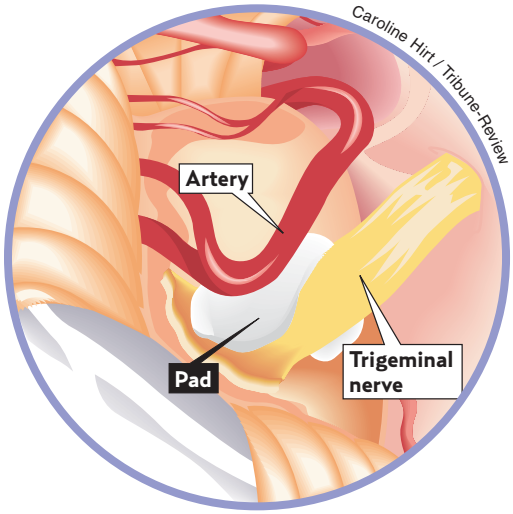
be at Penn Medicine. "I believed him," Jannetta says. "Penn was the intellectual center of the world."

Jannetta was fully trained first as a surgeon and then as a neurosurgeon. "That was very unusual and remains so," says Simeone. "Nowadays, general surgery training isn't mandatory for neurosurgeons."

Jannetta also finds himself in the rare company of doctors who have been the subject of a book – in this case, more than 300 pages long. *Working in a Very Small Place: The Making of a Neurosurgeon* was published by W. W. Norton in 1989, when Jannetta was in his prime at Pittsburgh's Presbyterian-University Hospital. The author, Mark L. Shelton, begins the book with a patient whose pain from trigeminal neuralgia is so intense that he considers suicide. Instead, he finds his way to Jannetta. The book proceeds to explain Jannetta's discovery and vividly describes several surgeries in the cerebellopontine angle, "a very small place on the underside of the brain." The account is by no means uniformly solemn. For example, in the course of the book, Jannetta is surprised to learn that, despite his denials, he routinely hummed and sang during his extremely delicate procedures. The videotapes did not lie!

On Saturday, October 13, 2007, more than 500 of Peter Jannetta's friends, colleagues, and family members convened in Pittsburgh to celebrate his career. Jannetta currently serves as vice chairman of the Department of Neurosurgery at Allegheny General Hospital. Maya Angelou, the former poet laureate of the United States and an old friend of Jannetta's, was the keynote speaker. The day consisted of a scientific symposium with presentations celebrating four decades of neurosurgical innovations. It was followed by the evening gala.

Simeone, who was a resident with Jannetta in the 1960s at Penn, credits



The surgeon makes a small hole in the skull behind the patient's ear. Using a microscope to see the nerves, blood vessels, and veins, he then repositions the blood vessel that is aggravating the nerve and puts a pad the size of a matchstick head between the nerve and vessel, fixing the problem.

Jannetta with making more clinically applicable discoveries — of procedures and techniques — than any other neurosurgeon. "His treatments are based on the mechanism. Most of us succeed by doing better operations or larger numbers of operations."

Before coming to Allegheny in July 2000, Jannetta spent many years at Pitt, serving as chair of neurosurgery from 1971 to 1997. In 1995, Governor Tom Ridge appointed him to be Secretary of Health for the Commonwealth of Pennsylvania. "I was appointed because of my interest in public health," says Jannetta, who held the position for a year.

Things have changed dramatically since Jannetta first presented his controversial procedure. In fact, in 1990, he received the Horatio Alger Award, which honors the achievements of outstanding individuals who have succeeded in spite of adversity.

The author of more than 250 scientific abstracts, articles, and book chapters, Jannetta has earned several of his field's most prestigious awards. In 2006, he was awarded the Zulch Prize for basic neurological research by the Max Planck Society. In presenting the award, the Society stated that his microvascular decompression procedure is a convincing example of how a novel theoretical concept can lead to a practical therapeutic innovation that relieves the suffering of many. In 1983, Jannetta was the first neurosurgeon to receive the Herbert Olivecrona Award from the Karolinska Institute in Sweden. (It is a committee of this institute that selects the laureates for the Nobel Prize in Physiology or Medicine.) And Pitt Med, Jannetta's longtime home, has endowed a chair in his honor.

Jannetta's current interest is applying his microvascular decompression to research as he attempts to determine the etiology of treatment for Type 2 diabetes. He is looking at the connection between vascular pressure on the brain and diabetes, and he presented initial results at the 2007 annual meeting of the Endocrine Society.

These days, however, Jannetta is also concerned that physicians no longer stand up for themselves or their profession. He cites a failure of leadership – especially in the face of a litigious environment. "We don't push back; we just roll over," he says. "It just burns me how poorly we are being treated. Physicians today are litigated to death."

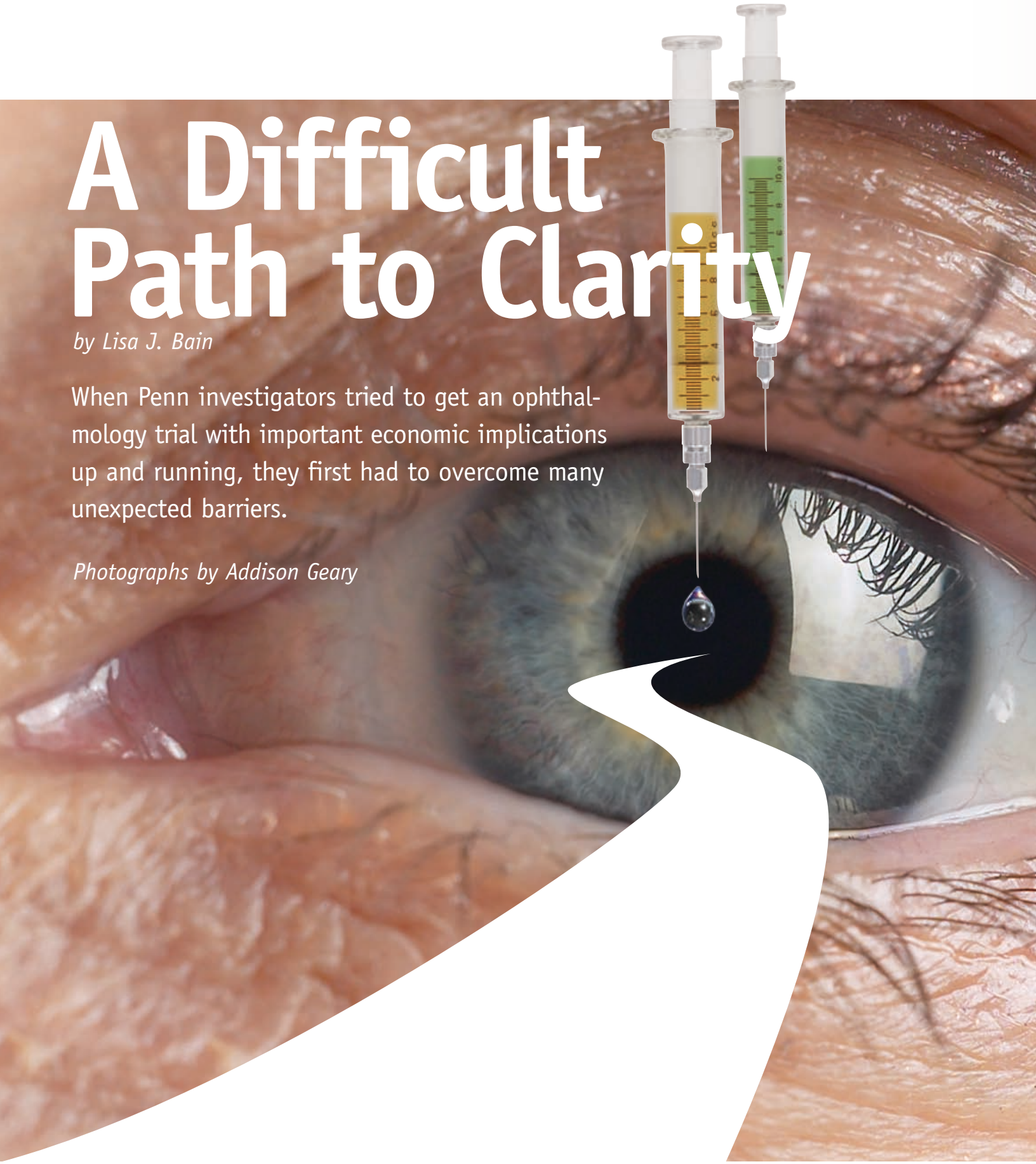
Still, the honors keep coming. Last spring, he received the Claire W. Patterson Award for Distinguished Service from the Trigeminal Neuralgia Association. Patterson, who lives in West Chester, Pa., was one of Jannetta's patients 20 years ago. She founded the association to provide support for people suffering from the disorder. The occasion marked Jannetta's stepping down as chair of the association's medical advisory board. And this year, on April 25, he received the 2008 Distinguished Citizen of the Commonwealth Award from the Pennsylvania Society. Jannetta is only the 15th recipient since the award was created in the Bicentennial Year. ■

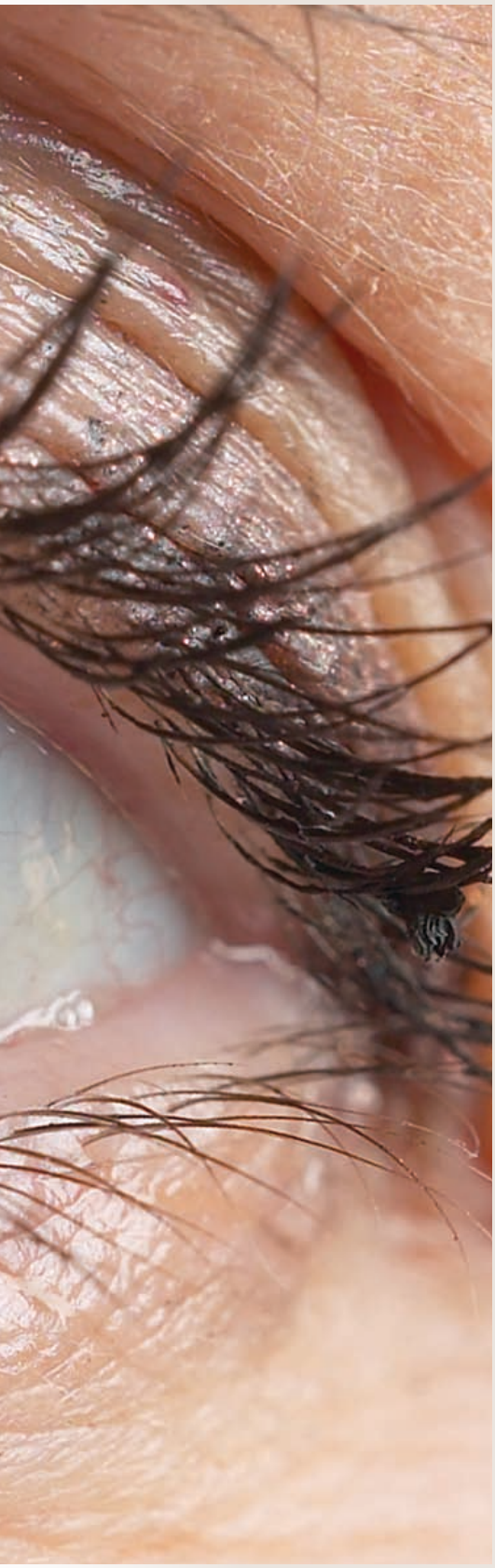
A Difficult Path to Clarity

by Lisa J. Bain

When Penn investigators tried to get an ophthalmology trial with important economic implications up and running, they first had to overcome many unexpected barriers.

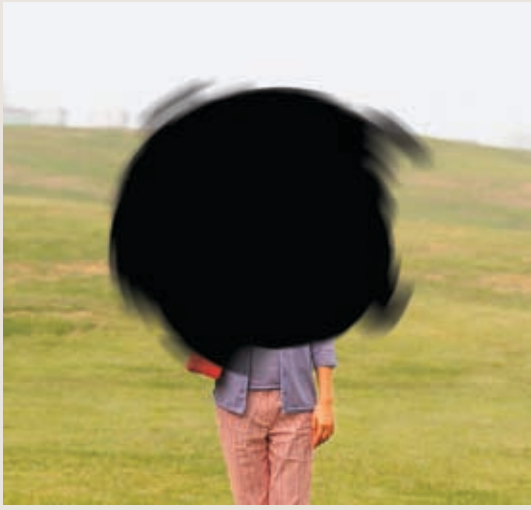
Photographs by Addison Geary





On a wintry day in February, a 75-year-old woman in Knoxville, Tennessee, became the first subject to begin a clinical trial that will test two drugs designed to treat age-related macular degeneration (AMD). Drops were put into her eye to dilate her pupil, and an anesthetic was given to numb her eye. Then, using a tiny needle, her ophthalmologist injected the drug directly into the jelly-like vitreous of the eye. If all goes as hoped, the drug will stop the leakage of blood vessels in the back of the eye, leakage that has blurred and distorted her vision.

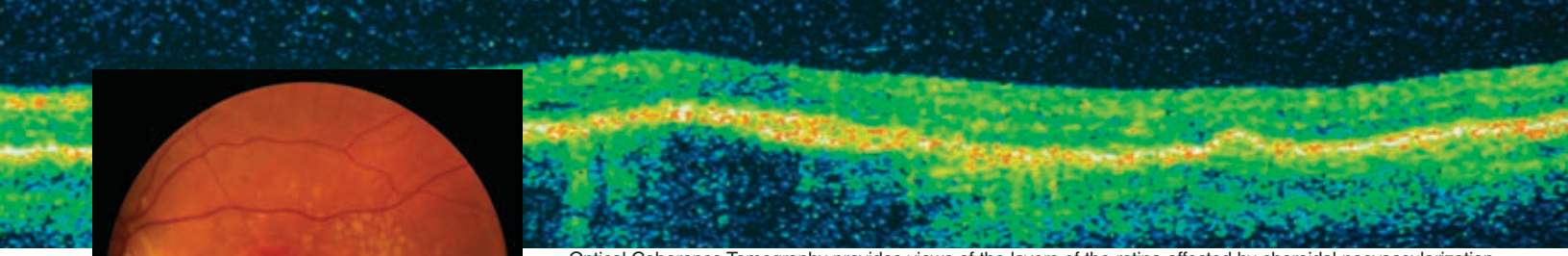
Like the other 1,199 subjects in this trial, Patient Number One has no idea which of the two drugs she has received. What she does know is that one of the drugs, Lucentis, has been approved by the Food and Drug Administration (FDA) to treat age-related macular degeneration and costs about $2,000 per dose. The other drug, Avastin, costs only about $50 per dose but has not been approved by the FDA for the treatment of that particular disease; it was developed as a cancer treatment but is used "off label" to treat other conditions. And she also presumably knows that the drugs have the same mechanism of action and, somewhat surprisingly, were developed and are marketed in the United States by the same company, Genentech, the biotechnology company based in San Francisco.



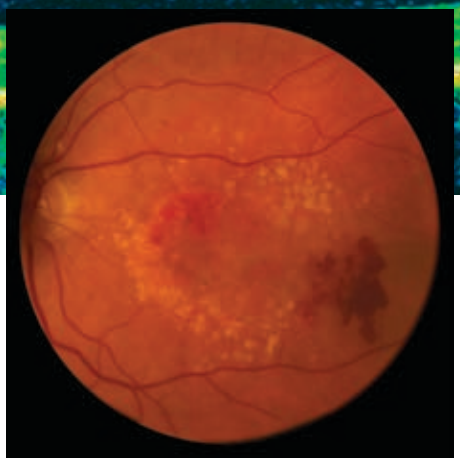
Most people with AMD have blurred central vision that may progress to a blurred spot in the center of the visual field.

Although – or perhaps because – the results of this trial have important implications not only for people with AMD but also for Genentech, health insurers, and Medicare (which covers most people with AMD), getting the trial off the ground has been anything but easy. According to Maureen G. Maguire, Ph.D., the Penn biostatistician who is directing the coordinating center of the trial, she and the study chair of the trial, Daniel Martin, M.D., of Emory University School of Medicine, originally applied to the National Eye Institute in January of 2006 to test the two drugs head to head.

"If we had been able to start the trial that summer as we had hoped, we would be done with the one-year results by now," said Maguire as the trial was about to begin in 2008. "But things got complicated."



Optical Coherence Tomography provides views of the layers of the retina affected by choroidal neovascularization.



The fluorescein angiogram shows the abnormal growth of blood vessels that characterizes wet macular degeneration.

The most common cause of blindness

Age-related macular degeneration is the most common cause of legal blindness in older people, affecting nearly two million Americans. According to some estimates, that number could climb to as high as three million by the year 2020 as the population rapidly ages. Most people with AMD have the early "dry" form that causes slightly blurred central vision and may progress to a blurred spot in the center of the visual field or even to loss of central vision. Early AMD can also progress to the more severe "wet" form, which is associated with a rapid loss of central vision. In both forms of AMD, the problem results from damage to the macula, a small (1.5 mm) spot in the center of the retina that contains the photoreceptors responsible for central vision and, in particular, for seeing fine detail. In dry AMD, these photoreceptors slowly break down. Wet AMD, in contrast, occurs when blood vessels behind the macula grow abnormally and begin to leak, lifting the macula from the back of the eye. This type of AMD is also called "neovascular" AMD, referring to the growth of new vessels. Both Lucentis and Avastin are effective only against the wet, neovascular form of AMD.

Until recently, the best treatment for neovascular AMD used lasers to seal the leaking blood vessels and to prevent their further growth. An improvement to this approach, called photodynamic therapy (PDT), added an intravenously injected compound that undergoes a chemical reaction when exposed to light from a laser. The activated compound clots the leaking blood vessels in the macula, arresting the fluid build-up and preventing the growth of new vessels. While PDT causes less damage to surrounding tissue than the standard laser treatment for AMD, both approaches are of limited use because they can be used only in the small number of people whose leaky vessels are limited to one or only a few small spots. Most people with wet AMD have diffuse neovascularization. Moreover, while both treatments slow the progression of the disease, neither improves vision. It was clear that the ever-growing number of people who were losing their vision to AMD needed better treatments.

Late in 2004, words was spreading in the ophthalmology community about Genentech's Lucentis trial. Lucentis (ranibizumab) is derived from a monoclonal antibody that binds and inhibits Vascular Endothelial Growth Factor (VEGF), a protein involved in angiogenesis, the growth of new vessels. Injected directly into the eye, the drug was designed to inhibit neovascularization in the entire macula, rather than at a single spot. Theoretically, this meant that anyone with the neovascular form of AMD could benefit.

Although results from the trial had not yet been announced, many ophthalmologists had begun to draw their own conclusions, said Stuart L. Fine, M.D., the William F. Norris and George E. DeSchweinitz Professor and Chair of Ophthalmology at Penn. "It's unusual to do a clinical trial where people can figure out what is working just by looking at the 10 or 20 patients at their own center. But many of the people participating in the Lucentis trial knew that *something* was happening because some of their patients were having dramatic, almost immediate improvements in vision."

In May 2005, Genentech released initial results from its Lucentis trial. Then in July the company presented the results from the first pivotal study at a meeting of the American Society of Retinal Specialists in Montreal. The study exceeded the expectations even of Genentech scientists: after one year of treatment, the drug not only prevented further deterioration of vision, but most patients actually could see better.

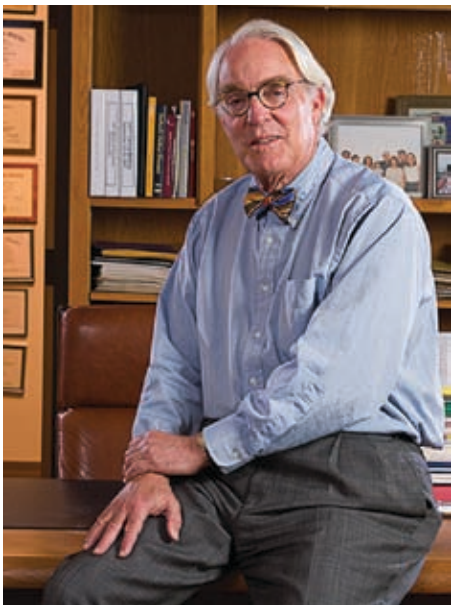
"It just knocked everyone's socks off," said Maguire, the Carolyn F. Jones Professorship of Ophthalmology and director of Penn's Center for Preventive Ophthalmology and Biostatistics. "In the past, when we would speak to patients we would say, 'This will not make you better – it will slow down how fast you get worse.' Lucentis was a complete change. Most patients pick up a little bit of visual acuity, so rather than facing a steady de-

cline for the next couple of years, they were facing a little bit of improvement over the next few months and then plateauing at that good level. So that was fantastic, and the whole ophthalmology world was taken aback and thrilled."

Right after Genentech presented its results, Philip J. Rosenfeld, M.D., Ph.D., an ophthalmologist from the Bascom Palmer Eye Institute in Miami, got up to speak. He had come up with a possible alternative to Lucentis, another VEGF inhibitor called Avastin (bevacizumab), which was already on the market and far less expensive than Lucentis. Avastin had been developed by Genentech for the treatment of colon cancer; in fact, it was derived from the same monoclonal antibody that was later used to design Lucentis. Rosenfeld wondered if Avastin's anti-angiogenic properties might also reach the eyes of people with AMD. After showing benefits using intravenous injections of Avastin, Rosenfeld injected a small amount of Avastin into the eyes of two AMD patients. The results were dramatic, similar to those seen with Lucentis.

"What happened after that was truly amazing," said Maguire. Within six months, perhaps as many as 10,000 patients around the world were treated with intraocular injections of Avastin, despite the fact that it had not been developed or tested for intraocular use nor were safety data available. But ophthalmologists, described by Fine as normally a very medically conservative group, knew Avastin's similarity to Lucentis and knew that Lucentis was unlikely to be available for at least one year.

But there were questions: Would Avastin be as effective as Lucentis? Would it result in adverse side effects not seen with Lucentis? Should the dosing regimen be similar? And, of course, there was the cost factor. According to Fine, if Avastin is as effective as Lucentis, the annual savings to Medicare would be somewhere between $3 and $6 billion



per year. A head-to-head comparison of the two drugs was the obvious solution. It is not surprising, then, that Genentech balked at conducting such a trial. Lucentis, the company's representatives argued, was designed specifically for intraocular use and was thought, therefore, to have a better safety and efficacy profile. Moreover, Lucentis was predicted to be a blockbuster drug for the company.

A long road to approval

Maureen Maguire conducted her first clinical trial related to AMD some 30 years ago when she began to work with Stuart Fine at Johns Hopkins. Since then, she has become a specialist in ophthalmology, running countless clinical trials and coordinating multi-center trials for AMD and other eye disorders (such as glaucoma) as well as a multi-center trial of corneal transplantation. In 1994, she followed Fine to Penn, working with him on AMD prevention trials and on a trial of thalidomide for treating AMD. Fine speaks glowingly of Maguire's acumen and skill in conducting trials: "I can't say she's the best, but in the whole world, there's no one better."

Searching for a better treatment for AMD was one of Maguire's passions. By early 2005, she and her colleagues had designed two or three full trials of potential AMD treatments, only to reject them when preliminary data showed that the drugs were not as effective as originally thought. When the first results of the Lucentis trials were announced, her group stopped everything else. "We said, nobody is going to want to look at anything else but this drug." Avastin changed all that, but Maguire's advanced preparation left her group ready to launch a Lucentis/Avastin trial, since much of the infrastructure was in place and decisions about outcome measures had already been made. So in January 2006, even before Lucentis had been granted FDA approval, Maguire's group applied to the National Eye Institute for permission to conduct a study to compare the two drugs.

The primary hurdle was financing the study. At $2,000 a dose, given every 28 days for two years, the cost of Lucentis alone would be $52,000 per subject – and that did not include injection fees, diagnostic imaging costs, and the myriad of other costs to run a clinical trial. Because most people in the study would be covered by Medicare, Maguire reasoned that as soon as Lucentis was approved, the Center for Medicare and Medicaid Services (CMS) would be eager to cover the cost of the trial because of the huge claims they would be facing. After obtaining approval from the trial from the National Eye Institute, Maguire's team started meeting with CMS. By this time, the summer of 2006, Lucentis had been approved. That was when they found out there was a problem: CMS said Medicare would not pay for the drug. According to the CMS interpretation of existing policy, an investigational drug could not be covered by Medicare. That eliminated payment for Avastin, which was not FDA-approved for AMD as well as for Lucentis, which was.

"We were flabbergasted," said Maguire. "Probably the first five times they said that to us, we didn't believe them." The intent of that policy, formulated under President Clinton's directive to Medicare, was to expand access for patients under Medicare so that they would not be penalized for participating in clinical trials. But the CMS lawyers did not see it that way, and it would be more than a year before a new policy was expected to be in place. "We said that would be far too long to wait," said Maguire.

While continuing to search for a resolution to the financing issue, Maguire's team continued to work with CMS on designing an acceptable trial. Another problem emerged regarding the masking of participants in the trial so that none of the parties involved – the subjects, the clinicians treating them, the people evaluating the results – would know which treatment an individual patient had received. Typically this is called "blinding," but for obvious reasons, Maguire pointed out, the ophthalmology community prefers the term "masking." The problem is that Medicare typically sends a notice to clients saying that it has paid 80% of the cost of a specific drug, making it difficult to shield subjects from knowing if they were receiving Lucentis or Avastin.

From August 2006 through September 2007, Maguire's team worked with people at CMS to devise a plan that would solve the financial and masking issues. As many as six to eight plans were developed, and each one had to be carefully considered from different perspectives by a number of people and offices at Penn: Glen Gaulton, Ph.D. executive vice dean and chief scientific officer; the offices of Human Research, Research Services, Billing, Compliance, and Legal Affairs; and the Investigational Drug Service. Penn put quite a lot of time, effort, and support into getting this trial off the ground, said Maguire, but eventually she was told not to come back until she had a plan approved, in writing, by CMS.

In the meantime, Maguire, Fine, and other members of the team were lobbying Congress and the White House. They met with Elias Zerhouni, M.D., director of the National Institutes of Health, and had conversations with Leslie Norwalk, acting administrator for Medicare. Everyone agreed that the trial should go forward, but finding a way to make it happen was proving difficult. When CMS finally approved a demonstration project, the Department of Health and Human Services lawyers refused to approve it. At one point, Genentech indicated that it would provide the study drug but later reversed its decision. Eventually, after months and months of aborted plans, long negotiations, and repeated disappointments, Maguire and colleagues devised a plan that did not depend on any special treatment from CMS beyond approval of the study. By that time, the new clinical trials policy was in place; it allowed Medicare to pay 80% of the cost of Lucentis, and supplementary insurance would pick up most of the rest. The cost of Avastin is covered by NEI.

One last hurdle remained. Avastin is packaged by Genentech in large vials for use in treating colon cancer. To be used for AMD, the drug must be repackaged into much smaller vials. Physicians who are using Avastin off label for their AMD patients rely on compounding pharmacies to do this repackaging. At Penn and other larger hospitals, the hospital pharmacist repackages the drug. The FDA objected to the use of compounding pharmacies for distribution, so Kenneth A. Rockwell Jr., Pharm.D., HUP's director of the Investigational Drug Service, came up with a plan that was eventually approved. Avastin is sent to a company that uses good manufacturing practices to fill the vials, which are then sent to Rockwell's service for distribution to study sites.

The team settled on what could be called "partial masking." While the ophthalmologists and the people who evaluate data from visual acuity and imaging tests are masked, and the patient is masked at least at the outset, the clinic coordinator is not masked. He or she is told to which treatment "arm" the patient has been randomized, obtains the correct vials, fills syringes with the appropriate drug, and gives them to the ophthalmologist for the injections. Because both drugs are clear and colorless, have the same viscosity, and take up the same volume, only the clinic coordinator knows which drug has been provided.

Only time will tell

Now the trial begins. While many clinical trials have difficulty enrolling sufficient numbers of subjects, so far this appears not to be the case for the CATT (Comparison of AMD Treatments Trials) study. Patients understand that the drugs given in both treatment arms are highly effective, said Fine. Moreover, they understand that only a head-to-head comparison of the drugs will answer the question of whether one is more effective than the other. And there are other important questions to be

answered as well – for example, whether the dosing regimen for the two drugs is similar. Lucentis is given every 28 days, regardless of whether the disease is continuing to progress, but it may be that Avastin would require less frequent dosing because it is a bigger molecule and possibly more likely to persist in the eye. Genentech developed Lucentis based on the supposition that Avastin, being a larger molecule, would not be able to penetrate the retina to reach the macula, but that supposition was subsequently disproved.

As a result of these questions, CATT has been designed with four treatment arms. One group will get injections of Lucentis every 28 days; one group will receive Avastin every 28 days; and two other groups will receive one of the two drugs on an as-needed basis. In these "variable dose" groups, after the first treatment, the treating ophthalmologist will evaluate test results each month to determine whether there is active new vessel growth. If not, the subject will skip that dose of the drug. A reduced dosing schedule might not only save money, but might also substantially reduce the burden and risks to patients. Each subject enrolled in the trial will be followed for a total of two years. Fine said that in addition to clarifying the effectiveness of the two drugs and the best dosing regimen, he hoped that data from the trial would allow the researchers to construct a risk profile to identify which patients are likely to need monthly injections and which could benefit from less frequent treatments.

A question of science – or policy?

Completion of the trial is not expected until early 2011, and regardless of the results, there will still be questions to be answered. When two drugs are equally effective for an illness that affects millions of people and one of them is significantly cheaper than the other, what is the responsibility of the drug companies, the FDA, health insurers, and the federal government to determine which one should be used? After Genentech took steps to limit the availability of Avastin to compounding pharmacies in October of 2007, Senator Herbert Kohl of Wisconsin, who chairs the U.S. Senate Special Committee on Aging, entered the fray. In November, he made public copies of letters he sent to CMS, the FDA, and Genentech expressing "great concern" about Genentech's intention to limit access to Avastin.

"I take very seriously the Committee's responsibility to protect and advocate on behalf of our nation's seniors," he wrote to Genentech. "Part of this responsibility is ensuring that seniors are receiving appropriate and cost-effective prescription drugs."

Genentech subsequently reversed its decision, stating that the company "believes physicians should be able to prescribe the treatment they believe is most appropriate for their patients." Yet this may be only a temporary solution. Even if the Lucentis/Avastin trial were to show that Avastin was equivalent to or better than Lucentis, it would still be up to Genentech to apply for FDA approval and labeling for Avastin as a treatment for AMD. At this point, that step seems highly unlikely because it could only hurt sales of Lucentis. And Genentech will still be able to control the packaging and marketing of the drug.

"It's hard not to get incensed by this," said David Asch, M.D., M.B.A., the Robert D. Eilers Professor of Health Care Management and Economics at the Wharton School and the School of Medicine. As Asch, who directs Penn's Leonard Davis Institute of Health Economics, put it, "It's a marketing strategy that far more supports the bottom line of the company than it supports the interests of society."

Which may leave ophthalmologists, at the end of this trial, with the same choice they face now: prescribing an approved drug or an off-label drug, albeit one that has been fully tested for effectiveness and safety. For Stuart Fine, whether a drug has been approved for that indication or not has little bearing on what he tells his patients. "Treating patients is a partnership," he said. Fully tested or not, all drugs have beneficial effects as well as side effects. By taking the time to explain the benefits and risks of each treatment and making sure that his patients are fully informed, he and his patients can decide together which treatment to choose. The choice can be highly individual, he added. For example, one patient might place a high value on the convenience of less frequent dosing even if it resulted in slightly poorer results, while another patient might think the inconvenience a small price to pay for even slightly improved vision.

Fine does not expect a better drug to come along. On the other hand, he does foresee better delivery systems in the future, such as an implantable pellet or even topical administration. "In terms of effectiveness, it's going to be hard to beat this drug. This is a silver bullet that we've been waiting for for 25 years." •

Changing the Paradigm – Preparing

By Nan Myers

Despite the challenging and often frustrating nature of the health-care marketplace these days, Mark A. Kelley, M.D., G.M.E. '79, believes there are ways for a health system to manage what he called the coming health-care crisis or at least to withstand its worst effects.

According to Kelley, who serves as executive vice president for the Detroit-based Henry Ford Health System (HFHS) and chief executive officer of the Henry Ford Medical Group, the Henry Ford experience can serve as an example.

Kelley, a longtime member of Penn's medical faculty, was the featured speaker at this year's Samuel P. Martin III, M.D., Memorial Lecture. The annual event is one of the highlights of the Health Policy Seminars sponsored by Penn's Leonard Davis Institute of Health Economics. The title of Kelley's talk was "Health Care in Detroit: A Preview of the Impending National Crisis."

His blunt warning: "We need to make a paradigm shift."

Introducing Kelley was a former colleague, Sankey V. Williams, M.D., the Sol Katz Professor of General Internal Medicine and Health-care Systems. Kelley, said Williams, brought to Henry Ford the management skills that Dr. Martin, the namesake of the memorial lecture and a former director of the Leonard Davis Institute, thought were so necessary for instilling some order and economic know-how in medicine. In addition, said Williams, Kelley has been able to preserve the all-important academic values.

"Mark had an interesting career at Penn because it involved all the pieces of an academic health center," added Williams. "Among his positions were program director of the residency program, vice chair of the Department of Medicine,

vice dean for clinical affairs, and chief of medicine at the V.A."

In 2000, when Kelley arrived in Detroit after 27 years at Penn, the car companies that are virtually synonymous with Detroit were beginning to suffer greatly because of declining sales and increasing health-care costs for retirees.

As Kelley put it, "I was under the delusion that the leaders of the car companies – some of whom were even Wharton M.B.A.s – knew something about the management of health care. After all, they were managing the coverage for thousands of employees. Instead," he continued, "I learned what they did know – it was about costs."

In his lecture, Kelly used the experiences of the auto manufacturers to illustrate the issues and difficulties that caused major problems for HFHS. In his view, they are the same issues that are contributing to our current national crisis in health care.

The auto industry was the largest employer in Michigan. From 2000 to 2007, because of many factors, the state lost 402,000 jobs, mostly in the auto industry. The Big Three (as General Motors, Ford, and Chrysler were known) were not prepared for foreign competition. At the same time, not only were health-care costs rising for employees, but job reductions often resulted in early retirement. That meant a burgeoning of the retiree population, whose health-care costs were covered by the car companies. (And many people no longer had health insurance because they lost their jobs.) As a result, the car companies made the decision to shift monies from union pay to health-care payments for current and retired union workers.

The challenges faced by the Big Three reflect those of Medicare and the nation. "One problem is that our life expectancy is improved; people were supposed to die by age 67," Kelley pointed out. Another problem was the rising costs of new technology and drugs. "We are the only developed country where the big pharmaceuticals are so strong. It is a sad state when people can't afford their medications. Medicare beneficiaries spend so much more on their meds than the younger generation."

Today, as it is in Philadelphia, health care is the largest industry in Detroit. Unlike what is happening in Philadelphia, however, young, healthy workers are leaving the Detroit area. And in both metropolitan areas, the cost of health care is rising faster than wages.

Kelley believes that Penn's health system, like HFHS, will have to change the way it operates because of factors out of its control. On the other hand, he said, Penn has an advantage over Henry Ford because of its history and its excellent reputation.

It is an "unhealthy environment that we live in," he continued. Both public and employer funding are shrinking. Most Detroit city hospitals – both private and not-for-profit – have closed, and 50 percent of the population is underinsured or uninsured. Medicare and

for the Crisis

Medicaid are assuming the role of payers. Malpractice is very costly, although tort reform has helped.

With seven hospitals, the non-profit HFHS is the largest system in the region. It offers its own health plan. The Henry Ford Medical Group, its employed physician practice that is similar to Penn's primary-care network but much larger, has 1,100 physicians. Henry Ford Hospital is affiliated with Wayne State University School of Medicine. Like Penn's health system, HFHS is dominant in its region and operates in an urban setting. On an annual basis, Henry Ford admits two million patients, compared to Penn's nearly 1.4 million.

To succeed in this difficult environment, the Henry Ford Health System took a number of steps. Kelley suggested that, in the near future, UPHS will also have to reinvent parts of itself to retain its dominance. HFHS began by emphasizing quality as a differentiator and has re-engineered some of its processes, including a redesign of its primary-care services to feature easier access for appointments. "We learned the importance of patient satisfaction," said Kelley. "We like to say that we can't treat a patient who doesn't choose to see us."

Especially if patients are forced to accept the burden of paying for more of their health-care costs, Penn, too, will have to figure ways to become more efficient, Kelley explained.

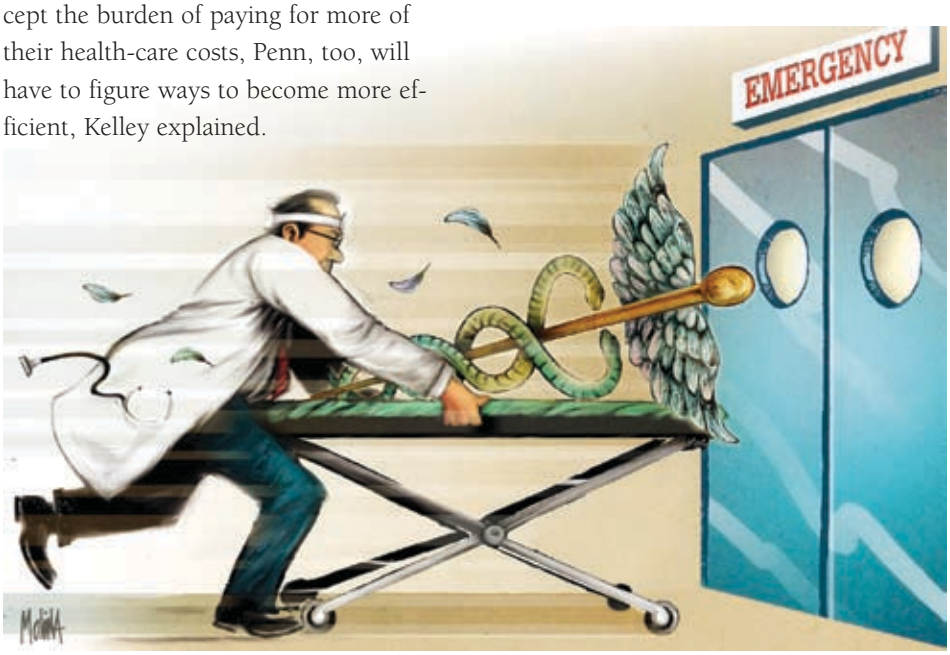
For its part, HFHS adopted electronic prescribing, developed a program for managing chronic disease, standardized MRI treatment, and reduced overall ICU and surgical infections.

Even with the successful changes, which he explained are widespread across the U.S., primary care as a practice remains in danger. Higher co-pays result

"To remain profitable, hospitals will have to convince patients of their quality and superiority and be able to control their costs."

in fewer office visits. Then there are too many "non-revenue" patient demands, such as fielding telephone calls, providing social services, filling in forms, and reporting lab results. And these responsibilities come in the face of reimbursements that are flat – or worse. "Small primary-care practices will probably disappear," Kelley predicted, "because there are none of the necessary economies of scale."

In discussing the success of HFHS, Kelley highlighted e-prescribing. In this process, a physician sends the prescription directly to the pharmacy by computer. It eliminates the need for the pharmacist to call the doctor for an explanation of what is written on the prescription. "We did a pilot study and found that although it does not provide time-saving for physicians, e-prescribing does provide an overall cost savings to the system. It also eliminates errors."



Kelley quoted the saying from an earlier era: As goes Detroit, so goes the nation. In the near term, systems of care as well as doctors and hospitals must become aligned with information systems and financial incentives. To remain profitable, hospitals will have to convince patients of their quality and superiority and be able to control their costs. In addition, as Kelley asked rhetorically, "Who will rescue the Federal Government from its legacy costs? Care for Baby Boomers will flood Medicare, and, like the Big Three, the Federal Government has an unsustainable entitlement."

One of Kelley's main points came in response to a question: "We have to take politics out of the picture," he said. "I think that we will have to raise taxes to take care of the older population. Medicare won't exist in its current form. Nothing I have seen in the proposed political agenda is reality. The presidential candidates are flip-flopping around the real health-care issues.

"The problem is who will pay. The insurers won't get on board unless they feel they will get a quick payback. If Medicare takes the lead, the insurance companies will follow. Congress will have to pass some mandates – for example, about diabetes care.

"We need a catalyst to affect this shift."

Kelley concluded his talk with an admonition to his audience. "As health-care providers," he said, "we should do more to affect health-care costs. We know where there are problems. We have to be vocal in the efforts to change them." ●

Development Matters

PENN Medicine Turns to Simulators for

PENN'S NEW CLINICAL SIMULATION CENTER IS WHERE MEDICAL PROCEDURES BECOME PRACTICE

For more than 200 years, PENN Medicine has expanded the frontiers of medicine and medical education. That tradition continues with the multi-million dollar PENN Medicine Clinical Simulation Center, opening this summer. Located at PENN Medicine at Rittenhouse, the center will feature 21,000 square feet of space for simulation training and continuing medical education programs. Here practitioners and residents from across the health-care field will turn to Penn to master the most advanced techniques in medicine.

The Center is a shared endeavor – by the University of Pennsylvania Health System, the Clinical Practices of the University of Pennsylvania, and the School of Medicine – that will further improve patient safety and enhance medical education. Such innovations are made possible thanks to the support of "Making History: The Campaign for Penn" and its focus on providing funding for educational advancements as well as PENN Medicine's outstanding faculty and clinicians.

PENN Medicine at Rittenhouse will be the site for the multi-million dollar PENN Medicine Clinical Simulation Center: 21,000 square feet of space for simulation training and continuing medical education programs, opening this summer. The Center will be a shared endeavor by the University of Pennsylvania Health System, the Clinical Practices of the University of Pennsylvania, and the School of Medicine that will further improve patient safety and enhance medical education.

A simulated operating room, emergency department, intensive-care unit, and labor and delivery room are planned for the center, which will integrate different approaches – from responsive mannequins to high-tech simulators – across its research and education programs. Physicians, nurses, residents, and other professionals will be able to rehearse:

- general surgery
- interventional radiology
- ear-nose-throat and oral and maxillofacial surgery
- obstetrics and gynecology
- ophthalmology
- emergency medicine
- and other invasive medical procedures such as endoscopy, bronchoscopy, and cardiac catheterization.

These hours of training in the simulator will translate into greater safety and better outcomes for PENN Medicine's patients.

Improved Training

The PENN Medicine Clinical Simulation Center, located at PENN Medicine at Rittenhouse, will feature 21,000 square feet of space for simulation training and continuing medical education programs.

Photo courtesy of Laerdal Medical Corporation. All rights reserved.

Training for the Constant Evolution of Medicine

Put simply, "simulation technology is the future," says James L. Mullen, M.D., professor and vice chair of surgery and chair of the Simulation Center Steering Committee at the University of Pennsylvania Health System. At the new PENN Medicine Clinical Simulation Center, human patient simulators will mimic operating conditions, even responding to anesthesia and drugs according to dosage. Training sessions can be viewed, recorded, and replayed through the technologically advanced control center located in the core of the facility.

For example, the rise of robotic surgery is just one sign that medicine and surgery are constantly advancing, with innovative technologies, devices, and procedures that offer new hope to patients with life-altering illnesses. "PENN Medicine has a true, multi-specialty robotic surgery program," says Mullen. "Our surgeons are performing more and a broader range of procedures than most of our peer institutions."

Indeed, PENN Medicine utilizes robotic surgery in a number of disciplines – cardiology, gynecology, and otorhinolaryngology, to name only a few – and is one of a small number of training centers for robotic surgery serving the East Coast. So training in these new techniques now has to be built in to all levels of medical education.

Another example can be found in Penn's Department of Obstetrics and Gynecology. The simulation center will provide an opportunity for the residents and students to practice basic skills and procedures (such as normal deliveries, laparoscopy, and suturing techniques) and to introduce new clinical skills. The simulation center may also be used to offer refresher courses for obstetricians who are returning to the work force after taking leave to spend time with their families.

Practice Makes Perfect for Health-Care Teams

Perhaps the most significant opportunity afforded by the new center is the ability to train physicians, nurses, and technicians in operating as a well-rehearsed team. "During the past two years, we have focused on providing patient-centered care using a team approach on labor and delivery," says Deborah A. Driscoll, M.D., chair of the department.

The department plans to use the simulation center to create scenarios with a focus on developing clinical and communication skills. After these drills, teams of physicians and nurses should be prepared for, and perform more effectively in, crisis situations in the real-life setting.

Technology, however, is only one part of creating excellence in patient care and education. "What will truly make the PENN Medicine Clinical Simulation Center a model for training and education is the PENN Medicine faculty," notes Mullen. "We are very fortunate to have leaders in practically every medical

According to one of the pioneers in the field of simulation training, "There's a transformation going on globally that challenges the way we practice health care. . . . We [can't] rely on live operations as the only training tool or the only place to introduce new techniques."

discipline as part of the simulation training process, and their knowledge and experience will be key to the center's success."

Just as important as providing the opportunity to learn and practice individual surgical techniques, the Center will enable whole medical and surgical teams to rehearse difficult procedures and stressful scenarios, planning for any number of possible complications. Mullen also sees the current live, interactive surgery telecasts, funded by The Benjamin & Mary Siddons Measey Foundation, as "a major leap – a revolutionary approach to medical education." The Foundation also supports the Measey Surgical Skills Suite, which will be part of the new simulation center, and the Measey Medical Simulation Center at the School of Medicine, which opened in October 2006.

In order to build a successful program, PENN Medicine turned to a pioneer in the field, Richard Reznick, M.D., from the University of Toronto. There, he leads a team of up to 80 faculty members who use their simulation laboratories as the hub for training and continuing medical education. He presented many of his surgical training ideas, insights, and experiences at Penn's 2007 Agnew Surgical Society Lecture.

"There's a transformation going on globally that challenges the way we practice health care," he explains. "I trained in a bygone era. . . . We [can't] rely on live operations as the only training tool or the only place to introduce new techniques."

Reznick also notes "Penn is ahead of the game, since it is already dedicating part of the curriculum to simulation. That's rare." Penn Surgery's residency program is among a select few nationwide with a dedicated simulation rotation – a month-long, full-time component of general surgery training. Simulation will also be a vital part of Penn's OB/GYN residency training program.

Introducing simulation into obstetrical training at Penn "will help us achieve our goals of providing high-quality care and improving patient safety," says Driscoll. "We will be using what's learned through simulation training to help prevent or reduce adverse events through prompt recognition and better management of any medical situation."

According to one of the pioneers in the field of simulation training, "There's a transformation going on globally that challenges the way we practice health care. . . . We [can't] rely on live operations as the only training tool or the only place to introduce new techniques."

Jon B. Morris, M.D., professor of surgery and program director for general surgery in the division of gastrointestinal surgery, agrees that the new simulation center presents tremendous potential. "While we're seeing this growing body of evidence that surgical simulation will enhance not only the quality, efficiency, and effectiveness of the clinical care for our patients, we're also seeing enormous opportunities to promote greater patient safety and improved surgical outcomes."

Incorporating simulation into the PENN Medicine curriculum, Morris continues, "marks the dawning of a new era in surgical education."

For more information about supporting the new PENN Medicine Clinical Simulation Center, PENN Medicine's surgical or medical education programs, or its faculty, please contact the ***PENN Medicine Office of Development and Alumni Relations*** *at (215) 898-5164 or 3535 Market Street, Suite 750, Philadelphia, PA 19104-3309.*

The Benjamin & Mary Siddons Measey Foundation – A Comprehensive Approach in Supporting Medical Education

In October 2006, PENN Medicine dedicated the **Measey Medical Simulation Center**. There, technology allows Penn's medical students to practice a variety of procedures – until the movements and processes become second nature – before ever touching a live patient. Remarkably, this is just one example of The Benjamin & Mary Siddons Measey Foundation's commitment to advance medical education in the Delaware Valley.

At PENN Medicine alone, the Foundation supports 11 endowed chairs, including:

- **The William Maul Measey Professorship in Surgery**, held by Michael A. Acker, M.D., chief of the division of Cardiothoracic Surgery;
- **The Brooke Roberts/William Maul Measey Professorship in Surgery**, held by Joseph E. Bavaria, M.D., director of PENN Medicine's Thoracic Aortic Surgery program;
- **The William Maul Measey Professorship in Surgical Research**, held by Jeffrey A. Drebin, M.D., Ph.D., F.A.C.S, chief of the division of Gastrointestinal Surgery; and
- **The Clyde F. Barker-William Maul Measey Professorship in Surgery**, held by Ronald M. Fairman, M.D., chief of the division of Vascular Surgery and Endovascular Therapy.

In addition, there are hundreds of medical students, residents, and fellows who have received generous **scholarship support** from the Measey Foundation and who have made an impact in the Delaware Valley community – and beyond. Many of these talented physicians and researchers wouldn't have been able to receive a Penn education without that vital support.

"I am honored to work with people who are utterly committed to the future of medicine and medical education," says Dean Arthur H. Rubenstein. "The Measey Foundation has invested in people and in the medical knowledge they can acquire and create. And through the Measey Medical Simulation Center, it is also supporting state-of-the-art educational technology."

"As the world changes, the medicine we practice within it must change as well," Rubenstein continues. "The need for simulation technology arises from such change, and we deeply appreciate the Measey Foundation's willingness to embrace it with us."

Recent Gifts

The Robert Wood Johnson Foundation awarded the African American Collaborative Obesity Research Network (AACORN) a five-year, $3.5 million research grant to generate and conduct community-partnered research to reduce obesity in African American children and adolescents. The network was founded by and is under the direction of Shiriki Kumanyika, Ph.D., M.P.H., professor of epidemiology at Penn.

The estate of **Evelyn S. Butterworth** continues to support Penn's Department of Genetics with gifts this year totaling $4.9 million. The estate has given the department more than $12 million over the past three years.

Patricia Dunn-Jahnke has made a $1.8 million pledge to raise or personally support the Ovarian Cancer Vaccine Initiative at Penn's Abramson Cancer Center, under the direction of George Coukos, M.D., Ph.D. This initiative supports the testing of an autologous vaccine that uses the patient's own tumor tissue to direct the patient's own immune cells to deploy more of the patient's own tumor-specific killer T-cells to attack the cancer.

Theodore Aronson and his wife, Barbara, have contributed $1.1 million to support acute stroke care and the research of Scott E. Kasner, M.D.

The Harold B. Robbins estate recently contributed $1 million to its Neurology Research Fund, which supports research into the care and prevention of cerebral atherosclerotic disease with associated brain degeneration.

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

Alumni Events

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

August
Friday, August 15 – Parents and Partners Program, Philadelphia
Friday, August 15 – White Coat Ceremony, Philadelphia

September
Tuesday, September 23 – Otorhinolaryngology Reception, 7:00-9:00 p.m., Chicago

October
Friday, October 3 – Fall Medical Alumni Advisory Council Meeting, 8:00 a.m. – noon, Philadelphia
Friday, October 3 – Gamble Scholars & Medical Alumni Advisory Council Luncheon, 12:00-2:30 p.m., Philadelphia
Tuesday, October 14 – American College of Surgeons Reception, 6:00-8:00 p.m., San Francisco

November
Sunday, November 2 – American Association of Medical Colleges, Alumni Reception, 6:00-8:00 p.m., San Antonio
Saturday, November 8 – Ophthalmology Reception, 7:00-10:00 p.m., Atlanta

Progress Notes

Send your progress notes to:
Andrea Pesce
Assistant Development Officer
PENN Medicine Development and Alumni Relations
3535 Market Street, Suite 750
Philadelphia, PA 19104-3309

'50s

John R. Senior, M.D. '54, G.M.E. '59, residence, received the Outstanding Service Award from the Food and Drug Administration's for superior performance and outstanding national leadership in studying the effects of pharmaceuticals on the liver and for contributing to public health safety. Senior is associate director for science in the FDA's Office of Surveillance and Epidemiology.

Tsung O. Cheng, M.D., G.M. '56, professor of medicine (cardiology) at The George Washington University, was honored with its first Lifetime Achievement Distinguished Research Award. He received the award at the 12th Annual George Washington University Medical Center Research Day in recognition of his outstanding research achievements in cardiology over a long period of time. He has more than 1,400 peer-reviewed publications.

Jules B. Puschett, M.D. '59, was promoted to vice dean for program development at the Texas A&M Health Science Center College of Medicine. Puschett trained in internal medicine at the University Hospital in Baltimore and in renal-electrolyte medicine at HUP, sponsored by the National Institutes of Health. He was chief of the renal-electrolyte division at the University of Pittsburgh School of Medicine from 1980 to 1990. From 1990 to 2005, he was chairman of the Department of Internal Medicine at the Tulane University School of Medicine. Now a professor of medicine at Texas A&M Health Science Center, he also maintains a research laboratory that focuses on the pathophysiologic mechanisms and novel treatments of volume expansion-mediated hypertension.

'60s

Spencer Foreman, M.D. '61, retired in January 2008 as president of Montefiore Medical Center (the university hospital for the Albert Einstein College of Medicine) after nearly 22 years of "healthcare statesmanship and service to the hospital and community." Montefiore is the largest healthcare provider and employer in the area, serving more than 1.5 million residents of the Bronx and parts of Westchester County, N.Y. Under Foreman's leadership, the hospital added an adolescent AIDS program, a Child Advocacy Center to protect at risk children from abuse, the largest School Health Program in the U.S. and a program that gave respite and housing to families and their children who were at risk for lead poisoning.

'70s

Vanessa Northington Gamble, M.D. '78, Ph.D. '87, has been appointed the University Professor of Medical Humanities at the George Washington University. A historian, she specializes in the role of race and racism in American medicine and public health. Previously she had been director of the National Center for Bioethics in Research and Health Care at Tuskegee University in Alabama. A health commentator for NPR, she served as an associate professor of health policy and management at the Johns Hopkins University since 2002.

Richard C. Wender, M.D. '79, professor and chair of the Department of Family and Community Medicine at Thomas Jefferson University, served as co-chair of the Dialogue for Action Conference, sponsored by the Prevent Cancer Foundation in April. The event in Baltimore focused on screening for colorectal cancer – "Despite a Broken Health-Care System." He is a member of the foundation's medical advisory board.

'80s

Carol Beer Benson, M.D. '80, and her husband, Peter M. Doubilet, M.D., Ph.D., both professors of radiology at Harvard Medical School and the Brigham and Women's Hospital, are the authors of *Your Developing Baby: Conception to Birth* (McGraw-Hill, 2008). The book, written with Roanne Weisman, uses two- and three-dimensional ultrasound images to show the development of a baby over the course of nine months. Beer is director of ultrasound and co-director of high-risk obstetrical ultrasound at Brigham and Women's Hospital.

Frank G. Haluska, M.D. '89, Ph.D. '89, was appointed senior medical director of ARIAD Pharmaceuticals, Inc. Haluska will be responsible for leading multiple clinical trials of oral deforolimus as part of the joint global development plan with ARIAD's partner, Merck & Co., Inc. He is a recognized authority on the targeted therapy of kinase abnormalities in solid tumors. Most recently, Haluska served as a senior faculty member in the departments of medicine and genetics at Tufts University School of Medicine, where he was clinical director and deputy director of the Tufts-New England Medical Center Cancer Center. He is also a major in the Medical Corps of the United States Air Force and the Massachusetts Air National Guard.

OBITUARIES

Elizabeth Kirk Rose, M.D. '26, G.M.E. '30, Kennett Square, Pa., emeritus associate professor of community health and pediatrics at the University of Pennsylvania School of Medicine; February 23, 2008. At the age of 106, she was Penn's oldest alumnus/alumna. When she completed her internship at HUP, she was the only woman of 28 on the staff. She married a colleague, Dr. Edward Rose, and then completed a year of residency at The Children's Hospital of Philadelphia. For two decades, Rose was a practicing pediatrician at HUP and a member of the faculty of the School of Medicine. She also served on the staff of both Children's Hospital and Presbyterian Hospital. In 1950 she was appointed by Mayor Joseph Clark to head the Division of Maternal and Child Health at the Philadelphia Department of Public Health. In 1956 she joined Penn's Department of Public Health and Preventive Medicine. She later moved to the Department of Community Health and helped lay the groundwork for involving medical students and residents in community-based learning and outreach. In 1974, both Dr. Roses retired from their practices and faculty positions at Penn. A strong advocate for women in medicine, Rose held picnics for female medical students and alumnae of the medical school in 1962. This event evolved into the annual Elizabeth Kirk Rose Women in Medicine Dinner, to celebrate Rose and to bring medical school alumnae back to campus to advise and serve as mentors for female medical students. In addition to serving as a mentor, Rose was the long-time secretary of the Class of 1926. In 1983, both Elizabeth Rose and Edward Rose received the medical school's highest honor, the Distinguished Graduate Award. She was active in many professional and civic organizations, among them the Philadelphia United Cerebral Palsy Association, the Society for Prevention of Cruelty to Children, the Philadelphia Pediatric Society, the Penn Alumnae Association, the Philadelphia-Camden Social Service Exchange, the Mulberry Tree Nursery School, the Shut-In Society, and the Philadelphia Youth Hostel Association. She was president of the Penn Women's Faculty Club from 1968 to 1970). A member of many medical societies as well, Rose received the Distinguished Daughter of Pennsylvania Award in 1993, honoring her leadership and contributions to the state.

Allen Wilson Cowley, M.D. '29, G.M.E. '33, Naples, Fla., former chief of the Department of Medicine at Harrisburg Polyclinic Hospital; October 10, 2007. He maintained an active practice in Harrisburg for 42 years. He established the first free clinic in cardiology in the 1940s at Polyclinic Hospital. A former president of the Dauphin County Medical

Society, the Pennsylvania Heart Association, and the Pennsylvania Medical Society, he had also been chairman of the board of Pennsylvania Blue Cross and Blue Shield. In his retirement years, he devoted his efforts to the application of biomedical engineering to medicine and was one of the founding board members of the Whitaker Foundation, on which he served for 50 years.

Sidney D. Apt, M.D. '32, Philadelphia, an art director who later owned an advertising firm in the city; May 30, 2007.

Felda Hightower, M.D. '33, Winston-Salem, N.C., emeritus professor of surgical sciences at Wake Forest University; May 30, 2007. He was governor of the American College of Surgeons from 1963 to 1975. A lectureship at Wake Forest was named in his honor in 1989.

Francis F. Hart, M.D. '36, G.M. '46, Ambler, Pa.; October 13, 2005. He was former chief of radiology at Montgomery Hospital in Norristown, Pa.

J. George Teplick, M.D. '36, G.M. '42, Philadelphia, a retired professor of radiology at Hahnemann University Hospital; May 17, 2007. Author of *Lumbar Spine: CT and MRI*, he was coauthor of several other books in the field of radiology.

John E. Dotterer, M.D. '38, Sanford, N.C., March 23, 2007. He had been associated with Center County Hospital. A life member of the North Carolina Literary and Historical Association, he had served as a county commissioner of Lee County.

John J. B. Light, M.D. '38, G.M. '46, Lebanon, Pa.; September 23, 2001. Known as a physician with a passion for caring for his patients, he often based his fees on their ability to pay. He was board certified in radiology and ophthalmology, and he was on the staff of Wills Eye Hospital in Philadelphia at the time of his death.

Maurice L. Zox, M.D., G.M.E. '38, Columbus, Ohio, July 16, 2006. A surgeon, he had retired from the Ohio State University College of Medicine.

Charles E. Myers, M.D. '39, Larksville, Pa.; December 9, 2006. In April 1942, he entered the U.S. Medical Corps as a paratrooper with the rank of first lieutenant. In 1945, he was awarded the Legion of Merit Award for his care of psychiatric causalities in the Mediterranean Theater. He was discharged from the military in 1946 with the rank of lieutenant colonel. In 1950, he entered into private practice, specializing in internal medicine and chest disease. In 1962, he founded and organized the Associate Internists of Wyoming Valley. He served as vice president of the Health and Hospital Planning Council of Northeastern Pennsylvania; was chairman of the Long-Range Planning Committee at Wilkes-Barre General Hospital; and served as chief of staff and as the chief of the Department of Medicine at Wilkes-Barre General Hospital, where he was also the founder and chief of the Anthracosilicosis Clinic. A former president of the Pennsylvania Thoracic Society, he also served as president of the Wyoming Valley TB Society. In 1975, he received the Environmental Leadership Award of the NEPA Environmental Council; and in 1983, he won the Distinguished Internist Award of the Pennsylvania Society of Internal Medicine.

Harry A. Pfingst, M.D., G.M. '39, Chittenden, Vt., a retired ophthalmologist; April 19, 2004. The first director of the Louisville Lions Eye Clinic, which was established to diagnose eye disease for needy patients, he had a private practice in Louisville. He also taught ophthalmology at the University of Louisville.

Edward A. Bershof, M.D., G.M. '40, Denver; May 30, 2001.

Edward Kulczycki, M.D. '40, Athens, Pa., retired head of ophthalmology at the Guthrie Clinic in Sayre; February 5, 2007. During World War II, he was a flight surgeon at the U.S. Naval air station in Pensacola, Fla., before becoming a medical officer of Patrol Bombing, Squadron 11 (the Black Cat Squadron) of the Seventh Fleet. After serving in the South Pacific he became senior medical officer on the aircraft carrier *U.S.S. Saipan*. He took his residency in ophthalmology at the U.S. Naval Hospital in Philadelphia and was then assigned to the U.S. Naval Hospital in Charleston, S.C. as chief of the eye, ear, nose, and throat department. He joined the Guthrie Clinic in 1954 and was on the staff for 28 years.

Edward F. McGrath, M.D. '40, Milton, Mass., a retired pediatrician; November 12, 2003. He was appointed to the Carney Hospital staff in 1950 and was a physician in chief of the pediatrics department from 1955 to 1958. A former chairman of the hospital's laboratory committee, he was on the intern and resident committee and the pharmacy committee. He was also on staff of St. Margret's Hospital in Dorchester, Children's Hospital in Boston, and Milton Hospital.

Salvatore Cucinotta, M.D., GM '41, Cherry Hill, N.J., a decorated World War II battlefield physician who delivered babies in South Philadelphia for more than 50 years; December 30, 2007. He learned to use hypnosis to eliminate patients' pain and helped establish the Philadelphia Hypnosis Society in 1972. He taught obstetrics to medical students at Hahnemann University Hospital and directed a research project on cervical cancer at HUP.

Roy J. Grubbs Jr., M.D. '41, Sylacauga, Ala.; March 21, 2001.

Jay W. Fidler Jr., M.D. '42, Pompano Beach, Fla., February 18, 2007. A retired psychiatrist, he had taught in the School of Occupational Therapy at Misericordia University in Dallas, Pa. He was a co-editor of *Group Psychotherapy and Political Reality: A Two-Way Mirror* and *Group Processes and Political Dynamics*. He had been a fellow of the American Group Psychotherapy Association.

Harry Green, Ph.D. '42, Boynton Beach, Fla., vice president of scientific liaison and technology at the old Smith Kline Corp. (now GlaxoSmithKline), until his retirement in 1983; February 19, 2006. At Penn he was awarded the Harrison Fellowship in Chemistry in 1940 and served as an assistant professor in the Graduate School of Medicine. He began his 25-year career at Smith Kline in 1958 as a senior research biochemist, after having served as chief of biochemical research at the Wills Eye Hospital in Philadelphia. He co-wrote 60 publications, including four with former Penn professor and Nobel Prize-winner Otto Meyerhof.

Horace C. Reider, M.D. '42, Bryn Mawr, Pa., a retired physician; May 9, 2007.

L. John Bingham, M.D. '43, Salt Lake City; July 7, 2007. He took over a family practice in Idaho Falls in 1955 and practiced there until 1983, when he semi-retired to St. George, Utah, with a group of emergency room physicians. He accepted a Latter Day Saints mission to the Manila Mission in the Philippines, where he served as the area medical coordinator from 1989 to 1991.

John Gray Hunter, M.D. '43, G.M.E. '50, Albemarle, N.C., a former surgeon; September 26, 2007.

Frederick M. Owens Jr., M.D., G.M.E. '43, St. Paul, Minn., a former surgeon.; June 4, 2004. He had been a clinical professor of surgery at the University of Minnesota.

Floyd M. Hess, M.D. '44, San Antonio; June 17, 2004.

Warren L. Candela, M.D. '46, Stockton, Calif.; January 22, 2007.

Walter C. Klingensmith, M.D. '46, G.M.E. '50, Gladwyne, Pa., January 1, 2007. An internist, he had been a clinical associate professor of medicine at Penn.

Anna Kane Laird, M.D. '46, Ph.D., Madison, Wis., a retired psychiatrist; June 10, 2007. She had been with the Division of Biological and Medical Research of Argonne National Laboratory and published in *Nature* and *Science*.

Edward B. Price Jr., M.D. '46, Omaha, Neb., a former pathologist; October 11, 2007. He had worked at the National Cancer Institute.

John "Jack" W. Alden Jr., M.D., G.M. '47, Wilmington, Del, a

retired radiologist; October 20, 2007. He joined the staff of the Delaware Hospital in 1947 and later became the head of its Department of Radiology. In 1969, he went into private practice with Papastavros Associates. In 1976, he retired to Ft. Lauderdale, Fla.

Edward K. Atkinson, M.D. '47, founder and former director of the Greenville Hospital Department of Anesthesiology, Berea, Ky.; December 5, 2005. He entered active duty with the U.S. Marine Corps in 1950 and eventually became chief of anesthesiology at the U.S. Naval Hospital at Camp Pendleton in Oceanside, Ca. After returning to civilian life, he moved to Greenville, Pa., where he practiced until 1973. He subsequently continued to practice in the Drexel Hill and Hazelton, Pa., areas. He retired from anesthesiology in 1993 and established a private medical practice in Berea, treating a variety of ailments with chelation therapy and nutritional supplements.

Milton A. Kamsler Jr., M.D. '47, G.M. '51, St. Augustine, Fla., a physician who had maintained a practice in Burlingame, Calif., for more than 30 years; March 23, 2007. He served in the U.S. Army in Germany during the post-World War II era.

Andrew W. Lawrence, M.D. '47, Centerport, N.Y., a retired orthopaedic surgeon; November 11, 2007. He was a former member of the Scoliosis Research Fellowship, dedicated to the education, research, and treatment of spinal deformity.

Russell P. Sinaiko, M.D., G.M. '47, a retired surgeon, Los Angeles; September 21, 2002.

Max J. Fischer, M.D., G.M. '48, former chief of the ear, nose, and throat division at Children's Hospital, Washington D.C.; December 15, 2007. He was chief resident at Georgetown University Medical Center before taking over the ear, nose, and throat practice of his uncle, Dr. Aubrey Fischer. He worked there for the next 55 years and retired in spring 2007. In addition to running the otolaryngology division at Children's, he also was director of the speech and hearing department and helped establish the hospital's first school for autistic children. He was an attending physician at Washington Hospital Center and was a clinical assistant professor at George Washington University Hospital.

Albert P. Giannini, M.D., G.M. '48, Fort Collins, Colo., a former thoracic surgeon; February 29, 2004.

George W. Moore, M.D. '48, Venice, Fla., a retired urologist; August 1, 2007. He completed tours in the Navy and Marines, attaining the rank of lieutenant, and was honorably discharged from the Navy in 1951. He completed his internship and residency at Geisinger Hospital in Danville, Pa., and joined a urological practice in 1955. A former chief of staff at both the Jameson Hospital in New Castle, Pa., and St. Francis Hospital, he had also been president of the Lawrence County Medical Society.

William A. Robie, M.D., G.M.E. '48, Cary, N.C., a former pediatrician; December 28, 2006. He had been a medical director at Wake Med health system and a consultant for North Carolina's Disability Determination Service.

Robert H. Shedd, M.D. '48, Punta Gorda, Fla.; October 23, 2007. He served as a surgeon with the United States Marine Surgical Unit during the Korean War. In 1953, he moved to Punta Gorda, becoming only the third doctor in the area. During that period, he made house calls to families and delivered more than 1,000 babies. He served on the Charlotte County Commission from 1972 to 1982, was mayor of Punta Gorda for two terms, and was an active member of its city council. For four years, he was chief of staff at the Charlotte Regional Medical Center, and he founded the Charlotte County Medical Society. He was the medical director for the Life Care Center of Punta Gorda, the Port Charlotte Care Center, and St. Joseph Nursing Care Center, and also served as staff physician for South Port Nursing Center.

Carroll F. Burgoon, M.D., G.M.E. '49, Chester Springs, Pa., retired professor of dermatology at Temple University; September 28, 2007.

Charles A. Doehlert, M.D. '49, Sarasota, Fla.; April 13, 2007. A former adjunct professor of clinical medicine at the University of Wisconsin Medical School, he took his internship at Evanston, Ill., Hospital. During the Korean War, he was a Navy physician on the aircraft carrier *Franklin Delano Roosevelt*. After an honorable discharge, he served a fellowship in cardiology at the Mayo Foundation and earned his M.S. degree from the University of Minnesota. He went on to practice internal medicine with Associated Physicians in Madison, Wis., for 36 years. He retired from active practice in 1991.

Coleman W. Kovach, M.D., G.M. '49, Jamison, Pa.; February 10, 2007. A retired physician, he practiced in Philadelphia and was associated with Thomas Jefferson University Hospital throughout his entire career.

Jordan Thompson, M.D. '49, New Orleans, a specialist in internal medicine; April 2, 2001.

David L. Hearin, M.D., G.M.E. '50, Alpharetta, Ga.; July 19, 2006. After completing his residency in dermatology he maintained a private dermatology practice in Atlanta until 1985. He served as head of the Department of Dermatology at the VA hospital in Decatur and served as a dermatology consultant to the hospital, conducting weekly dermatology clinics until fully retiring with 37 years of service in 1988. In recent years, he delivered Meals on Wheels to home-bound residents of the Alpharetta area.

William F. Monroe, M.D. '50, Cincinnati; April 23, 2006.

H. Luten Teate Jr., M.D., G.M.E. '50, Decatur, Ga., a former pediatrician; September 3, 2006. For seven summers he headed to Central America to treat children through Care-Medico and Amigos de las Americas. He is believed to be the first doctor in Georgia to perform a blood exchange transfusion on a newborn baby to save the lives of babies born to Rh-negative mothers.

Albert S. Terzian, M.D., G.M. '50, Wilmington, N.C., a retired psychoanalyst who practiced for more than 35 years; April 8, 2007. He received his undergraduate degree from the University of Pennsylvania and his medical degree from Hahnemann Medical College. He went overseas as a member of the Medical Corps of the Army in World War II.

Robert M. Akey, M.D., G.M. '51, Topeka, Kan.; February 14, 2007. He completed a fellowship at the Mayo Clinic in internal medicine. He then went on to practice as an internist/diagnostician with a cardiology specialty at the Watson Clinic for 40 years until retiring at age 70.

Robert Balin, M.D., G.M.E. '51, Las Vegas, a psychiatrist; July 1, 2003.

Lewis P. Frank, M.D., G.M. '51, Lebanon, Pa., a retired surgeon; February 1, 2003. He retired as a staff physician at the Coatesville Veterans Administration Medical Center in 1982. He was a decorated World War II Army captain, serving in the Pacific theater as a combat military surgeon from 1942 to 1946. He opened a practice in Lebanon, Pa., in 1948.

William H. Hulet, M.D. '51, Ph.D., Key West, Fla.; April 15, 2000. He completed his internship and residency in internal medicine at G. F. Geisinger Memorial Hospital in Danville, Pa. For a time, a member of the Department of Medicine at New York University, he was interested in research and physiology. In 1969, he took a permanent leave of absence from human medicine and pursued a Ph.D. degree in marine science at the University of Miami.

David G. Rimer, M.D. '51, Santa Monica, Calif., a retired gastroenterologist; February 17, 2007. He was the first G.I. fellow and chief resident at UCLA. He maintained a private practice in Santa Monica for most of his 44-year professional life. A clinical professor of medicine at UCLA, he was chief of G.I. service at Harbor/UCLA Medical Center in 1963 and served as director of the Medical Ambulatory Care Center and associate director of the General Internal Medicine Residency

Training Program at UCLA. He was the first full-time gastroenterologist at St. John's Hospital. He founded and was director of the G.I. lab at St. John's and was chief of G.I. He also served as chief of G.I., director of G.I. training, and chief of medicine at Santa Monica Hospital.

Luis F. Sala, M.D., G.M. '51, Ponce, P.R., former head of Puerto Rico Board of Medical Examiners; June 23, 2005.

Bernard Shapiro, M.D. '51, G.M.E. '55, Lower Merion, Pa.; November 27, 2007. A pioneer in nuclear medicine, he retired in 1998 after 40 years at Albert Einstein Medical Center, where he had been chief of the Division of Nuclear Medicine. His research on radiation protective agents received support from the N.I.H., the American Cancer Society, the Army, and the Air Force. After retiring as division chief, he remained on Einstein's board of trustees. He was a former president of the Pennsylvania College of Nuclear Medicine.

Edward C. Sutton, M.D. '51, Burlington, N.C., a retired obstetrician-gynecologist; February 16, 2007.

William Beautyman, M.D., G.M.E. '52, Blue Bell, Pa.; September 5, 2000. He had been chief pathologist, director of laboratories, and chair of the pathology department at the former Pittsfield General Hospital, which later became Berkshire Medical Center. He was highly regarded for having introduced computers into the pathology laboratory in the 1960s, in a way that became a model for others. He served on the board of governors of the College of American Pathologists from 1974 to 1980. After retiring in 1993, he lectured on apoptosis, a type of cell death.

Gumersindo Blanco, M.D., G.M. '52, San Antonio, Tex.; September 22, 2007. He specialized in thoracic surgery in Philadelphia and New Jersey. He was co-author of more than 40 articles in his field. His last appointment was as chief of surgery at the University of Puerto Rico, from which he retired in 1986.

Samuel H. Horton, M.D., U.S.N.M.C. (ret.), G.M.E. '52, Beaufort, S.C.; March 16, 2007.

Lewis G. Richards Jr., M.D., G.M. '52, Hardy, Va.; October 10, 2004. He served four years as a medical doctor in the Navy during World War II. He practiced surgery in Lynchburg, then Roanoke, retiring to Franklin County in 1983.

Gustave T. Anderson, M.D., G.M.E. '53, Calminesa, Calif., a former dermatologist; November 13, 1999. He was a physician for 45 years, 12 of those for Kaiser Permanente Fontana Medical Group in Fontana. Anderson served in the U.S. Navy Medical Corps for 25 years, spanning World War II, the Korean War, and the Vietnam War.

F. Wilson Daily, M.D., G.M. '53, Savannah, Ga., February 22, 2007. He had set up the obstetric anesthesia department at Candler General Hospital and had been associated with Obstetric Anesthesia of Savannah.

Julio A. Ayulo, M.D., G.M. '54, Harbor City, Calif., a former gastroenterologist; May 10, 2004.

Jerome I. Brody, M.D., G.M.E. '54, Bala Cynwyd, Pa.; September 20, 2007. He studied violin at the Manhattan School of Music before earning his degree from Jefferson Medical College. In addition to his medical training at Penn, he completed a hematology fellowship at Yale University. For almost 30 years, before retiring at 75, Brody was a professor of medicine at the Medical College of Pennsylvania. Earlier, he had been an associate professor in Penn's School of Medicine, where he was a National Institutes of Health fellow. For the last several years, Brody, author of more than 100 medical articles, had been writing a book profiling physicians who were also writers, artists, and musicians.

Frederick R. Haase, M.D., G.M. '54, Toms River, N.J., a former otolaryngologist; October 7, 2007.

John "Jack" T. Reeves, M.D. '54, Denver, a former professor of medicine, pediatrics, and surgery at the University of Colorado Healthy Sciences Center; September 15, 2004. He had been on the faculty of the University of Colorado since 1972 and was an emeritus professor at the time of his death. For many years he was a senior member of the Cardiovascular Pulmonary Research Laboratory in the Department of Medicine. He had been an integral part of the Developmental Lung Biology Laboratory in the Department of Pediatrics, and most recently he played a significant role in establishing the Colorado Center for Altitude Medicine and Physiology in the Department of Surgery.

Isadore Brodsky, M.D. '55, Narberth, Pa.; October 6, 2007. He served for two years in the U.S. Public Health Service in Bethesda, Md., and was a National Cancer Institute fellow in hematology before joining Hahnemann Medical College in 1962. He performed the first stem-cell transplant in the Philadelphia area more than 30 years ago. Before retiring last January, Brodsky had been chair of hematology and oncology at Drexel University's College of Medicine, medical director of its Isadore Brodsky Institute for Blood Diseases and Cancer, and managing partner in an oncology and hematology practice at Hahnemann University Hospital. Since 1976, he and his medical team had performed more than 1,000 bone-marrow transplants on patients with leukemia and other types of cancer. His research projects included the study of retroviruses to control cancer and the use of interferons to treat cancer, leukemia, and AIDS. In 2003, he and his son Robert, a hematologist and oncologist at Johns Hopkins University, developed a chemotherapy drug treatment for multiple sclerosis.

David G. Ostrolenk, M.D. '55, Monmouth Beach, N.J.; September 27, 2007. After taking his radiology residency at New York Hospital, he worked at various hospitals, including Mount Sinai Hospital and Jersey City Medical Center. He finished his career at the Veterans Administration Hospital in Columbia, S.C.

Paul Forrester Williams, M.D. '55, Burlington, N.C.; January 11, 2007. He completed his internship and residency at the University of Michigan Hospital in Ann Arbor, then spent two years in Morocco as a United States Air Force Captain and head of the medical services at the 3922nd Air Force Hospital. He returned home to practice medicine in Burlington, N.C., where he served as chief of staff at Memorial Hospital.

Samuel H. Black, M.D. '56, Ph.D., College Station, Texas; March 30, 2007. A faculty member of Texas A&M Health Science Center College of Medicine since 1975, he was an emeritus professor of medical microbiology and immunology and of humanities in medicine. After serving two years in the U.S. Army Medical Corps, he received his Ph.D. degree in microbiology from the University of Michigan. He taught at several other schools before coming to Texas A&M, where he served as professor and head of medical microbiology and immunology from 1975 to 1990. Among the positions he held there were assistant dean for curriculum and undergraduate medical education; interim dean of the College of Medicine; associate dean of the College of Medicine; and associate dean for academic affairs. He was speaker of the Faculty Senate from 1986 to 1987. His many honors include the Faculty Distinguished Achievement Award in Teaching from Texas A&M University in 1982 and 1989. A lecture hall was dedicated in his name in May 2003.

Louis E. Goldberg, M.D., G.M. '57, Hatfield, Pa., a former ophthalmologist; July 11, 2001.

Paul M. Mitchell, D.D.S., G.M. '57, Yardley, Pa., October 17, 2007.

Lloyd David Hall, M.D. '59, Columbus, Ohio, a retired obstetrician-gynecologist, June 3, 2006.

Robert J. Kirschner, M.D., G.M. '59, Bryn Mawr, Pa., an ophthalmologist who had served on the faculties of Graduate Hospital and the Wills Eye Hospital; September 4, 2007.

Kirk P. Kalemkeris, M.D., G.M. '62, Ho Ho Kus, N.J., a general surgeon and oncologist who specialized in cancer surgery for four

decades; July 19, 2002. He served on the staff of The Valley Hospital in Ridgewood and Pascack Valley Hospital in Westwood.

Sherwood V. Cohen, M.D., G.M. '63, Elkins Park, Pa., a retired ophthalmologist; May 9, 2007. He earned his medical degree from the State University of New York at Syracuse. He had been on the staffs of several hospitals in the Philadelphia area, including Graduate, Holy Redeemer, and Rolling Hill. During the Vietnam War, he served in U.S. Army hospitals, stateside. Cohen wrote medical columns *for The Jewish Exponent* and *The Northeast Jewish Times*.

Lorenzo G. Runk III, M.D. '63, G.M.E. '67, Lansdowne, Pa., a retired neurologist; August 29, 2007. After serving in the Air Force for two years in Alabama, he returned to the Philadelphia area to do clinical research at Graduate Hospital. He joined a neurological practice in South Philadelphia in 1972 and was associated with St. Agnes Medical Center and Methodist, Mercy Fitzgerald, and Misericordia hospitals. He taught neurology at Penn in the 1970s and later was a clinical assistant professor of neurology at Thomas Jefferson University. According to his wife, Nancy Gordon Runk, his great love was music, and he played the French horn with the Lower Merion Concert Band for 26 years.

Peter R. Kaplan, M.D. '64, Gross Pointe, Mich., a former cardiologist; March 2, 2006. He had been a teacher and physician at St. Thomas Hospital in Nashville since 1972.

John R. Scott, M.D. '64, Delmar, N.Y., a radiologist; February 12, 2007. At one time he had been clinical associate professor of radiology and clinical associate professor of radiology in pediatrics at Penn.

Harvey A. Koolpe, M.D. '73, Elkins Park, Pa., an interventional radiologist at Albert Einstein Medical Center; October 18, 2007. He was the inventor of several catheters now widely used in the field. His articles appeared in many professional journals, including *The American Journal of Radiology* and *The Journal of the American Medical Association*, and he was an invited as a guest speaker at national seminars. Koolpe had academic appointments at Temple University, Albert Einstein Medical Center, and the University of Medicine and Dentistry of New Jersey.

Saroja D. Adusumilli, M.D., G.M.E. '02, Westlake, Mich., a clinical assistant professor of radiology at the University of Michigan Medical School; March 3, 2007. An authority on magnetic resonance imaging, she was a member of her department's abdominal imaging group.

FACULTY DEATHS

Jerome I. Brody, M.D. See Class of 1954.

Alfred Gellhorn, M.D., New York City, former dean of the School of Medicine; March 24, 2008. He came to Penn as the first director of its Medical Center and served as dean of the medical school from 1968 to 1973. He was credited with introducing new dimensions of social thinking into many aspects of curriculum and health-care delivery, including reviving the Department of Community Medicine. His focus on collaboration with the local community led to the creation of such programs as the West Philadelphia Community Mental Health Consortium, the Health Education Program, and Gateway to Higher Education, which encouraged minorities to pursue medical degrees. While serving as dean, he held an appointment as professor of medicine and pharmacology. Gellhorn served a 25-year tenure at Columbia University; was founding director of the Sophie Davis School of Biomedical Education of the City College of New York; and was director of medical affairs at the NY State Department of Health. He received his medical degree in 1937 from Washington University in St. Louis. In 1993, Penn awarded him an honorary degree for his contributions to medicine and to physician education in the service of humanity.

Elizabeth Kirk Rose, M.D. See Class of 1926.

LEGACY GIVING

With Gratitude

Drs. David and Kathy Guarnieri have always placed great value on education. They support their private high school in Scranton, Pa., and they also donate to their undergraduate alma mater. Despite earning medical degrees from different schools, they agree that the University of Pennsylvania School of Medicine prepared David extremely well for his profession.

"I would not be where I am without my degree from the School of Medicine," says David, a member of the Class of 1984. "It was a basis, a wonderful beginning for my profession. And even though she did not attend, Kathy has a great appreciation for the School as well."

The Guarnieris decided to transform their heartfelt appreciation into a scholarship that is included in their will. The David M. and Kathleen M. Guarnieri Scholarship will provide a world-class School of Medicine education to many students who otherwise could not afford it.

"We decided to make a planned gift, which we feel is a wonderful way to perpetuate our name and to extend our gratitude to the School of Medicine," says Kathy.

In 1994, the Guarnieris, who are both anesthesiologists, moved to Scottsdale, Arizona. Even though the move was more than 2,000 miles away, the Penn name resonated among David's peers. "The University of Pennsylvania School of Medicine is an incredible name to put behind you," he says. "To this day, it continues to open a lot of doors."

The Guarnieris want future generations of medical students to experience "the best of the best" with the same high-caliber education, admiration from their peers, and pride a University of Pennsylvania School of Medicine education can bestow.

"We have taken stock of our lives, and we are happy with where we are. It now feels like the right time to give back. The only way we got to be where we are is through Penn. Through the wonderful vehicle of planned giving," says David, "we will be able to give others the same opportunities we had."

The Guarnieris have chosen one of a multitude of creative gift opportunities that benefit both the School of Medicine and its donors. As you plan your financial future, 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., Associate Director of Planned Giving at 215-898-9486 or at PENN Medicine, 3535 Market Street, Suite 750, Philadelphia, PA 19104-3309. You can e-mail Christine at cewan@upenn.edu. Also, you can visit the Office of Planned Giving's web site at www.med.upenn.planyourlegacy.org.

Conflict of Interest

In this issue, you can read that our School of Medicine was ranked among the top five research-oriented medical schools by *U.S. News & World Report* and the Hospital of the University of Pennsylvania earned a spot on the *U.S. News* Honor Roll of best hospitals (p. 3). Those are tremendous achievements. But Penn recently received another high grade from a less widely known organization, and its implications are worth considering.

The organization is the American Medical Student Association (AMSA). In late May, AMSA published its PharmFree Scorecard 2008, which evaluated conflict-of-interest policies in 150 medical colleges and colleges of osteopathic medicine. Given the public's interest in the integrity of our institutions of higher learning, it was not surprising that *The New York Times* reported on the survey. Its headline was sober: "Survey of Medical Schools Is Critical of Perks" (3 June 2008). The scorecard assessed policies on accepting gifts and meals from industry; consulting relationships; speaking relationships; disclosing financial conflicts; pharmaceutical samples; financial support for educational events (both on campus and off); industry support for scholarships and trainee funds; and access of industry sales personnel to the medical school or hospital. Schools were also asked whether the academic curriculum includes materials on conflict of interest and whether individuals with financial conflicts participate in an institution's purchasing decisions. These are problematic areas, although sometimes the issue is one of degree and transparency.

AMSA specifically referred to a widely publicized article that appeared in *The Journal of the American Medical Association* two years ago, "Health Industry Practices That Create Conflicts of Interest: A Policy Proposal for Academic Medical Centers" (25 January 2006). That article focused on the efforts of manufacturers of pharmaceuticals and of medical devices to sell their products to institutions like ours, which the authors believe "pose challenges to the principles of medical professionalism." The AMSA survey, in contrast, was limited to the pharmaceutical industry.

As the *Times* headline intimated, the results of the PharmFree Scorecard are somewhat grim. Our School of Medicine was one of only seven in the country to receive an "A" for its conflict-of-interest policies. Only one other medical school in the state, the University of Pittsburgh, received an "A." Surprisingly, 60 schools across the nation received a failing grade; some schools received an "F" because they had weak policies or no policies, and some did not respond despite repeated requests. PENN Medicine has worked hard to eliminate potential conflicts of interest of this kind, and AMSA's initiative was something we applauded. For those reasons, it is gratifying to see our efforts recognized.

Those efforts go back a few years, when the seriousness of the matter was becoming clearer. Our medical students had an important influence on our new policies, and P. J. Brennan, M.D., professor of medicine and senior vice president and chief medical officer for the Health System, took the lead among our faculty members. In October 2004, our institution held what we believe was the first symposium in the nation that brought together representatives from academic medicine and the pharmaceutical industry, specifically to consider how to handle our interactions. As such an event suggests, PENN Medicine did not take an accusatory approach. Two years ago, Dr. Brennan told *Physician's News Digest* that although we had some policies in place, they were not being enforced well enough. As he put it, Penn needed to review and revise its policies, "not to demonize pharmaceutical companies, but to bring their interactions with physicians closer in line with evidence-based content rather than marketing" (September 2006). There is certainly a need for medicine and industry to interact, and when it is done properly, our patients benefit. We would not have established the Office of Corporate Alliances in 2003 if we thought otherwise. In fact, the meeting in 2004 and a second forum in April 2006 were ably assisted by that office.

Speaking of evidence-based policy, one of the reasons for a stricter approach to gifts is based on recent research in social science and psychology. As the *JAMA* article put it, "the impulse to reciprocate for even small gifts is a powerful influence on people's behaviors." Free pens and meals, that is, can have more impact on the recipients than they are aware.

Soon after AMSA's survey appeared, the Association of American Medical Colleges issued a fuller report that covered similar ground, "Industry Funding of Medical Education." Here, too, the call is to maintain professionalism and to have full transparency and disclosure by personnel of academic medical centers. I should note that Dr. Brennan was a member of the AAMC's task force that issued the report.

Receiving an "A" is very nice, but we must remain vigilant and work to achieve the best relationship with industry. To that end, Glen Gaulton, Ph.D., our executive vice dean and chief scientific officer, and I recently issued a memorandum to our faculty on extramural consulting activities. As we note, we have seen a significant increase in the number and complexity of consulting arrangements. Our institution has resources, such as the Office of Corporate Alliances, the Office of Faculty Affairs, and the Office of General Counsel, to advise our faculty in this sometimes ambiguous area. Our goal is a simple one: to avoid even the appearance of a conflict of interest and maintain the public's trust. ▪

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

Some 20 years after the idea first came to them, Jean Bennett, M.D., Ph.D., and Albert M. Maguire, M.D., have used gene therapy to restore partial sight to patients with Leber's congenital amaurosis (LCA). A severe form of retinal degeneration, the condition leads to total blindess. The preliminary results set the stage for further studies of an innovative treatment for LCA and possibly other retinal diseases.

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