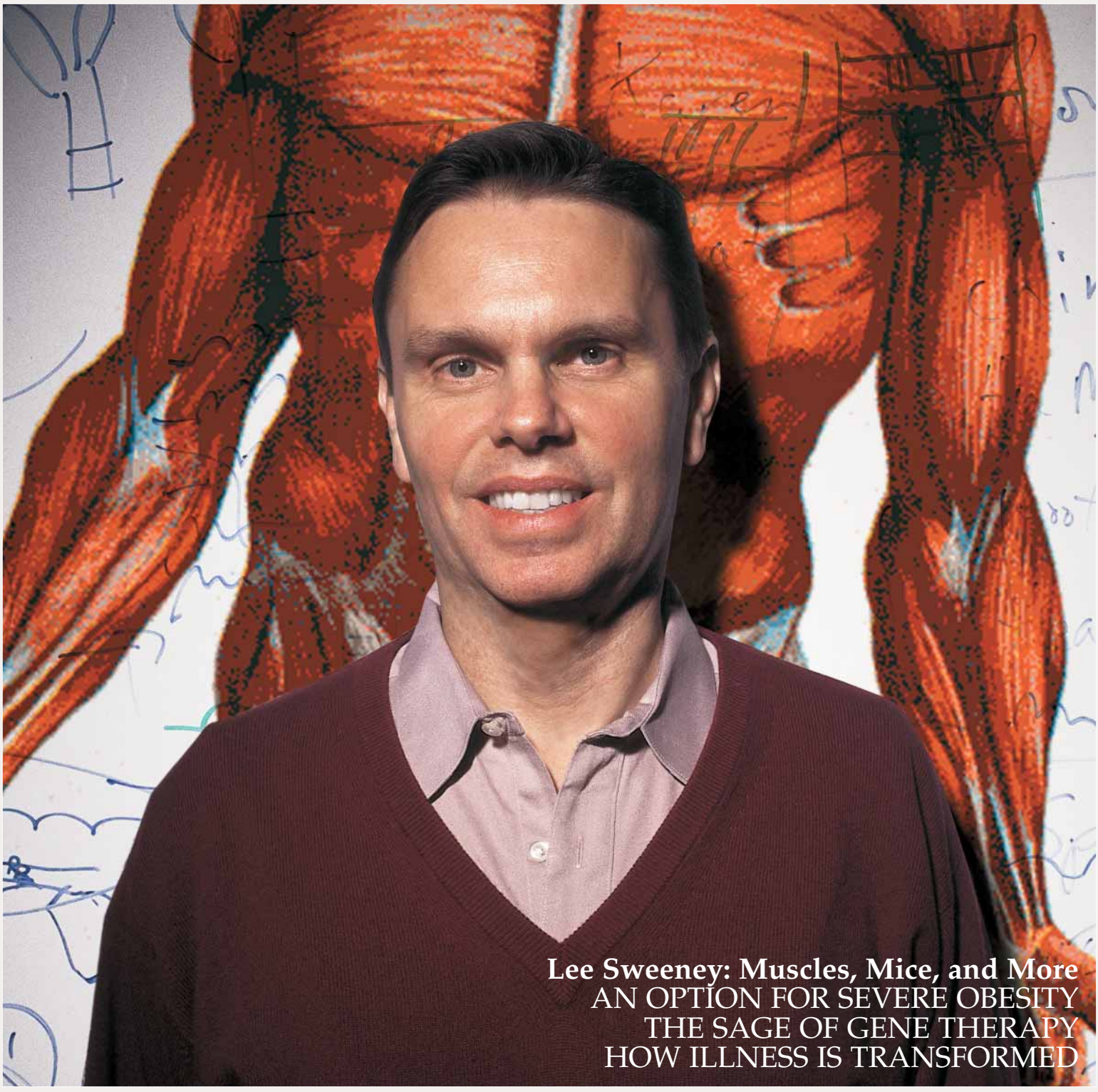
PENN MEDICINE

UNIVERSITY OF PENNSYLVANIA MEDICAL CENTER ▪ SPRING 2004



Lee Sweeney: Muscles, Mice, and More

AN OPTION FOR SEVERE OBESITY

THE SAGE OF GENE THERAPY

HOW ILLNESS IS TRANSFORMED

Senior Resources


Robert Clink

When PENN Medicine formally launched the Association of Senior and Emeritus Faculty (ASEF) earlier this year, it was an acknowledgment that we recognized all that this experienced group has to offer. I was very happy to speak at the Association's first meeting in March, and I am sure I join many alumni and junior faculty in wishing the Association a long and productive existence. As far as the organizers can tell, ASEF is the first such association in the country specifically for medical faculty.

As its mission statement puts it, ASEF's goal is to initiate and coordinate activities that encourage and permit senior faculty (defined as being 55 years of age and older) and emeritus faculty to remain engaged in our School's community of scholars and to encourage them to remain a part of the life of our school. In some ways, we in PENN Medicine have known all along that our group of senior and emeritus professors can be a marvelous resource with much to offer. We have many instances of their meaningful contributions. The late Jonathan E. Rhoads, M.D., G.M.E. '40, for example, was a towering presence as a senior faculty member at Penn for decades, attending a variety of forums, serving on committees, mingling with alumni at events. In fact, Dr. Rhoads never took emeritus status.

Two years ago at our White Coat Ceremony, Sylvan Eisman, M.D. '41, G.M.E. '45, and Truman G. Schnabel, M.D. '43, G.M.E. '47, received the Lifetime Humanism Award. The awards honored, among other things, their example to students and their invaluable assistance as mentors to our younger faculty. Twenty-seven years after receiving the University's Lindback Award for Distinguished Teaching, Microbiology's Helen C. Davies, Ph.D., now must find room for more than a dozen Excellence in Basic Science Teaching Awards, presented by the Medical Student Government. She earned her most recent one this year. And whenever there is a period between deans in the School of Medicine, everyone knows that Arthur K. Asbury, M.D., is the person to contact: he served as acting dean of our School of Medicine in 1988-89 and again in 2000-01. This very selective list only begins to hint at the contributions our senior and emeritus faculty have made in the last several years.

The challenge has been to tap into that great human resource in a systematic fashion. We need to help our faculty in the transition to emeritus status and make them feel part of our school.

All that is now beginning to occur. A crucial first step was taken with Faculty 2000, which the chair of the project, James C. Saunders, Ph.D., professor of otorhinolaryngology, described as "a faculty-based vision for the future of the faculty." One of the project's four working groups focused on senior faculty, and one of the resolutions put forth was to develop an Office of Senior Faculty Affairs and an Association of Emeritus Faculty. This particular resolution received a faculty approval of 92 percent.

That groundwork was laid before I arrived at Penn, but I am proud that the strategic plan developed since then has built on the valuable work done for Faculty 2000. As the Plan for PENN Medicine states, one of our specific goals is to "develop programs and activities that make the transition to emeritus faculty by senior faculty a natural and attractive proposition and process." That document identifies emeritus and senior faculty as "a great but often underutilized resource for PENN Medicine." To give only a couple of examples, more of those faculty members could be mentors for younger faculty and ambassadors of good will with our alumni. Our strategic plan even recommended creating a forum for senior and emeritus faculty – in other words, something much like ASEF.

The Association's appeal seems to have been successful. So far, there are 214 faculty members. John J. Mikuta, M.D. '48, G.M.E. '54, the Franklin Payne Emeritus Professor of Gynecological Oncology, is the current president. The president elect is Marvin E. Steinberg, M.D. '58, G.M.E. '63, professor of orthopaedic surgery. Serving as treasurer/secretary is Marilyn E. Hess, Ph.D., emeritus professor of pharmacology. The council members are Howard Goldfine, Ph.D., professor of microbiology; Nicholas A. Kefalides, M.D., Ph.D., emeritus professor of medicine; and Rob Roy MacGregor, M.D., professor of medicine. At present there are four committees: education (chaired by Martin Pring, D.Phil., associate professor of physiology); service (Arthur F. Whereat, M.D. '51, G.M.E. '55, emeritus associate professor of medicine); data collection (Peter H. Arger, M.D., emeritus professor of radiology); and social activities (Anna T. Meadows, M.D., professor of pediatrics, and Goldfine). As you can see, this group comes with impressive credentials and a wealth of experience. The Office of Faculty Affairs and Professional Development provides administrative support for ASEF.

One of the primary goals of the Association is to demystify the School's and the University's policies on retirement options and benefits. ASEF's next event, in fact, is scheduled to feature a senior benefits specialist from the University's Human Resources office as well as people who will provide an overview of the Faculty Income Allowance Plan, the "Reduction in Duties" policy, and other issues pertinent to faculty retirement.

According to its mission statement, the Association will "celebrate the careers of our emeritus faculty by encouraging them to remain a part of the life of the School in new, interesting, and important ways." On with the celebration! ■

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

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LETTERS

A SHIFT SORELY NEEDED

I studied with great interest Dr. Hansen-Flaschen's photographs of post-call residents in the MICU ("Counting the Hours," Fall/Winter 2003).

What an elegantly simple way to document a fundamental paradigm shift in the way house officers are trained. A shift that, in spite of the doggedly stubborn comments of some of the residents quoted in the article, was sorely needed.

When I was an intern and junior resident in general surgery, there was no mandated 80-hour work week, no required one day off out of seven, no 30-hour shift limit. The size of the inpatient census, the operative schedule, and the whims of the chief residents dictated when we would leave the hospital.

On several rotations, the last vestiges of the every-other-night call schedule were still clinging to existence. Since the every-other-night system would otherwise result in no days spent out of the hospital for an entire month, my colleagues and I would double up our on-call nights in order to secure one precious day off out of 14. This system resulted in our frequently working two nights and three days in a row on call – a frenetic 60-hour shift – with little or no sleep. Ten hours after finally leaving the hospital, we would return, and the cycle would start again.

Did these relentless work marathons forge camaraderie and grant us bragging rights to the most time spent in the hospital by any of the house officers at our institution? Absolutely. Did they make us better doctors? Absolutely not.

I wonder now what my photograph would have looked like, after 48 hours in the hospital with no sleep and another 12 yet to work before going home.

And I'm thankful that our current residents will never have cause to ponder that question.

J. Kellogg Parsons, M.D. '97
Department of Urology
Johns Hopkins School of Medicine

A VOTE FOR MORE HUMANE SCHEDULES

In "Counting the Hours," it is apparent that implementing an 80-hour work week for residents has been done only grudgingly. This, from an institution with one of the leading sleep study centers in the world, is saddening and frustrating. The same decision-makers who would be appalled if the semi-truck drivers next to them on an interstate were sleep-deprived are quite at ease with their least-trained physicians wielding scalpels, calculating drug doses, and counseling grievously ill patients while half-asleep.

Regarding continuity, ignore for a minute the irony of administrators who are embracing hospitalists and physician extenders of every description, all of which disrupt the continuity which is held to be so important in the case of house staff care. Taking continuity as valuable on its face, a night float system would actually improve this by ensuring that only two teams follow a patient rather than the three or four under current every third- or fourth-night call schedules. During my own residency we found that a large majority of patients could be admitted during daytime and early evening hours, limiting handoff issues even further.

Finally, think of the consequences for house staff. Beside the anger and dysphoria that has been documented, they pose a risk to themselves. I counted over a dozen acquaintances during my training who were involved in auto accidents post-call. Thankfully, most were minor. But two resulted in admissions to intensive care and chronic disabilities. I hope it will not take another expensive lawsuit to finally bring training programs to the realization that more humane schedules are right for everyone and should be embraced.

Frederick Jones, M.D. '83, M.B.A.
Wyeth Pharmaceuticals
Collegeville, Pa.

THE FUTURE FOR CANCER SURVIVORS

Congratulations to Dr. Meadows for her accomplishments ("A Champion for Survivors," Fall/Winter 2003). It is heartening to learn that she espoused such research to explore what is hidden in the future for cancer survivors. Cancer is a disease that frightens many people, even those who pursue a degree in medicine, such as my son Samer, who attended U. Penn Medical School, but dropped out after learning that his mother had breast cancer. I wish he had read this wonderful article and learned from the dedication of this wonderful doctor.

If I may ask Dr. Meadows a personal question, is there some similarity between pediatric and adult survivors regarding the reoccurrence and the down-the-road complications due to radiation? Or due to adriamycin or chemotherapy cocktails? Would they also develop heart problems, such arrhythmia and palpitation, and chronic fatigue? Did she also notice any skin changes, such as dryness and scales forming in some parts of the body or over all?

E. Ismail
Watson Pharmaceuticals, Inc.
Brewster, N.Y.

Dr. Anna Meadows replies: The recognition that pediatric tumors responded to treatment with drugs and radiation began more than 30 years ago. Since then we have been studying children who received such treatment, and know much more about their late complications than adult oncologists know about what happens to their patients treated with the same drugs and radiation. It has been assumed that younger patients have more serious complications of therapy, but studies of adults are lagging behind those in children. Steven Hancock at Stanford has studied many adults treated with radiation, and he does have data that points to some serious complications of high-dose heart and lung irradiation. Dry skin is a complication of ageing and overheated buildings for everyone.

THANKS FOR THE MEMORIES

On February 1, I assumed a new position as a senior major gifts officer with the Grateful Patient Program in the PENN Medicine Development and Alumni Relations Office. As I made the transition, I reflected on the many experiences that I had over the past 16 years as the director of Medical Alumni Relations and Institutional Events. When I joined the office, Edward J. Stemmler was dean. I also had the pleasure of working with Arthur K. Asbury on two occasions when he served as interim dean, William N. Kelley, Peter Traber, and Arthur H. Rubenstein. During the 16 alumni weekends we hosted, I met alumni from across the country and beyond.

Another group that I enjoyed working with I affectionately refer to as PENN Medicine's Living Legends. This group is composed of senior faculty members, many of whom are emeritus; Sylvan Eisman, Britton Chance, Clayton Kyle, Nipper Schnabel, John Mikuta, Robert Austrian, Peter Nowell, Cletus Schwegman, Chris Lambertsen, Luigi Mastroianni, Libby Rose, Helen Davies, and Robert Mayock, as well as Jonathan Rhoads and Brooke Roberts, who are deceased. Their contributions have earned them very special places in the history of the School.

I want to express my sincere gratitude to the executive committee of the Medical Alumni Society, who provided advice and leadership on alumni issues. They are a dedicated group led by these presidents I have worked with: Ken Brayman, Joe Gordon, Henry Jordan, William Schwartz, Diane Jorkasky, John Mikuta, William Beck, Arthur Altman, and Edward Viner.

I look forward to many more great experiences at PENN Medicine in my new role.

Marcia Roberts Battista
PENN Medicine Development & Alumni Relations

COMPLICATED ISSUE

Thanks to [John Shea], John Hansen-Flaschen, and the residents for the nice article in *Penn Medicine* entitled "Counting the Hours" – it's a tough and complicated issue that will continue to evolve.

David F. Dinges, Ph.D.
Chief, Division of Sleep and Chronobiology
Department of Psychiatry
University of Pennsylvania School of Medicine

University Nominates its Next President

Amy Gutmann, Ph.D., has been nominated by the executive committee of Penn's Board of Trustees to be the next president of the University of Pennsylvania, scheduled to succeed Dr. Judith Rodin on July 1, 2004. Gutmann is currently the provost and the Laurance S. Rockefeller University Professor of Politics at Princeton University. As provost, she serves as Princeton's chief academic and chief budgetary officer, reporting to the president.

"Amy is a brilliant scholar with a demonstrated commitment to undergraduate and graduate education, a proven and skilled administrator who understands the challenges of running a major research university and an articulate spokesperson about the essential role of higher education in our lives and in the future of our society," said James S. Riepe, chair of Penn's trustees. "She is widely regarded as a world-class scholar whose research addresses many of the key issues facing our society today – from religious freedom, to race

and affirmative action, to ethics and public affairs."

According to 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, "Professor Gutmann's appointment as president of the University of Pennsylvania represents a truly extraordinary partnering of one of the nation's most respected leaders in academia with one of the nation's most revered institutions of higher education."

"Penn has enormous energy and a dynamic spirit," said Gutmann. "Under Judy Rodin's leadership, Penn has established itself in the top rank of institutions, well positioned to face the opportunities and the challenges that lie ahead." Gutmann received her B.A. degree from Radcliffe College; her M.Sc. degree from the London School of Economics, and her Ph.D. degree from Harvard University. ■

Lucky Seven for the School of Medicine

For the seventh year in a row, Penn's School of Medicine was ranked among the top five research-oriented medical schools in the nation by *U.S. News & World Report*. According to the magazine's most recent annual survey of graduate and professional schools (published in its April 12th issue), Penn was ranked fourth, in a tie with Duke University. Ahead of Penn and Duke were Harvard, Washington University in St. Louis, and Johns Hopkins. *U.S. News* conducted a

comprehensive review and analysis of 125 accredited medical schools.

Penn was tied for 46th in the category of medical schools oriented to primary care.

The *U.S. News* survey also lists several specialty programs, ranked by deans and senior faculty at peer institutions. This year, Penn had four programs ranked in the top 10: pediatrics (3rd); women's health (2nd); drug/alcohol abuse (6th); and internal medicine (6th).

In announcing the news, 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, noted, "While such published surveys have their limitations, it is gratifying to see – via independent reviews – that our efforts have been recognized by our peers." ■

New Chair of Anesthesia

Lee A. Fleisher, M.D., was appointed chair of PENN Medicine's Department of Anesthesia. A graduate of Penn's School of Arts and Sciences and a native Philadelphian, Fleisher earned his medical degree from SUNY Stony Brook and completed his residency at Yale. Before his return to Penn, he served as professor of anesthesia, vice chair for clinical investigation, and clinical director of operating rooms for The Johns Hopkins School of Medicine. He also held an appointment in health policy and management at The Johns Hopkins School of Public Health since 1997.

Fleisher's future goals as chair include continuing the department's tradition of outstanding basic science research and enhancing its clinical, health services, and translational medicine components.

His professional interests include the study of how to predict and prevent cardiac complications in patients with cardiac disease who are undergoing operations not related to their heart conditions. He is an expert in both clinical research and medical decision theory, focusing on perioperative cardiovascular management as well as the examination of surgical cost effectiveness. Fleisher is also interested in the surgical treatment of patients over 65 and has served on numerous governmental (Medicare) committees to determine how to make the safest and most appropriate insurance decisions for this patient population.

Fleisher is the co-medical director of the Global Perioperative Research Organization and is a Fellow of the American College of Cardiology. ■

Taking the Initiative Against Alzheimer's

The University of Pennsylvania announced the establishment of the Marian S. Ware Alzheimer Program, a set of collaborative initiatives between PENN Medicine and the School of Nursing to advance drug discovery, clinical research, and patient care related to Alzheimer's disease. The program is created through a $6 million gift from Marian S. Ware, a long-time supporter of the University and advocate for progress in medical research and treatment for Alzheimer's disease.

"With our aged population projected to expand dramatically in the coming years, and with Alzheimer's disease research showing great potential, now is the time to focus increased resources and energies on uncovering the mysteries of this devastating disease and offering new hope to its patients and their loved ones," 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. "The timely and extraordinarily generous gift from Marian S. Ware will be invaluable to advancing Penn's contributions to several realms of this vital work."

The Marian S. Ware Alzheimer Program will build on the recognized expertise and research strengths at Penn's Alzheimer's Disease Center, the Center for Neurodegenerative Disease Research, and collaborating faculty and centers within Penn's schools of Medicine and Nursing.

One component of the Program is drug discovery, which will attempt to identify novel compounds that may prevent or ameliorate the onset or progression of Alzheimer's disease. This work will be led by two people whose research in the last decade has helped lay the foundation for this initiative: Virginia M.-Y. Lee, Ph.D., M.B.A., the John H. Ware 3rd Professor in Alzheimer's Research and director of the Center for Neurodegenerative Disease Research; and John Q. Trojanowski, M.D., Ph.D., the William Maul Measey – Truman G. Schnabel Jr., M.D., Professor of Geriatric Medicine and Gerontology, who serves as director of the Institute on Aging and co-director of the Center for Neurodegenerative Disease Research. Both are professors in the Department of Pathology and Laboratory Medicine.

A second main component of the Program is clinical research. One goal is developing a reliable, easily administered, and safe test to detect Alzheimer's disease and to measure its progression. This work will be led by Christopher M. Clark, M.D., associate professor of neurology, and Jason H. Karlawish, M.D., assistant professor of medicine. Both are affiliated with the Memory Disorders Clinic of Penn's Alzheimer's Disease Center.

The third main piece focuses on developing a comprehensive, coordinated, and cost-effective model of care management for Alzheimer's patients. Mary D. Naylor, Ph.D., R.N., the Marian S. Ware Professor of Gerontology in the School of Nursing, recently completed a pilot study in this area. She will lead

a program to implement and evaluate a care coordination model for patients throughout Penn's Health System.

Approximately 4.5 million Americans have Alzheimer's disease today, and it is estimated that 13 million will be afflicted by the middle of this century unless a cure or prevention is found, according to the Alzheimer's Association. U.S. society spends at least $100 billion a year on Alzheimer's disease. ■

Mitchell A. Lazar, M.D., Ph.D.

Penn Researchers Establish Hormonal Link Between Obesity and Diabetes

Three years ago, a team of researchers at the University of Pennsylvania School of Medicine discovered resistin, a hormone secreted by fat cells in mice. Since then, they have focused their studies on the role of resistin in glucose metabolism, obesity, and Type 2 Diabetes Mellitus, using mouse models. According to Mitchell A. Lazar, M.D., Ph.D., chief of the Division of Endocrinology, Diabetes, and Metabolism at Penn's Medical Center, collectively, these studies point toward resistin as a new target for treatment of endocrine diseases.

Lazar's team developed and compared a strain of mice lacking resistin with those having normal levels, seeking to determine resistin's role in maintaining proper levels of glucose. Because resistin is the fuel that allows the body to function, it is essential to have glucose available in proper amounts. During a period of fasting – such as sleep – the liver is able to generate glucose from fats and protein. Significant differences in the blood glucose levels of the two groups of mice became evident after both fasted for periods of four hours or longer. In the mice lacking resistin, the process was severely impaired, suggesting that the hormone acts as a key regulator of glucose metabolism.

One of the recent studies was published in the 20 February 2004 issue of *Science*. The results, says Lazar, were remarkable. When both groups of mice were fed diets high in fat, those without resistin showed a significantly lower relationship between weight and blood glucose levels. This indicates a positive correlation between the presence of resistin and insulin resistance, a reduced sensitivity by tissues to this hormone.

"Circulating hormones, some only recently discovered, clearly combine to create metabolic havoc," says Lazar. "In our modern environment, characterized by nutritional excess, these hormones may be specific targets for prevention and treatment of obesity and diabetes."

Some observers have questioned the role of resistin in humans because it is secreted by macrophage cells in humans, rather than by fat cells, as in mice. Regardless of where the hormone originates, Lazar argues, elevated levels of resistin are present in the obese and correlate positively with insulin resistance. In addition, some drugs currently used to treat diabetes lower resistin in both mice and humans.

Future research in this area will aim to establish the role of resistin in human diseases. Measuring resistin in a simple blood test may then be useful in detecting insulin resistance and pre-diabetic conditions. Looking forward, Lazar suggests that counteracting resistin's effects on the body might be a new approach to preventing and treating diabetes. ■

Transition at the School

Michael E. Black, who had been vice dean for administration and finance, has left the School of Medicine to join the School of Medicine of the Washington University of St. Louis. There, he will serve as the associate vice chancellor/associate dean for administration and finance and as chief financial officer for the Faculty Practice Plan. Christopher P. Kops, executive director of finance for the School of Medicine, was named as Black's successor.

Black came to Penn's School of Medicine in January 1998. During his tenure, the school has modernized its financial functions, making them responsive to the School's budgeting, monitoring, and reporting needs. Black established the Office of Research Support Services, the Office of Compliance, and the Office of School of Medicine Human Resources and Training, all of which have enabled the School to support its rapidly growing academic programs, while providing stewardship of the related resources.

Kops joined the staff of the School of Medicine in July 1998 and has led the successful evolution of its finance function since that time. Formerly, he was at the firm then known as Coopers and Lybrand, where he was a partner in the Healthcare

Legislative and Regulatory Group. At the School of Medicine, he has worked to integrate the School of Medicine's financial administration with the educational, research, and other administrative functions of the School.

Toward a Vaccine for Breast Cancer

Researchers at Penn's Abramson Cancer Center have begun a Phase I clinical trial to evaluate the effectiveness of a telomerase peptide as a possible vaccine against breast cancer. The trial will measure the potential shrinkage of tumor cells in patients after an immune response has been triggered to an antigen – the telomerase peptide – that is found in more than 90 percent of breast cancer tumors.

"This is the first clinical study to use a telomerase peptide as a possible vaccine against breast cancer," said Robert Vonderheide, M.D., D.Phil., lead researcher on the study. Vonderheide, assistant professor in the Department of Medicine, is affiliated with the Abramson Family Cancer Research Institute. "Our hope is that the immune response will kill the cancer and improve the health of patients."

Twenty-eight patients with metastatic breast cancer will be enrolled in the study, which is expected to last two years. Patients will be injected with one of three escalating doses of the telomerase antigen in combination with adjuvant therapies (granulocyte-macrophage colony stimulating factor, GM-CSF) over a period of seven months. The immune and tumor response to the telomerase-based vaccine will be compared to a control response to an injection of cytomegalovirus peptide.

The results of an earlier feasibility study – also led by Vonderheide and published in the 1 February 2004 issue of *Clinical Cancer Research* – showed immune responses with little toxicity in seven breast and prostate cancer patients after they were injected with small amounts of a similar telomerase peptide vaccine.

"One breast cancer patient in the earlier study showed temporary tumor regression, prompting us to accelerate research into the possibility of a vaccine," said Susan Domchek, M.D., assistant professor of medicine and the trial's principal investigator.

The study is made possible through a $500,000 grant from the Avon-NCI Progress for Patients Awards program.

Vonderheide, left, and Domchek


Strom

Two More Hats for Strom

Brian L. Strom, M.D., M.P.H., has been appointed associate vice dean of the University of Pennsylvania School of Medicine and associate vice president for integrated program development for the University of Pennsylvania Health System. Strom will be responsible for the integration of the research, clinical, and educational activities of the medical school and Health System.

"Dr. Strom's primary charge in these positions is to ensure that we take full advantage of our system-wide resources in mission planning and operation," 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. According to Rubenstein, Strom will review existing activities and look to generate new opportunities from the perspectives of the various users throughout the institution.

Strom's first specific project in this new position is to develop an integrated vision for medical/biomedical informatics at PENN Medicine (the School of Medicine and the Health System). According to Ralph Muller, CEO of the Health System, "Dr. Strom will be reaching out to all components of this area for participation, from patient registry and care to health services and genomics research and education."

"Penn's School of Medicine is well recognized as one of the very best medical schools in the country, and the Hospital of the University

of Pennsylvania is recognized as one of the nation's best hospitals," said Strom. "PENN Medicine is now one of the few truly integrated academic health-care systems. This creates tremendous opportunities for further cross-fertilization, resulting in enormous benefit for both the clinical and academic parts of our operation. The results will be better for our patients, for our students, and for the patients of the future, who will benefit from our research."

Strom is the George S. Pepper Professor of Public Health and Preventive Medicine and chair and professor of the Department of Biostatistics and Epidemiology, as well as professor of medicine and of pharmacology. In addition, he serves as director of the Center for Clinical Epidemiology and Biostatistics and chair of the Graduate Group in Epidemiology and Biostatistics at the School of Medicine. He will retain these existing responsibilities while fulfilling the demands of his new positions. His research interests span many areas of epidemiology, including pharmacoepidemiology.

Widely honored in the profession, Strom serves on the Drug Safety and Risk Management Advisory Committee for the United States Food and Drug Administration. A member of the Institute of Medicine of the National Academy of Sciences, he chaired the institute's Committee to Assess the Safety and Efficacy of the Anthrax Vaccine and is currently chair of its Committee on Smallpox Vaccine Program Implementation. ■

Cryoplasty: Using Sub-Zero Cold to Open Blocked Arteries

In February, physicians at the Hospital of the University of Pennsylvania performed the city's first cryoplasty procedure. The patient, a 73-year-old male, had a severely blocked artery in his right leg. Like angioplasty, cryoplasty restores blood flow by carefully positioning a tiny balloon inside the vessel, at the site of the blockage, and then slowly inflating the balloon to expand the diameter of the vessel. Traditional angioplasty uses a saline-contrast solution to inflate the balloon, while cryoplasty uses nitrous oxide, which cools to a temperature of –10 degrees Celsius.

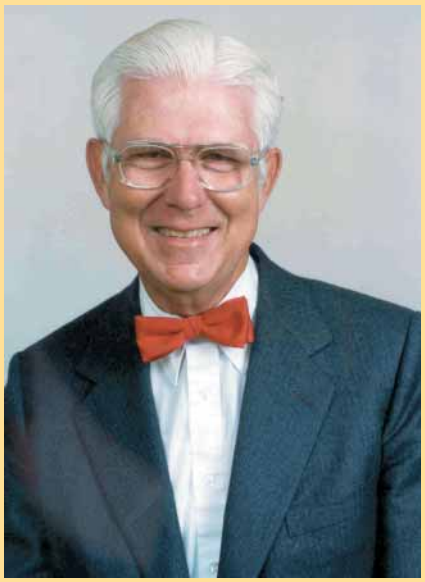
The sheer coldness of nitrous oxide appears to limit restenosis (late re-narrowing of the artery) by reducing tearing and subsequent inflammation of the affected vessel. In traditional angioplasty, the inflation of the balloon causes uncontrolled tearing of the vessel wall and triggers inflammation and, consequently, the formation of scar tissue. Nitrous oxide, on the other hand, is associated with more controlled tearing and little or no inflammation. It appears to work, in part, by selectively destroying the cells involved in scar formation (endothelial and smooth-muscle cells).

"Cryoplasty is a new tool for opening blocked arteries, and it appears to be a very promising approach in the treatment of peripheral vascular disease," says Herbert Aronow, M.D., M.P.H., an interventional cardiologist who led the cryoplasty procedure. As Aronow, director of HUP's Peripheral Intervention Program in Cardiovascular Medicine, explains, "Preliminary data suggest that cryoplasty may be superior to traditional angioplasty or stenting."

Indeed, in a study of 91 patients treated with cryoplasty for leg-artery blockages – which was presented at the International Symposium of Endovascular Therapy in January – 75 patients, or 85 percent, showed no signs of restenosis nine months after treatment. This figure compares favorably to those in traditional angioplasty and stenting series, where the rates of restenosis have ranged from 40 to 50 percent.

More than 12 million Americans suffer from peripheral vascular disease, also known as atherosclerosis of the blood vessels of the arms, legs, and other branches of the aorta. "As many as one in three of those patients have pain so severe that it affects their quality of life and limits their functional status," says Aronow, who is also an assistant professor of medicine in Penn's School of Medicine and director of the Cardiac Catheterization Laboratory at the Philadelphia Veterans Administration Medical Center. "Cryoplasty appears to be a significant advance in the treatment of this painful, debilitating disease."

The cryoplasty performed at HUP in February used the PolarCath™ System, manufactured by Boston Scientific, Inc. ■



More Honors for Beck

Aaron T. Beck, M.D., emeritus professor of psychiatry at the University of Pennsylvania School of Medicine, has received the Rhoda and Bernard Sarnat International Prize in Mental Health for the Year 2003 from the Institute of Medicine. The prize consists of a medal and $20,000. He was also selected by the University of Louisville to receive the Grawemeyer Award in psychology for the Year 2004. This award is a prize of $200,000. Both honors recognize Beck's outstanding and far-reaching contributions to psychiatry and mental health.

Known as the "father of cognitive therapy," Beck sidestepped the accepted theories of the day, most of which relied heavily on Freudian analysis, and developed a pragmatic and highly productive technique for helping patients deal with emotional disorders. ■

W

Photographs by Addison Geary

What Lee Sweeney discovers about muscles in mice is likely to have a bearing on muscles in humans.

What Makes Lee Sweeney Run?

By Lisa J. Bain

In scientific circles, Lee Sweeney has built a reputation investigating Duchenne muscular dystrophy and hypertrophic cardiomyopathy – but he is best known in the wider world for his work with "mighty mice," treated to gain muscle mass and stave off many of the effects of aging.

What makes Lee Sweeney run? Muscles. H. Lee Sweeney, Ph.D., chair of Penn's Department of Physiology, has spent his whole career learning how muscles work at a molecular and cellular level. And what he's found has revealed new insight not only into what can go wrong in muscles, but also how non-muscle cells communicate and carry out many essential functions.

Along the way, muscles have carried Sweeney into what is usually unknown territory for most basic scientists. He is as likely to be spotted at meetings of politicians, policy makers, ethicists, parents, and athletes as at meetings of his cellular biology colleagues. Yet this should not be surprising, given that dysfunction of muscles is responsible for so many human diseases and disabilities. Heart disease, the leading killer of people in America, is essentially a disease of a large muscle. And many conditions that bedevil the ever-growing aging population result from loss of muscle mass.

"My intellectual love is the very basic work that I do," he says, but he concedes that "it would be a stretch to see how the basic work that I do would impact society or the health of society in the next few centuries." On the other hand, Sweeney also has what he calls his "more applied work" and his work to try to help patient groups that are interested in diseases of the muscles. That activity started, he says, as a means "to do something that would be a little more relevant to the society that supports me in my ability to spend most of my time doing things that I find intellectually challenging."

Running on molecular motors

Sweeney came to Penn in the late 1980s, at a time when the study of physiology was moving rapidly into the realm of molecular biology. Yale Goldman, M.D. '75, Ph.D., now professor of physiology and director of the Pennsylvania Muscle Institute (P.M.I.), recruited him, recognizing that he had both a strong foundation in physiology and had begun using molecular techniques

to study the problem of muscle contraction in skeletal muscle. Penn and the P.M.I. had a long tradition of excellence in research on muscle physiology, and Goldman rightly sensed that expertise in molecular biology was essential for continuing that tradition.

Goldman and Sweeney took parallel paths to study a group of muscle proteins called myosins. Sweeney focused on molecular aspects, while Goldman undertook biochemical and structural studies. Myosin is called a molecular motor because it transforms chemical energy into movement along tracks made up of another protein called actin. In this way, myosins power the movement of muscle fibers during muscle contraction. But myosins do much more: they are responsible for cellular motion during cell division as well as for the movement of different structures within the cell.

"Lee had a brilliant insight about the tilting motion of one of the subunits," says Goldman. "A lot of us had been looking for angle changes in myosin, but the evidence was slim." Sweeney's work with colleagues at The Scripps Research Institute in La Jolla, Calif., provided some of the most direct evidence that a part of the myosin molecule acts as a rigid lever arm, swinging the myosin down the actin track. Meanwhile, work in Goldman's lab using a novel technique called fluorescence polarization also helped solidify the idea that a central feature of motility involves a lever-arm motion of myosin.

According to Goldman, Sweeney and he are planning future collaborations studying non-muscle myosins in the brain. These proteins carry cargoes around inside of cells. Sweeney and Amber Wells, who had been a graduate student in Sweeney's lab (she completed her Ph.D. degree in 2002) discovered a novel feature of one of these myosins, called Myosin VI. Unlike all other known myosins, Myosin VI walks backward on actin, giving rise to novel functional properties.

The discovery, says Wells, "opened up a whole new way to think about how myosin may be acting." This new concept may help explain how mutations in the protein can cause deafness in both humans and mice. At least two other myosins have been linked to deafness, pointing to an essential role for the protein in the development of the ear. Mice with a mutation in myosin VI, called Snell's waltzer mice, also have balance problems, run in circles, and show signs of anxiety, suggesting even further intrigue in the myosin story.

Alternate paths

Within a few years of coming to Penn, Sweeney had made an impression on other investigators within the University community. Alan Kelly, B.V.Sc., M.R.C.V.S., Ph.D., now dean of the School of Veterinary Medicine, convinced him to apply his knowledge of muscle physiology to a fatal, degenerative disease – muscular dystrophy. Sweeney also initiated studies of myosin contractility in heart muscle, eventually leading to collaborations with Timothy J. Gardner, M.D., now the William Maul Measey Professor of Surgery and chief of cardiac surgery at the Hospital of the University of Pennsylvania. And, as he began to

Sweeney and the Hulk

Sweeney's mice have shared the spotlight on TV.

In May 2003, the Discovery Channel aired a program called "Kapow! Superhero Science." The question it examined was "can science replicate the powers of comicbook superheroes?" (For unexplained reasons, all the superheroes cited come from Marvel.) One of the program's segments focused on strength well beyond normal, as embodied by the Hulk, the massive green creature with an unfortunate tendency to lose his temper. The scientific background featured the work of H. Lee Sweeney, Ph.D., chair of Penn's Department of Physiology. As the Discovery narrator put it, "It appears that to really change human to Hulk, you're going to have to tamper with the genes, which is where the real super-science comes in. Dr. H. Lee Sweeney of the University of Pennsylvania has already created the Hulk – or at least his rodent equivalent."

Filmed in his laboratory, Sweeney demonstrated one of the mice used in his experiments aimed at slowing the loss of muscle strength. If you shaved off the fur of a treated and an untreated mouse, he said, "there'd be no comparison. I mean, the muscles are huge in the treated ones vs. the untreated ones."

The narrator filled in some of the details: "The scale tells the tale: a normal mouse weighs in at 27 1/2 grams; the genetically engineered ones, 41 grams – or 40 percent

think more and more about treating these debilitating diseases, Sweeney began collaborating with James M. Wilson, M.D., Ph.D, the John Herr Musser Professor of Research Medicine who headed Penn's Institute for Human Gene Therapy.

Sweeney's early work in muscular dystrophy remained on a basic science level. "My interest in trying to develop something therapeutic didn't come until I was first asked to speak to some of the parent groups," he says. "It was the personal contact that sort of changed my views."

There are actually several forms of muscular dystrophy. All are inherited, many in an x-linked fashion, meaning they affect only boys and are passed through mothers. Duchenne muscular dystrophy (DMD), the most common and severe form, affects about 1 in every 3,500 male births. Affected boys may appear normal until they begin walking. Sometime between the ages of one and three, they begin to show signs of weakness and may have trouble standing. As the disease progresses, skeletal, respiratory, and cardiac muscle are all destroyed. By age 10, most boys with Duchenne muscular dystrophy are confined to a wheelchair, and they rarely live past their early 20s.

Lee Sweeney confers with Carl Morris, a postdoctoral fellow in physiology.

beefier than the average. How do you get the gene into the mouse? You smuggle it in, on a virus."

Sweeney explained that the virus "goes inside the cell looking like a normal virus, but, lo and behold, when it opens up, it's got a new gene in there that wouldn't have normally been there. So you can view it as a Trojan horse, if you like."

Narrator: "The mouse gets mighty – and stays that way."

In fact, Sweeney continued, "Their muscles never get weaker when they get old. They are just as strong when they're the equivalent of an 80- or 90-year old human as when they are the equivalent of a 20-year-old."

The reason is insulin-like growth factor-I, injected into the specific muscle. The muscle, in the words of the narrator, then grows "at superhuman rate." Pulling back a moment from the world of superheroes, the narrator noted that the first use the IGF-I treatment is likely to be in treating muscular dystrophy.

But Sweeney reported that some people have considered different uses of the treatment: "Through e-mail, I've been approached by a lot of people, mostly weight-lifters, but even once a coach for a high-school football team." The coach asked Sweeney to inject his whole team "because he thought they could benefit from being a bit stronger." ■

— John Shea

Sweeney's work with parent groups finds him not only meeting with parents to tell them about progress in the field, but also lobbying Congress for more funds to support muscular dystrophy research. "With the form of muscular dystrophy that I've been working the most with, the patients themselves don't live long enough to lobby Congress," he says. "And by the time they die, most of the parents never want to think about it again. So historically, there has been very little voice for that community in Congress because of the nature of the disease."

Pat Furlong, president of Parent Project Muscular Dystrophy (PPMD), says that Sweeney backs his words with action. At the first PPMD conference he attended, says Furlong, Sweeney sat through the entire conference, not just the scientific sessions. "I was thrilled, pleased, amazed," she says. At one point, "he stood up and said, 'The only way you're going to get sufficient money for us to do something about this disease is to lobby in Congress.'" And that is exactly what Sweeney has done. Says Furlong, "Of all the researchers in the world, I admire him the most because if he promises something, he'll deliver." Sweeney now serves as the group's scientific director.

Duchenne muscular dystrophy is caused by mutations in the gene for dystrophin, a protein that is needed for the structural support of muscles. Without dystrophin, muscles deteriorate and weaken. Although some early work suggested that gene therapy might be used to replace the mutated dystrophin with normal protein, several factors – including the large size of the protein – have led researchers to look for other therapeutic strategies.

About 15 percent of boys with DMD have a genetic mutation called a "premature stop codon" that instructs the protein-making machinery of the cell to stop building dystrophin before the protein is complete. In the late 1970s, scientists found that in yeast, certain

antibiotics called aminoglycosides allow the cell machinery to ignore premature stop codons and continue to build proteins. More recently, scientists showed that this approach could be used to trick cells with similar mutations in the gene that causes cystic fibrosis to read through the mutation and produce the full-length protein that is absent in people with the disease. Sweeney reasoned that a similar approach might work in muscular dystrophy. Studies conducted in his lab demonstrated – first in cultured cells, then in a mouse model of muscular dystrophy – that the drug did induce the production of full-length dystrophin. More important, the muscles of mice treated with gentamicin resisted damage.

While potentially useful, aminoglycosides can also cause hearing loss and kidney damage when used in high doses. Because of this danger, Sweeney is working with a small biotechnology company to try to develop new drugs that have some of the same properties, but without the toxic side effects. He says he expects to be able to initiate clinical trials of these drugs within the next year.

Meanwhile, Sweeney is also pursuing his interest in gene therapy with an approach that could help people with another form of muscular dystrophy, called limb girdle muscular dystrophy (LGMD). The disease is caused by one of about a dozen genetic mutations. Both males and females can be affected by the illness, which leads to a weakening of voluntary muscles, primarily in the shoulder and hip "girdles." Unlike Duchenne muscular dystrophy, LGMD is usually not fatal, and its symptoms range from mild to severe disability.

Some people with LGMD have mutations in genes called sarcoglycans. These are proteins in the membranes of muscle cells. When they are defective, the muscle cells are not able to react normally to the stress of muscle contraction. Sweeney has focused on mutations in one particular type of sarcoglycan, called gamma-sarcoglycan. His laboratory is working with gene-therapy colleagues at Penn to develop vectors that will deliver normal gamma-sarcoglycan to the muscles of people with this mutation. The vector they are using is called adeno-associated virus (AAV). AAV has shown particular promise in gene therapy trials because, unlike some other potential viral vectors, AAV does not in itself cause human disease, nor does it provoke an immune response from humans.

The researchers have shown that injecting the vector carrying the normal gamma-sarcoglycan gene into the limbs of mice lacking the gene prevents degeneration of the muscles. They have also engineered the vector so it expresses gamma-sarcoglycan only in muscle cells, rather than in all types of cells. As a result, the gene therapy does not provoke an immune response.

Sweeney says he hopes that human trials of this approach can start soon. As he puts it, "This is our entry point using AAV as a vector. If it goes well, we'll probably try to do something with Duchenne muscular dystrophy and AAV as well." One possible approach would be to put into the vector a factor that would stimulate the production of eutrophin, a protein related to dystrophin that may be able to compensate for its loss. "We're trying to find things that will be more generic for all of the Duchenne patients and, for that matter, for Becker patients as well." Becker muscular dystrophy is a less common and much milder form of MD that is also caused by a defect in the dystrophin gene.

Rescuing aging muscles

Sweeney's interest in muscle physiology intersects with his own life in other ways beyond his work with parent and advocacy groups. Watching his grandmother grow older, in fact, prompted him to ask questions about what could be done to rescue the waste of muscle that occurs naturally as people age. "My grandmother had total use of her mental faculties, but became wheelchair bound just because of progressive muscle weakness that no amount of her trying to exercise was able to overcome," he recalls.

Elisabeth Barton, Ph.D., carried out critical gene-therapy experiments that showed increased muscle mass and strength in mice.

In fact, all mammals lose up to a third of their muscle mass and power as they age. A few years after his grandmother died, Sweeney says, he started thinking about how to approach the problem of muscle wasting, as well as the potential for gene therapy as a means to deliver factors that might reverse it. The question was, what sort of gene delivery might be useful in an aging setting?

Insulin-like growth factor I (IGF-I) is a substance that stimulates growth and repair of the muscles. Produced both by muscles themselves and by the liver, IGF-I drives protein synthesis and suppresses protein degradation. Perhaps more important, it stimulates cells called "satellite cells" in the muscle to divide, differentiate, and regenerate muscle. Researchers at other institutions had shown that injection of IGF-I into the damaged muscles of mice improved both the structure and function of those muscles.

Sweeney thought gene therapy might be a better way of delivering the factor. Elisabeth Barton, a postdoctoral fellow in Sweeney's lab, carried out the critical experiments along with colleagues at Massachusetts General Hospital. Using the AAV virus as a vector, Barton injected the IGF-I gene into one leg of mice ranging from 2 to 24 months of age. The ages of the mice chosen represented the equivalent of adolescent, 55-year-old, and 70-year-old humans. The other leg of each mouse was left untouched as a control. (Barton is now assistant professor of anatomy and cell biology in Penn's School of Dental Medicine.)

All of the mice showed increases in muscle mass and, most important, the injections completely prevented the age-related loss of muscle mass and significantly boosted muscle strength in the oldest mice. Sweeney presented the results of this research at the annual meeting of the American Society for Cell Biology in December 1998, which coincided with the publication of the research in the *Proceedings of the National Academy of Science*. It did not take long for news about these "mighty mice" to leak out to the popular press around the world – and for people involved with groups like the International Olympic Committee and World Anti-Doping Agency to voice their concerns.

When his lab group first started this line of research, Sweeney says, "I didn't really think about the athletic implications. But when we started analyzing the young mice that we were doing it in, it became pretty clear that they were getting strong without doing anything. So then, overnight, it became clear that there was going to be some interest in this from an athletic standpoint."

"Some interest" is an understatement. Sweeney's work has been featured in publications ranging from *Science News* to *The New York Times* to *Sports Illustrated* and broadcast on BBC News and CNN. In fact, in 2002, CNN ran what it calls an on-line "quickvote" on Sweeney's research: "Do you think something like IGF-I – if it's found to work in humans as it does in mice – should be applied to athletic performance?" The CNN web site tallied 6,522 votes. Twenty-eight percent voted "Yes, absolutely"; 30 percent voted "Under certain circumstances – like pure fitness – but not for competition"; and 42 percent voted "No way." The *Weekend Australian* began an article in 2002 in dramatic fashion: "Lee Sweeney guards a genetic fountain of youth. In his Pennsylvania laboratory, the elite biotechnologist is testing a muscle-building gene designed to fend off frailty in the elderly." In addition, Sweeney has been asked to speak about his work at meetings of the World Anti-Doping Agency, The National Human Genome Research Institute, and the President's Council on Bioethics, among others.

"The availability of this sort of technology to an athlete in this country is not going to happen any time soon," said Sweeney in his address before the President's Council on Bioethics. "But on the world stage, in a world where countries in the past have shown that they want their athletes to win no matter what, and they will give them any experimental drug that might be performance enhancing no matter what the long-term

consequences, one can imagine that with enough money you could put together a program to genetically engineer your athletes and do it in such a way that it would be totally undetectable unless you were to remove tissue from that athlete. There would be nothing in the blood, no signature in the blood or urine to indicate that the tissues had been genetically manipulated."

Nonetheless, Leon Kass, M.D., Ph.D., chairman of the President's Council, reminded the council that the ethical issues are significant. According to Kass, an ethicist from the University of Chicago, "What's in a way at stake in this is something like the view of the life cycle and, forgive me, a place of decline in the overall shape of a life. While nobody from a medical point of view or even from an experiential point of view would choose debility given the opportunity to avoid it, one at least has to wonder what the world would be like if you've got 75-year-old men quite happily playing ice hockey; and what the view of the life cycle would be if in a way what you are really aiming for – never mind the immortality research – but you're going to get everybody up to the brick wall sort of looking and acting as if they were 30."

The controversy surrounding the idea of genetic enhancement has obscured some of the other implications of Sweeney's IGF-I research. In addition to helping the aged, IGF-I treatment shows promise in helping people with muscular dystrophy. Sweeney and colleagues have genetically engineered the mdx mouse (mice with the mouse version of muscular dystrophy) to churn out high levels of IGF-I as well. Sweeney reports that these mice show increases in the size and strength of their muscles, better regeneration, less muscle wasting, and less buildup of scar tissue.

Despite the publicity and controversy, Sweeney says that ethical concerns will not stop his research. "I think it's unethical *not* to try to do something to help a population that needs medical assistance just because there might be fallout in sports. I have no ethical dilemma. It's up to the agencies to do what they can; but it can't stop me or other people from trying to develop treatments that will benefit people."

Racing towards the future

In addition to the basic research about myosin, the anticipated clinical trials studying the use of aminoglycosides in people with Duchenne muscular dystrophy, and the gene therapy trial in people with limb girdle muscular dystrophy, Sweeney has been working for several years with Tim Gardner, a Penn cardiac surgeon, to develop gene therapy approaches to treating heart dis-

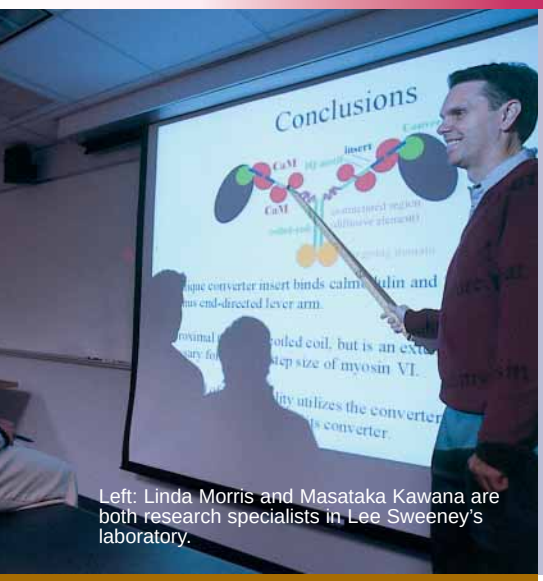
Sweeney Among the Ethicists

Some biomedical pioneers would hesitate to go anywhere near Penn's Center for Bioethics. Yet last spring, H. Lee Sweeney, Ph.D., ventured to the very center of the Center to make a presentation to graduate students and other interested listeners. Among them was Arthur L. Caplan, Ph.D., director of the center and one of the most quoted bioethicists in the nation. Sweeney, chair of Penn's Department of Physiology, was there to talk about what he called "the growing concern in the use of gene technology" when it is used not to target a specific disease or a defective gene but for "genetic enhancement." The irony is that Sweeney's own basic research has helped raise some of those concerns.

In the laboratory, Sweeney has introduced insulin-like growth factor I (IGF-I) into the muscles of mice by way of a viral vector. Not only did the treatment basically halt many of the effects of aging in mice, it increased their strength by some 30 percent and more. Sweeney's hypothesis when he began this research was that the treatment might lead to better maintenance; might increase muscle regeneration after injury; and, in the young, might increase the rate of growth. One of the ethical issues Sweeney himself raised at the Center for Bioethics is that the gene therapy has to be done *before* the loss occurs – otherwise, the loss cannot be recovered. In muscular dystrophy, Sweeney noted, "the block on fibrosis is indirect": the IGF-I does not prevent the muscle degeneration but increases the ability of muscle to develop. In Sweeney's view, there is less of an ethical issue when IGF-I is given to help counter muscular dystrophy. But, he continued, what about its use in young animals – and young humans looking to be stronger and faster?

According to Sweeney, the United States Olympic Committee is upset because the use of IGF-I does not change blood levels and cannot be detected without a muscle biopsy. "Athletes, I think, are always willing to take these chances," Sweeney told the group. But, he added, this approach is more available to governments than individuals. He cited the example of East Germany, which subjected its Olympic athletes to steroids. Such treatment could provide "a little bit of a competitive edge" – but that might be all an athlete needs to win. What Sweeney called the larger ethical issue is: if the treatment is safe, why not introduce it as early as possible? Won't it be something that everyone, some day, will want?

Noting that the technology itself



Left: Linda Morris and Masataka Kawana are both research specialists in Lee Sweeney's laboratory.

does not appear to be hard, Caplan asked about the cost involved. "Not trivial," said Sweeney, estimating that to treat an athlete's two legs might cost $100,000.

Another person wondered about the risk of cancer in the IGF-I treatment. Sweeney said it was not common; he has not seen it in mice that have two-to-three times the normal levels of IGF-I.

The guardians of the Olympics, suggested Caplan, seem primarily concerned about the distortion of body endowments and issues of fairness and "naturalness." He wondered whether the current vogue of "extreme sports" might lead people to try genetic enhancement – for example, if a producer said, "I'd like to see someone carry four cars up a ladder." But "where the pressure may come more," he added, was in the matter of aging, especially if wealthy individuals are involved. Said Sweeney, "Frankly, I'm a little surprised it hasn't happened."

Sweeney also briefly described his meeting with the President's Council on Bioethics. His sense was that the council on the whole was opposed to genetic manipulation of the sort that IGF-I treatments would make possible. It would force us to redefine "what we know as human," whereas those on the council view aging "as a normal part of life." Yet Sweeney did not seem persuaded. Shouldn't it be a matter of individual choice? No one *has* to undergo the IGF-I treatment.

On the other hand, suggested one of the bioethics students, if you refuse the treatment, are you in effect making yourself a burden on society as you age?

Would the treatment lengthen life? Again, Sweeney reported that his research group has not seen evidence among the animal models. If there was any difference in life spans, he speculated, it would be a trivial amount.

Caplan argued that our notion of "what's normal aging is a modern construction." In fact, for much of humanity's past, people did not live much beyond 40 or 50. Yet he said he could understand how the prospect of seeing elderly people in the future blithely rope-climbing could "freak people out."

The session closed as Caplan asked how many scientists were working in this area so far. "Probably just half a dozen," replied Sweeney. In clinical trials, dogs will be next, and he estimated that human trials are about four years away. In the meantime, joked Caplan, referring to the Center for Bioethics and the budding ethicists in the room, "you're generating business for us." ■

— John Shea

ease. They have begun to identify genes that produce factors that can rescue and stabilize hearts after a major heart attack.

If there's a downside to Sweeney's relentless pursuit of, well, everything, it's that there is not enough time in a day to accomplish all he's set out to do. "I like the advocacy groups and I like the research," he says. "You just run out of time is the problem."

Since he was named chairman of the Department of Physiology in 1999, the demands on his time have only increased. But it's the demands from outside the University that are really taking their toll. During a recent one-month period, says Sweeney, he was only in town for three days. First, he was in Japan to give a keynote address at one scientific meeting. Because it was an exciting time for a project with collaborators in France, he went from Japan to France; and then to Berlin to speak at another meeting. Then it was back to Washington, D.C., to review grants for the NIH, and then back to Japan to give another talk at a meeting.

He has cut out, for now, his training of graduate students, feeling that he does not have the time to serve as a mentor properly. "I have to make appointments with his secretary now," says Amber Wells ruefully. She was the last graduate student to complete her doctorate in his lab. But it was not always that way, she notes. "He's brilliant and fun to talk to and bounce ideas off," she says. "He's a cerebral kind of guy."

With so much on his plate, Sweeney says he finds little or no time to enjoy his beloved opera or devote sufficient time to his other passion, wine. Nevertheless, says Wells, he is a true wine connoisseur. "It's amazing what the man can keep in his brain," she says. "He remembers every vintage he's tasted, and where and when he had it. It's like he has an amazing database in his brain."

Sweeney says he does not think that splitting his time between basic science, applied science, and public advocacy has detracted from the work he does. "I think the travel does hurt my research to some extent, but it has its plusses too." For one thing, the public exposure brings in additional money from private donations. And his stature in the science community does not seem to have suffered.

"His basic, fundamental research is top end," asserts Yale Goldman. While many scientists might find tackling both basic and applied research too demanding, continues Goldman, Sweeney seems to thrive. "It's impressive that he is making an impact in both of these areas. He covers a broad range, and he does it very well." ■

Bariatric Surgery:

Because she was obese, Gabrielle Niemiec had sleep apnea, joint aches, Lupus, anxiety, and high blood pressure. That was bad enough. But the worst pain from being overweight, she says, was when her two young sons, Joey and Erik, asked her not to come to their soccer games.

"Their friends made fun of them," says Niemiec. "They teased them about how fat their mom was."

At one point, Niemiec carried 279 pounds on her five-foot, four-inch frame. That pain, along with the health-related problems from being overweight, led the Philadelphia resident to have a bariatric bypass operation at the Hospital of the University of Pennsylvania. The procedure, limited to those the program calls "severely obese" people, restricts their food intake and helps them lose weight. It is offered as an option when dieting, medications, and behavior modification have failed. One year after undergoing the procedure, Niemiec now weighs 115 pounds, and her health is fine. But when you listen to her talk about her new life, going to her sons' games might give her the most joy.

"My sons," she says, "now call me 'Sexy Moma.'"

Before the operation, Niemiec had been a virtual recluse, often remaining in her house for days at a time. Now she and her husband go out often, and the confidence she gained enabled her to start her own catering company.

Niemiec says she was always "large," but carried the weight well, even at 200 pounds. But when she gained more weight, her health began to suffer. Traditional diet and exercise programs didn't work for her.

Noel N. Williams, M.D., director of HUP's Bariatric Surgery Program, says that when he first met Niemiec, "She was beside herself. Certainly she wanted to change, to get life back together again."

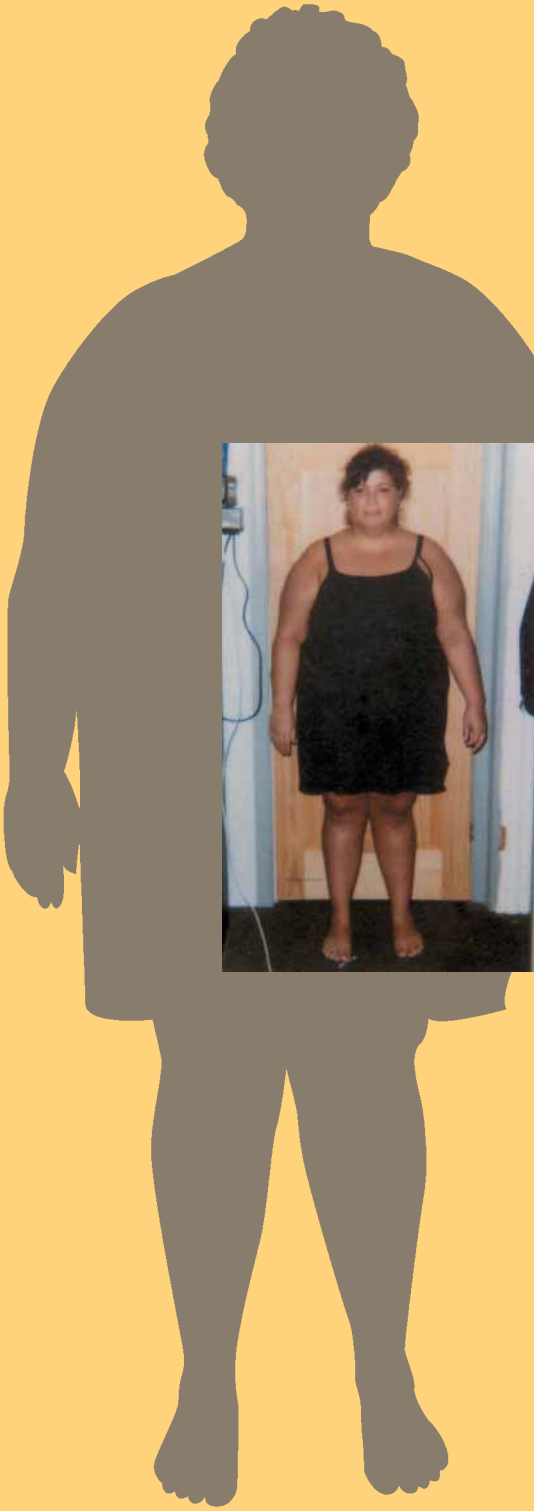
Niemiec was taking several medicines for the obesity-related conditions and even took valium to treat her anxiety. "I knew something had to be done," she says. In March 2002, she met with Williams to see if she met the criteria for bariatric surgery. The surgery would help her lose weight, Williams told her, but she would have to make significant lifestyle changes to assure she wouldn't gain it back. Candidates for the operation are required to undergo a screening process with the program's psychologists and nutritionists. Some people are turned down because they suffer from eating disorders or depression, or they would be unlikely to make the necessary diet restrictions after the operation.

"Dr. Williams was very helpful, explaining everything to me," says Niemiec. "He makes you feel very comfortable in every step. He has an excellent bedside manner, and I felt comfortable with him from the first time I met him."

After the careful screening process, Niemiec underwent the operation on July 17, 2002. Williams reconfigured her stomach, making it much smaller by stapling portions of it together to make a pouch. Because the new stomach takes in less food, the person feels "full" sooner and eats less. The particular surgery Niemiec had is called Roux-en-Y Gastric Bypass; the program's other main procedure is Vertical Banded Gastroplasty.

Typically, Williams will see patients 10 days after the surgery, to remove a drainage tube from the stomach; after that point, he will see them again every two months, then every six months – for the rest of their lives. The first month after surgery, Niemiec lost 14 pounds. After six months, she had lost 80 pounds, and one year later, she has shed 160 pounds.

That kind of weight loss is impressive, but it is by no means rare in Penn's Bariatric Surgery Program. On its web site, the program maintains a "photo album" of some of its clients who, as the site puts it, "are proud of their



Gabrielle Niemiec, before and after her surgery.

When Other Ways Have Failed

Daniel Burke

progress." For example, "David" went from 411 pounds to about 165. (See www.uphs.upenn.edu/surgery/bariatric/photoalbum.html.)

Just as important as the loss of weight, however, is the change in lifestyle. Before her bariatric surgery, Niemiec's typical breakfast would have included two eggs, sunny-side up; two pieces of toast; and sausage links. Lunch would have been a hoagie or cheesesteak with chips and soda. For dinner, she might have had a whole pork chop and servings of potatoes and vegetables, along with bread and butter. For a late-night snack, she would eat a bowl of cereal. Now, breakfast consists of half an egg scrambled with half a piece of toast. Lunch is half a sandwich, and dinner is three tiny pieces of a pork chop, with a forkful of vegetables and a forkful of potatoes. Between meals, she has a tiny amount of cheese or peanut butter to increase her protein intake.

"I've completely cut out carbonated beverages, cakes, cookies, and pies," says Niemiec, who notes that her family as a whole now eats healthier. She can have snacks, such as potato chips or even candy, but she's careful to make sure she eats those things after she's had a regular meal, to get her nutrients.

For the rest of her life, she will need to take vitamin supplements and have a monthly B-1 vitamin shot. But except for her Lupus medication, she no longer needs all the medicines she took before surgery.

"It was amazing how my body started feeling when the weight started coming off," says Niemiec. "My health got better very quickly. I felt my body becoming stronger each day and I had lot of energy." Williams, too, sees a clear difference: "She has an incredible personality, she's a very bubbly individual," he says. "She's obviously a different person. She had no confidence before."

In a recent *New England Journal of Medicine* (March 11, 2004), Robert Steinbrook, M.D. '79, began a "Perspective" in a provocative manner: "The epidemic of obesity in the United States has spawned a second epidemic – of bariatric surgery. The number of gastrointestinal surgeries performed annually for severe obesity increased from about 16,000 in the early 1990s to about 103,000 in 2003." Although Steinbrook does not caution against the procedure, he does warn that there are concerns that some surgeons may not have adequate training for these operations. One of the two major challenges that Steinbrook sees is the need to improve safety. The other "is to learn more about the long-term outcomes, which approaches are best, the mechanisms through which bariatric surgery results in weight reduction, and the effects on coexisting conditions."

Since her operation, Niemiec has recommended six people to Williams for bariatric surgery, including her mother. From his busy schedule, it is clear that Williams's reputation is stellar: he performs about 500 such operations a year, and his time is booked for appointments six months in advance. He says his program receives up to 100 calls a day from interested people. Nor is HUP the only hospital in Penn's Health System where bariatric surgery is done. Two surgeons there, Matt L. Kirkland, M.D., and Alan L. Schuricht, M.D., perform about 500 cases a year.

For Gabrielle Niemiec and her husband, Joseph, the one-year anniversary of her surgery came upon them before they realized it, but that doesn't bother them. As she puts it, "Every day since has been a celebration." ■

— Jon Caroulis

Bittersweet

By Chris Feudtner, M.D. '95, Ph.D., M.P.H. From *Bittersweet: Diabetes, Insulin, and the Transformation of Illness*, by Chris Feudtner, M.D.
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The prognosis for people with diabetes was forever rewritten in the summer of 1921 and the year that followed with the discovery and initial development of insulin by Frederick G. Banting, Charles H. Best, James B. Collip, John J. R. Macleod, and other researchers in Toronto. By the autumn of 1922, insulin was being made commercially. Among the initial medical reports on insulin, perhaps most compelling was Ralph H. Major's introduction to the readers of the *Journal of the American Medical Association* regarding the drug's miraculous effects, communicated with two contrasting photographs: "The boy shown in Figure 1 is an example of severe juvenile diabetes. At the time the picture was taken, Dec. 7, 1922, he had had diabetes for two years, and it had been impossible to render [his urine sugar-free] except on a diet of 5 per cent. vegetables [such as lettuce, cucumbers, water cress, broccoli, and the like], with days of complete starvation. His weight at this time was 15 pounds."

Not quite three months after the first picture was taken, the unnamed child was photographed again on 26 February 1923. He had doubled his weight to 30 pounds and was consuming a diet of nearly 1,500 calories a day.

The two portraits are stunning. The boy's gain in weight alone was sufficient to impress even the most skeptical readers. Beyond this obvious improvement, other aspects of the photographs further intensified their impact. Before insulin, emaciated and naked, the youngster clung to his mother, supported by her stout arm, his entire body on display; his closed eyes and fixed grimace, set alongside his mother's stoic gaze, heighten the sense of his suffering. After insulin, he was photographed sitting by himself, no longer dependent, peering at the camera, clothed in a sailor suit. Not only had his facial features filled out, the enlarged scale of the photograph made him look nearly twice as large. The message was clear and incontrovertible: insulin worked wonders.

Major was not alone in employing this powerful visual rhetoric. Several other physicians, whose pioneering accounts of treating diabetics with insulin appeared in the *Journal of Metabolic Research* during the late spring of 1923, also resorted to dramatic before-and-after pictures. . . . These photographs and verbal portraits of miraculous therapeutic success present a modern yet mythic account of diabetes history, accentuating the potency of insulin as a heroic wonder drug to rescue patients, vanquish disease, banish suffering, and finally secure an implied but unexamined "happily-ever-after" ending.

Mythical storytelling elements such as these permeate much of our current appreciation of other medical technologies. When pharmaceutical companies launch promotional advertising campaigns showing pictures of bald yet smiling cancer survivors; or when proponents of the human genome project speculate how gene therapy will eliminate certain inborn diseases; or when former trauma patients testify how they were saved by the latest radiographic machines that swiftly provide remarkably precise body images; or even when the biotechnology industry shows film clips on television of children spared from blindness due to rice supplemented with vitamin A, these examples of scientific achievement

are all presented in the mythical aura of an idealistic quest for a better world. As they tap into our fears and desires, these stories about medicine reflect a broad technology ethos in our culture, the American propensity to embrace more technology as the best solution to our problems.

Perhaps no story of medical progress, though, has been more influenced by this technology ethos than the history of diabetes. Stories of insulin have served various needs while reinforcing deeply held beliefs of 20th-century Americans. A parable of salvation, the tale of diabetic deliverance has spoken to the imagination of doctors and laypeople alike, serving as a potent and often-cited symbol of scientific progress and the prospect of human mastery over disease. One of the most impressive stories about modern medical miracles, the tale of insulin saving diabetics has legitimated the prestige and power that Americans have invested in scientific medicine and its technical wizardry.

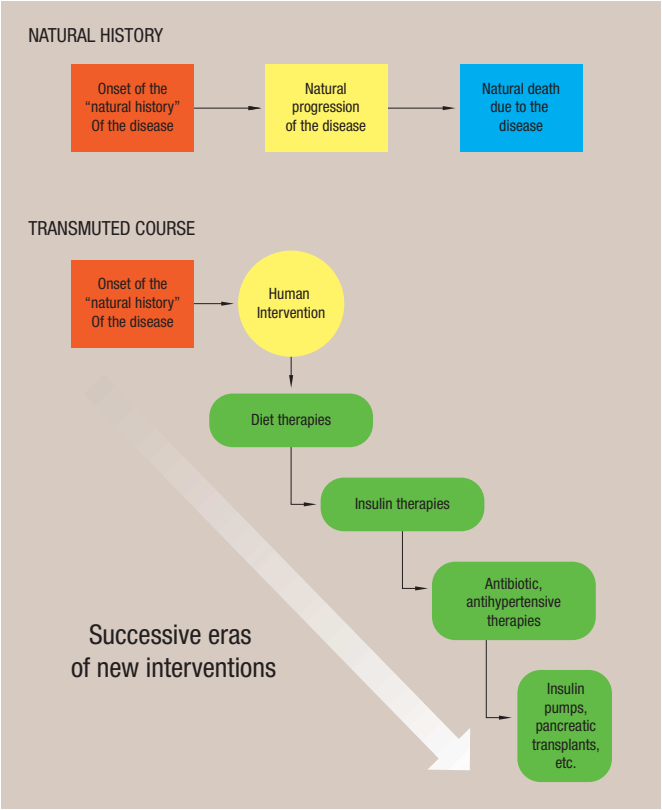
The mythically framed accounts of diabetes history, however, conceal more than they reveal. Focusing on a wonder drug, they distract from the human realities of living with diabetes – all the people involved in the mundane yet challenging realities of daily diabetic work and their personal struggles with illness that continued well after the discovery of insulin. Emphasizing a miraculous event, these accounts ignore the more sober legacy of this "miracle" – all the problems that remained, all the new problems created by the transmutation of diabetes into a chronic disease. Exulting in an unexamined belief in progress, they fail to grapple with the difficult task of weighing the mixed consequences of medical intervention – all the years of life added poised against all the ramifications of living with a chronic, often debilitating disease.

Simply put, we need to reappraise the happily-ever-after ending: diabetes still devastates lives. Approximately 1 million Americans currently have juvenile-onset, Type 1, diabetes mellitus, with perhaps another 10 million afflicted with the adult-onset, Type 2 form of the disease. Although much of the public believes that diabetes has been cured or at least tamed, the health statistics present a very different picture: Diabetes today is the primary cause of new-onset blindness in adults, accounts for a third of all cases of kidney failure, leads to half of all non-traumatic limb amputations, and overall stands as the seventh leading cause of death. Diabetics live with a substantial risk of heart attack, heart failure, and stroke. Infants born to diabetic mothers are more likely to have congenital abnormalities and to die either *in utero* or shortly after birth. Even for those patients who do not develop complications, their lives are irrevocably altered by the diagnosis of diabetes, for they must monitor their diets and often either take oral medicine or inject or infuse insulin – and hope that they remain well. The "cure" of insulin has become the accomplice to a newly created disease of complications.

This contradictory legacy of insulin – of general triumph mixed with individual tragedies – challenges our views about technology and its impact on human health and hope. The most reasonable perspective seems to literally hang in the balance – the balance between acknowledging the remarkable benefits of technology and realizing the incompleteness and often ironic deleterious consequences of technological "solutions," the balance between questing for that better world and working to better the world that we have, the balance between the bitter and the sweet emotions that suffuse the modern history of diabetes. Striking this balance requires that we move beyond the ready-made but incomplete answers to our health and health-care problems offered up by the technology ethos.

In recounting the history of juvenile-onset diabetes in 20th-century America, I have sought to strike such a balanced perspective. . . . I have been more concerned, however, with the clinical realities and experiences of patients. . . . My focus has been on the changes that occurred throughout the 20th century that affected people living with diabetes, changes that extended well beyond the discovery of insulin. Other historical studies have filled in some of the detail, focusing on famous specialists in diabetes or a particular diabetes institution, such as the American Diabetes Association, or chronicling the succession of medical ideas and technical developments. These accounts are all a part of the broader story of diabetic patients, their families, and doctors – a collective history of biology and society, of therapeutics and technology, of

Chris Feudtner, M.D. '95, assistant professor of pediatrics at the University of Pennsylvania, recently published *Bittersweet: Diabetes, Insulin, and the Transformation of Illness* (University of North Carolina Press). Feudtner's book examines the remarkable therapeutic triumphs of insulin – as well as what he calls "the more sober legacy of this 'miracle.'" Although he describes the benefits of insulin, Feudtner also shows how advances in medical technology have often brought unforeseen changes, such as the transformation of diabetes from an acute disease to a chronic disease. "Simply put," he writes, "we need to reappraise the happily-ever-after ending: diabetes still devastates lives."



Courtesy of *Bittersweet*

medical culture and private experience, of scientific knowledge and human belief. I sought to synthesize these diverse elements, joining different yet complementary views and experiences of diabetes into one unified and coherent perspective: the human consequences of transformed disease.

By the time that insulin was discovered in 1921, Dr. Elliott Joslin had already been caring for diabetics – several thousands of them – for more than twenty years. When insulin arrived, Joslin stood at midcareer, having already made his mark as America's foremost expert on diabetic care. During much of the 1910s, this meticulous clinician had championed the use of stringent dietary regimens to eke out additional months and even years of life for young diabetics. Ever so gradually, the life expectancy of juvenile patients under his care had improved. . . .

Nevertheless, insulin arrived like a thunderbolt. Joslin quickly perceived that his world had changed – changed utterly. Within a year after first administering insulin in 1922, Joslin declared, "A new race of diabetics has come upon the scene." Prior to the introduction of insulin, his patients had lived with the disease, on average, about three and a half years after the diagnosis; by 1923, the average duration of illness had already been extended another two years by pancreatic extract. . . .

As Joslin himself realized, this prolongation of diabetic life was one aspect of a larger phenomenon, namely the aging of Americans that has reshaped the U.S. population during the 20th century. "In North America," he noted presciently in 1924, "we are to dwell more and more with the old. A generation ago the average expectation of life was 38 years and now it is 57." This aging, he predicted, would cause much social tension, for "although we as a nation want to live to be old, we do not want to be old too soon."

Joslin turned out to be a true prophet regarding these matters. The life expectancy of Americans has risen substantially from 1900, and, consequently, older Americans have composed an increasing percentage of the U.S. population. As Americans have survived illnesses that once would have killed them, the pattern of causes of death has changed dramatically. Instead of succumbing to the major killers of bygone eras – diarrhea, respiratory infections, tuberculosis – Americans increasingly die from chronic diseases such as heart failure, cancer, emphysema, dementia – and diabetes.

This transition, in which the leading causes of death shifted from acute infectious disease to more chronic ailments, is what we might think of as the *diminishment* or *substitution* of disease. In these reciprocal processes, the decline of one disease enables people to live longer, allowing another disease to rise to prominence, substituting for the diminished disease. Given that diabetes is more prevalent among older individuals, it was this model that Joslin evoked when he wrote that "diabetes ought, therefore, to be and is many times as frequent in the community today as heretofore, and with increasing longevity is destined to be more common." Simi-

A Pediatrician and M

In 2002, seven years after finishing the M.D./Ph.D. program at Penn, Chris Feudtner left the pediatric faculty at the University of Washington and returned to Penn as an assistant professor in the Department of Pediatrics. He also holds an appointment at The Children's Hospital of Philadelphia. There, he serves as director of research and attending physician for the Pediatric Advanced Care Team, which provides decision-support, palliative, end-of-life, and bereavement-care services. In addition, he is an attending physician for the general pediatric and the "pediatric complex" services.

Feudtner's research has been varied. When Feudtner was a medical and dissertation student, Charles Rosenberg, Ph.D., author of influential studies like *The Cholera Years* and *The Care of Strangers: The Rise of the American Hospital System*, was at Penn as a professor of history and sociology of science. He supervised Feudtner's doctoral dissertation. Feudtner's recent book, *Bittersweet: Diabetes, Insulin, and the Transformation of Illness* (University of North Carolina Press), comes out of his longstanding interest in the history of medicine.

Feudtner has also published work in the field of medical ethics, on

lar arguments have been made about the rise of other chronic diseases.

The processes of diminishment and substitution are only two of the patterns by which diseases afflicting Americans have changed. Demonstrating a third pattern, diseases such as cholera and influenza have also *relocated* from one part of the globe to another, altering world history in their wake. A fourth pattern occurs when diseases *emerge de novo*. Lung cancer, for instance, was exceedingly rare until after the First World War, when many former soldiers had begun their habits of smoking tobacco while serving overseas; similarly, the epidemic of AIDS, as well as outbreaks of other new infectious ailments, represents disease emergence. A fifth pattern reflects the *reemergence* of diseases, such as tuberculosis, gonorrhea, syphilis, or measles through drug resistance and lapses of social policy.

In the background, another process of disease change has gradually reshaped many of the illnesses that Americans encounter. The increasingly common process of disease *transmutation* has altered already existing diseases into essentially new entities – transmuted diseases. These transmuted diseases have been changed by medical therapeutics so that they progress along a diverted course of either recovery or complications. This diversion suggests that the old notion of natural history does not accurately represent the realities of modern-day diabetes or of most other treated diseases; we now rarely allow a serious disease to follow its natural history. In each instance, medical therapy alters the fundamental biology of the disease, thereby warding off certain "natural" problems while allowing new problems to surface. The patient experiences an illness with a transmuted course.

The difficulties that diabetic patients have encountered with their transmuted disease do not stem, for the most part, from medical, "man-made" errors; rather, transmuted diabetes presents novel challenges because medical therapy has enabled diabetics to live longer with their disease than the ailment's natural history once permitted. Indeed, this biological change from natural history to a transmuted course has been, overall, a godsend to patients. Unlike other diseases that have been turned from bad to worse by medical therapy – such as the tragedies wrought by thalidomide, diethylstilbestrol (DES), the artificial heart, or the program to immunize against swine flu – diabetes is, by almost any criteria, an "improved" disease compared to what it was one hundred years ago. And diabetics are certainly better off now than in the past. Nevertheless, transmuted diabetes is not an immaculate good – for within this new disease lurks the possibility of debilitating complications.

Diabetics are not alone in confronting transmuted disease. From premature infants cared for in neonatal intensive care nurseries, to children who have been cured of cancer, to adults on dialysis for end-stage renal failure, many patients now live with the ironic consequences of "successful" therapeutic interventions that have transmuted their underlying conditions from an acute to a chronic ailment. In each of these cases, new therapies divert the disease away from its so-called natural history, as drugs and other medical interventions interrupt the pathological sequence of events so that the disease is shunted along a new and uncharted course.

For the past 90 years, this process of transmutation has reshaped the experience of being diabetic in a manner sometimes dramatically obvious, at other times elusively subtle. Examining how diabetics fared during the first ten years of their illness drives this point home. From the turn of the century through 1919, half of newly diagnosed diabetics were dead within two years, and fewer than 5 percent were still alive after ten years. Compare these dismal figures with the group of diabetics diagnosed between 1939 and 1959; in this later group, most survived their first ten years of living with diabetes.

Another way to gauge how much diabetes has changed during the 20th century is to study the shifting pattern of lethal diabetic complications. In the early years, almost all diabetic patients who died did so in ketoacidotic coma; by 1950, fewer than one in ten fatal cases died comatose. But in place of coma, other menaces had emerged, such as cardiac arrest or nephritis and renal failure. Infections, which had been causing more death during the 1920s and 1930s, receded as sulfa antimicrobials became available in the late 1930s and penicillin arrived in the early 1940s. Not only was the length of diabetic life transformed but also the kind of life – and ultimately, the cause and kind of death. ■

edical Historian

such topics as the ethical development of medical students and, more recently, on the interface of ethics and public health policy regarding immunizations.

Feudtner's main research efforts, however, have been to investigate the epidemiology and health-care experience of children with complex chronic conditions, with a particular emphasis on palliative and end-of-life care. His current work has examined trends over time in the demographic and diagnostic features of children who have died, the location where they died (home, hospital, or elsewhere), the distance from home for those children who died in the hospital, and the hospital services they received prior to death. Feudtner was recently funded by the National Institute of Nursing Research to develop a system for predicting the pediatric risk of death after hospitalization; if successful, the system would allow supportive care services to be targeted to those with the greatest likelihood of need. He is also beginning a series of studies designed to deepen the understanding of how parents of chronically ill children make difficult decisions. The goal is to develop means to assist them in this demanding task while marshalling hope. ■

FROM FORESIGHT TO OVERSIGHT:

Ted Friedmann and the Rise of Gene Therapy

By Debbie Goldberg

For more than 30 years, Theodore Friedmann, M.D. '60, has been a strong presence in gene therapy, as one of the writers of a "founding statement" in the field, as a researcher, and as chair of the NIH's Recombinant DNA Advisory Committee.

Back in 1972, when the field of genetics was still in its infancy, Theodore C. Friedmann, M.D.'60, and Richard Roblin, Ph.D., two young researchers, wrote a remarkably prescient paper that suggested that genetic disorders could be corrected by using viruses to carry new genes into a person's body – and that the new genes would override the defective genes and thus cure the genetic disease.

At the time, the scientific technology didn't even exist to accomplish what Friedmann and Roblin proposed. The paper, in fact, was titled "Gene Therapy for Human Genetic Disease?" The question mark was no accident. Yet, more than 30 years ago, Friedmann and Roblin had envisioned and clearly identified not only many of the clinical stumbling blocks in what we now know as the gene therapy field, but also many of the thorny ethical issues such genetic treatments would raise along the way to reaching maturity as a clinical option.

That landmark paper, published in *Science* magazine, has been referred

Photographs by Kevin Walsh

to as "a founding statement of the field of human gene therapy" by Alan N. Schechter, M.D., chief of the Laboratory of Chemical Biology at the National Institute for Diabetes, Digestive, and Kidney Diseases. Yet, at the time, Friedmann recalls, the paper "just came and appeared and went away."

Since then, Friedmann, now a professor of pediatrics, holder of the Muriel Jeannette Whitehill Chair in Biomedical Ethics, and director of the human gene therapy program at the University of California at San Diego, has continued to be one of the leading players in human gene therapy. He has made his mark both in the laboratory – searching for better ways to deliver therapeutic genes to humans safely and efficiently – and through his involvement in numerous bodies that oversee clinical research in the field and help set the ethical boundaries for human gene therapy.

Recently, Friedmann completed his term as chair of the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health, which is responsible for reviewing all NIH-funded human gene therapy trials to ensure the safety and efficacy of these experiments. The 21-member committee, made up of scientists, clinical investigators, ethicists, and public policy experts, not only evaluates protocols for clinical trials involving the transfer of genetically modified tissue into humans, but also considers safety standards, potential hazards, and methods for monitoring and minimizing risks associated with gene therapy research. Another Federal agency, the Food and Drug Administration is responsible for approving clinical trials.

Yet, although the RAC has reviewed close to 600 gene therapy trials since human studies commenced around 1990, Friedmann acknowledges that none has yet worked convincingly. Nevertheless, he believes U.S. researchers are tantalizingly close to achieving some success in the field. Medical breakthroughs tend to come slowly and build on years of basic research, and the field of gene therapy has been no different.

At the 6th Annual Meeting of the American Society of Gene Therapy in Washington, D.C., last spring, Friedmann spoke of the course of events after Roblin's and his early paper. "One of the things that held up development of the field for the next 30 years is that the science wasn't ready," he said. It would not be long, however, before the development of recombinant DNA technology – which allowed researchers to isolate and recombine pieces of DNA – would enable the field of gene therapy to start moving ahead.

Now, fast forward to 2003. Despite those descriptions three decades ago of the potential for gene therapy, it is only very recently that scientists have achieved the first clinical successes using this type of therapeutic treatment. A group of French-based researchers have been able to cure 10 children of the devastating X-linked SCID (severe combined immune deficiency, located on the X chromosome) disease – a remarkable feat because the disease is usually fatal. But even this tremendous advance has come at a cost – two of the children who were cured of the genetic disease have since developed leukemia. The problem, it turns out, is that the virus used to deliver the new genes to the young children with X-linked SCID (more commonly known as the "bubble boy syndrome") has a tendency to "sit" near and turn on the expression of a cancer-causing oncogene.

Friedmann hails the French study as the "first clinical success in gene therapy." But at the same time, he cautions that it underscores the point that "the technology is very, very risky, experimental, and dangerous, and should be used very carefully only for dire diseases." Nonetheless, Friedmann is thrilled that the French study "removes any doubt that the principle is real – that we can cure disease by introducing new genes."

Gene

Theodore Friedmann goes over work with Dr. Shaochun Song, a postgraduate research associate in Friedmann's group.

The X-SCID study also is important because it allows researchers to do a cost-benefit analysis of the results: the very real benefit of curing the debilitating and often fatal X-SCID disease versus the chances of contracting another, albeit more treatable, disease. "The patient has been cured of the genetic disease, yet unequivocally harmed by the gene transfer," Friedmann explains. "We can accept the risk as long as the benefits are much greater."

Probing the ethical depths of such dilemmas is one of Friedmann's strengths as a scientist. He is chair of the ethics committee of the American Society of Gene Therapy, a group of almost 3,000 scientists and researchers committed to developing new gene therapies. And, although Friedmann remains ultimately optimistic about the prospects for gene therapy to cure disease, he acknowledges that, in the end, "nothing we do to interfere with nature doesn't come at some cost."

"That's Ted's strength, his vision of all of the aspects of clinical gene transfer," says Claudia Mickelson, Ph.D., deputy director of environmental health and safety at Massachusetts Institute of Technology, who chaired the RAC for five years just prior to Friedmann's term. "He is one of the early investigators in the field of gene therapy and in the development of the field, and he has proved to be a benchmark for investigators in terms of melding the science and technology expertise with the sensitivity to research responsibilities and human subject protection." He prizes openness as well, she continues, noting Friedmann's "strong commitment to public access to the information on clinical trials."

In an article in *Science* (24 March 2000), Friedmann delicately described what he called "an important difference" between the RAC and the Food and Drug Administration: "the RAC reviews of proposals and adverse-event reporting are public and open, whereas FDA is required by statute to carry out these functions privately and without provision for public disclosure. In a field as immature and filled with public interest and concern as gene therapy, more, rather than less, public review seems desirable."

Therapy and the Biotechnology Industry

One area that we did not fully appreciate in 1972 was the extremely powerful role that the commercial world would come to have in the development of the gene therapy technology. The modern biotechnology industry, which existed only in the most rudimentary form in 1972, is now playing as powerful a part in the development of new gene therapy techniques as is the academic world. This development might have been anticipated from a realization that gene therapy is an area of medicine that, more than many others, requires not only novel concepts and demonstration of proofs of principle, but also a great deal of expensive implementation, scale-up, and the manufacture of clinical-grade gene transfer reagents. Neither academia nor the commercial world alone is able, by virtue of its ethos, strength, or technical capabilities, to carry out all of these activities effectively. In many cases, some aspects of gene therapy that cannot and probably should not be carried out in academia – e.g., large-scale development – are rapidly being moved, often by academic centers themselves, into the commercial arena. Conversely, although it is disingenuous to claim that novelty and innovation are exclusive activities of academia, it is true that most adventuresome, high-risk, and high-payoff studies that depart from conventional therapies are still more likely to arise in the somewhat less fettered world of academia and research institutes than of industry. In the general area of biotechnology and particularly of gene therapy, eventual broad-scale clinical success will require a heavy collaboration between these two disparate but mutually dependent and more and more interactive worlds. ■

— from "The Origins, Evolution, and Directions of Human Gene Therapy," by Theodore Friedmann, in *The Development of Human Gene Therapy* (Cold Spring Harbor Laboratory Press, 1999)

Despite his many years living near the stunning beaches of La Jolla, California, Friedmann, soft-spoken and professorial-looking at 68 years, is a Philly kid at heart. Raised in the Oxford Circle area of the city, Friedmann graduated from Olney High School, the University of Pennsylvania (1956), and, finally, Penn's medical school. As a teenager, he spent hours each day practicing the piano and had dreams of attending the city's renowned Curtis Institute of Music. But he soon discovered there weren't enough hours in the day for everything he wanted to do, and his interest in science and medicine won out.

It was at Penn, in his final year of medical school, that Friedmann's career-long interest in pediatrics, disease, and genetics came together when he had the opportunity to observe the work of Dr. Giulio Barbero. Then a professor of pediatrics, Barbero was caring for children suffering from cystic fibrosis. Friedmann fondly refers to him as one of his first "medical idols."

Friedmann's career, however, was sidetracked when the Berlin Wall went up and he was drafted into the U.S. Air Force midway through his pediatric residency at Boston Children's Hospital. He ended up working in a pediatric clinic on a military base near Cambridge, England. After his discharge, Friedmann was able to stay on at Cambridge University on a fellowship from Harvard University and got to work alongside the world-class genetic researchers there, including Frederick Sanger, who had by then won his first Nobel Prize in chemistry for his work on the structure of proteins. The stay in Cambridge was fortuitous for another reason: it was at a party there that Friedmann met a Swedish woman, Ingrid, who was an occupational

therapist at a nearby hospital. They fell in love and married – and today have two grown sons.

During a second postdoctoral fellowship at the National Institutes of Health, in 1966-67, Friedmann started his long-standing work on Lesch-Nyhan disease, a debilitating kind of pediatric Parkinson's disease (similarly characterized by a dopamine deficit in the brain) in which the children exhibit aggressive, self-mutilating behavior. At that time, Friedmann was working with J. Edwin Seegmiller, M.D., who had just discovered that a deficiency of the enzyme HPRT causes Lesch-Nyhan disease, and Scottish researcher John Subak-Sharpe. They tried an experiment involving skin cells from some of the Lesch-Nyhan children, culturing the cells in the lab and then flooding the cells with DNA from normal cells. When they viewed the results using radioactive detection methods, they found that perhaps one in a million of the defective cells appeared to express HPRT, demonstrating that the cell had taken up the foreign gene it had lacked. "We took that as the first evidence that an enzyme deficiency could be corrected as least temporarily by the addition of foreign DNA," Friedmann says of this early attempt at gene manipulation. "It was obvious the system was very ineffective, but it was kind of a *eureka!* moment for me."

A few years later, Friedmann was working at The Salk Institute in La Jolla, investigating ways to modify tumor viruses to function as gene transfer agents. It was there that Friedmann and Roblin put together their paper – which started out as an in-house think piece – laying out a blueprint for the field of gene therapy. The paper's basic elements hold up surprisingly well today. Still, despite three decades of research, there are still two major challenges holding back the field – target and delivery of the corrective genes. In Friedmann's laboratory at U.C. San Diego, where he was a founding member of the medical school faculty, he and his colleagues are focusing on just these core problems: designing better vectors (delivery vehicles) and better ways to deliver therapeutic genes more efficiently and more safely into the human body.

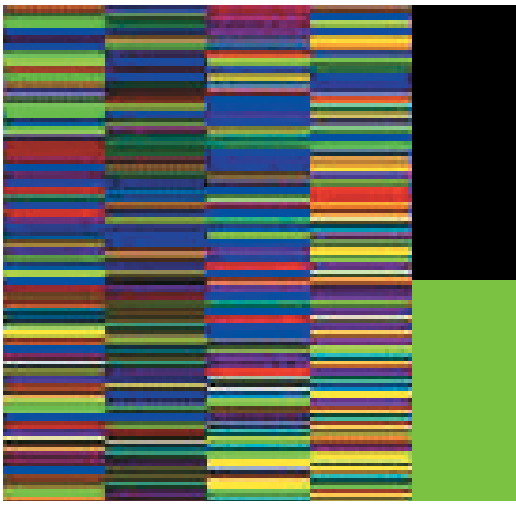
As Friedmann explains, the challenge is to direct the payload – in this case the new genes – to the right spot in the body while ensuring that the delivery system – now most typically a virus – does not turn on the expression of an unwanted gene, such as an oncogene, as happened in the X-SCID study.

With chemotherapy for cancer patients, for example, the trick is to get the right gene to the right spot, while doing the least amount of residual damage to otherwise healthy genes in the body. "The other challenge," he adds, "is to figure out what about these viruses is dangerous."

From the start, it was clear that viruses would be the natural choice to try to deliver genes to humans. "We knew viruses would be useful, because that's what they do for a living – carry genes into cells." Friedmann likens the virus to a Trojan horse that stealthily delivers its contents into human cells. Today, viruses remain the most commonly used vectors for transferring genes into humans. Still, researchers have continued to work on other possible methods – for example, delivering the genes on their own, coated in a fatty residue.

In his laboratory, Friedmann is looking into the basic mechanisms by which viruses choose which cells to infect and how they attach to and enter such cells. The goal is to be able to instruct the virus on exactly which cells to infect, while keeping them away from healthy cells they could possibly harm. Friedmann and his colleagues are working on ways to change the molecules on the outside surface of the virus. The goal is to wipe out its ability to interact with its usual cellular receptors and replace it with the ability to interact with the specific receptors the researchers want to target.

In another study, Friedmann is exploring the ways in which viruses are assembled in the cell to try to build a virus particle entirely from scratch. The goal, he explains, is to try to take advantage of the most

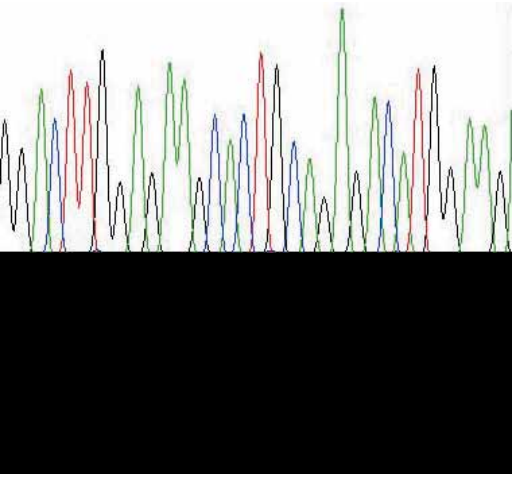


desirable aspects of viruses (they are very efficient) while eliminating their undesirable features (they can be harsh, toxic, and promiscuous). The next step would be to add the positive traits of non-viral gene transfer agents to form a synthetic, or semi-synthetic, kind of vector that would possess the best possible features of all these agents.

Melding his overlapping interests in both the science and ethics of gene therapy, Friedmann also is working on a new study that will consider some of the issues raised by the potential use of gene therapy for enhancing athletic performance. In this study, Friedmann and his colleagues will introduce a new growth-inducing gene into muscle, which they hope will enable them not only to understand how such an agent acts in the body, but also will provide some valuable information that will help set a framework to detect the use of drugs to boost athletic performance.

Although gene therapy does not yet have a proven track record, its potential use by athletes already is a concern, one taken very seriously by the International Olympic Committee and the World Anti-Doping Agency. (Friedmann is a member of the latter's health, medicine, and research committee.)

In fact, Penn researchers H. Lee Sweeney, Ph.D., chair of the Department of Physiology, and physiologist Elisabeth Barton, Ph.D., already have created "super" mice by injecting them with muscle-enhancing IGF-I (insulin-like growth factor I),



using an adeno-associated virus as a vector. (See pp. 8-15.) With the genes enhanced by IGF-I, young mice achieved at least a 15 percent increase in muscle size and strength, and older mice were able to maintain their muscle mass. This is a significant achievement considering that humans lose about one-third of their muscle mass as they age. The process eventually could help people suffering from muscle disorders and weakness – but it could also be used by athletes to improve performance.

Already, says Barton, now assistant professor of anatomy and cell biology in Penn's School of Dental Medicine, it is believed some athletes are injecting IGF-I protein into their muscles, which offers a short-term gain. But the potential ability to genetically introduce IGF-I into muscle – and have it reproduce there indefinitely – would likely be even more appealing. It also would be difficult to detect without doing a muscle biopsy. "It's always a concern," Barton acknowledges. "Anything that helps in muscular disease is likely to help the athletic community as well. But we can't stop doing this because someone is going to run a race faster or throw a javelin farther."

Friedmann's concerns are both for the safety of athletes and the spirit of sportsmanship. In addition, as with the use of performance-enhancing drugs such as steroids, Friedmann says there would be an ethical price to pay for using gene therapy to boost athletic performance. "What's the difference between sport and biotechnology if one were to modify performance?"

The next step would be to use gene therapy for enhancement in general. "Once we know how to move genes around to cure really terrible diseases," says Friedmann, "presumably we will use the technology for less terrible diseases and then non-disease traits."

Although it would be easy to decry all non-medical uses of gene therapy, Friedmann understands the nuances of some of the thorny issues. "Your idea of a disease may not be my idea of a disease," he says, turning his head to hear better. (He explains that, years ago, he sneezed and blew out the round window in his left ear, leaving him partially deaf.) "There may be enhancement of some traits, not disease traits, that we want to manipulate, such as intelligence or cognition, which are genetic to some extent." In the case of patients with Alzheimer's disease, for instance, Friedmann raises the question of whether trying to genetically restore a patient's memory functions might be considered a medical treatment, rather than an enhancement. Or how about a memory injection for an actor trying to remember all those lines? Would that be a justifiable use of gene therapy?

His concerns notwithstanding, when it comes to gene therapy's potential for enhancing human traits, Friedmann acknowledges that ultimately "some use of this sort is inevitable." After all, he points out, "We do cosmetic surgery, take Viagra, and take psychopharmacological drugs to reduce tension and make us feel happier."

In some ways, Ted Friedmann is a man of contradictions. Over the years, he has been one of gene therapy's most ardent supporters, working in the laboratory and serving on scientific committees and government-appointed commissions to further the development of the field. "Medicine needs this technology," he says. "It's not just a choice."

But Friedmann is also one of the field's toughest critics, which is why his voice is almost unanimously respected as the voice of reason. He has urged caution many times over the years – caution against overly optimistic hopes for a quick clinical answer; caution against the premature use of the technology that he says at this time would cause much more harm than good; and caution against what he sees as potentially unethical uses of gene therapy technology, particularly as a tool of human enhancement – say, to build a better athlete or create a smarter, better-looking person. That kind of application, he feels, would smack of eugenics.

Indeed, Friedmann is quick to decry what he calls the hype that surrounded some of the earlier experiments that prematurely raised the public's hope for an easy cure and created a media backlash against the field. Another major setback came when Jesse Gelsinger, an 18-year-old patient with ornithine transcarbamylase deficiency, died in 1999 as a result of his participation in a clinical trial at the University of Pennsylvania Medical Center. Gelsinger was given what turned out to be a lethal dose of adenovirus vector. His death, thought to be the only human casualty resulting from a clinical gene therapy trial, was a crisis for Penn's gene therapy program, but also, in Friedmann's words, "a real body blow to the field." The Penn study was later found by the Food and Drug Administration to have numerous flaws. Despite this setback, Friedmann published an article in *Science* in 2000 in which he argued that human experimental studies by their very nature involve risks and that adverse results do not invalidate the rationale of gene therapy. In the case of a death or other serious adverse event, he wrote, "It is vital to understand the reasons for unexpected results or clinical failures to allow the development of corrected procedures and improved experimental methods."

It is this ability to look both thoughtfully and critically at the field he helped create that has won Friedmann many admirers over the years. "Ted's a very thoughtful person. He considers all sides of an issue – that's one of the reasons he's so highly respected," says Stanley N.

Cohen, M.D. '60, a classmate and friend. A geneticist at Stanford University, Cohen developed the recombinant DNA technology that is so vital to the gene therapy field. Even back in medical school, Cohen says, "Ted was viewed as a quiet thinker – he spoke up when he had something to say, and it was usually important, so people listened."

Richard Roblin, now scientific director of the President's Council on Bioethics in Washington, D.C., which has considered such controversial issues as cloning and stem cell research, believes his and Friedmann's paper has held up well over the years. In particular, he points to the paper's admonitions to proceed cautiously with human experiments, and he lauds Friedmann's role in the development of the field. "He's been a major contributor, both on the experimental side and on the ethical side," says Roblin. "He's written books on the history of gene therapy, served on the RAC, and his lab at U.C.S.D. has continued to do experimental work directed toward making gene therapy a reality."

In addition to chairing the Recombinant DNA Advisory Committee, Friedmann was a member of the Committee on Germline Genetic Modification of the American Association for the Advancement of Science. The committee issued a report in 2000 that concluded that genetic alterations aimed at improving future generations – for instance, removing a gene from the family tree – cannot be attempted safely at this time.

Yet despite all the caveats and warnings and questions that Friedmann has raised regarding the scientific, safety, and ethical issues in the field of gene therapy, it is clear that he believes wholeheartedly in its potential. As he put it in the first chapter of *The Development of Human Gene Therapy*, "Medicine is on the brink of a new era – that of molecular genetic medicine. As in the case of previous conceptual and technical revolutions, we are witnessing the early stages of a quantum change in the way in which we understand and confront human disease." The conceptual part of the revolution, he continued, "is essentially over" and the remainder of the revolution "now lies in the hard work of implementation." Edited by Friedmann and published by Cold Spring Harbor Laboratory Press, the 729-page book was called "a benchmark in the field for 1999" by *Nature Medicine*. *Science* praised it for highlighting "the significant recent advances in the field" while illuminating "the important hurdles that remain to be overcome."

Today, Friedmann remains convinced that gene therapy will be able to provide good treatment options for many diseases, ranging from cancer to arteriosclerosis and diabetes, as well as for the genetic diseases that affect far fewer people. "I don't think there's too much of a limit," he says, "but the application for many of these diseases is going to be difficult and time-consuming."

And, at 68 years, Friedmann is conscious of how long the clock has been ticking since he first raised the question of treating diseases through gene manipulation. "I thought it would move more quickly," he acknowledges. "The thing I most dearly love to see is for it to move quickly enough for me to still have a clinical role." ■

Principles of Human Gene Therapy Studies

In March 2000, Theodore Friedmann published an article in *Science* in which he articulated and commented on seven principles that, in his words, "constitute the foundation of clinical research in gene therapy." The article appeared at a time when, as Friedmann put it, "the human gene therapy community finds itself struggling with technical and policy problems arising from several recently publicized adverse events in human gene therapy studies." These included the tragic death of Jesse Gelsinger. According to Friedmann, the principles are:

- Human Experimentation Requires Careful Patient Selection
- Human Experimentation Involves Risks
- Adverse Results Do Not Invalidate the Rationale of Gene Therapy
- Informed Consent Is Crucial to Patient Protection
- Dealing with Financial Conflict of Interest ("At minimum, involved investigators should disclose direct commercial ties in the informed consent process. Those investigators with direct financial interest in the study outcome should recuse themselves from patient selection, the informed consent process, and study directions.")
- Improvements Are Needed in Review and Regulation
- Gene Therapy Trials Require Improved Monitoring ■

— from "Principles for Human Gene Therapy Studies," by Theodore Friedmann, in *Science*, Vol. 287, No. 5461 (24 March 2000), pp. 2163-2165

Fiery Folk Art for a Good Cause

Where's the fire?

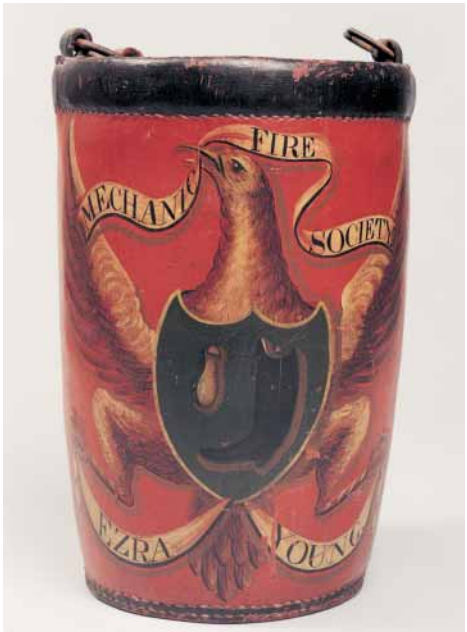
This year, it was at the 43rd annual Philadelphia Antiques Show. Each year, the show features a special loan exhibition, and for 2004 the theme was "Folk Art on Fire," capturing the colorful heritage of America's early firemen. The 18th- and 19th-century artifacts on loan from private collections included weather vanes, paintings, portraits, presentation pieces, panels from fire engines – as well as parade fire hats and leather fire buckets embellished with painted scenes and symbols.

The treatment of the theme varies. For example, a bucket from the City Fire Society (1822) depicts several city buildings aflame. Yet the parade hat celebrating the Northern Liberty Hose Co. shows a calm allegorical figure in Grecian-style dress, with the American flag draped loosely around herself; no fires are visible.

The theme of the loan exhibition was especially pertinent because Philadelphia was the first American city to establish a volunteer fire department (1736) as well as the first to have a successful fire-insurance company in America (1752).

Since 1962, the Philadelphia Antiques Show has served as one of the most reliable and remarkable fund-raising events for the University of Pennsylvania Medical Center. In those 40-plus years, proceeds from the show have contributed more than $11 million to advance patient care throughout the Medical Center. This year's proceeds will go to the ultrasound section of Penn's Department of Radiology, which will use the donation to buy state-of-the-art scanners. The ultrasound section performs more than 20,000 examinations per year on patients. The new scanners will allow the health-care professionals to make critical decisions on a more timely basis.

Beginning with a preview gala on Friday, April 16, the 43rd Annual Philadelphia Antiques Show ran from April 17-20, at the 33rd Street Armory (33rd & Market). In addition to the loan exhibition, the show featured 56 of the nation's leading antiques dealers. The presenting sponsor for the 2004 show was The Glenmede Trust Company. More information about the 2004 Philadelphia Antiques Show can be found online at www.PhilaAntiques.com. ■



Mechanic Fire Society Bucket (1811), leather


Dalmation (c. 1880-1890), carved and painted

Don Roman


Pumper Model (early 19th century), painted wood and metal


Chalk Fireman (late 19th century)

Sotheby's


Trumpeting Fireman Weathervane (third quarter 19th century), molded copper

Franklin Black Hat (Franklin Hose Company, founded 1838)

Progress Notes

Compiled by Erin Hennessy

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

40's

William North Sterrett, M.D. '43, was profiled in the January 13, 2004, edition of *The New York Times* for his unique volunteer efforts. When Sterrett, former physician to Dwight and Mamie Eisenhower, retired as a family doctor in his native Central Pennsylvania in 1990, he decided to volunteer his time at the Eisenhower home and farm in Gettysburg, which he had visited so often as a physician. The staff quickly realized that it had a natural tour guide on its hands.

50's

H. Robert Davis, M.D. '53, received the Molly Pitcher Award from the Carlisle Exchange Club for his contributions to the region as a physician, veteran, community leader, land developer, elected official, businessman, and philanthropist.

William F. Ted Young, M.D. '54, G.M.E. '58, Sumter, S.C., has received the Career Achievement Award from the South Carolina Chapter of the American Academy of Pediatrics. A clinical professor at the University of South Carolina School of Medicine, he previously was honored with the school's William Weston Distinguished Service Award for a career of excellence in pediatrics. He recently retired from his general pediatric group after 44 years of active practice.

Norman N. Cohen, M.D. '56, G.M.E. '60, became president of the Pennsylvania Society of Gastroenterology in September 2003 and will serve until 2005. He has a private practice in gastroenterology and is clinical professor of medicine at Drexel University College of Medicine and chief of the GI department at Mercy Catholic Medical Center.

60's

Daniel D. Rabuzzi, M.D. '61, was presented with the Presidential Citation of the American Academy of Otolaryngology-Head and Neck Surgery during its annual meeting in September 2002, in Orlando. The citation, given to acknowledge expertise as a surgeon and educator, stated: "Through his efforts, a generation of residents has been successfully mentored." Since leaving clinical practice in 1997, Rabuzzi has been the medical director of the Harrison Outpatient Surgery Center in Syracuse, N.Y.

Pierre L. Leroy, M.D., G.M.E. '63, received the John C. Liebeskind Award from the American Academy of Pain Management for his "significant lifelong contributions on medical education and research in pain medicine."

Bennett Lorber, M.D. '68, the Thomas Durant Professor of Medicine and professor of microbiology at Temple University School of Medicine and chief of the infectious diseases division, recently received two professional honors. At the annual meeting of the Infectious Diseases Society of America in October 2003, he received the Bristol Award, the society's highest honor. He also was presented with the Clinical Practice Award of the Pennsylvania College of Internal Medicine for service to patients, the community, and the profession. Lorber notes that he also received his 10th Golden Apple Teaching Award from Temple's School of Medicine.

70's

Robert O. Bonow, M.D. '73, G.M.E. '77, served as president of the American Heart Association 2002-2003. Currently the Goldberg Distinguished Professor at Northwestern University Feinberg School of Medicine and chief of the cardiology division at Northwestern Memorial Hospital, Bonow has served on the Association's board of directors since 1999. He is also a member of the Board of Extramural Advisors of the National Heart, Lung, and Blood Institute. Among his recent honors are the 2000 Distinguished Fellowship Award of the American College of Cardiology and the 2002 Coeur d'Or Award of the American Heart Association.

Stephen C. Rubin, M.D. '76, has been named to the Franklin Payne Professorship of Gynecologic Oncology at Penn, where he is professor of obstetrics and gynecology and chief of gynecologic oncology. One of the country's leading gynecologic cancer specialists, he is an internationally recognized expert in the clinical management and experimental therapy of ovarian cancer, having published more than 250 papers and five textbooks in the field. He joined the faculty at Penn in 1993, after spending the early part of his career at Memorial Sloan-Kettering Cancer Center.

Vanessa Northington Gamble, M.D. '78, G.M.E. '87, associate professor of health policy management at the Johns Hopkins Bloomberg School of Public Health, was quoted in the 23 October 23 2003 issue of *The Philadelphia Inquirer* regarding a conflict with a patient at Abington Hospital: "The racial incident at Abington involves a patient's bigotry, but it also points out that because you are wearing a white lab coat and scrub suit and a stethoscope around your neck doesn't mean you are race-neutral or objective." Having written extensively about race, medicine, and public health, Gamble pointed out that the nation is only about 35 years removed from the days when medicine was largely segregated. Whites did not want to be treated in the same hospital as blacks, and they did not want to be treated by black doctors and nurses.

James Nestor, M.D. '78, is finishing a 10-year term as physician-in-charge at a large multispecialty Kaiser-Permanente clinic in Milpitas, Calif. The clinic cares for 70,000 patients and employs 81 providers of direct patient care, including 53 physicians. After leaving his administrative role, Nestor plans to return to practice as a full-time internist in the same clinic.

Andrea Baldeck, M.D. '79, G.M.E. '84, and her husband, William Hollis, donated a large bronze sculpture by Philadelphia artist Arlene Love to the Kimmel Center for the Performing Arts. *Eight Figures*, which sits midway along the north side of the first tier, consists of eight life-size female nudes in various poses.

80's

Michael A. Golden, M.D. '81, has been appointed chief of the division of vascular surgery at the University of Pennsylvania Medical Center-Presbyterian.

Christopher T. Born, G.M.E. '85, was one of 60 American doctors sent to Iran to provide emergency health care to survivors of a recent earthquake. Born, an orthopaedic surgeon and co-director of Temple University Hospital's orthopaedic trauma service, spent 13 days at the site of the quake that killed more than 30,000 Iranians, setting broken bones and performing surgical operations where necessary. "We saw 727 patients in four days, and did eight operations, including two cesarean sections," reports Born. "I don't know what will happen as a result of this crack in the door. Personally, I felt honored to be there."

Mehmet Oz, M.D. '86, has been elected to the board of directors of Osiris Therapeutics, which is known for its

adult stem-cell therapy treatment. Oz is currently vice chair of surgery and professor of cardiac surgery at Columbia University College of Physicians & Surgeons and director of Columbia's Cardiovascular Institute. His research interests include heart replacement surgery, minimally invasive cardiac surgery, complementary medicine, and health care policy.

William Winkenwerder Jr., M.D., G.M.E. '86, writes: "I have been serving for the past two years as the Assistant Secretary of Defense for Health Affairs, with responsibility for the Military Health System and worldwide Department of Defense health operations. It has been a very busy time with the conflicts in Iraq and Afghanistan, new immunization programs for smallpox and anthrax, the overhaul of all TRICARE private-sector health contracts, and rebuilding the health system in post-war Iraq. In addition, we have been working closely with the departments of Health and Human Services and Homeland Security to bolster civilian bio-defense capabilities and programs. The work has been challenging, sometimes exhausting, but generally rewarding."

Paul G. Curcillo II, M.D. '89, chief of surgery at the Medical College of Pennsylvania, has been appointed secretary of the Metropolitan Philadelphia Chapter of the American College of Surgeons. Curcillo's wife, **Stephanie A. King**, M.D. '83, G.M.E. '88, a gynecologic oncologist with the Kimmel Cancer Center at Thomas Jefferson University Hospital, was listed among *Philadelphia* magazine's "Top Docs 2002."

90's

Scott Silvestry, M.D. '91, has joined the division of cardiac surgery in the Department of Surgery at Thomas Jefferson Hospital. Silvestry, who is board-certified in general surgery and thoracic surgery, has also been named assistant professor of surgery in Jefferson Medical College of Thomas Jefferson University. His areas of research and clinical interest include valvular heart disease and heart failure.

After four years of internal medicine practice, **Patrick J. Curran**, M.D. '94, has decided to go back and do a cardiology fellowship, which he will be completing this year.

Deborah Julie Franklin, M.D. '96, Ph.D., was appointed assistant professor of rehabilitation medicine at Penn's School of Medicine. She has joined the physical medicine and rehabilitation section at Pennsylvania Hospital, one of the hospitals in Penn's Health System. Franklin, a former Harrison Fund Fellow in cancer rehabilitation at Pennsylvania Hospital, has a special interest is the rehabilitation of patients with cancer diagnoses. She earned her doctorate in the history and sociology of science from the University of Pennsylvania.

After finishing his urology residency this June, **Zachary V. Zuniga**, M.D. '98, will be starting a two-year fellowship in pediatric urology at Texas Children's Hospital, Baylor College of Medicine, Houston, in July.

00's

Kevin J. Chang, M.D. '00, recently transferred from Northwestern to Boston University Medical Center to attend a residency program in radiology.

Gayle Skinner, M.D. '00, is a resident in obstetrics and gynecology at King-Drew Medical Center in Los Angeles.

Soo Kim Abboud, M.D., G.M.E. '02, has joined the Department of Otorhinolaryngology at the University of Pennsylvania Medical Center – Presbyterian. She is an assistant professor of otolaryngology in Penn's School of Medicine. She is also author of *Heart Block* (Treble Heart Books, 2002), a medical thriller.

OBITUARIES

W. Harding Kneedler, M.D. '26, Raleigh, N.C.; March 21, 2002.

H. Victor Adix Jr., M.D., G.M.E. '32, Portland, Ore.; March 20, 2001.

Maurice M. Steinberg, M.D., G.M.E. '38, Omaha, Neb.; January 18, 2000.

Arthur Morton Greene, M.D., G.M.E. '40, Omaha, Neb.; April 26, 2002.

A. H. Steinberg, M.D., G.M.E. '40, Sylvania, Ohio; July 13, 2000. Steinberg practiced obstetrics and gynecology in Toledo and delivered more than 10,000 babies during his career.

Paul Theodore Strong, M.D., G.M.E. '40, Dallas, Texas; August 22, 2002.

Paul E. Vaughan, M.D. '40, Beckley, W.Va.; June 20, 2000.

Miles D. Garber, M.D. '41, Albuquerque, N.M.; January 1, 2003.

Max H. Rosenblum, M.D., G.M.E. '41, Steubenville, Ohio; July 29, 1998.

John W. Irwin, M.D. '42, Boston; May 12, 2003.

John A. Johnston Jr., M.D., G.M.E. '46, Pittsburgh; January 4, 2000.

William C. Owsley Jr., M.D. '46, G.M.E. '50, Bedford, Texas; November 26, 2001.

Arthur R. Paterson, M.D. '46, Highlands, N.C.; May 25, 2001.

R. Sidney Amritt, M.D. '49, Gwynedd, Pa.; April 4, 2003. Amritt was former chief of anesthesiology at Northeastern Hospital in Philadelphia; upon his retirement in 1988, he was honored with the Asa M. Lehman Award for outstanding service. In addition, he was on the staff at Jeanes Hospital from 1985 to 2000.

Henry Douglas Beale, M.D., G.M.E. '49, Durham, N.C.; October 16, 1998.

Louis R. Dinon, M.D. '49, Drexel Hill, Pa.; March 26, 2003.

John S. Moore, M.D., G.M.E. '49, Roswell; N.M., July 1, 1987.

Chester M. Trossman, M.D., G.M.E. '49, Palo Alto, Calif.; January 15, 2002.

Richard D. Bush, M.D. '50, Falmouth, Mass.; May 1, 2001.

George Bruce Lemmon Jr., M.D., G.M.E. '50, Springfield, Mo.; March 3, 2001.

William H. Garner Jr., M.D., G.M.E. '51, New Albany, Ind.; August 1, 2003. Garner was chief of staff and chief of surgery at Floyd Memorial Hospital. A member of several professional groups, he was also a veteran of the United States Air Force.

Matthew B. Moore, M.D., G.M.E. '51, Tulsa, Okla.; August 8, 2002.

Guido A. Vanni, M.D., G.M.E. '51, Genoa, Italy; October 20, 2001.

Louis Kadas, M.D., G.M.E. '52, Kissimmee, Fla.; March 9, 2001.

Joseph Riemer, M.D., G.M.E. '52, Norristown, Pa.; December 16, 2002.

Thomas H. Smith, M.D. '52, Brigantine, N.J.; June 21, 2002.

Richard D. Murray, M.D., G.M.E. '53, Girard, Ohio; May 20, 2002.

Jonathan A. Hammond, M.D., G.M.E. '54, New Hope, Pa.; August 20, 2001.

Miroslaw W. Hnatiuk, M.D., G.M.E. '54, Livonia, Mich.; July 31, 2001.

L. Richard Schumacher, M.D. '54, Peachtree City, Ga.; December 17, 2002.

Dale R. Snyder, M.D. '54, Fredericksburg, Va.; October 27, 2002.

John S. Cowan, M.D., G.M.E. '55, Mecosta, Mich.; February 29, 2000.

Mary Futrell Eggers, M.D., G.M.E. '55, Columbia, Mo.; November 11, 2000.

Lewis J. Ledden, M.D., G.M.E. '55, Saint Augustine, Fla.; February 20, 2003.

Dominic Lim, M.D., G.M.E. '57, Temple, Texas; September 25, 2000.

Dan Zavela, M.D., G.M.E. '58, Detroit, Mich.; November 19, 2002.

Juan F. Calzada, M.D., G.M.E. '59, Caguas, Puerto Rico; January 1998.

Melissa L. Buchan, M.D. '61, Portland, Ore.; December 20, 1998.

Charles R. Cox, M.D. '61, Folcroft, Pa.; August 25, 2002.

Robert E. Cott, M.D., G.M.E. '62, King of Prussia, Pa.; October 7, 2000.

William E. Hoy Jr., M.D., G.M.E. '63, Ashland, Ky.; January 25, 2001.

Vincent B. Pica, M.D., G.M.E. '64, Dayton, Ohio; October 18, 2001.

Earl Frederick Barrick, M.D. '66, McLean, Va.; April 15, 2003.

Joseph P. Atkins Jr., M.D. '66, Wayne, Pa., January 19, 2004. A professor of otorhinolaryngology at the University of Pennsylvania and a surgeon at Pennsylvania Hospital, he was a pioneer in the development of endoscopic sinus surgery. He joined Pennsylvania Hospital and the Penn medical faculty in 1974. At the time of his death, he was clinical professor and vice chairman of otorhinolaryngology and head and neck surgery at Pennsylvania Hospital and executive director of the Penn Center for Voice. He was awarded the American Cancer Society's Humanitarian Award, the Resident Teaching Award from the University of Pennsylvania School of Medicine, and the Jacob Ehrenzeller Award for achievement and service in medicine. His major contributions to the field of otorhinolaryngology include his pioneering development of CO2 lasers and CO2 laser bronchoscopes, and the use of endoscopic sinus surgery for the management of sinus disease.

Harvey David Silberman, M.D., G.M.E. '68; Elkins Park, Pa.; August 31, 2002.

Gordon P. Buzby Jr., M.D. '74, Bala Cynwyd, Pa.; October 31, 2003. An attending surgeon at the Hospital of the University of Pennsylvania since 1981, Buzby became director of the surgical residency Program two years ago. He was an expert on nutritional support for cancer patients. He had also served as chairman of the medical legal committee and director of the Department of Surgery's Clinical Effectiveness and Quality Improvement.

Amos Okrah, M.D. '74, Memphis; December 10, 2002.

Patricia A. Gibbons, M.D., G.M.E. '83, Uniontown, Ohio; August 7, 2002.

Kevin B. Hughes, M.D., G.M.E. '80, Glen Oak, N.Y.; June 20, 1995.

FACULTY DEATHS

Joseph P. Atkins Jr., M.D. See Class of 1966.

Gordon P. Buzby Jr., M.D. See Class of 1974.

The Good Son

Frixos C. Charalampous, M.D., grew up in a rural village on the island of Cyprus, off the coast of Greece. "My father wanted me to follow him the import/export business, to raise a family in Cyprus – to live his life," he recalls. But Charalampous had another future in mind: to become a doctor.

It was his mother, whom he calls the "great inspiration and force" of his life, who encouraged him to follow his dream . . . and who persuaded his father to let Charalampous attend medical school.

Last fall, Charalampous made a gift to the Department of Ophthalmology in her honor, donating his interest in a parcel of real estate from a property he owns in New Jersey. "Scheie Eye and the School of Medicine have the enviable reputation of being the centers of leadership in research and medical education," he says. "I wanted to do whatever I could to promote its growth."

Charalampous received his M.D. degree from the University of Athens shortly after World War II. He recalls that among the first patients he saw were resistance fighters. He moved on to Harvard University, where he completed post-graduate work. In 1953, he joined Penn's Department of Biochemistry and Biophysics and spent his entire professional career there, becoming an emeritus professor in 1988.

"You learn a lot in a lecture hall," he says. "The immediate feedback you receive from your students makes you a better teacher and it makes you strive to be the best you can be." Of his colleagues in Biochemistry and Biophysics, he says: "We were like a family, and our commitment to our work and our camaraderie made a wonderful combination. They have given me a lifetime of memories."

By giving to Penn, says Charalampous, "I am doing my part to uphold the School's position as a brilliant institution." Above all, he hopes to honor the person who made it all possible, decades ago in a tiny village an ocean away. "By enabling me to go to medical school, my mother put me on a path that led me to a satisfying, wonderful career."

Dr. Charalampous' charitable gift is just one of the creative gift opportunities that would benefit both the School of Medicine and its alumni. As you chart your financial future, the Planned Giving Office is ready to assist in developing an appropriate strategy: ***Contact Marcie Merz, Director of Planned Giving, PENN Medicine Development and Alumni Relations, 3535 Market Street, Suite 750, Philadelphia, PA 19104-3309. Phone: 215-898-9486. Email: mmerz@ben.dev.upenn.edu.***

Sally Sapega

Left to right: Metz; Beverly Ginsburg, M.B.A., executive director of the Abramson Cancer Center; Hampshire; and John H. Glick, M.D., director of the Cancer Center.

A Decade of OncoLink

Whether for professional or personal reasons, I'm sure many of you have used OncoLink, the web site of the Abramson Cancer Center of the University of Pennsylvania. Certainly, you would be far from alone. At last report, according to James Metz, M.D., OncoLink's editor in chief, "We've grown from receiving a few thousand page views a month to up to two million per month today."

OncoLink celebrated its tenth anniversary with a reception in March, and several speakers at the event praised the site for its popularity, resiliency, and reliability. Just surviving for 10 years and outlasting many of the web sites that sprang up in those heady early years of the World Wide Web is an accomplishment. Yet OncoLink has done much more than survive – it has basically established a new standard for online health web sites, as attested by awards from several organizations and links from many other reputable sites, such as that of the National Cancer Institute. And it is clear that OncoLink's popularity has much to do with its reliability. The people who access the site are confident that the information they receive during their interactions with OncoLink is state of the art. It can be so authoritative only because of the efforts and expertise of the PENN Medicine faculty, editors, nurses, administrators, designers, and computer technicians who give their time to OncoLink.

Early on in OncoLink's existence (as reported in the Winter 1996 issue of *Penn Medicine*), there was a disagreement among its creators on what material should be posted on the site. The decision was made in favor of full editorial review. As two of the early editors, Joel W. Goldwein, M.D., and Ivor Benjamin, M.D., put it in a letter to *The New England Journal of Medicine*, "We discovered that Internet publishing tests the fine line between free speech, academic freedom, and responsible dissemination of clinically relevant information." Maintaining editorial review appears to have served OncoLink – and the many people who visit it – very well.

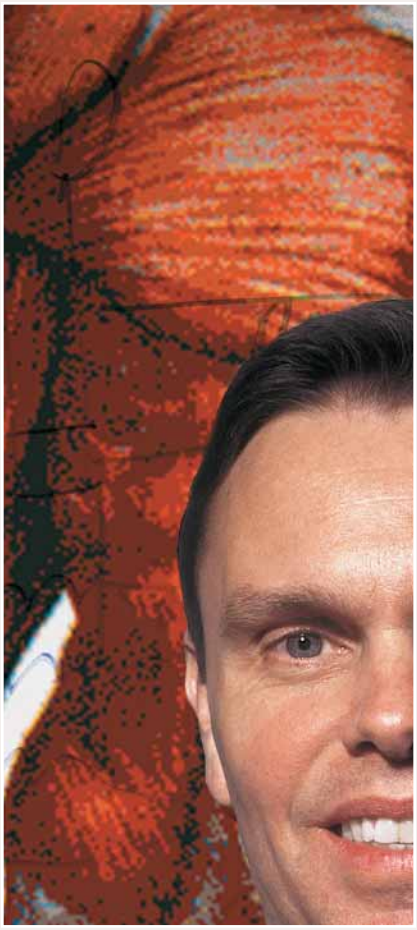
One of OncoLink's features is "Ask the Experts." According to Maggie Hampshire, R.N., the site's managing editor, many faculty members contribute to make that feature so effective. Metz, who is an assistant professor of radiology, notes that the people who write for OncoLink are active clinicians who continue to see patients; they are always considering how to integrate their clinical work into their work for OncoLink. In addition, these experts know that to be effective and helpful, they must speak in jargon-free language that patients will understand.

A new development is the OncoLink Patient Guide series, geared to readers who don't use the Internet or who are more comfortable reading a book than searching on line. The guides are compiled by OncoLink's editors, drawing from Ask the Experts and other materials, and each book will focus on a particular form of cancer. The first book published in the series is on colorectal cancer.

In the first year of OncoLink's existence, it was hailed as "Best of the Web" in the category of best professional service by those who attended the first World Wide Web Conference. A year later, OncoLink was rated in the top five percent of *all* sites – and the highest of all cancer-related home pages – by Point Survey, an independent agency. Subsequently, OncoLink was named a "Forbes Favorite" by the business magazine, praised for combining "top-quality medical information with the human side of understanding cancer." In a report in *JAMA* that was conducted by researchers at the RAND Corporation, OncoLink scored among the highest of the 25 sites reviewed.

Perhaps most important, though, are the individuals who visit the site. In this age of the informed patient and what Metz describes as "patient empowerment," they continue to appreciate that OncoLink provides the best information available. As *Pennsylvania Medicine*, the publication of the state's medical society, once put it, OncoLink's popularity "shows a tremendous hunger for specialized information on the part of patients – and, for that matter, on the part of nonspecialist physicians, nurse, and other health professionals." ■

Cover: H. Lee Sweeney, Ph.D., chair of Penn's Department of Physiology. Photograph by Addison Geary.



H. Lee Sweeney, Ph.D., chair of Penn's Department of Physiology, has spent his career learning how muscles work at a molecular and cellular level. Along the way, he has ventured into what is usually unknown territory for basic scientists – meeting with policy makers, ethicists, parents, and athletes in addition to his professional colleagues. In the wider world, he's become known for "mighty mice" that were treated to gain muscle mass and stave off many effects of aging.

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