# EINSTEIN

SPRING 2006



GLOBAL HEALTH AT EINSTEIN: THE WORLD AS CLASSROOM



DEWPOINT PROGRAM: FIELD OF DREAMS FOR WOMEN AND MINORITIES



DR. ALLEN M. SPIEGEL: A JOURNEY WELL TRAVELED







#### EINSTEINCONTENTS

SPRING 2006



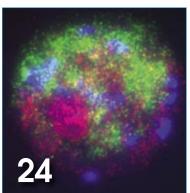
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EINSTEIN: A publication for faculty, students, alumni, friends and supporters of the Albert Einstein College of Medicine of Yeshiva University.

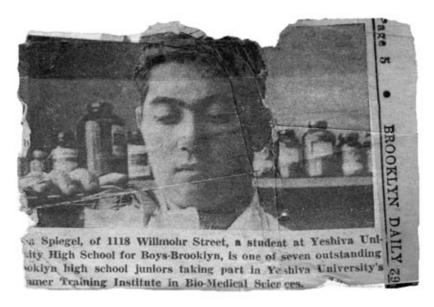
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# EINSTEIN'S NEW DEAN ALLEN M. SPIEGEL, M.D.

#### A Journey Well Traveled

t was the summer of 1962. Sixteen-year-old Allen Spiegel had just completed his junior year at Yeshiva University High School in Brooklyn and was embarking on a new adventure: participating in a National Science Foundation-supported program to encourage bright young students to pursue careers in science. Mornings were spent attending lectures at Yeshiva University in Washington Heights. Afternoons found him traveling to the University's Albert Einstein College of Medicine in the Bronx where he would work in a pathology laboratory studying the effects of barbiturates on enzymes.

The trip from Brooklyn to Manhattan to the Bronx may have been daunting for most youngsters, but Allen Spiegel had already traveled a very long distance in his young life.



Sixteen year-old Allen Spiegel in an Einstein pathology laboratory, summer, 1962. Daily News photo.

On June 1, 2006, Dr. Spiegel assumes office as The Marilyn and Stanley M. Katz Dean of the Albert Einstein College of Medicine. e was born in May, 1946, in a displaced persons camp in Landsberg, Germany, the son of Holocaust survivors. His parents had been sent to Auschwitz in 1944 and were separated during the war. His father, Julius, survived the "death march" from Auschwitz to Buchenwald and was eventually liberated by advancing American forces. His mother, Esther, who had been transferred to a forced-labor camp in Czechoslovakia, was liberated by the Russian army.

Julius and Esther each found their way back to Lodz, Poland, where they had lived in the early years of their marriage, and were reunited there. Hoping to get to America, they traveled to Germany, landing in the Landsberg DP camp. Dr. Spiegel later recalled his mother telling him that he was the first child born in the camp.

In 1949, at age three, Allen Spiegel made his first "big trip," from Bremen, Germany to Boston, from which the family would make its way to 555 West 155th Street, their first New York home, and then to 96 Wadsworth Terrace, in Washington Heights. A few years later, another "trip"—this time to a new home in Brooklyn. By the time he was 16 and ready to journey from Brooklyn to Einstein's pathology laboratory in the Bronx, Allen Spiegel was already a very seasoned traveler.

His interest in science intensified as time passed. After graduating as valedictorian of his high school class, he was accepted by Columbia University, where he enrolled as a premed student with a special interest in comparative literature. His summer work experiences while at Columbia mirrored his eclectic interests. "After freshman year," he recalls, "I was a bus boy at Kutscher's Country Club in the Catskills. The next summer, I was at the Max Planck Institute in Biophysics in Frankfurt, Germany, studying the effect of radiation on yeast cells."

Dr. Spiegel graduated from Columbia in 1967, summa cum laude, Phi Beta Kappa, and salutatorian of his class. He then entered Harvard Medical School, on a full scholarship, and earned his M.D. degree cum laude in 1971. Remaining in Boston, he completed his internal medicine training at Massachusetts General Hospital. "From the very beginning of my career," Dr. Spiegel says, "I have had an abiding interest in the science of medicine and in how that science could improve the care of patients.

#### Who knew, in 1962 when I first entered an Einstein lab, that 44 years later I would be given this exceptional opportunity? What a gift, and what a responsibility!

Fortunately, as a physician-scientistadministrator at the NIH for more than 30 years, I have been able to pursue this interest by conducting my own research, by overseeing the research of scientists within NIH, and later as an Institute Director, by helping shape programs for support of research at academic health centers across the country."

r. Spiegel began his career at the NIH in 1973 as a clinical associate in the Endocrinology Training Program of the Institute that is now named the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK). He then served as a senior investigator in NIDDK's Metabolic Disease Branch from 1977 to 1984. In 1985 he was appointed Chief of the Molecular Pathophysiology Section, and then Chief of the Metabolic Diseases Branch. In 1990, he was also appointed Scientific Director of the NIDDK's Division of Intramural Research, a position in which he had responsibility for more than 20 Laboratories and Branches, performing research in areas ranging from basic structural biology to clinical trials for treatment of hepatitis and sickle cell anemia. In 1999, he was named Director of the NIDDK by then NIH Director Harold Varmus (currently President of Memorial Sloan-Kettering Cancer Center).

An internationally recognized researcher and endocrinologist, Dr. Spiegel has given award lectures in Japan, Australia, and at major European and American academic health centers. He has been elected to the American Society of Clinical Investigation, the Association of American Physicians, and the Institute of Medicine of the National Academies. Dr. Spiegel's work has helped illuminate how hormones and other signals are received and

interpreted by cells, and has identified genetic defects in signaling that lead to a number of human diseases. The first of his more than 280 published papers (in 1969, in Endocrinology) resulted from his work with Dr. Mark Bitensky (then at New York University Medical School) that began while Dr. Spiegel was still a Columbia underaraduate.

This initial paper involved glucagon, the pancreatic hormone that converts stored sugar in the liver into glucose, the body's energy source. Dr. Spiegel looked at how chemical and enzymatic modifications of glucagon affect its ability to activate adenylyl cyclase, an enzyme found in the membranes of virtually all mammalian cells. Adenylyl cyclase is responsible for producing one of the most famous of all cellular molecules: cyclic AMP, a so-called second messenger chemical that plays a crucial role in signal transduction.

rn 1973, Dr. Spiegel joined the NIDDK laboratory of Gerald Aurbach, who had first purified parathyroid hormone (PTH), a key regulator of calcium metabolism. Although it was clear by that time that hormones like PTH and glucagon act on proteins in the cell membrane to generate cyclic AMP inside the cell, how they did so was a "black box," until Martin Rodbell, also at NIDDK, first identified G proteins (guanine nucleotide binding proteins) as key intermediaries between hormonebinding receptors and the cyclic AMP generator, adenylyl cyclase. (The discovery of G proteins earned a shared Nobel Prize for Martin Rodbell and Alfred G. Gilman, whose father—Alfred Gilman—was founding chairman of the pharmacology department at Einstein.)

Dr. Spiegel's work on G proteins and the hormone receptors to which they couple focused on the

disturbances in the structure and function of these proteins that can lead to human disease, particularly diseases of the parathyroid and other endocrine glands. This research has helped to clarify the genetic basis of several human endocrine diseases including pseudohypoparathyroidism, McCune-Albright syndrome and nephrogenic diabetes insipidus.

Throughout his career as an endocrinologist, Dr. Spiegel has focused on and championed the link between basic research and patient care. This emphasis on translational medicine is vividly illustrated by his involvement with MEN1 (multiple endocrine neoplasia type 1), a hereditary disease



Allen M. Spiegel, M.D.

characterized by multiple benign tumors of the parathyroid and pituitary glands as well as pancreatic islet cell tumors that can lead to cancer.

Dr. Spiegel and his NIDDK colleagues had treated patients with MEN1 at the NIH Clinical Center for many years. Studying tissues and blood samples from more than 65 families with MEN1 they had cared for over more than 20 years, they mounted a sustained effort to find the

(Continued on page 19)



## GLOBALHEALTH ATEINSTEIN:

#### The World As Classroom



Ph.D., arrived at Albert Einstein College of Medicine and ever since he has made a world of difference for Einstein students. As the medical school's first Associate Dean for Educational Affairs, Dr. Kuperman established a fellowship program through which students could travel to less developed or emerging countries to assist in providing medical care and/or participating in research and public health projects. At the time he joined the Einstein faculty, Dr. Kuperman had just returned from seven years in Southeast Asia where, as a member of the Rockefeller Foundation's field staff, he helped establish medical education programs at local universities. He knew the valuable lessons that can be learned from hands-on experiences in developing nations. As a result, from the mountains of El Salvador to the heart of the Amazon, and from small villages in Thailand to remote outposts in Cameroon, medical students at Albert Einstein College of Medicine have had the opportunity to gain a more global perspective of how medicine is practiced throughout the world.

hirty years ago, Albert Kuperman,

It all began in 1976, when eight fourthyear students became the first at Einstein to take advantage of the new concept of global medicine. "At the time, only a handful of medical schools were offering such opportunities," says Dr. Kuperman.

# ... Today, at least half the nation's medical schools promote global medicine for their medical students. But Einstein was and remains at the forefront.

"Einstein, Harvard, Duke and Johns Hopkins and a few others. It wasn't until the 1990s that interest in global health exploded. Today, at least half the nation's medical schools promote global medicine for their medical students. But Einstein was and remains at the forefront."

ndeed, during the 30 years since its introduction, the Global Health Fellowship Program at Einstein has blossomed, with approximately 25 seniors traveling overseas annually, for periods ranging from two months to a year, and about 40 first-year students spending their summer break abroad. Many of these students take advantage of opportunities to strengthen their medical Spanish through programs in Mexico and South and Central America. These student globetrotters are supported by the College of Medicine along with funding from the Milton Rosenbluth Foundation, the Abraham Kuperman International Health Fellowship, and the Arnold Penner Fund.

"Once a student is interested in global health, there's no better school in the world for pursuing that interest," says Dr. Lanny Smith, global health advisor at Einstein as well as assistant professor of medicine and family and social medicine. And Dr. Smith should know: he is also a member of the governing council of the Global Health Education Consortium and founder of Doctors for Global Health (DGH), an entity through which Einstein and others can get firsthand experience in caring for individuals living in Third World countries.

Prior to establishing DGH 10 years ago, Dr. Smith found that many similar healthcare-providing organizations were reluctant to involve students. "They only wanted fully trained physicians and didn't see students as part of their mission," he says. When he went about forming DGH, Dr. Smith

not only sought student participants for his program, he included several as members on its original board. (Alumnus Dr. Stephen Miller, Class of 1996, was among the first students to volunteer with DGH. He then succeeded Dr. Smith as president of the organization and currently serves on its board.)

"Students have a vitality and an energy that you don't find in most other people. And they are humble in a way that most doctors are not," adds Dr. Smith. "They are eager to learn and to assist the health promoters who work with patients in the communities where we offer medical assistance."

r. Smith is not the only Einstein faculty member to spearhead international efforts to aid underserved populations.

Dr. Matthew Anderson, assistant professor of family and social medicine, established HIV Medicines for Guatemala in 1995 while a fellow at Harvard. Einstein's Department of Family and Social Medicine has since developed an active collaboration

with the Luis Angel Garcia Clinic at the Hospital General San Juan de Dios in Guatemala. This clinic provides HIV testing and both ambulatory and inpatient HIV care, diagnosing approximately 700 new cases of AIDS each year and offering more than 6,000 outpatient consultations. In addition, through the HIV Medicines for Guatemala program, approximately \$500,000 worth of muchneeded HIV medicines—donated unused from sites in the United States—is flown to Guatemala by American Airlines Ambassadors, an organization of stewards from the airline.

"Since the clinic's inception,
Einstein students have participated
in a variety of capacities. They have
helped with an epidemiologic study
on inpatient admissions to the hospital
and with analysis of the use of recycled medicines in treating the pediatric population," notes Dr. Anderson,
who also serves as advisor for the
medical school's social medicine
course, designed with student input
and offering pertinent information on
global health.

#### A hammock is used as a makeshift stretcher to transport a patient in Peru.





Einstein student Greg Simmons examines a young patient during his elective in El Salvador.

aking a more global perspective, Dr. Carol Harris, professor of clinical medicine, is now establishing Einstein's Institute of Global HIV Medicine. It will encompass both educational and humanitarian endeavors, with a primary goal of affecting the HIV pandemic. Still in its infancy, the Institute has already begun offering an annual CMEaccredited HIV management course, called "HIV Management—The New York Course." It is also developing the Global AIDS Learning and Evaluation Network project, in conjunction with the International Association of Physicians in AIDS Care. During 2006, the Institute will inaugurate a two-month fellowship for pairs of medical students who will travel to Ethiopia, in conjunction with Einstein's Global Health Fellowship Program and the African Forum of Faith-Based Organizations in Reproductive Health and HIV/AIDS.

"Our goal is to break the barrier of ignorance that so often plays a role in both HIV infection and failure to seek treatment," says Dr. Harris, who conducts her research and her internationally based health care in Ethiopia.

"In the process, we're seeking to improve the quality of life for patients and their families, while acting as a force for change regarding the prevention and treatment of AIDS, based on understanding and respect for differing cultural and political environments," Dr. Harris adds.

Another new Einstein program, the AIDS International Training and Research Program, will train one medical student per year at a site in India. Both clinical and research training will be offered, including collaborative studies that the student will take part in through laboratories both at Einstein and in India.

Respect for differing cultures and politics is also reflected in Einstein's participation in MEDICC, or Medical Education and Cooperation with Cuba, a program established in 1997 with Dr. Kuperman and others from both American and Cuban health care institutions serving on its Academic Council. Through MEDICC, first- and fourth-year medical students were able to travel to Cuba where they could observe how the small Caribbean nation provides effective universal health care in spite of limited resources and a USA-imposed embargo on health care supplies, equipment, and food.

he program also offered immersion in medical Spanish. However, recent changes in State Department travel permits—one must visit Cuba 10 weeks or longer to obtain permission—have greatly diminished possibilities for participation among first-year students, who typically would go for four- to eightweek periods.

"The program was amazing," says third-year student Casey Barbaro, Class of 2007, who was in the last round of first-year students permitted to go. "In the one month we were there, we got a complete immersion in medical Spanish, including lectures on the health care system and observational site visits to local

clinics. During our third week, we were assigned to a specific doctor's office where we observed and occasionally assisted.

"The wildest thing, though, was learning that the top neurosurgeon there makes just \$17 a month. In comparison, a janitor makes \$8 a month. We asked, 'Why would you want to do this?' and they told us, 'Because we love it. It is our heart.' Cuban doctors also work with fewer resources, yet they still do a lot in the way of prevention and dealing with social issues. I learned so much and it's a shame that participation by first-year students is now limited."

ot to be deterred, a research team comprised of faculty from Einstein and Yeshiva University's Wurzweiler School of Social Work visited Cuba in December 2005, where plans were discussed to establish long-term research collaborations between members of the Einstein/YU team and counterparts in Cuba. Research projects will focus on the Cuban health system, the role of social workers in that system, and the interaction between communities, physicians, and other health care workers in promoting the health of the people.

"The research trip to Cuba was very successful and is likely to lead to long-term and productive collaboration with our Cuban counterparts," notes Dr. Kuperman. "Both Einstein and Wurzweiler are ideally positioned to conduct important interdisciplinary-based research in Cuba and here in New York, given some of our shared community-based interests such as cultural diversity, mental health, HIV/AIDS, social justice, and substance abuse. Planning for specific projects will be further delineated in follow-up meetings, and we plan to find ways to involve students in some of them."

... I truly want to change the 'fate' of my future patients and give them the opportunity to live happier, healthier and fuller lives.

In addition to these varied opportunities afforded students through connection to the global health efforts of Einstein faculty, Einstein students can participate in other programs, such as Amazon Promise and Partners in Health, whose humanitarian pursuits in developing nations offer them similar hands-on experiences. "There are a wealth of opportunities that students can pursue, limited only by their research and imagination," says Dr. Kuperman. "They present the project that most interests them and, if approved, the school supports them with a fellowship."

Above and beyond supporting the pursuit of greater knowledge in settings far removed from the Bronx, the medical school also reflects a worldly view of medicine through its curriculum. Since its establishment in 1955, Einstein has included a course in parasitology for its students, and it is still one of only a few US medical schools to do so. The course, offered in the second year, has evolved to include various aspects of global medicine. This year the course will



#### CHRIS CARPENTER

Awarded Inaugural Albert S. Kuperman Award for Field Work in Global Health

hristopher Carpenter, M.D., Class of 2005, is the inaugural recipient of the Albert S. Kuperman Award for Field Work in Global Health. The award was established to honor the tremendous influence that Dr. Kuperman, associate dean for educational affairs, has had in creating opportunities for Einstein students to take part in global health programs abroad, particularly in poor nations whose populations are largely underserved. The award recognizes an Einstein student who, through fieldwork and other activities, demonstrates an interest and exceptional aptitude for the practice of global medicine.

At the award presentation, Dr. Carpenter was cited as an accomplished young man who has traveled widely and who is perhaps more at home in less developed nations than he is here in the U.S.

Indeed, Dr. Carpenter, who is a native of the Bay area, has been to 40 countries, including Cambodia, Cameroon, Vietnam and India. Between his first and second year of medical school, he ventured to Rwanda and Tanzania, and after his third year he traveled to Botswana and Zimbabwe. He also took a year off to earn a Master's degree in international health at the Harvard School of Public Health.

His interest in the world beyond the United States was instilled during family trips abroad. At age 18 he bought a Eurail pass, and used it to visit Sweden, Germany, Italy and Greece. During college, he also traveled on his own to various parts of Asia, Latin America, and Africa. Just before beginning his medical studies at Einstein, he met up with a research team in Cameroon, a small country in West Africa, and worked with a midwife helping to teach villagers about sanitation.

Following the completion of his Master's degree, Dr. Carpenter spent five weeks on a medical mission in Sitkim, a section of northern Chris Carpenter, M.D., recipient of the inaugural Albert S. Kuperman Award for Field Work in Global Health, on a medical mission in Sitkim, northern India.



introduce a case-based approach to global health problems that focuses on diagnosis and treatment options and is supported by a website solely for students.

"Today, there is no place on earth that you can't go. People travel to these formerly hard-to-reach locales and return with parasites or illnesses previously unheard of here," says Dr. Murray Wittner, professor of pathology, who has taught the parasitology course since its inception. "So the course will look at all issues of disease, including how opportunistic infections compromise the immune system as well as approaches to treatment."

Interested students can also take a parasitology elective allowing them to observe the operation of the tropical medicine clinic, headed by Dr. Wittner at the Jacobi Medical Center. "We see patients from everywhere —Russia, Albania, Africa, and the Middle East—who are referred to us from throughout New York, Connecticut and Pennsylvania," says Dr. Wittner. "They come to us with

health issues relevant to the parasitology course, such as schistosomiasis, malaria, and intestinal parasites."

The website supporting the new case-based curriculum is still under development and expected to go online this year. "The site will incorporate course material and experiences from the tropical medicine clinic to reinforce what students learn in lectures, and it will offer useful background information to students preparing to go abroad," explains the website's developer, Dr. Christina Coyle, who also is associate professor of clinical medicine at Einstein.

In his work overseas with Medicins Sans Frontieres (Doctors Without Borders), alumnus Jason Wong, Class of 2000, observed that his Einstein training in tropical medicine was superior to that of other doctors. "As I met others in the medical profession, I realized that our parasitology class at Einstein was unusual in its scope," says Dr. Wong. "Most people had a token one-hour on malaria and that was it."

The learning is reciprocal as well: While students see what they learned

India, where he helped to set up mobile clinics in the area's rural villages. And since graduating from Einstein last June, he has been busy with his residency in pediatrics at the University of California, San Francisco, and takes part in a pediatric international health interest group. He also plans to apply to Doctors Without Borders once he has completed their requirement of at least two years of postgraduate training.

"My travels definitely inspired my interest in health issues abroad," said Dr. Carpenter. "I realized how fortunate we are here, and I knew I wanted to practice overseas when I applied to medical school. That knowledge was only reinforced by my experiences overseas while at Einstein."

He then recalled a house call he and several colleagues made to the home of a 25-year-old woman in the eastern Himalayas. "She was in acute renal failure because she had received an inaccurate dosage of medicine on a previous visit to a local hospital. She was extremely ill and needed intervention quickly, which we urged her to get. She knew that dialysis or a transplant was necessary and life saving, but told us it would be too much of a burden on her family to pay for such treatment.

Instead, she chose to accept her 'fate' and resigned herself to die.

"When I think back on this young patient's story, my motivation for working abroad greatly intensifies. I truly want to change the 'fate' of my future patients and give them the opportunity to live happier, healthier and fuller lives."

As the first recipient of the Albert S. Kuperman Award for Field Work in Global Health, Dr. Carpenter not only lived up to the award's ideals as a student at Einstein, he continues to do so in his ongoing endeavors.



in class being applied in the field, they also bring what they observed in the field back with them. "It makes a huge difference in their ability to provide excellent medical care across cultures within the U.S.," says Dr. Smith. "That's very important given the diverse cross-section of cultures we have here."

Adds Dr. Kuperman: "It's also true that there are plenty of experiences that our students can and do get working with underserved populations right here in the Bronx." He cites the work of many students in conjunction with local health promoters through their ECHO Clinic in the South Bronx as

an example. (ECHO stands for Einstein Community Health Outreach.)

He adds, "But when you go overseas and experience a village in Peru or Ethiopia, it puts the Bronx experience in a very different perspective, one that we hope enriches and emboldens our students in their overall approach to practicing medicine as doctors."

With that goal in mind, as well as enthusiastic support from Dean Purpura, a group of faculty convened by Dr. Kuperman last November is drafting a proposal to establish a Global Health Center. According to Dr. Gerald Paccione, professor of

medicine and the proposal's lead writer, the Center "will foster global perspectives in medical education at Einstein, facilitate international clinical and research experiences for students and faculty, and form collaborative relationships that promote the ideals of health for all with like-minded individuals in institutions and communities in the developing world."



In the process, we're seeking to improve the quality of life for patients and their families, while acting as a force for change ... based on understanding and respect for differing cultural and political environments.





Above and top right: Members of the Amazon Promise team make a house call in the stilt-house community of Belen, Peru.

Bottom Right: Einstein student Eleanor Chung ('07) administers an I.V. to a patient being transported to the hospital by boat in Iquitos, Peru.



#### EINSTEIN'S Student GLOBETROTTERS

or the past 30 years, students at the Albert Einstein College of Medicine have been traveling the globe, learning about the practice of medicine in places where technology is limited or nonexistent and where doctors are sparse or nonexistent. Supported by fellowships from Einstein's Global Health Fellowship Program, each year dozens of students travel to the four points of the compass and beyond to assist with care-giving, patient education, and research while learning about how health care is administered in remote regions of the world. Following are vignettes detailing the adventures and experiences of Einstein students who, through Einstein's Global Health Fellowship Program, sought a more global perspective of the practice of medicine.

#### **ELEANOR CHUNG, Class of 2007**

In the summer preceding her second year at Einstein, Eleanor Chung traveled to Iquitos, Peru, where she split her time between two "jobs"— helping to provide care for residents of Belen (a town on the outskirts of Iquitos) and conducting a health census of that community of approximately 7,000 people to prepare for the opening of a free medical clinic. She worked with members of Amazon Promise, a non-governmental organization dedicated to providing medical assistance to the indigenous people living in the remote villages of the Upper Amazon River Basin.

"A tourist brochure advertises Belen as 'the Venice of Iquitos'," says Ms. Chung. "And it is the largest city in the world with no road access, so there is indeed truth to the advertising. But the brochure fails to mention that the river is the source of everything in the community, since the people drink from it, bathe in it, and even dump their waste in it. Homes are on stilts along the river's edge and the only modes of transportation for most villagers are boats and canoes. There is no escaping the trash or human excrement, both of which contribute to infections and illnesses."

Ms. Chung worked under the supervision of Patty

Webster, Dr. Javier, and other team members of Amazon Promise, who for 11 years have been making medical house visits to the homes in Belen, helping to treat the myriad illnesses that would otherwise only be treated by home remedies and spells offered by the local shaman. For four weeks, Ms. Chung visited households along with her translator Jose Luis and attempted to piece together an in-depth portrait of the life and health of the community.

"We asked people about their perceptions, concerns and hopes for a better life, while also cataloging the illnesses that are predominant in the community," she says. "Among the 75 households we visited, we chatted with families cramming 17 members into the already-cramped quarters of a stilted house and to a 72-year-old shaman who lived alone in a sparse, floating home. We chronicled ailments as varied as constant headaches and respiratory ailments to skin infections and dysuria (difficult or painful urinating), to relapsed tuberculosis, end-stage lymphoma, and hydrocephalus. We also found that because of lack of money, few families seek help at the local medical post until the point of emergency. By and large, sickness has become a way of life."

In addition, Ms. Chung and Jose Luis joined Dr. Javier in visiting with doctors in the community and in speaking with government officials from the municipality of Belen. "We discussed the idea of the new, free clinic, the data on illnesses and number of people that would be served, and the construction of roads. It was fascinating to encounter responses ranging from enthusiasm to apathy to outright objection: 'Roads would disrupt the harmony of Belen,' one official declared."

Most poignant in her memory are the resiliency of the people and the dedication and resourcefulness of the doctors. "The medicine they do brings you back to the core of medicine. We used camping headlamps to illuminate a pelvic exam and, on one occasion, we used a hammock in lieu of a stretcher to transport a man with a painfully strangulated scrotal hernia to Iquitos Hospital, three hours away by boat. We admin-

istered antibiotics through an I.V. that was hooked to the rafters of the boat. It was a stroke of luck that we were even there at the time he needed assistance."

She adds, "I went into Peru without much clinical knowledge. I came away gaining a lot from my experience, and what I learned put much of my second-year coursework, particularly parasitology class, into context. It also opened many possible career avenues, in government, health education, community development, and fundraising, for medical students to consider. And seeing the multiple social, economic, and political factors influencing access to health care has strengthened my belief that universal health care must be made a priority. One thing is sure. My experience in Peru continues to shape my career, and I will be able to use these new perspectives of medicine whether in the international setting or locally, right

#### GARRY CHOY, Class of 2005

here in the Bronx."

An hour north of Bangkok, Thailand, is the village of Singburi, with an estimated population of 75,000. Garry Choy spent two months of his senior year at Singburi's small, rural hospital, which featured 100 inpatient beds and a very active outpatient clinic. While shadowing a local attending, Kanya Karoonuthaisiri, M.D., and attempting to communicate in his limited, basic Thai, Dr. Choy noted the profound relationship between doctor and patient. "The physicians talk to their patients about their lives, feelings, and concerns. This is something that I felt, at times, was lacking in the hectic pace of healthcare in the U.S."

While in Singburi, he also conducted research evaluating the utility of hemoglobin AlC, or HbAlC, in the management of diabetes within the local community.

"In the U.S., HbA1C is a low cost, common lab test that is used for assessing glucose control." explains Dr. Choy. "The test can help physicians and patients regulate sugar levels, thereby minimizing and preventing complications of diabetes from occurring. By contrast, the test is not used in Thailand because of its high cost and the patients' perception that its expense can't be justified."

The goal of Dr. Choy's research was to measure HbA1C levels in all the diabetes patients who visited the hospital, to determine whether the test could aid local physicians in treating patients' diabetes while also adequately measuring each patient's medical complications and medication compliance.

He notes that results, thus far, demonstrate that HbA1C did correlate to complications, but the experience also offered other important insights. Most notably, Dr. Choy found that the simplest of lab tests, such as a CBC or basic metabolic panel, is ordered so routinely in the U.S. that it resembles a reflex. In Thailand, this practice did not occur largely because patients could not afford the entire CBC at one time. Physicians had to creatively triage the tests doing the most important first.

"I also met doctors who could diagnose a multitude of diseases and conditions without imaging or tests. Seeing medicine practiced very effectively at its basic level without the tremendous cost and reliance on technology was humbling," he says. "In particular, my time in Thailand taught me that technology, if not used right, is of no use and technology isn't always necessary to heal a patient."

The experience has shaped how Dr. Choy—who currently is completing an internship at Harvard Medical School in internal medicine, after which he will concentrate full-time on a residency in radiology—approaches both the ordering of tests himself and by colleagues and how he will practice his chosen specialty, diagnostic radiology.

"Diagnostic radiology is a field highly based on advancing technology. We have wonderful, though often expensive tools at our disposal that can help answer specific questions about a patient's case. They can also be put to use simply because they're available. My experience in Thailand has helped me to question whether a test being ordered is clinically useful and justified, or whether it is extraneous. It also left me with a better understanding of the true need, limitations and benefits of diagnostic technologies, so long as we are conscientious and thoughtful in our use of them."

# ... When Gregory Simmons arrived in El Salvador, he could not know the role he would play in the tragic life of a little baby girl named Sulma.

#### **GREGORY SIMMONS, Class of 2006**

When Gregory Simmons arrived in El Tablon, El Salvador, at a clinic that had been set up by Einstein's Dr. Lanny Smith, assistant professor of family and social medicine and of medicine, he could not know the role he would play in the tragic life of a little baby girl named Sulma. With four exam rooms, the clinic is equipped to provide medical assistance in obstetrics and gynecology, pediatrics, and general medicine. It also houses a pharmacy with medications that have been donated by American physicians. The clinic

is run by Medicos por El Derecho a la Salud (Doctors for the Right to Health), a non-governmental organization that also provides community health promoters to assist the student volunteers.

During the first four months of his seven-month elective, Mr. Simmons worked with an El Salvadoran medical student and an attending physician. The latter three months he worked with an attending physician, assisted by community health promoters.

"The health promoters act as sentinels," says Mr. Simmons. "They have the trust of the community and they are a tremendous help in so many ways because they are trained by us to identify problems that may require a visit to the clinic. As a result, more people get medical attention when they need it."

According to Mr. Simmons, there are approximately 1,500 people in the immediate area serviced by the clinic and a total of about 4,000 in the surrounding communities that access the clinic. Roads are mostly dirt, making access difficult. There is no phone or e-mail, although there is electricity. Each day, some 10 patients make their way to the clinic, though sometimes their arrival occurs during the middle of the night or in the early hours of the morning. And sometimes the volunteers and health promoters go to the patient.

Such was the case with Baby Sulma. In February 2005, at the suggestion of a health promoter, Mr. Simmons paid an after-hours visit to her home where

her parents were concerned about the bluish coloring at her fingertips and mouth. He examined the baby and found that she had an unusually high respiratory rate of 30 to 45 breaths per minute—which is not typical for a baby. He then learned that following a visit to a doctor in San Salvador the baby had been placed on medications typically prescribed for patients with heart failure—also unusual for an infant.

Conducting his interview with Sulma's parents in Spanish, Mr. Simmons learned the more complete history of the young infant, which included an eight-

day hospital stay at the San Miguel Health
Center prior to being transported to San

Salvador for more extensive testing.

(San Salvador is home to El Salvador's only children's hospital.) Ultimately, he learned that because of a lack of resources for treating the baby's problem—she had both transposition of the aorta and pulmonary arteries and a ventral septal defect (a hole in her heart)—the doctors had not fully informed the parents of their child's problem.

"Had we been in the U.S., the

defects that were preventing blood from reaching baby Sulma's lungs, could have

been corrected within the first two months, and she could have enjoyed a normal life expectancy" says Mr. Simmons. "But sadly, the lone pediatric cardiothoracic surgeon at the hospital admitted that he lacked the equipment to do the complicated procedure in a time frame that could save Sulma. He was devastated and so was I. To know there is something that can be done yet to feel so helpless at the same time; I don't think there is a worse feeling. My experience with him taught me a lot about diplomacy in the face of advocating for a patient."

At the end of March, just weeks before Mr. Simmons was to return home, a fourth-year physician assistant from Washington, D.C., Edward Horgan, arrived at the clinic. Together, he and Mr. Simmons determined they would find a doctor and/or organization that could help Sulma. Eventually, they identified a physician—Dr. Aldo Castaneda, former head of Pediatric Cardiothoracic Surgery at Children's Hospital in Washington, D.C.— who committed to doing the sur-

gery in Guatemala for \$7,000. (The procedure typically costs \$70,000 to \$100,000 in the U.S.) They also found an organization that would consider funding the surgery if Simmons and Horgan could get Sulma to the U.S.

The two spent the next two weeks fundraising among their family and friends. They raised \$12,000 — \$2,000 of which came from the generosity of Mr. Simmons' fellow Einstein students. They decided to allocate \$8,000 for Sulma's surgery and post-operative care and to place the remainder of the money in a fund to help future children in circumstances like Sulma's. The surgery was to take place on May 12, 2005, but Mr. Simmons has since learned that the baby was inoperable because she lacked enough of her myocardial septum to close the big hole between both compartments of her heart. When he last spoke with volunteers in Tablon, in February, 2006, Sulma was still alive, though very cyanotic from lack of oxygen and fighting monthly lung infections.

"Her parents wrote me, expressing their gratitude. They knew that everything that could be done for their little girl had been done and will never have to wonder why she died," says Mr. Simmons. Meanwhile, the money Mr. Simmons and Mr. Horgan raised is part of the Sulma Blanco Fund, which will be used to help other impoverished children in El Salvador in need of surgery—beginning with a little boy who needs gall bladder and liver surgery.

#### JASON WONG, M.D. Class of 2000

As a first-grader, Jason Wong was assigned a book report on the biography of Dr. Albert Schweitzer. He recalls that the experience had a profound impact on him.

"After reading about Dr. Schweitzer's life and his dedication to health care in the third world, I realized that it was a dream I shared" he says. "I knew right then and there that I wanted to be a doctor like Dr. Schweitzer."

Some fifteen years later, Dr. Wong entered Albert Einstein College of Medicine in pursuit of his dream. And since graduating five years ago, Dr. Wong has volunteered with the Nobel-winning organization Medicins Sans Frontieres (Doctors Without Borders) on missions in the Cote d'Ivoire and in Darfur, Sudan.

Currently, he is a member of Group Health Cooperative, a family medicine practice in urban Seattle, but he hopes to continue his alliance with Medicins Sans Frontieres (MSF) through a two- to three-month mission every few years.

Dr. Wong's entree into international health began during his fourth year at Einstein, when he applied for and received the Albert Schweitzer Fellowship—which he notes "is supposed to be for New England students only, but they allowed for my faulty sense of geography and accepted me." The fellowship involved spending three months at L'Hopital Schweitzer, the hospital of his childhood hero, located in the West African nation of Gabon.

While in Gabon, Dr. Wong was exposed to the world of tropical diseases, such as malaria, schistosomiasis, and filariasis, while also treating more common problems like diarrhea and respiratory infections and following chronic diseases like diabetes and hypertension. For two weeks, he shadowed experienced physicians, after which he spent the next month as a preceptor. During the remaining four months, he rotated between an outpatient clinic, inpatient hospital, and mobile clinics, seeing patients largely on his own but with backup assistance available.

"The set up of things allowed me to be exposed to the world of tropical medicine in a safe environment with expertise around me," he says. "It also was helpful, as a student, to see how medicine is practiced in different countries and how well some people have honed their skills in the absence of technological advances."

Dr. Wong's exposure to tropical medicine became firsthand experience as well, when he learned he had Loa loa, a mosquito-borne parasite, also called African Eye Worm. More irritating than dangerous, Loa loa can be treated with an oral medication taken over an extended period. He is particularly grateful to Drs. Murray Wittner, professor of pathology, and Christina Coyle, associate professor of clinical medicine, for treating his Loa loa, as well as for their fun and stimulating parasitology lectures.

"As I met others in the medical profession, I realized that our parasitology class at Einstein was unusual in

... It is easy in this world of fee for service and finance-dominated health care to lose sight of the reason most of us got into medicine in the first place—to use our skills and education to help those who need it.

its scope," he says. "Most people had a token one-hour on malaria and that was it. I felt that our class piqued my interest in tropical medicine in spite of my prior interest through Dr. Schweitzer."

Other coursework also proved helpful abroad, particularly the first-year ICM course and the internal medicine rotation at Montefiore. "The first-year ICM helped with the cultural sensitivity necessary to succeed abroad, particularly the ways in which Michelle Rottenstein taught us how to talk to patients and, more importantly, how to listen," says Dr. Wong. "And the internal medicine rotation was invaluable for its excellent teaching of clinical skills, bedside

rounding, and diverse pathology. Gerry Paccione is unparalleled as a clinical teacher. He taught me that you don't really need tests except to help confirm clinical impressions. A world away, where instinct is in much greater supply than technology, that kind of information makes a tremendous difference."

Following graduation, the lessons from Einstein continued to serve Dr. Wong well during his MSF missions in the Cote d'Ivoire and Sudan. So did his fluency in French,

which stemmed from his interest in the language while growing up in northern California along with a year abroad in France during college.

"I expressed interest in going to Africa, preferably a French-speaking country, and to a region affected by war," says Dr. Wong of his association with MSF. His decision was based in part by the skills he felt he could offer and in part by what work would prove stimulating and meaningful. Having already worked in locations where the primary issues were nutrition and isolation, he was eager to be in an environment that dealt with emergency situations. "MSF is known to respond very well to emergency situations and I wanted to be a part of that," he says. "The Ivory Coast fit that bill."

During six months in the Ivory Coast, Dr. Wong oversaw the medical activity in a war-torn region along the country's western boundary, where approximately 60,000 Ivorian IDPs (internally displaced people) and Liberian refugees sought treatment for malnutrition, malaria, respiratory infections, diarrhea, skin infections and trauma. Medical activities included an outpatient clinic that saw approximately 120 patients per day, an inpatient adult hospital with 10 to 20 patients at a time, an inpatient pediatrics and nutrition ward with 20 to 40 children, a maternity clinic at which 10 deliveries were made per week, mobile clinics, active nutritional screenings, and an on-site vaccination



program that was complemented by regional measles vaccination campaigns. Initially, Dr. Wong was the only physician, working with a nurse and a logistician/field coordinator, but during the final month of his mission, two Ivorian doctors joined the team. Still, Wong found that most of the team had minimal to no medical training.

"Our goal was to recruit motivated and intelligent people and train them to work in our health center," he says. "The most challenging aspect of things was doing the work we did in relative isolation, especially since in the States you quickly become accustomed to working in a large academic facility with colleagues and resources everywhere."

Dr. Wong also was challenged to diagnose and treat

diseases he'd never seen before, and to know that so much more could have been done for many patients if only they lived in a more medically developed country.

"I was pushed emotionally to deal with death on a level previously unknown to me, without the moral support of fellow physicians," he says. "Over time, I learned to deal with the uncertainty and the insecurity, but it took time."

At the same time, Dr. Wong notes, "There is no doubt that you are needed and it is impossible to measure the gratitude from the community. Moment by moment you can feel your impact."

For his second MSF mission Dr. Wong only had a couple of months he could volunteer before finding work in the States, so he requested Darfur knowing how dire the situation was there. He worked with one nurse/field coordinator, one logistician, and one other doctor, administering to health needs similar to those in the Ivory Coast, but also including ambulatory feeding programs, the distribution of food, and sanitation.

"I saw sides of people I did not think would still exist in such horrific conditions," he says. "In the face of unimaginable terror, there remained such a spirit of hopefulness and goodwill toward each other."

In particular, he was most inspired by the mothers with their children in the feeding program. Upon admission, children are so sick and need to take so

many medications that it is a real struggle. The mothers are frightened to be with foreigners, taking medications and eating foods that are not familiar to them. And the admissions can last two months.

"As they get better, they start to gain weight, smile, walk, and play," says Dr. Wong. "And by the second month, the mothers are so experienced and comfortable that they take over some of the teaching of new moms. They help watch over the children, exchange tips about how to get the kids to swallow their medication, or how to get them to eat the fortified foods, and they support each other. Discharges are always big celebrations."

While witnessing such progress is always rewarding, a benefit Dr. Wong hadn't anticipated was the pleasure that came from working with a group of similarly minded international humanitarians. "It is easy in this world of fee for service and finance-dominated health care to lose sight of the reason most of us got into medicine in the first place—to use our skills and education to help those who need it," he says.

"Dr. Schweitzer embodies the sense of mission and purpose as a pioneer in medicine," he adds, "and it is a rare privilege to have skills that are so useful in so many situations and places. To volunteer my skills as a physician was truly an honor."



#### Allen M. Spiegel, M.D.

#### A Journey Well Traveled

(Continued from page 3)



Dr. Spiegel, right, testifying before Congress in June 2005 on behalf of increased funding for diabetes research, along with, left to right, Mary Tyler Moore, International Chairman of the Juvenile Diabetes Research Foundation; film producer Douglas Wick; and Olympic gold medal swimmer Gary Hall, Jr.

Photo courtesy Camera One NYC

gene that, when mutated, is responsible for the disease.

This research by Dr. Spiegel and his colleagues—a tour de force demonstration of the power and scope of genetic technologies—culminated in a 1997 Science paper that identified the MEN1 gene and found that mutations in this tumor suppressor gene are responsible for the disease. Working in the MEN1 program with Dr. Spiegel were Stephen J. Marx, a senior investigator at the NIDDK and one of Dr. Spiegel's main collaborators during his three decades at the NIH, and Francis Collins, director of the National Human Genome Research Institute.

Thanks to this discovery, doctors now can readily screen families at risk for MEN1. Further study of the *MEN1* gene and its protein product, menin, will lead to insights regarding the growth of endocrine tumors in particular and cancer in general. The discovery of the *MEN1* gene also provides a target for designer drugs that may be able to treat or even prevent both benign and malignant endocrine tumors.

"My time at the NIH," Dr. Spiegel says, "has been extraordinarily fulfilling. The people who work at the Institutes are enormously dedicated to its mission of performing and supporting research to improve diagnosis, treatment and prevention of dis-

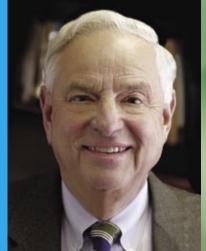
I am now very much looking forward to a new challenge, one that will enable me to focus on a broader array of diseases and a broader scope of responsibilities, including educating the next generation of physicians.

ease, and they do a terrific job of it. As Intramural NIDDK Scientific Director, I was able to recruit many of those people, and even to create a new Branch focused on autoimmunity, pancreatic islet and kidney transplantation. As NIDDK Director, I was able to help shape new programs for support of research on disorders such as diabetes, polycystic kidney disease, and Crohn's disease. Testifying in Congress, as I did on numerous occasions in support of the NIH research budget, gave me a keen sense of the importance of making the case for the value of biomedical research to the public and its elected representatives. But I am now very much looking forward to a new challenge, one that will enable me to focus on a broader array of diseases and a broader scope of responsibilities, including

educating the next generation of physicians.

"I feel especially privileged that I will be able to do all of this at a great medical school, Einstein. Extraordinary things have been accomplished here over the past fifty years, but we must do even better in the future to realize the full benefits of medical research. Who knew, in 1962 when I first entered an Einstein lab, that 44 years later I would be given this exceptional opportunity? What a gift, and what a responsibility!"

Dr. Spiegel and his wife, Rita, were married in 1969, and they have two children, a daughter, Rachel, and a son, Daniel. Mrs. Spiegel has worked for many years at The World Bank, an international development organization in Washington, D.C.



Irwin R. Merkatz, M.D.

## **FIELD** of **DREAMS**

Innovative **DEWPoint Program** in **Obstetrics &** Gynecology and Women's Health Serves as a Field of Dreams for Women and Minorities

> ention the name Irwin Merkatz among the faculty of Obstetrics & Gynecology and Women's Health and one word emerges in describing their Einstein department chair: visionary. For twenty-five years, Dr. Merkatz has employed his unique insight to shape the department, to guide young physicians and researchers, and to create programs aimed at addressing healthcare disparities among women and infants in the Bronx. His most recent innovation, conceived in collaboration with Dr. Karla Damus, associate professor of obstetrics & gynecology and women's health, has been the formation of a new division —the Division of Equity in Women's Health and Perinatal Medicine, or DEWPoint Program.

> Chief among the new division's training objectives is to enhance the career advancement of women and minority physicians by offering them more formalized clinical and research training opportunities. In carrying out these objectives, the DEWPoint Program's ultimate goal is twofold: to broaden the scope of the healthcare that these young doctors provide for women and to establish them as leaders in their field.

"As academic leaders, members of the Einstein community must be proactive, particularly when serving families in the diverse community of the Bronx. One way in which we can do this is by providing postgraduate education and producing culturally sensitive obstetricians and gynecologists who can play a pivotal role in these efforts," says Dr. Merkatz.

He adds, "Our goal is to provide an integrated training site for a significant segment of the health force of the future and to equip them with the tools needed for providing more equitable and culturally sensitive care."

An important part of the DEWPoint Program has been the establishment of DEWPoint scholars, promising young African American and other minority physicians who are mentored and supported by various grants and Einstein programs to aid their academic growth, practice, and research endeavors. Each year, the program supports as many as nine Einstein faculty members through DEWPoint scholarships.

"Our hope," notes Dr. Merkatz, "is that the Program will become a national model for offering women and minority physicians greater opportunities for advancement in academia and in their medical practices."

The prospect for advancement is already a sweet reality for former DEWPoint scholar Dr. Dineo Khabele, who completed a fellowship in gynecologic oncology at Einstein. In addition to winning a Robert Wood Johnson Minority Scholar Development Award while at Einstein, Dr. Khabele received a job offer from Meharry Medical College where she is now director of gynecologic oncology and heads a laboratory studying ovarian cancer. It's a position she never envisioned achieving so early in her career.



Dewpoint Scholars with Drs. Merkatz and Damus, left to right: Dr. Setul Pardanani, Dr. Nereida Correa, Dr. Marsha Guess, Dr. Lubna Pal, Dr. Karla Damus, Dr. Genevieve Neal-Perry (seated), Dr. Irwin Merkatz, Dr. Rodney Wright, Dr. Garfield Clunie (seated), Dr. Wendy Wilcox, Dr. Ashlesha Dayal, and Dr. Gloria Huang.

"As academic leaders. members of the Einstein community must be proactive, particularly when serving families in the diverse community of the Bronx...Our hope is that the Program will become a national model for offering women and minority physicians greater opportunities for advancement in academia and in their medical practices."

Irwin R. Merkatz, M.D.

"I would not be where I am without the support, training, and opportunities that I received as a DEWPoint scholar at Einstein," she says. "Dr. Merkatz is a visionary, and he has designed the DEWPoint Program to provide junior ob/gyn faculty at Einstein with the resources and support that allow them to pursue their research and to establish themselves as clinical investigators."

Another DEWPoint scholar, Dr. Marsha Guess, agrees. Thanks to the support from the DEWPoint Program, Dr. Guess—who completed a fellowship in Urogynecology at Einstein in June 2004 and is now a member of the division of pelvic medicine and reconstructive surgery—was better able to pursue her research interests. She first realized her interest in research while still a medical student at UCLA School of Medicine, leading her to seek the fellowship at Einstein. With Dr. Merkatz's encouragement and mentorship, she was on her way, becoming one of two DEWPoint scholars enrolled in Einstein's Clinical Research Training Program.

"I would not be where I am without the support, training, and opportunities that I received as a DEWPoint scholar at Einstein,"

- Marsha Guess, M.D.



"Urogynecology has several surgical therapies but little concrete knowledge of why problems develop," she says. "And since problems like incontinence are more prevalent in women than high blood pressure, but people are reticent to discuss this issue, I felt compelled to explore it. My fellowship helped pave the way for my research track, and the CRTP provided me with critical guidance and support to pursue my research interests."

Her research recently produced landmark findings, which demonstrated that neurological problems might, in fact, be at the root of female sexual dysfunction, rather than the vascular connection previously believed to be the cause. That research, which was published in the American Journal of Obstetrics & Gynecology, was instrumental in getting the National Institutes of Health to fund clinical trials of an herbal remedy that purportedly improves sensation for women with dysfunction.

The opportunities for DEWPoint scholars go beyond patient care and research, since each scholar also serves as a mentor to high school and college students who have shown an interest in medicine. "It's a great feeling being able to give something

back," says Genevieve Neal-Perry, M.D., Ph.D., another DEWPoint scholar and Robert Wood Johnson award recipient who is an obstetrician/ gynecologist and a neuroscientist. "It's not an experience that I had as a young person, so being able to interact with young students is extremely rewarding."

For the DEWPoint scholars, mentoring is a two-way street. Dr. Neal-Perry has two mentors: Dr. Nanette Santoro, director of reproductive endocrinology and infertility, is her clinical mentor, while Dr. Anne Etgen, professor of neuroscience, is her research mentor. Dr. Neal-Perry has received a grant from the National Institutes of Health to support her research on the role of the central nervous system in reproductive aging. This research recently produced a paper published in the journal *Endocrinology*, for which she was first author.

he DEWPoint Program is one of many that Dr. Merkatz has introduced since becoming chairman at Einstein in 1982. As head of the department, he quickly expanded its mission to focus on the persistent disparities in health outcomes for women and infants in the Bronx. Since then, he has launched initiatives to provide the programs, education and research necessary to support the mission.

To begin with, he changed the formal title of the department by adding "women's health" to the traditional "obstetrics & gynecology." As a result, Einstein became the first medical institution in the nation to encompass this holistic notion of what is needed to impact on perinatal health for mothers and babies.

"There was a lack of emphasis on the overall health of women in society and I felt we needed to address it. By broadening the perspective to include women's health, we are better able to address issues of health that can have impact on pregnancies and on the health of both the fetus and the baby," he explains. "Promoting good health in women translates to a continuum of good health being passed on to their children and the entire family."

This is a common theme in the weekly departmental grand rounds, and it is at the heart of the department's nationally renowned annual postgraduate conference, "Autumn in New York."

The positive effects of this approach to women's health also are apparent to another DEWPoint scholar, Dr. Rodney Wright, in his everyday practice. An expert in HIV infection, Dr. Wright serves as co-chair of an AIDS clinical trial group studying transmission of HIV from mother to child. In this capacity, he sees about 90 pregnant women a year who have HIV.



"It's not an experience that I had as a young person, so being able to interact with young students is extremely rewarding."

- Genevieve Neal-Perry, M.D.

"Being a DEWPoint scholar helped me to more clearly define my goals and has tremendously changed my views of how I can accomplish those goals."

- Rodney Wright, M.D.



"While we have been able to get transmission rates from mother to child down from 25 percent to less than one percent, we're still seeking ways to minimize complications for both mothers and their unborn children," he says. "We also hope to identify more effective, long-term options for moms, since we find that most resistance to treatment occurs when the woman's virus is not completely repressed."

Dr. Wright first considered conducting HIV research at the suggestion of Dr. Merkatz. "At the time," Dr. Wright says, "Dr. Merkatz and I were discussing career paths. He suggested the DEWPoint fellowship (in maternal fetal medicine)."

Dr. Wright adds, "Being a DEWPoint scholar helped me to more clearly define my goals and has tremendously changed my views of how I can accomplish those goals. Before, my perspective was more local, while now it is global. And the potential for reaching and helping more patients has also grown."

Within obstetrics & gynecology and women's health, Dr. Merkatz also has applied a global approach that goes beyond the department's name. Through another initiative, he has established a core of divisions

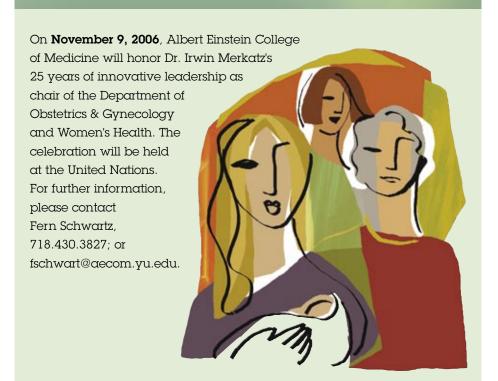
specific to disciplines within the field of obstetrics and gynecology that are critical to addressing the many facets of women's health - namely, maternal fetal medicine, gynecologic oncology, reproductive genetics, reproductive endocrinology and infertility, and female pelvic medicine and reconstructive surgery.

He notes, "Each division offers its own training program, which is a unique aspect of our program among traditional postgraduate programs in ob/gyn. And we've got faculty who are leaders in their respective disciplines who are teaching young physicians the intricacies of providing women's health. As a result, trainees come away better equipped to provide excellent care to their patients."

Dr. Neal-Perry agrees, noting, "Within Einstein there is a wonderful diversity of people, junior and senior faculty, who offer support, advice and opportunities for collaboration." And she attributes her positive experience at Einstein and those of her colleagues to the vision of Dr. Merkatz. "His enthusiasm is infectious, and he has encouraged so many people to achieve beyond what they might initially see for themselves."

In addition to Drs. Guess, Neal-Perry and Wright, current scholars of the DEWPoint Program include Drs. Francine Einstein, Ashlesha Dayal, Garfield Clunie, Lubna Pal, Nellie Correa, Wendy Wilcox, Setul Pardanani, Kavitha Ram, and Gloria Huang.

#### SAVE THE DATE



# **EVERYTHING** EVERYONE NEEDS TO **KNOW** ABOUT

## **EPIGENETICS**



John Greally, M.B., Ph.D.

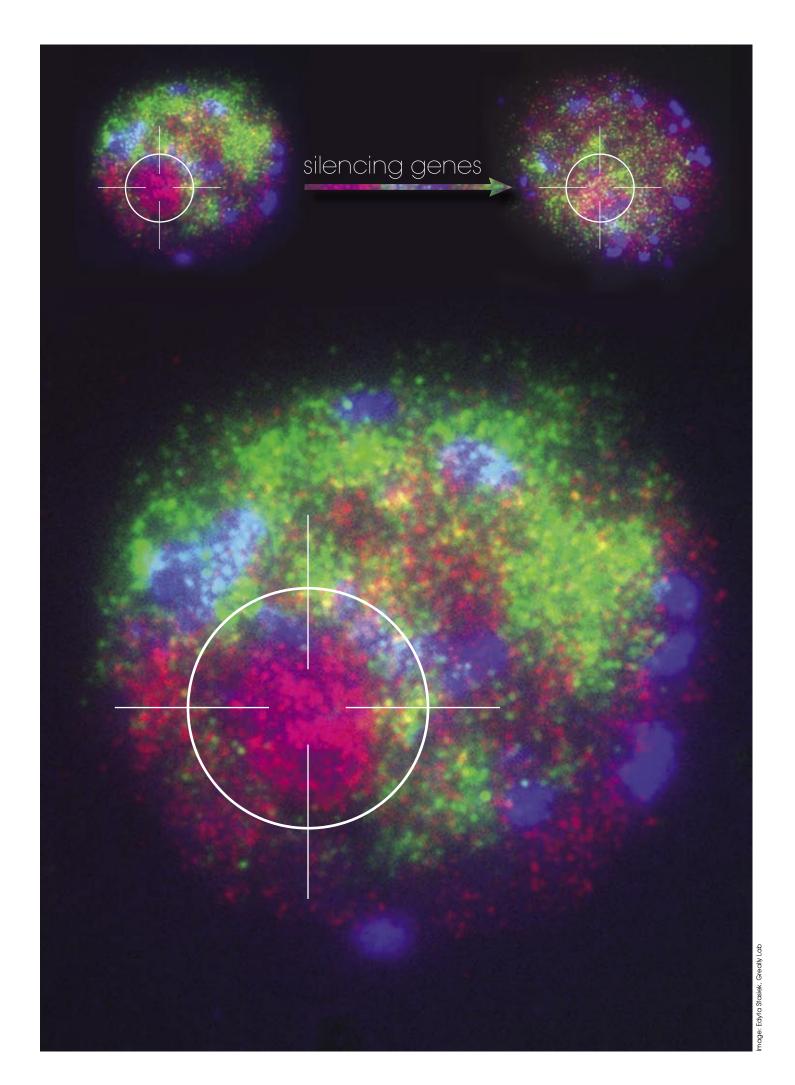
enes have long reigned as the ultimate
"players" in living systems. Duplication of
their DNA insures that replicating cells form
identical daughter cells and that parental
traits are passed to offspring. Species evolve through gene
mutation and natural selection. The proteins spawned by
genes govern the structure and functions of all organisms.

But now, genetic sovereignty is being challenged by research in epigenetics, which is revealing a level of biological authority that controls genes themselves. Epigenetics is proving to have a crucial role in development, in cancer and other diseases, and possibly even in evolution.

The Albert Einstein College of Medicine is becoming a leading center of epigenetics study. Spearheading this research effort is Dr. John Greally, assistant professor in the departments of medicine and molecular genetics. In introducing Dr. Greally when he lectured on epigenetics last January, Dr. Jack Lenz (interim chair of molecular genetics) noted that "John has brought a lot of enthusiasm here and has pushed all of us to move into hot and exciting areas that we all needed some pushing in."

We recently sat down with Dr. Greally to find out what all the excitement is about.

Opposite page: mouse cells from the pachytene stage of spermatogenesis. Blue shows nuclear DNA, while areas stained green (by use of an antimethylcytosine antibody) indicate methylated DNA. Within each nucleus, the bright red circled area is the X chromosome, identifiable by its unusually high density of repetitive sequences known as L1 LINEs. X chromosomes of cells observed early in pachytene (below and upper left) contain relatively few methylated (silenced) genes. During pachytene, X-chromosome genes become progressively silenced as shown by increased presence of green on X chromosome region of later-stage cell at upper right.



#### What is epigenetics?

Epigenetics is usually defined as the study of changes in gene expression that don't result from changes in DNA sequence and that can be passed on from one cell generation to the next. Epigenetic control fundamentally involves silencing genes. The main epigenetic modification—adding methyl groups to cytosine bases of DNA—acts like a switch to turn genes off (see illustration above).

#### Why is it called "epigenetics"?

The "epi" in epigenetics is from the Greek, meaning "above, upon or higher than." So, for an existing set of genes, epigenetics is an additional, higher set of controls that says, 'I'm going to use this group of genes in this way in this situation but can use different genes if circumstances change.' The critical issue that makes epigenetic gene silencing so important is that it's not that far a leap to go from appropriate gene silencing to inappropriate gene silencing that leads to cancer and other diseases.

#### Is that why epigenetics is such a hot area of research right now?

Primarily. Studies over the past few years have implicated epigenetic gene silencing in many if not all types of cancer. Overlooked sometimes in this focus on cancer is the fact that the epigenetic orchestration of genes is an essential physiological process for controlling normal development and insuring survival. One way to appreciate this crucially important role is to contrast epigenetics with genetics.

Genetics deals with DNA—a molecule designed to be dull and boring, like your computer's hard drive: You

don't want your hard drive to have any personality or to try to improve your data in some way, but just to keep on doing its data-management job.

DNA's repair mechanisms are aimed at protecting it against mutations, but that doesn't help us confront changing conditions. By contrast, epigenetics is all about helping us adapt—routinely adding or subtracting the methyl groups and other chemical "marks" on genes so that just those genes needed under particular conditions are actually switched on.

#### Which of our cells are likely to be affected by epigenetic control?

Epigenetic gene silencing is happening in every cell type in our bodies right now to suppress the majority of genes in those cell types where their expression is not needed. Consider the fact that your brain cells and liver cells are genetically identical, yet they are starkly different in phenotype and function. When we study the genomes of genetically identical animals and look at livers and brains, we find big differences in methylation patterns, which tells us that different versions of epigenetic control have yielded brain cells on the one hand and liver cells on the other.

So cell fate is fundamentally an epigenetic phenomenon: Cell types are determined by patterns of expression rather than by the genes themselves.

Epigenetics also exerts a major influence on cell-fate decisions during fetal development. The methylation marks on DNA can be detected, and my lab and others have developed techniques for studying tissues and determining the cytosine methylation of their entire genomes. Early

Cytosine methylation is a major epigenetic mechanism for silencing genes. It occurs when DNA methyltransferase enzymes catalyze the covalent binding of a methyl group to the 5-position of cytosine's sugar to form 5-methylcytosine.

in embryogenesis, if you look at the patterns of epigenetic marks that are laid down, you see massive changes as you go from the blastocyst to the implanted embryo to the embryo when it's forming more complex structures.

#### Are there other "normal" epigenetic occurrences?

Yes, and two in particular should be mentioned—X-chromosome inactivation and gene imprinting.

In X-chromosome inactivation, one of the two X chromosomes in the cells of female mammals is 80 percent shut down due to DNA methylation, presumably to prevent cells from getting a double dose of X-linked genes. This X inactivation occurs early in embryonic development, and whether a cell's maternal or paternal X chromosome is affected appears entirely random. Subsequent daughter cells all retain the same inactive X chromosome as their parent cells.

In gene imprinting, whether a gene is active or not depends on whether you inherit it from your mother or from your father. Here you have a difference in expression between basically identical pieces of DNA—one on your father's chromosome, the other on your mother's—and switching one or the other off involves epigenetic mechanisms. The silenced gene shows high levels of DNA methylation, as you would expect. About one percent of our genes are imprinted, and it can happen to them individually or in large clusters. We don't know why imprinting occurs, but it seems to be necessary for normal development.

#### What plant or animal models are used for studying epigenetics?

Many of our insights into epigenetics come from plant genetics. Plants don't have legs and so can't walk away when there's no water or when other plants block out the sun by



#### ... epigenetics is all about helping us adapt.

overgrowing them. The plant must take the genome it has and work with it.

In rice, for example, part of their natural history is spent under water, due to flooding. Having lost its oxygen supply because it's covered with water, the rice switches to anaerobic metabolism. Within minutes, genes that code for enzymes that carry out aerobic metabolism are repressed due to changes in chromatin conformation that prevent their transcription; conversely, previously silenced anaerobic enzymes are expressed because their genes have been switched on.

It's the same genome in both situations, but the way the rice uses it is different. Epigenetic gene regulation allows the rice to be flexible and to adapt rapidly to a drastically altered environment.

#### What directs this rapid epigenetic reshuffling of silenced and switchedon genes?

That's not at all clear yet. We know that the changes occur, and we recognize certain molecular events that can switch genes on and off, but we have a chicken and egg problem—the molecular mediators that can target specific sequences (like transcription factors or short RNAs) need to be switched on to induce an effect. If that requires a change in transcription, something is controlling these mediators at a higher level. If I had to guess, I'd speculate that transcription factor activation by cell signaling is the initiating event resulting in a cascade of epigenetic events, but that's unproven at the moment.

#### How about epigenetic adaptation in mammals?

The rice example illustrates epigenetic regulation at its most flexible, allowing these plants to adapt on the fly. Epigenetic control can also

involve more stable gene regulatory changes, as a fascinating story out of Canada illustrates.

A group of Canadian researchers was looking at a rat model of anxiety and had made a couple of observations. The glucocorticoid receptor seemed to be a good candidate for mediating anxiety, and poorlymothered rat pups tended to be more anxious than well-mothered ones. Good mothering behavior was defined as maternal licking and grooming of the pups and what is referred to as "arched-back nursing."

The researchers studied whether the expression level of glucocorticoid receptors in the pup hippocampus could discriminate between the wellmothered and the poorly-mothered pups. They found that the glucocorticoid-receptor gene in well-mothered pups had become relatively inactive due to gene methylation, the basic epigenetic gene-silencing mechanism. By contrast, the neglected pups had very little inactivation of that gene, so they had glucocorticoid receptors in abundance that could be stimulated to mediate the effects of anxiety.

Even more interesting, differential expression of glucocorticoid receptors in these rats persisted well into adulthood. So environmental influences can trigger epigenetic gene regulatory changes that are long-lasting and perhaps even permanent.

#### What about other environmental influences on epigenetic regulation?

A number of studies have shown that things like diet and nutrition influence the epigenetic control of our genes. There's a lot of evidence, for example, regarding pregnancies complicated by a partial tear in the placenta that reduces the flow of nutrients to the fetus from the mother's blood supply.

Surviving babies are born under-

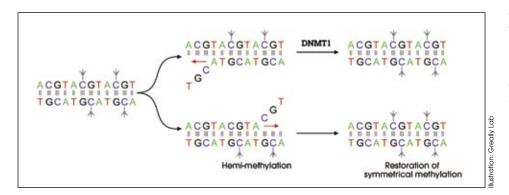
sized and malnourished and on reaching adulthood have a much higher risk of developing obesity and diabetes. There has apparently been an epigenetic resetting of the genes to conserve calories—clearly a lifesaving adaptation. But after babies are born and start eating a normal diet, they accumulate calories much more efficiently than other people, which can give rise to obesity and other problems.

Dietary fiber offers another example of nutritional influences on epigenetic gene regulation. When I was chatting recently with John Mariadason who works with Len Augenlicht at Montefiore, he pointed me to studies suggesting that fiber in the diet is good for more than just moving things through the digestive tract. When dietary fiber is acted on by the gut bacteria, you get high concentrations of a natural drug called butyric acid, which influences the epigenetic regulation of genes.

Immature cells of the intestinal epithelium always run the risk of becoming cancerous because they proliferate rapidly. Butyric acid lowers that risk by prompting these cells to differentiate into mature epithelial cells. So with dietary fiber producing this drug that induces differentiation, you have a very healthy epigenetic influence from the environment. Take away the fiber and you're reducing this influence and increasing the cancer risk.

#### Since epigenetic changes can be transmitted from one cell generation to the next, the methylated cytosines presumably are replicated as cells

Yes. Not all of DNA's cytosines are subject to methylation, just some of those that are followed by a guanine on the DNA strand—a dinucleotide symbolized as CpG. And since about three percent of the cytosines in



When cells divide, their methylation marks are faithfully transmitted to the next generation. The newly synthesized DNA strands have a cytosine methylation mark on only one of the two strands (hemi-methylation). This hemi-methylated state is recognized by DNA methyltransferase1 (DNMT1). This enzyme adds methyl groups to appropriate cytosine bases, assuring that symmetrical methylation occurs in daughter cells.

our genome are methylated in this way, methyl cytosine is referred to as our fifth nucleotide. During cell division, the "memory" of gene control exerted by these methylated CpG's is faithfully passed on to the daughter cells. This transmission also requires DNA methyltransferases, the enzymes that add methyl groups to the cytosine at CpG dinucleotides (see illustration above).

#### Are there other epigenetic mechanisms besides cytosine methylation?

DNA methylation seems to be the main epigenetic mechanism, but it's not the whole story. Chemical alterations to proteins in chromatin—the DNA-protein complex that comprises each chromosome—also play a key role.

In the chromatin, the double helix of DNA is wrapped tightly around groups of proteins called histones to form a continuous chain of bead-like structures called nucleosomes. This is how the two meters of DNA in each of our cells can be sauished down into a cell nucleus a few microns in diameter.

Until a few years ago, chromatin was thought of as merely an ingenious but basically static means of packaging DNA. But now we know that chemical modifications tacked on to the "tails" of histone proteins can dramatically affect genes by controlling access to them—sometimes blocking their transcription, other times allowing previously silenced genes to be expressed. Some of these histone tags are methyl groups, but other chemicals, including acetyl groups and phosphates, also decorate histone tails (see illustration at right).

How do DNA methylation and histone modifications actually turn genes off? It's not clear. DNA methylation leaves a methyl group sitting in the major

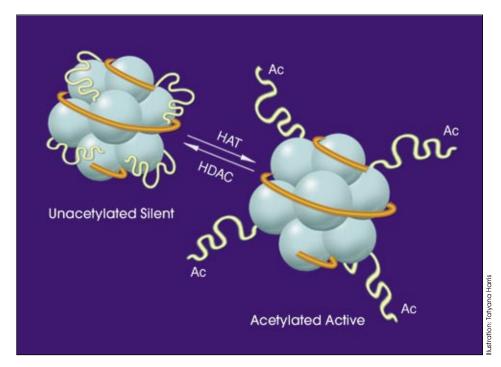
groove of the DNA double helix-—the place transcription factors normally dock—so methylation may interfere with the binding of transcription factors to DNA and their potential to activate genes. How acetylation and other chemical modifications of histone tails cause genes to switch on as well as off is also uncertain. It used to be thought that it involved altering the charge of the histone tails. But more recent data suggest that specific histone tail modifications can attract other proteins such as heterochromatin protein 1 (HP1) to the chromatin locally, and these proteins may actually mediate the transcriptional effects, perhaps by changing chromatin's conformation.

In addition to being transmitted to daughter cells, can epigenetic patterns be passed to the next generation through the germline?

There's emerging evidence that this can happen. Much of this is coming from studies of plants, but there are also examples closer to home. One of my favorites involves a mouse model called the viable yellow mouse. It has a gene mutation that causes it to have a yellow coat color and to develop obesity and diabetes later in life, so it's a very useful model for diabetes research.

Depending on how this mutated gene is methylated, genetically identical littermates can develop fur color ranging from yellow to brown. Mice in which the effect of the mutation has been epigenetically released will have yellow fur along with obesity and diabetes later in life; but their dark-furred, genetically identical brethren won't develop obesity or diabetes.

But here's the really interesting part: Rather than giving birth to a litter



Histone tails (yellow) in the nucleosomes of chromatin can be acetylated [addition of acetyl groups, Ac] by acetyltransferase enzymes (HATs), or they can be deacetylated by deacetylase enzymes (HDACs). The acetylation state appears to influence chromatin's organization. The more open, acetylated configuration may encourage gene expression by making DNA (shown in orange) more accessible to transcription factors



# So far, we know of nearly 70 genes that are epigenetically altered in cancer.

of the normal proportions of different-colored mice, yellow mothers are much more likely to have offspring that are yellow and therefore the same as they are epigenetically. Similarly, the darker mice are much more likely to give birth to mice that—like them—are brown and don't develop obesity or diabetes. So the DNA methylation patterns in the somatic tissues of these mothers is clearly being retained in their ova and then inherited by their offspring.

If you combine this evidence for inheritance of epigenetic marks with accumulating evidence for dietary and other influences on these marks, we end up with the intriguing possibility that epigenetic changes resulting from our behavior may be passed on to later generations.

We're not yet positive that this can happen in humans, but a provocative study published in February in the European Journal of Human Genetics suggests that it might. This study of men living in northern Sweden found that those men who started smoking before age 11 had sons with a greater body mass index at age nine than did men who started smoking later. Daughters apparently were not affected.

Of course, the possibility of epigenetic germline inheritance gets us into Lamarckianism, the discredited theory that evolution occurs when parents pass on to their offspring the characteristics they've acquired during their lifetime. And it doesn't fit with the neo-Darwinian idea of natural selection sorting through random mutations and then passing on only the beneficial ones. We may find that epigenetics is not actually directing evolution but instead is modifying the way future generations use a particular genome.

Certainly, the notion of epigenetic germline inheritance suggests that we're not just custodians of

our genomes, but also of our epigenomes—the epigenetic profile of our entire genomes. And if our irresponsible behavior predisposes our offspring to health problems, then future epigenetic research may raise very interesting ethical issues.

# You've said that epigenetic research has focused mainly on cancer. How important are epigenetic modifications in causing cancer?

Critically important. It's not too broad a statement to say that epigenetic changes have been found in every cancer that people have looked at. So far, we know of nearly 70 genes that are epigenetically altered in cancer, although this number is increasing almost weekly. They're mainly tumor suppressor genes that are silenced due to aberrant methylation. But in some cases, these abnormal epigenetic changes involve demethylation of certain loci that allows oncogenes to be switched on.

We know from our research that the biggest epigenetic change a cell can undergo is to become a cancer cell. In fact, for any individual, the differences in epigenetic patterns between a normal cell type and its cancerous counterpart will always be greater than the differences in epigenetic pattern between, say, that person's brain cells and spermatogenic cells. Cancer is definitely an outlier on the epigenetic spectrum.

#### So can cancer be triggered without gene mutations?

No one has yet proven that cancer can be caused solely by epigenetic changes, so we still believe in a cancer model that requires DNA mutations as part of the process along with epigenetics. However, there are several reasons why epigenetics seems to be a much more powerful force for dysregulating what goes on in the cell.

A mutation can affect just one gene allele at a time. But the broad, nonspecific dysregulation involved in epigenetics can literally take out hundreds or thousands of genes at once. In addition, a DNA mutation makes a gene go directly from "on" to "off". And while epigenetic changes can do that as well, they can also create intermediate levels of expression; and these more subtle effects may accumulate to create conditions favoring tumorigenesis.

Finally, it's becoming clear that epigenetic changes occur very early in cancer progression--perhaps even before mutations occur, suggesting that cancers might be preventable if epigenetic dysregulations could be prevented or corrected.

#### How do epigenetic changes lead to cancer?

As we've noted, epigenetic gene silencing—aberrant and otherwise—occurs mainly through methylation of cytosines in CpG dincucleotides. Those CpG dinucleotides in the genome that are normally unmethylated tend to cluster in small stretches of DNA referred to as "CpG islands."

These "hypomethylated" CpG islands are found mainly in promoter regions—stretches of DNA where the transcription of DNA into RNA is initiated. In fact, about half of the genes in our genome are believed to have promoter regions rich in these unmethylated CpG islands. When these normally unmethylated CpG islands become methylated, genes that once were active become silenced. And quite often, the genes that are silenced in this way are tumor suppressor genes.

Yet this hypomethylation that we see in promoter DNA, and in protein-coding regions as well, is actually an anomaly. When you look at the other 98 percent of the genome, you find that heavy cytosine methylation is the



#### ... epigenetic marks, on the other hand, are inherently meant to be malleable and reversible.



normal or default condition.

So hypermethylation prevails in the vast, noncoding areas of DNA generally referred to as "junk" DNA and serves to keep it in a transcriptionally inert state. That's probably just as well, since about half of junk DNA consists of transposons, virus-like repetitive sequences that can cause serious problems when released from suppression—inserting themselves into genes to cause mutations, for example, or creating chromosomal instability causing chromosomes to break and then recombine.

We now suspect that demethylation of noncoding regions of the genome may be linked to some types of cancer. In addition, we know that demethylation of oncogenes is also involved in cancer.

So abnormal epigenetic gene regulation actually contributes to cancer in two seemingly contradictory ways: aberrant methylation that silences previously active tumor suppressor genes, and aberrant demethylation that awakens previously silenced transposons or oncogenes. Sometimes both types of aberrations are found in the same tumors.

#### What are the underlying causes of aberrant methylation?

Methylation is definitely not a random event. It has to be influenced or directed in some way, and one of the major influences on methylation appears to be the aging process. Basically, the fidelity of the epigenetic marks that we're born with and retain during early adulthood starts to decay over time.

Last year, the Spanish investigator Manel Esteller published a study in PNAS in which he looked at two groups of identical twins: six-year olds and 60-year olds. Monozygotic twins are very close to being genetically identical; and Esteller found that young twins were also pretty much

indistinguishable epigenetically. But by the time twins were 60 years old, epigenetically they were no more similar in the tissues he was studying than any two unrelated individuals in the population.

These remarkable epigenetic variations could explain the curious differences in disease susceptibility so often observed in older identical twins. And since aging seems to affect our methylation patterns, agerelated epigenetic decay at critical loci may explain why cancer and so many other complex diseases tend to occur late in life.

#### What about other influences?

Gender may also affect methylation patterns. The investigator Peter Laird has shown that you can see sexspecific differences if you look at the epigenetic organization at different loci in the genome. Laird found that males tend to have one pattern, and females tend to have a different one. Hormonal differences may be responsible for these different patterns. Obviously, this is very interesting in terms of finding the underlying cause of autoimmune diseases such as lupus that have a sex-specific predilection for women.

Not surprisingly, genetic mutations also appear to play a role in triggering abnormal methylation. For example, the chromosomal translocation causing acute promyelocytic leukemia involves the fusion of a gene called PML with the retinoic acid receptor gene. The retinoic acid receptor drags the PML protein around the genome with it, homing to the usual sites to which it attaches, but PML in turn drags DNA methyltransferases with it, causing abnormal methylation of these sites. In this way, the magnitude of a single genetic event is amplified by means of epigenetic effects on a large number of loci. This leukemia is unusual

for being responsive to retinoic acid. After treatment, a striking finding is the reversal of this abnormal methylation, strengthening the case for the causative role of epigenetics in this leukemia.

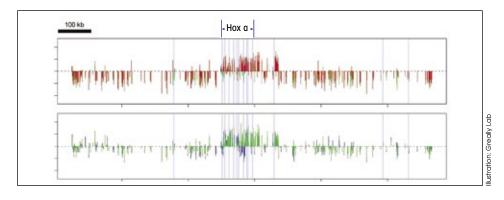
#### Could you describe the part of your epigenetic research that involves cancer?

Essentially, we're trying to profile tissues based not on how they look or function but instead on the basis of the methylation patterns on their genes. Even though a particular gene may appear perfectly normal, with no mutations, its abnormal methylation pattern compared with normal tissue—either hypomethylation or hypermethylation--may tip us off to its role in causing that tumor.

The way cell types are classified has changed dramatically in just the past couple of decades. Not that long ago, we separated tissues simply according to their phenotype. Later, gene-expression analysis using microarrays allowed us to classify cell types based on the different sets of genes that are switched on within them. These microarrays, or gene chips, can measure the expression of tens of thousands of genes by looking at mRNA levels.

Measuring mRNA output using gene chips helps differentiate subclasses of tumors that were previously impossible to separate. But the chips have serious drawbacks for cancer research. For one thing, microarrays can't detect small changes in gene expression. And if a gene is not expressed, the chip can't tell us why. So chips are merely inferential—they don't tell us whether that gene has been deleted, mutated or maybe silenced by methylation.

To overcome those drawbacks, Ari Melnick and I have established a collaborative research platform that combines gene expression analysis



Genes in the HOX A cluster are implicated in human breast cancer. Here, using a mouse model, Dr. Greally's HELP technique compares methylation states of HOX A genes in normal breast tissue (red), a localized breast cancer (green) and a metastatic breast tumor (dark blue). Light-blue bands are gene promoter regions. Less-methylated sites are upward bars, and methylated sites are downward bars. Promoter regions of some gene loci change methylation state in transforming from a normal cell to a cancer cell and then to a metastatic tumor cell, reflected by changes in gene expression that contribute to the disease.

with techniques that can detect the epigenetic marks on genes. My lab focuses on cytosine methylation, and we've developed a technique, called the HELP assay, that is able to look at cytosine methylation at every promoter region in the genome. Ari focuses on the other important epigenetic mechanism—histone modification—and is analyzing the chromatin structure at every promoter in the genome.

So, for example, we can say that the reason a gene is switched off in a breast tumor but not in normal breast tissue is functionally related to the methylation of cytosines at the promoter region of that particular gene. The illustration above shows the sorts of research results that we're obtaining.

#### What are the practical implications of mapping the epigenetic markers in tumors?

For one thing, we feel that analyzing the epigenetic signatures of tumors will greatly help in tailoring cancer therapies and predicting outcomes. A tumor in children called neuroblastoma, for example, will either melt away on its own or require years of very aggressive chemotherapy. For many years oncologists have been using amplification of a gene called *n-myc* as a marker for this cancer: having a tumor exhibiting *n-myc* amplification is usually associated with a good prognosis following chemotherapy.

The Japanese researcher Kazu Ushijima recently investigated whether differences in methylation at certain gene loci could help differentiate between good and bad prognosis in neuroblastoma. He came up with a screening panel consisting of several loci that did a much better job than *n-myc* in predicting the response to chemotherapy in these children.

#### How feasible are therapies that might correct epigenetic dysregulation and thereby help in treating cancer?

That question highlights one of the most significant differences between genetic and epigenetic changes. It's very difficult to reverse a DNA mutation—gene therapy, as we know by now, is a very hard thing to do. But epigenetic marks, on the other hand, are inherently meant to be malleable and reversible. Research right now is focused on finding drugs that can activate silenced tumor suppressor genes, either by removing methyl groups on DNA or by influencing the chemical tags on histone tails.

For example, a new class of drugs called hypomethylating agents work by inhibiting DNA methyltransferases. Over the past two years, the U.S. Food and Drug Administration has approved two of these drugs—azacytidine and decitabine—for treating a pre-leukemia condition called myelodysplastic syndrome. Other hypomethylating agents are in clinical trials, and so are drugs called histone deacetylase inhibitors, which activate silenced genes by preventing histone deacetylases from removing acetyl groups from histone tails.

Ari Melnick and I are involved in a multicenter clinical trial, based at Johns Hopkins, in which patients with myelodysplastic syndrome are being treated with both types of drugs: decitabine to hypomethylate DNA and an experimental drug called MS-275 that inhibits histone deacetylase enzymes. We're hopeful that epigenetic therapy, using drugs capable of targeting aberrant epigenetic changes, will ultimately make a real difference in cancer treatment.

#### What is your overall research goal?

My colleagues and I want to study the epigenome—the methylation profile and other epigenetic modifications of the entire genome. This

effort will actually be much more complex than the human genome project, since there is no single epigenome. Rather, every cell type has a different epigenome, and every cell type that you expose to different conditions will potentially have yet a different epigenome. So the sheer amount of experimentation that must be done—and the management of data afterward—is a daunting task that is far beyond the capacity of any one lab.

Two years ago, a number of European research centers organized a human epigenome project. Because of their initiative—and the realization that this is a worthwhile task—a few months ago the American Association for Cancer Research convened a meeting to discuss enlarging the scope of the project. There were about 40 of us from the U.S., Europe and Asia at this meeting, and we talked about what would be required. We held a subsequent meeting, sponsored by the NIH, where we saw that this initiative is gathering momentum.

One thing that is abundantly clear: this human epigenome project will require spending a massive amount of our time just working with the data. If you really want to be systematic about studying the epigenome—in terms of looking at large regions of the genome, at lots of people, lots of different health conditions, lots of different cell types—you'll be confronting massive data management and data analysis issues. So bioinformatics and the computation work it involves will play a vital role in this project. But at the end of the day I'm convinced it will be worthwhile and will provide a map for exploring the epigenome in human disease.

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#### FACULTY HONORED AT 50<sup>TH</sup> ANNIVERSARY CELEBRATION

series of exceptional special events to mark the 50th anniversary of the College of Medicine in 2005 culminated in December with a reception at the medical school in honor of Einstein's illustrious faculty. The occasion followed a year-long 50th anniversary celebration that included an on-campus party under a "big tent" for nearly 4,000 faculty, students and staff, a  $50^{\text{th}}$  Anniversary Scientific Symposium in which the speakers included four Nobel Laureates and two nationally prominent former members of the Einstein faculty, and an anniversary gala dinnerdance at the Waldorf-Astoria attended by nearly 700 members of the Einstein "family."





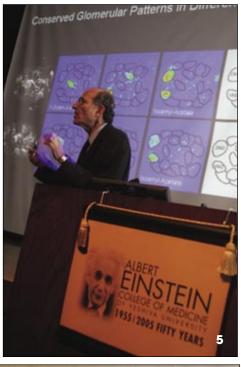






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t the reception honoring faculty, Dean Dominick P. Purpura announced the appointment of four members of the Einstein faculty as newly designated "Distinguished Professors," and the awarding of the College of Medicine's first Lifetime Achievement Award for Medical Education. The newly named Distinguished Professors, all of whom are members of the National Academy of Sciences, are:

MICHAEL V.L. BENNETT, D. Phil., Professor of Neuroscience and Sylvia and Robert S. Olnick Professor of Neuroscience, whose research has increased understanding of the biophysics and molecular structure of gap junctions and their roles in intercellular communication and electrical transmission:

SUSAN B. HORWITZ, Ph.D., Co-Chair of Molecular Pharmacoloav and Rose C. Falkenstein Professor of Cancer Research, whose research demonstrated how Taxol, a compound isolated from the bark of the Pacific yew tree, inhibited the uncontrolled cell division that characterizes cancer. leading to an entirely new class of chemotherapeutic drugs;

#### **CELEBRATING 50 YEARS**

Photos: 1-2-3, The entire College community gathers under the big tent; 4, the elegant anniversary gala at the Waldorf-Astoria; 5, the allday scientific symposium attracted an overflow audience to Robbins Auditorium; 6, the 50th anniversary year concluded on a high note with a reception honoring the faculty. See story this page.

STANLEY G. NATHENSON, M.D., Professor of Microbiology & Immunology and Samuel H. Golding Professor of Microbiology, whose research has helped reveal the immunological basis for the body's rejection of transplanted tissues and organs and led to therapies that can overcome the rejection process; and

MATTHEW D. SCHARFF, M.D., Professor of Cell Biology and Harry Eagle Professor of Cancer Research/ National Women's Division, whose research on the synthesis and assembly of antibody molecules and whose pioneering work in developing monoclonal antibodies has proven extremely useful in disease diagnosis.

At the special reception, Dr. Purpura also presented Einstein's firstever Lifetime Achievement Award for Medical Education to ALBERT S. KUPERMAN, Ph.D., recognizing his innovative leadership during 30 years as Associate Dean for Educational Affairs and Director of the Office of Education at Einstein.



# Up CLOSE & PERSONAL with DOMPURPURA

#### by Ira Millstein

Editor's Note: Last February, Dean Purpura, the longest-serving medical school dean in the country, and his wife, Penny, were honored at the College's annual dinner/dance in Palm Beach, Florida. Nearly 300 guests were on hand to celebrate the Purpuras and to honor Dr. Purpura on the occasion of his upcoming retirement as Dean. Ira Millstein, Chairman of Einstein's Board of Overseers, delivered some personal reflections on his many years of friendship and collaboration with Dr. Purpura. His remarks follow:

I have known and worked closely with Dom for the 22 years of his Deanship, both as a Board member and as Einstein's pro-bono lawyer in every negotiation with hospitals and the city. We are close friends, and he has been a trusted advisor to me and my family for what seems like forever.

If what I am about to say is biased, so be it.

I am not going to recite his outstanding background, or list all his honors and achievements. You all know what they are. For me, they sum him up with the highest honorable appellation. He is a professional's professional, a wonderful life-long husband to Penny—a wonderful person in her own right—a devoted father and grandfather.

But that's just one piece of the picture. The other piece that characterizes Dom, quite coincidentally, was described in today's New York Times in an article describing the life of an academic leader. It read, in part: "...in many cases incompatible demands from the various factions—the administrative governing boards, the faculty, the students, the alumni, the donors and those holding the federal purse strings...' And to this list, in Dom's case, add the five teaching hospitals we do not own, nor do they

# So there is your Dean. After 22 years, loved, respected and trusted. An amazing accomplishment, possibly unparalleled.

own us, the diverse community which surrounds us, and our loving parent, the highly respected and to be preserved, Yeshiva University.

What qualities have made Dom so successful in leading this medical school with all of its pulls and tugs?

- First and foremost—recognizing that there is a polestar that is essential to the success of any academic enterprise. That polestar is the faculty and students.
- Selflessness in sticking to the polestar.
- Trustworthiness for all the extrinsics to see and experience.
- Humanity, without which the medical profession is the lesser.

A quick example of each:

The faculty and students. You are not likely to find a Dean lasting 22 years who is not loved and respected by those who teach and learn at the institution. I know that the words love and respect are not fanciful in his case. For our faculty and student body, over the years, those words are real. In every instance I know of, Dom has been in their corner, concerned with creating and supporting the best available. They are his real palpable polestar. He guided the institution for them with the highest standards of fairness and ethics. He demanded from them only collaboration and community. And he got it.

Selflessness. Many educational leaders look at their perches as a means of self-aggrandizement—books, articles, speeches, self importance. I know those types, having been a teacher at some great institutions. They lose their faculties pretty quickly . . . not Dom. He stuck to his polestar without deviation, always putting the successes of the faculty and the students up front. In all my years on the Board, I never heard Dom lobby for something for himself. It was always about a new recruit, a new lab, a new building, more space,

better facilities for the students. The list was endless, and expensive, but never did it include fancy perquisites for Dom.

Trustworthiness.
How in the world
did Dom convince
Montefiore to
accede to accepting additional
hospitals into our
training network. It
was essential that we
do this because we
had outgrown our
existing training sites.

But egos and history are powerful. Yet Dom did it. How? Because each of the hospitals trusted that Dom would do the 'right thing' for each of them, and he did.

**Humanity.** And this is personal anecdote time. My daughter Liz has always felt free to call Dom with medical questions, and he always answers with patience and understanding. Years ago when her first born, Kate, was three, Liz called Dom, thinking Kate had a hearing problem because Kate rarely listened to her mom. Dom could easily and properly have reminded Liz that she had a three year old. Instead, he patiently recommended a pediatric hearing specialist who tested Kate and reported to Dom, who gave Liz the diagnosis: Liz was the proud possessor of a willful, obstinate three year old, and Liz would just have to live through it. Dom was, of course, correct, and we are all living through it. Dom has handled these regular intrusions on his time for many people, both on and off our Board, but within his ambit, understanding that large or small, health problems are important to those who have them, or even think they have them.

Last anecdote. Some years ago I



Left to right: Ira Millstein, Dom and Penny Purpura

was representing the French Institut Pasteur in a dispute with the U.S. NIH as to who discovered the AIDS virus and was entitled to the royalties on the first test kit. Jonas Salk became involved in helping determine the history of the science, but needed library research to support him. When I explained to Dom that the dispute was holding up the science, and the test kit, he promptly sent a team to work in the library, helped Dr. Salk, and the dispute was resolved between President Reagan and Jacques Chirac with no mention of any of the helpers.

So there is your Dean. After 22 years, loved, respected and trusted. An amazing accomplishment, possibly unparalleled.

For me and for all of us, Dom, this is hardly a farewell. This dinner will help provide the support for your next incarnation. More research, more helping faculty and students when they walk through the always-open door in your new office. And assisting the new Dean, Allen Spiegel, as he assumes his role, which is made all the easier because of what you are bequeathing him and because you also understand that he has to find his own way.

#### **"TOPPING-OUT"**

#### Ceremony Marks Construction Milestone for **EINSTEIN'S NEW RESEARCH BUILDING**



n Monday, May 1, 2006, the Albert Einstein College of Medicine held a special ceremony markina the latest milestone in the construction of its Michael F. Price Center for Genetic and Translational Medicine/Harold and Muriel Block Research Pavilion. The highlight of the "topping-out" ceremony featured the placement of the last steel beam on the roof, or "topping-out," of the new building.

"The 'topping-out' of a building under construction is traditionally a symbolic milestone for construction workers at the site," said Samuel G. Weinberg, Chairman of the Building Committee of Einstein's Board of Overseers. "It's wonderful to witness the last steel beam being hoisted to the roof, and to see the progress we've made in creating an attractive state-of-the-art biomedical research building."

Those joining the festivities were invited to sign the last steel beam before it was hoisted to the roof of the five-story, 201,000 square-foot research building. Located directly opposite Einstein's Jack and Pearl Resnick Campus, the new \$200-million facility is being built on property near the corner of Morris Park Avenue and Eastchester Road in the Bronx.

Construction of this major new biomedical research building began in October 2004 and is scheduled to be completed in December 2007. Upon completion, the Price Center and Block Pavilion will house 40 high-tech laboratories in addition to research support facilities and a 100seat auditorium.

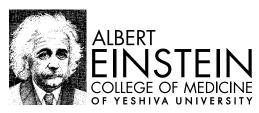
The building is named in honor of Michael F. Price, and Muriel Block and her late husband, Harold, who have made the two largest gifts in the 50-year history of the medical school,

totaling more than \$45 million. The Price Center/Block Pavilion also represents the largest medical research facility to be constructed in the Bronx since Einstein opened in 1955, and its design will further advance Einstein's long-standing emphasis on fostering scientific collaboration among its faculty and researchers. Each floor will contain "open laboratories" where biomedical researchers may easily consult with one another.

Tishman Construction Company is the construction manager of the building, which was designed by the architectural firm of Payette and Associates.

(Photo lower left): Drs. Purpura and Spiegel, with Board members, (1 to r) Philip Altheim, Burton P. Resnick, Michael F. Price, Samuel G. Weinberg, and Ira M. Millstein, chairman.





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