

Yale Medicine

spring 2007

The virtual patient

How digital simulators, actors and mannequins have transformed the teaching of medicine

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Town and gown come together for science education

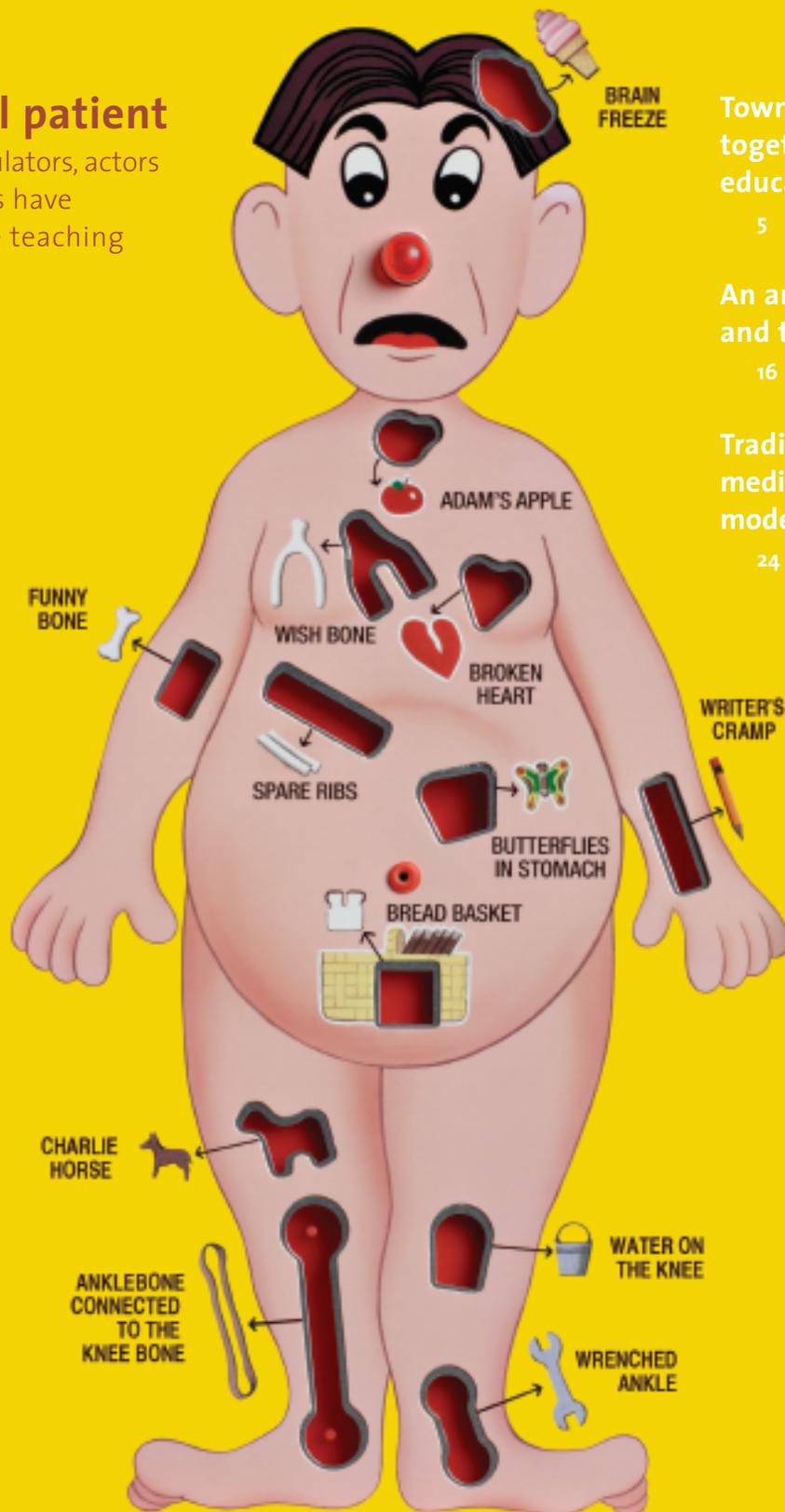
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SPRING 2007

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The goal of the Hasbro board game "Operation" is to complete a delicate procedure, using tweezers to remove a "body part" successfully, without tripping a buzzer. In the more serious matter of physician training, advances in computer technology combined with a game-like approach have changed the way skills are taught. Now medical students and residents can practice surgical techniques on computer simulators and mannequins and with standardized patients, actors who help students develop their clinical interview skills.

BACKGROUND

Body parts from "Operation" must be removed without touching the metal edges of a cavity in the game board.

Photographs by Frank Poole



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On the Web

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On our website, readers can submit class notes or a change of address, check the alumni events calendar, arrange for a lifelong Yale e-mail alias through the virtual Yale Station and search our electronic archive.

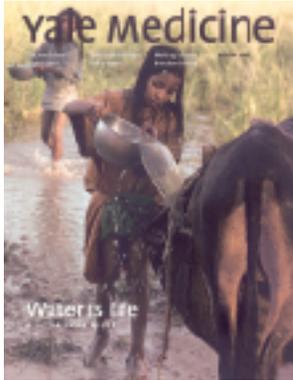
“Who among us would share?”

Please pass on my thanks to Ariane Kirtley for her article “Water is Life” [*Yale Medicine*, Winter 2007].

I was especially moved by her account of being invited to share a meal by two women in one of the villages she visited. Despite having had to scavenge for wild zucchini and wild grains during a time of famine, they were eager to share what they had with someone who to them must have seemed unimaginably prosperous.

Who among us would share what we had if we had so little? And who among us *will* share what we have, since we have so much?

*Michelle Sanders, M.D. '99
West Westford, Mass.*



HOW TO REACH US

Yale Medicine welcomes news and commentary. Please send letters (350 words or less) and news items to *Yale Medicine*, 300 George Street, Suite 773, New Haven, CT 06511, or via e-mail to yymm@yale.edu, and include a telephone number. Submissions may be edited for length, style and content.

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I wanted to congratulate the photographer Ariane Kirtley on the amazing cover photographs she took for the most recent edition of *Yale Medicine*. Simply amazing.

*Kevin M. Johnson, M.D. '03
St. Louis, Mo.*

Beeson article brings back memories

I read with more than passing interest the piece by Richard Rapport, M.D., on Paul Beeson, who was one of my real-life heroes [“Fever, Internal Medicine and Paul Beeson,” *Yale Medicine*, Winter 2007]. In it, he mentions the tragic case of the young woman who died from an overdose of intrathecal penicillin. I am certain that from that incident came the study that led to the paper by Elihu Schimmel, M.D. '54, HS '61, FW '64, titled “The Hazards of Hospitalization,” which appeared in the *Annals of Internal Medicine* in January 1964.

Each of Beeson's chief residents had a yearlong project that usually became the subject of medical grand rounds toward the end of the academic year. Schimmel's project was titled “The DOMP Syndrome,” the acronym referring to diseases of

medical progress, perhaps the precursor of the Institute of Medicine's volume *To Err is Human*. In-hospital complications of all sorts, including iatrogenic deaths, are front-burner items today. I hesitate to think of the reams of regulations that have been generated hoping to prevent, or at least minimize, these untoward occurrences.

As medicine becomes more technology-driven, the pace of hospital practice quickens and the severity of illness of those patients who are hospitalized increases, the health care professionals who battle to reduce in-hospital complications will be working against a considerable gradient. I wish them good luck in this difficult and worthwhile endeavor.

I enjoy *Yale Medicine* and read it regularly. Keep up the good work!

*James B.D. Mark, M.D., HS '60
Stanford, Calif.*

The obituary for Paul Beeson brought back many memories for me, and one of the anecdotes certainly rang a bell. When I started my internship in 1963, I learned that there were more interns than slots for residents and one intern would not be kept on.

One of my patients, who had alcoholic hypoglycemia, was chosen to be the subject of grand rounds that summer. Tom Ferris, my chief resident, told me to write the history and physical examination and then to come to his office to rehearse. The next day, the auditorium was packed. In the first sentence I extemporaneously described the patient as “an alcoholic bum.” There was an audible gasp from the audience and I knew I had done something wrong. On Monday, Tom told me that Beeson wanted me to know that there may have been bums at Bellevue but there were no bums in New Haven. I imagined then that my fate was sealed—I would be the intern who was cut because I was not enough

of a New England gentleman. Fortunately that did not happen. Before the year was out, however, I received a draft notice and went to see Beeson. He was able to get me reassigned to the Public Health Service at the Communicable Disease Center (which later became the Centers for Disease Control and Prevention), and he apologized to me for not being able to keep me out of the service altogether!

His advice was to make an opportunity out of what appeared to be adversity. I did, and that began my career in infectious diseases. I subsequently went to visit him in Oxford to ask his advice about where to do a fellowship. We had lunch at a pub; he was generous with his time and advice. He was so happy at Oxford, working on the immunology of eosinophilia in rats with trichinosis. He said he had left Yale so that he would have time to do research, rather than doing only administration for a department that had grown too large for his taste. I only regret not having had more time directly under his tutelage. He was a great teacher and a terrific role model.

*Joshua Fierer, M.D., HS '68
San Diego, Calif.*

Thank you very much for the magnificent article about Paul Beeson's tenure at the School of Medicine. The author, Richard Rapport, M.D., could not possibly express the awe that Dr. Beeson inspired in our entire class. It is no accident that a majority of my classmates chose internal medicine as their career choice—inspired, of course by the great physicians and teachers that surrounded Dr. Beeson.

We were thunderstruck by the fact that one of our classmates actually died as a complication of an infectious disease while a patient of Dr. Beeson's at the Grace-New Haven Medical Center! We could not imagine that Dr. Beeson could permit such a tragedy to occur!

*Fred M. Palace, M.D. '60, HS '64
Basking Ridge, N.J.*

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Simulation, Chinese herbs and a career studying killers

For our cover story this issue we asked writer Jennifer Kaylin to explore the ways in which simulation is used to train physicians. Simulation techniques range from mannequins that talk, breathe and even “die,” to sophisticated computer simulators that let residents and students test their skills at intubation and colonoscopy, to actors who take on the characters—and ailments—of patients in order to teach interview skills. These techniques have become standard training tools in medicine and, as medical education increasingly emphasizes clinical skills, a new way of evaluating students and residents.

We also focus on the meeting of mainstream medicine and traditional Chinese medicine. Since ancient times and all around the world, humans have found remedies in herbs and plants. As writer John Dillon reports, Yung-Chi Cheng, PH.D., the Henry Bronson Professor of Pharmacology, has taken the lead at Yale in seeking out Chinese herbal medicines that can enhance the effects of chemotherapy while mitigating toxic side effects.

Finally, writer Colleen Shaddox takes us into the world of Dorothy O. Lewis, M.D. '63, HS '70, who has spent her career studying killers. Since her childhood Lewis has been driven by a desire to know what makes society's outcasts tick. Although her initial theories fell outside what was then the psychiatric mainstream, her ideas have become accepted and even cited in Supreme Court decisions. Among those she has studied are serial killer Ted Bundy, John Lennon's assassin Mark David Chapman and Washington sniper John Muhammad. In all violent offenders she has found three elements that add up to a recipe for violence.

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SECOND OPINION BY SIDNEY HARRIS

"...AND I'LL KEEP SAILING THE SEVEN SEAS UNTIL I FIND
THE PERFECT PROSTHETIC DEVICES."

PET Center opens on Howard Avenue

New tools for diagnosis and treatment are available to clinicians and patients.

Despite recent advances in molecular medicine, physicians are still in the dark about many diseases, gleaning clues to a therapy's effectiveness only by studying changes in symptoms. Even as doctors seek the best treatment, patients may deteriorate. At Yale's new Positron Emission Tomography (PET) Center, researchers hope to bring light into this darkness by discovering novel diagnostic tools for otherwise hidden molecular abnormalities and speeding development of new medications.

PET imaging, said George Mills, M.D., director of the Division of Medical Imaging and Radiopharmaceutical Drug Products at the Food and Drug Administration's Center for Drug Evaluation and Research, is "the essential foundation" of the agency's efforts to modernize the process of developing new medicines. Mills spoke at the January 18 opening ceremony for the new 22,000-square-foot facility, located at 801 Howard Avenue.

PET is a noninvasive imaging technique that scans for minute amounts of radioactive material—radiotracers—that have been injected into a patient's body to bind to specific organ sites, providing images of molecular function. Researchers and clinicians use this information to study changes in organ function as a result of disease or in response to treatment. The radiotracer can also label a drug to determine whether and how much of

the compound has reached its target. Labeling enables researchers to study the safety and efficacy of different dose levels and identify biological markers of disease that can aid in diagnosis.

"The work we do here will build the knowledge we need to develop diagnostic imaging agents coupled to therapy," said J. James Frost, M.D., PH.D., professor of diagnostic radiology and psychiatry, chief of nuclear medicine at Yale-New Haven Hospital and director of the PET Center. Joining Frost as co-directors are lead physicist Richard E. Carson, PH.D., professor of diagnostic radiology and biomedical engineering; and lead radiochemist Yu-Shin Ding, PH.D., professor of diagnostic radiology. Completing the senior faculty team is Henry Huang, PH.D., a radiochemist and associate professor of diagnostic radiology.

The development of the center was made possible, in part, by Pfizer, the pharmaceutical company, which contributed \$5 million to establish it and provides \$2 million annually to support PET imaging studies of mutual research interest to both parties. Most research at the center will be supported by federal grants. The company has already used the PET facilities to study a small group of patients to determine how much of a new drug for depression would be required to reach its target in the brain, and how much would generate unacceptable side effects, said Diane K. Jorkasky, M.D., Pfizer's vice president of clinical pharmacology.

Researchers are usually required to give dosages that escalate over several months to large numbers of patients to establish the safest and most effective



TERRY DAGRADI

Robert Alpern, Diane Jorkasky, Richard Levin and Pfizer CEO Jeffrey Kindler cut the ribbon at a ceremony marking the opening of the medical school's new PET Center.

dose of a drug. "If we are able to avoid the need to do large-scale clinical studies like that, we'll be saving tons of money and time, and most important, we won't expose patients needlessly to a drug that may not have any benefit," said Jorkasky.

Frost said the center will serve as a core facility for the entire School of Medicine. Some biomarkers discovered in the course of research projects with Pfizer or other companies will be available for faculty research projects.

Along with cardiology and oncology, other major areas of focus are Alzheimer's disease, schizophrenia, depression, obesity, post traumatic stress disorder and other conditions that are difficult to diagnose and treat. Frost hopes that the center's research will help to identify biomarkers for subtypes of these diseases, which can help determine the best treatment for a given individual. "Ultimately this will benefit our patients," Frost said. "That's the key."

—Marc Wortman

Hands-on science program for local students brings town and gown together

The students who were asked to identify and explain the function of a muscle in the cadaver they've been working with in the School of Medicine's anatomy lab aren't enrolled at Yale, but they can take advantage of the school's offerings. They are high school students participating in the Anatomy Teaching Program, one of several ways in which the medical school collaborates with Hill Regional Career High School, a magnet school located just a stone's throw from campus.

Ten years ago Yale formalized a partnership with Career High that has enabled its students to benefit from the university's expertise and resources. The magnet school attracts students from New Haven and its surrounding suburbs who are interested in a career in health, business or computer technology. The partnership began informally with the anatomy program in 1993 and has expanded to include a variety of offerings.

Yale students and faculty instruct and mentor Career High students in a number of settings. In the medical careers class, for example, Yale public health students come to Career High to speak about medical career options during the first semester, while the high school students complete an internship at Yale in the second semester. The Department of Epidemiology and Public Health donated a research-quality electron microscope to help Career students understand molecular structures; it also recommended the types of equipment that would be most

appropriate for a certified nurse's aid room set up to look like a clinic. Another learning opportunity is offered to advanced biology students who come to Yale twice a month after school with their teacher, Shirley Neighbors, to work with medical students who help them with course material.

In the anatomy course, which is also taught by Neighbors, two classes meet twice each month in Yale's anatomy lab, where first- and second-year med students overseen by William B. Stewart, PH.D., associate professor of surgery and chief of the Section of Anatomy and Experimental Surgery, volunteer as instructors. In small groups, the students explore such topics as cardiovascular health, energy metabolism and infectious diseases. "One of the ideas is that these kids will become community ambassadors for health," said Stewart. For the students, it's a rare opportunity to see firsthand the effects of disease. "We actually get to touch the [cadavers] and feel what we're looking for," said Career High junior Lorraine Gabriel.

In the SCHOLAR (Science Collaborative for Hands-On Learning and Research) program, a three-week summer residential science program for students entering grades 10 through 12, Career students have a chance to become fully immersed in campus life. They not only study science subjects at the college level and conduct research under the supervision of Yale faculty, but they also get a taste of college life by living in the dorms. The students normally participate in the SCHOLAR program for three years. For Minerva Ruiz, who now works in the Family Support Services section of the Yale Child Study Center, the summer program was an eye-opening experience. Attending classes in which professors treated her as a college student, conducting a study on the ways in which smoking affects the brain and tasting ethnic food at local restaurants helped make her a more open person, she said. "We were able to



First-year medical student Terri Huynh leads students from Hill Regional Career High School through an exploration of the human body in the Anatomy Teaching Program.

go off to college and be comfortable with that."

Like many of her classmates, Ruiz, who graduated from Florida International University and plans on getting a PH.D. in psychology, takes education seriously. More than 96 percent of Career graduates went to college in 2005 (the college-bound rate for New Haven students in general is 83 percent); for those who participate in the SCHOLAR program, the college attendance rate is 100 percent.

The collaboration between Yale and Career High doesn't benefit only the high school students, however. As Neighbors watched second-year med student Rebecca Bruccoleri explain how food is converted to energy, she observed, "If they can find time to do this as a med student, you can imagine what kind of doctors they'll be."

—Jill Max

Training physicians—new ways of teaching in a changing medical landscape

For the past 32 years, Yale faculty from the Department of Internal Medicine have taught at 10 hospitals throughout Connecticut through the Yale Affiliated Hospitals Program (YAFP). Begun in 1975, YAFP is currently the largest consortium of internal medicine training programs in the United States. Its goal has always been to improve the quality of medical education throughout the state. With 446 full-time faculty among nine residency programs and more than 6,500 attending physicians, the program trains more than 450 residents in internal medicine each year. It also provides opportunities for collaborative clinical and educational research as well as selected subspecialty clerkships at Yale for affiliated medical residents. Each year 100 residents from other hospitals take electives at Yale-New Haven Hospital. Member hospitals include the Hospital of St. Raphael in New Haven, Bridgeport Hospital, Waterbury Hospital, Greenwich Hospital, Norwalk Hospital, Griffin Hospital in Derby, St. Mary's Hospital in Waterbury, Danbury Hospital and Lawrence & Memorial Hospital in New London.

"This is a very robust relationship," said Silvio E. Inzucchi, M.D., professor of medicine (endocrinology) and director of the program, speaking at YAFP's 30th annual symposium in November. "After 30 years, the program is still evolving—it is clearly of mutual importance to both the department and our affiliates." Asghar Rastegar, M.D., professor of medicine (nephrology) and associate chair for academic affairs, called it a "unique network." Yale's collaboration with smaller, community-based hospitals, he said, allows them to attract better faculty as well as trainees to their programs, enhance training of their residents and maintain academic links that serve as a resource. And, noted

Peter N. Herbert, M.D. '67, HS '69, vice president and chief of staff at Yale-New Haven Hospital, a vigorous educational program strengthens the overall enterprise. "Training programs are critically important to the retention of our faculty," he said.

But all is not well in the training of new doctors. More than a dozen speakers cited new challenges to medical education, not only in Connecticut but also in other parts of the country. Among those challenges are young doctors' desires for a less stressful and demanding lifestyle, lack of financial support for education and the shrinking emphasis on the hospital as the primary training setting. As Herbert noted, patient contact typically takes up an hour or two of a resident's day, while another six to seven hours are spent "doing largely clerical things that, in a practice setting, would be done by someone else."

Dean Robert J. Alpern, M.D., Ensign Professor of Medicine cited inadequate funding for education as a major problem, observing that tuition covers only half the cost of a medical education. Clinical practice, which has traditionally brought in money to fill that gap, is increasingly under financial pressure itself. "The ability of the clinical practice to subsidize education is going away," he said. "You can't run a medical school without a clinical practice, but what is optimal for education is not necessarily optimal for clinical practice."

Also of concern, said Jack A. Elias, M.D., the Waldemar Von Zedtwitz Professor of Medicine and chair of medicine, is the aging of the physician-scientist population, whose unique perspective bridges the lab and the bedside. Ten years ago, he said, 57 percent of the physician-scientists who received grants from the National Institutes of Health were 45 or older. "We are losing ground in this area at a time when translational research is blossoming."

Panelists also cited the importance of mentorship for medical students

and young doctors. Mary E. Tinetti, M.D., the Gladys Phillips Crofoot Professor of Medicine (geriatrics) and professor of epidemiology and public health, said that in the past students of either gender were linked with experienced older men, because the majority of available mentors were men. Today, however, there are women who can mentor other women and members of minority groups who can guide others from their respective backgrounds—even from afar—because they are "people who share many life experiences."

Despite their concerns about the future of medical education, speakers also noted cause for optimism in efforts to address the challenges. Elias cited a one-year master's program in public health at Yale that is geared to practicing physicians. Alpern said that while the financing of medical education is built on a shaky foundation, "each school figures out a way to get around it." And Rastegar, in an interview after the symposium, said that the education at Yale rests on a core belief shared by faculty.

"Everyone feels that there are significant structural challenges we are facing," said Rastegar. "A great deal of education depends on an environment that nurtures the trainees. Yale's power has always been that."

—John Curtis and John Dillon

Two decades after its founding, immunobiology becomes a department

Ever since Edward Jenner injected a young English boy with cowpox virus in the 1790s to prevent smallpox, scientists have tried to conquer infectious diseases by understanding and strengthening the human body's immune response. Yet as recently as three decades ago, the most basic principles of modern immunology eluded researchers.

All that would change, however, when the medical school decided to continue the work of the late Richard Gershon, M.D., who had established an immunology group within the pathology department. In 1988, a visionary scientist was recruited to create one of the first free-standing immunobiology sections in the world.

Almost 20 years later, Richard A. Flavell, PH.D., Sterling Professor of Immunobiology, remains chair, but in January the section became a full-fledged department in the School of Medicine. The group that started out as a handful of scientists has grown to include 13 world-renowned researchers, whose publications appear regularly in top-ranked scientific journals. "We strategized about it and planned very carefully what we wanted to build, and that's what we built," said Flavell.



TERRY DAGRADI

Almost 20 years ago Richard Flavell created one of the first freestanding immunobiology sections in the world. Now it is a department at the School of Medicine.

Representative of the group's far-reaching influence is the discovery of the workings of the innate immune system in the 1990s. While most researchers focused on the adaptive immune system, which creates B and T cells that target specific bacterial or viral invaders, the late Charles A. Janeway Jr., M.D., wondered how these immune responders are able to act so effectively and precisely every time the body is invaded by an infectious microbe. In a scientific tour de force, he and Ruslan M. Medzhitov, PH.D., professor of immunobiology, showed that components of the innate system known as *toll*-like receptors provide the adaptive system with the necessary advance intelligence to do its job.

"It was like saying there are only four planets in the solar system and then one day somebody comes along and says no, there are eight," said David G. Schatz, PH.D., professor of immunobiology.

Uncovering the role of *toll*-like receptors in the innate immune system is just one of the advances made by the department. Flavell's lab has identified molecules that are involved in activating and differentiating T cells and that could have implications for HIV and cancer.

Other areas of research are the similarities between allergens and microbes that jump-start the immune system; how proteins get broken down and then "presented" by antigen-presenting cells that allow T cells to recognize them; proteins that are involved in antibody production; and a protein that allows *toll*-like receptors to send signals and is involved in every inflammatory process.

The explosive growth of knowledge coming from the department over the last two decades has increased the awareness that the clinical relevance of immunobiology goes far beyond protection against disease. Immune mechanisms may lie at the root of numerous chronic diseases, including cancer, congestive heart failure and Alzheimer's disease.

—Jill Max

et cetera ...

NEW GRANT FOR RICKETS STUDY

Yale University has received a five-year, \$5 million grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases to form a Center of Research Translation (CORT), one of four in the country, to provide models of translational research in academic medical centers. The Yale CORT will focus on X-linked hypophosphatemic rickets (XLH), the most common form of inherited rickets in the United States. XLH can lead to deformed bones, fractures and debilitating arthritis.

The Yale Center for XLH, directed by Thomas O. Carpenter, M.D., professor of pediatrics, and co-directed by Karl L. Insogna, M.D., professor of medicine (endocrinology), has as its goals the identification and validation of mediators of skeletal disease in XLH and the development of therapeutics based on this knowledge. The center will support an educational program, a pilot projects program and three scientific studies, as well as a research core.

—J.C.

FOUR NAMED AAAS FELLOWS

Four Yale faculty members have been elevated to the rank of fellow by the American Association for the Advancement of Science.

Arthur L. Horwich, M.D., professor of genetics and pediatrics, was honored for contributions to the understanding of the role of chaperonins in mediating protein folding.

John R. Carlson, PH.D., the Eugene Higgins Professor of Molecular, Cellular and Developmental Biology, was cited for contributions to the molecular neurobiology of olfaction.

Oswald J. Schmitz, PH.D., the Oastler Professor of Population and Community Ecology in the School of Forestry & Environmental Studies, was named a fellow for his contributions to the understanding of the emergence and maintenance of ecosystem structure and functioning, and for relating ecosystem patterns to individual behaviors.

Kurt W. Zilm, PH.D., professor of chemistry and chemical engineering, was named a fellow for his applications of solid-state NMR spectroscopy to molecular structure and reaction mechanism determination.

—J.C.

Medicare coverage leads to more screening

With a change in federal policy, the number of early diagnoses of colon cancer has risen.

The expansion of Medicare in 1998 to cover colonoscopies appears to have led to both an increase in demand for the screening procedure and a rise in early-stage colon cancer diagnoses, according to a study by Yale researchers.

“We found that after the Medicare policy change, the use of colonoscopies went up and there was a corresponding increase in the likelihood that patients with colon cancer would be diagnosed at an early, curable stage,” said lead investigator Cary P. Gross, M.D., associate professor of medicine. His study

appeared in the December 20 issue of *JAMA: The Journal of the American Medical Association*.

In 1998 the Medicare reimbursement policy was changed to cover the procedure, which costs roughly \$800, for older patients with increased colon cancer risk. The policy was expanded again in 2001 to cover colonoscopy screenings for everyone 65 and older.

As a general internist at the Primary Care Center at Yale-New Haven Hospital, Gross sees firsthand how reluctant patients are to undergo a colonoscopy. “I thought it was important to test the assumption that reimbursement had been a major barrier to obtaining a colonoscopy,” he said.

The researchers studied patients in the Surveillance, Epidemiology and End Results Medicare-linked database

between 1992 and 2002. They adjusted for such factors as the increasing awareness of colon cancer screening during the study period, given the high-profile efforts of TV anchorwoman Katie Couric to draw attention to the importance of the procedure with an on-air colonoscopy in March 2000. (Couric’s husband had died of colon cancer two years earlier.)

Gross’ team found that the new Medicare policies were associated with a substantial increase in colonoscopy use among beneficiaries without cancer, as well as an increased likelihood of early diagnosis for patients who developed cancer. Before Medicare started covering the screening procedure, 22.5 percent of Medicare beneficiaries who developed colon cancer were diagnosed at an early stage. After Medicare began providing coverage for older at-risk patients, that number rose to 25.5 percent. When coverage was expanded again, to include all Medicare recipients over 65, 26.3 percent of patients diagnosed with colon cancer were diagnosed at an early stage.

“Our analysis suggests that the new Medicare policy was associated with improved health by identifying more patients with early-stage disease,” Gross said. But he was quick to add that, despite these encouraging signs, nearly three-quarters of all patients diagnosed with colon cancer still receive the diagnosis after the disease has spread beyond the early stage. Although his study suggests that cost had been a barrier for some patients, Gross said it also showed that “the new reimbursement policy was not a sufficient intervention to alter the decision process about having a colonoscopy for many older people.”

Noting that colonoscopies can also prevent colon cancer by removing precancerous lesions, Gross said the next step is to assess the impact of Medicare colonoscopy reimbursement on the incidence of colon cancer and to develop strategies to increase the use of screening colonoscopies at the population level.

—Jennifer Kaylin



et cetera ...

After 10 years of research, a rare skin disease is traced to a chemical used in MRIs

In 1997 investigators in California came across a mysterious skin disease. It often started with redness of the skin and warmth, but as it progressed, the skin swelled, tightened and turned brown, becoming almost “woody.” The unnamed disease led to disability, reduced mobility of the joints and could be fatal.

After almost 10 years of research, Shawn E. Cowper, M.D., assistant professor of dermatology and pathology, has provided additional evidence that the disorder affects a small number of patients with kidney disease who undergo magnetic resonance imaging (MRI) scans with contrast. The disease that he identified in 2001, with Philip LeBoit, M.D., of the University of California, San Francisco, is now called nephrogenic systemic fibrosis (NSF). Cowper started a registry of the disease that now numbers about 235 cases.

At first Cowper thought the disorder affected only the skin. It turns out that it is mediated by a cell involved in wound healing that was originally identified in 1992 by Richard Bucala, M.D., PH.D., professor of medicine (rheumatology), pathology and epidemiology (microbial diseases).

While pondering its causes, Cowper noticed that most of the patients in his registry had undergone vascular imaging. Working with investigators in Bridgeport, Conn., he examined the records of 467 patients receiving dialysis. Three developed NSF following MRI, and all three had received the contrast agent gadolinium. Another

84 patients received gadolinium but did not develop the disease. In March, Cowper published a study in the *Clinical Journal of the American Society of Nephrology*, linking gadolinium to NSF, which occurs only in patients with advanced kidney disease.

Based on Cowper’s work and a Danish study, the Food and Drug Administration issued a public health advisory last year warning of the dangers to kidney patients who receive a contrast-enhanced MRI. “What’s really key now, and what everybody is excited about finding, is what makes these 3 percent different than the other 97 percent who have renal failure and have been exposed to gadolinium without developing NSF,” said Cowper.

Understanding the mechanism behind NSF may explain why it occurs. In contrast agents, gadolinium is bound to a chelate, a molecule that keeps it from interacting with the body and allows it to be quickly eliminated by the kidneys. But patients with advanced kidney disease can’t efficiently rid themselves of such toxins as gadolinium, which may build up, dissociate from the chelate and do damage.

Unfortunately, all contrast agents used for routine MRIs in the United States contain gadolinium. Kidney patients who must undergo an MRI with contrast are advised to undergo dialysis immediately afterward, but no one is certain that this will decrease the chances of developing NSF. “There are a lot of questions that need to be answered before anyone declares this disease gone, or even this technique safe,” said Cowper.

—Jill Max

HIGHER RISK FOR CARDIAC PATIENTS

About a third of heart attack patients also have an active, noncardiac condition that could warrant admission to the hospital, Yale researchers reported in the *American Journal of Medicine* in October. And patients who have acute conditions such as stroke, kidney failure and pneumonia may have poorer outcomes, according to first author Judith H. Lichtman, M.P.H. ’88, PH.D., assistant professor of epidemiology. “Relatively little is known about the care and outcomes of heart attack patients who arrive at the hospital with an additional, active noncardiac condition.

Lichtman and colleagues studied 1,145 patients with acute myocardial infarction who were discharged from Yale-New Haven Hospital between January 1997 and June 2000, and rated the additional noncardiac conditions in these patients by severity. Life-threatening conditions included active bleeding, major stroke, metastatic cancer, abdominal aortic aneurysm rupture, acute psychosis, major trauma and others.

“More research is needed to describe these complex patients to identify opportunities to improve their clinical management,” said Lichtman.

—John Curtis

HIV SCREENING SHOULD BE ROUTINE

Voluntary screening for HIV should be routine for all adults, not just those at high risk, according to a study by Yale researchers. The team reports in the December 5 issue of the *Annals of Internal Medicine* that routine HIV screening is cost-effective, even in communities where as few as two in 1,000 people have undiagnosed HIV infection. Early identification of HIV leads to better health outcomes and longer life expectancies in HIV-infected persons.

The study provides strong support for the Centers for Disease Control and Prevention guidelines issued in September 2006 that recommend routine HIV screening of all persons age 13 to 64 in all health care settings.

“Early identification of HIV saves lives,” said principal investigator A. David Paltiel, M.P.P.M., PH.D., professor of public health and management sciences.

—J.C.

A clear solution to a protein puzzle

An enzyme's structure plus oil and water may yield a clue to Alzheimer's disease.

Several years ago, when researchers discovered intramembrane proteases—a class of hydrophilic enzymes that seemed to work despite being surrounded by cells' oily membranes—many scientists were perplexed. Some were downright skeptical. After all, oil and water don't mix.

Ya Ha, PH.D., assistant professor of pharmacology, and colleagues may have revealed the intramembrane proteases' recipe for success with their publication in October in the journal *Nature* of the protein's structure. In addition to providing a solution to a slippery biological mystery, Ha's work could shed light on the mechanisms underlying Alzheimer's disease.

The chewing up of proteins, a process known as proteolysis, is the job of proteases. But protein-splitting reactions require water, not normally found in the greasy interior of cell membranes. In 1997, Nobel laureates Joseph L. Goldstein, PH.D., and Michael S. Brown, PH.D., suggested in an article in *Cell* that a protease involved in regulating cholesterol somehow did its work within the cell membrane. This protease must be "unusual," they acknowledged, but they proposed that gamma-secretase, the enzyme that cleaves amyloid protein into the toxic fragments seen in the brains of Alzheimer's patients, might also operate in the same manner.

When he came to the School of Medicine from Harvard University five years ago, structural biologist Ha was convinced that gaining structural information through X-ray crystallography was the key to understanding intramembrane proteases. He started with gamma-secretase. But despite his best efforts, it could not be coaxed into forming crystals, the first step in determining a protein's molecular structure by X-ray crystallography.

When a family of bacterial enzymes with similar activity known as rhomboid proteins was discovered in 2001, Ha seized on those as an alternative. Over the next four years, Ha worked with postdocs Yongcheng Wang, PH.D., and Yingjiu Zhang, PH.D., to obtain the first X-ray data of the rhomboid enzyme molecules and created a visualization of the structure.

At last, they saw how an intramembrane enzyme is built: in the middle of a sea of fat, the rhomboid protease creates a protective bubble to shelter water molecules (whose source is unknown; they may come from a surrounding aqueous solution) in its active site. The enzyme is serpentine, crisscrossing the cell membrane six times. Five of these segments bundle together to create a water-filled chamber within the membrane.

However improbable this enzyme's mechanics, they are medically important because the enzyme belongs to the family that includes human gamma-secretase. "Compounds that inhibit the production of toxic amyloid peptides are now believed to be one of the most promising approaches to the development of drugs for Alzheimer's disease," says Vincent T. Marchesi, M.D.,

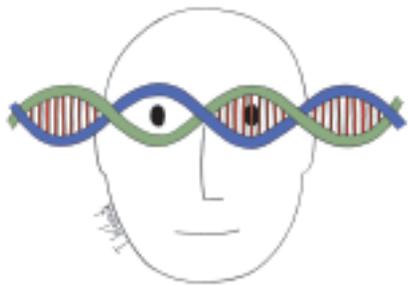
PH.D., the Anthony N. Brady Professor of Pathology and an expert on both membrane protein structure and Alzheimer's disease. "Ha's findings are an important contribution to this effort."

Ha says that the rhomboid protease is a good model system for intramembrane proteases in general, but he confesses that he still has his eye on gamma-secretase. "I would love to see it," he says. While the two enzymes are not related by their protein sequence or by evolution, Ha believes that they share common features because they face the same challenge of mixing water with oil. "Once you have a few structures, you'll see a pattern start to emerge," Ha explains. "That will give us a better understanding of how inhibitors might work. And then maybe we can design better inhibitors, and maybe those inhibitors can be used as drugs."

—Pat McCaffrey



Structural biologist Ya Ha produced this image of a hydrophilic enzyme that functions in a cell's oily, and hydrophobic, membrane.



Yale scientist finds two genetic anomalies linked to macular degeneration

In late 2004, Josephine J. Hoh, PH.D., associate professor of epidemiology and of ophthalmology and visual science, used new DNA chip technology to identify a gene for age-related macular degeneration (AMD). She found a single nucleotide polymorphism (SNP)—in this case a variant in the coding region of complement factor H (CFH) gene on chromosome 1—that is linked to an increased risk of developing both wet and dry forms of AMD.

Now, in findings published in the journal *Science* in October, Hoh has reported finding an independent SNP in a section of chromosome 10 that regulates the HTRA1 gene. The variant appears to increase the expression of the protein HTRA1 in the eyes of homozygotes, and people carrying two copies of the risk allele have a much higher risk of wet AMD.

“We found that patients with the HTRA1 SNP in both chromosomes were 10 times more likely to have wet AMD than those who have it in just one chromosome or no SNP,” said Hoh. “This may point to possible directions for effective treatment of wet AMD.”

AMD causes light-sensitive cells in the retina to break down, resulting in progressive loss of central vision. Of the two forms of AMD, the dry form is more common than the wet form. Wet macular degeneration can lead rapidly to blindness, while the dry form of AMD progresses more slowly.

The discovery marks the first time that a cross-ethnic approach was used to efficiently decipher a complex disease

such as AMD. Hoh exploited differences in the progression of AMD in Caucasian and Chinese patients. In Caucasians, the proliferation of abnormal blood vessels is compounded by the development of large waste deposits called drusen. Chinese patients, she said, develop little or no drusen and progress directly to wet AMD.

Using DNA samples from Chinese patients with AMD, Hoh discovered the disease-causing variant in the control section of the HTRA1 gene. She then hypothesized that this same genetic variant causes wet AMD in Caucasians. “Finding a gold mine is very much easier if you have a good map showing where to dig. The discovery in the Hong Kong Chinese samples gave me the map,” she said. The confirmation of her hypothesis that the HTRA1 variant causes wet AMD in Caucasians was done in collaboration with Kang Zhang, M.D., PH.D., of the University of Utah School of Medicine.

These studies demonstrate that each of these two major genes, CFH and HTRA1, affects the risk for a distinct component of the AMD phenotype: CFH influences the production of drusen associated with dry AMD, whereas HTRA1 influences blood vessel development, the hallmark of the wet disease type. When the two processes are combined, they lead to the composite characteristics seen in some cases of AMD.

“The marker variant we have identified in HTRA1 is very much associated with AMD, but function of the gene that causes wet AMD is unknown. We need to conduct further functional studies in order to understand the biological mechanisms,” said Hoh.

—Robin Orwant

et cetera ...

CANCER MUTATIONS COMMON

Cancer gene mutations are found in about 1 percent of the general population, more frequently than previously thought, according to Yale researchers.

The study published in the December 6 issue of the *Journal of the National Cancer Institute* looked for the presence and rate of BRCA1 and BRCA2 mutations in women with newly diagnosed ovarian cancer. Those mutations have been linked to elevated lifetime risks for breast, ovarian and other cancers.

The scientists screened for the most common mutations as well as rare or hard-to-distinguish variants. They then calculated the incidence of those variants in the general population and in individuals with family members who have had cancer. The Yale team found that the lifetime risk to age 80 is not the same for all mutations.

“The exact nature of the level of risk for the particular mutations needs to be further explored,” said lead researcher Harvey A. Risch, M.D., PH.D., professor of epidemiology. “This study is an important first step in that direction.”

—John Curtis

A GENE FOR NICOTINE ADDICTION

The World Health Organization estimates that more than 1 billion people smoke worldwide, and that smoking causes nearly 5 million premature deaths every year. Growing scientific evidence suggests a genetic link to nicotine addiction.

In findings published in the January issue of *Biological Psychiatry*, Joel E. Gelernter, M.D., professor of psychiatry, genetics and neurobiology, and colleagues reported on the risk of nicotine dependence in 634 small nuclear families with members who were also dependent on cocaine or opioids. In 507 of the African-American or European-American families, at least two members were nicotine-dependent. The researchers identified one significant genome-wide linkage on chromosome 5 for the African-Americans and a strong linkage on chromosome 7 for the European-Americans. “These data add to the growing evidence for specific locations for genes that influence risk for nicotine dependence,” said Gelernter.

—Amy Chow

A doctor learns to cope with death

In her new book, a surgeon explores the ways in which physicians respond to dying patients.

Pauline W. Chen, M.D., HS '98, often recalls the words of the late Yale surgeon C. Elton Cahow, M.D. She once heard him remonstrate with an exhausted resident for thinking he could head home without checking on a certain patient.

"Once you put your hands on a patient," Cahow said, "they're yours."

Chen liked to think she was keeping close watch over all her patients. But something was still wrong: "As early as internship," she said, "when patients were dying, I found it difficult to go into their rooms, to talk to their families, to discuss their diagnoses and prognoses." She even shunned a dear friend with terminal cancer.

And her fellow physicians generally shared her anxiety about death. "We're all susceptible to this," she said in a recent telephone interview from her home near Boston. "Dying is frightening."

This fundamental human anxiety, she said, is ratified by medicine's "hidden curriculum." When a patient's death was imminent, Chen often saw attending physicians close the curtain around the patient and the grieving family, and then depart. Chen did the same. "We thought that family members wanted to be alone at the end," she recalls. "It never occurred to most of us that the actual process might be frightening, and that we could alleviate that fear by being present. And perhaps too, some of us—I include myself here—did not have the insight to realize that we were also leaving them alone because it was easier for us to stay away from the dying altogether."

"This deeply rooted angst about death," she later wrote, was being passed on by doctors from one generation to the next "like some tragic hereditary disease."

Chen said that physicians recognize their limitations. Almost half the oncologists in one study described themselves as only "poor" or "fair" at breaking bad news. Chen



JOANNE CHAN

Pauline Chen's study of doctors and death began with her own difficulties in responding to the terminally ill.

herself abandoned a favorite patient to painful and futile end-of-life care because she could not bear to see him diminished by his cancer. In the idiom of her Taiwanese heritage, the young man became a *wan ong kwei*, a restless soul who haunted her.

Five years ago, pregnant with twins, she took time off from her work as a transplant surgeon at UCLA to care for her daughters and write about the ways in which physicians cope with death. Her book, *Final Exam: A Surgeon's Reflections on Mortality*, was published by Alfred E. Knopf in January.

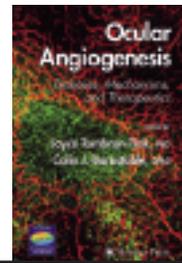
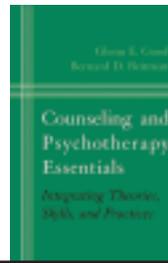
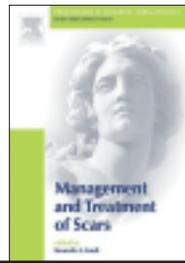
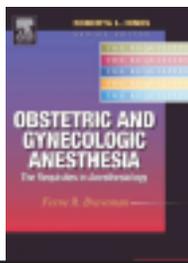
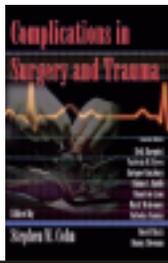
Chen begins *Final Exam* at the moment when she unveils the cadaver that she will dissect as a medical student. Through anecdotes from medical school at Northwestern and residency at Yale, she traces her growing awareness of the extent to which doctors deny death, and tells of the moment midway through residency when an attending surgeon provided a better model. The surgeon closed the bed curtain around a dying patient but did not leave. He remained inside the curtain, sitting with the patient and family during the final hour of the patient's life. "It was a major turning point," Chen recalls. "I realized that I could do more than just cure. I could be there for my patients and their families." She might offer what the medical anthropologist Arthur Kleinman, M.D., calls "empathic witnessing."

"My greatest hope for the book," she said, "is to get people to talk about the issue and to share their anxieties." Although she recognizes that complex cultural, psychological and institutional forces determine how we cope with death, "the more awareness there is, the greater the chance that we'll improve end-of-life care for all of us."

Chen now works full-time as a writer, lecturer and consultant. Her blog carries a link to an excerpt from the book, which was published in *The New York Times Magazine* last December: www.paulinechen.com.

—Cathy Shufro

Bookshelf focuses on books and authors at the School of Medicine. Send suggestions to Cathy Shufro at cathy.shufro@yale.edu.



Complications in Surgery and Trauma

edited by Stephen M. Cohn, M.D., with contributions by Edward Lubin, M.D., Ph.D., Deepak Narayan, M.D., M.B.B.S., assistant professor of surgery, John A. Persing, M.D., professor of surgery (plastic) and neurosurgery, Michael J. Robbins, Joseph H. Shin, M.D., HS '97, associate professor of surgery, and Raymond S. Sinatra, M.D., Ph.D., professor of surgery (Informa Healthcare) This text offers practical, detailed information on avoiding and managing complications resulting from surgical interventions in the operating room, emergency room and intensive care unit. It covers a variety of pre-, intra- and postoperative events, analyzing complications in all surgical disciplines and suggesting protocols for preventing them.

Colorectal Cancer: Evidence-Based Chemotherapy Strategies

edited by Leonard B. Saltz, M.D., with contributions by Edward Chu, M.D., professor of medicine and pharmacology, Richard Kim, M.D., FW '06, and M. Wasif Saif, M.B.B.S., associate professor of medicine (Humana Press) This evidence-based and data-driven guide presents reviews of cutting-edge therapies for colorectal cancer. The opening chapters outline contemporary thinking about the biology of colorectal cancer, screening and potential methods of chemoprevention. Subsequent chapters present uses of cytotoxic chemotherapy and weigh the potential for incorporating innovative biological therapy. The concluding chapter explores emerging drug paradigms and their potential for treating colorectal cancer.

Obstetric and Gynecologic Anesthesia: The Requisites

by Ferne R. Braveman, M.D., professor of anesthesiology and of obstetrics, gynecology and reproductive sciences (Mosby) This text discusses anesthesia for female patients during common surgical procedures, including oncologic and nonobstetrical procedures and fetal surgery. Other topics include pain management for high-risk obstetric patients and pharmacology. Each chapter includes case studies.

Management and Treatment of Scars: Procedures in Cosmetic Dermatology Series

by Kenneth A. Arndt, M.D. '61, HS '62 (Saunders) This reference presents practical guidance for revising scars using medical treatments, light/laser treatment and surgical and nonsurgical procedures. The book offers step-by-step guidance on proper techniques, pitfalls and "tricks of the trade," along with photographs and illustrations of cases discussed.

Counseling and Psychotherapy Essentials: Integrating Theories, Skills and Practices

by Glenn E. Good, Ph.D., and Bernard D. Beitman, M.D. '68 (Norton Professional Books) This textbook aligns students' classroom experience with the demands of actual clinical practice, in which clinicians do not hew to a single theoretical line but, rather, mix schools and methodologies in order to address their clients' needs.

Ocular Angiogenesis: Diseases, Mechanisms and Therapeutics

by Colin J. Barnstable, D.Phil., professor of ophthalmology and visual science and of neurobiology, and Joyce Tombran-Tink, Ph.D. (Humana Press) This book surveys current clinical and basic knowledge concerning abnormal growth of blood vessels in the eye. The authors also identify and assess the most promising approaches and discuss the challenges encountered in developing therapeutics for ocular neovascular diseases. This text includes a CD with color versions of figures used in the book.

Visual Development, 2nd ed.

by Nigel W. Daw, Ph.D., professor emeritus of ophthalmology and visual science (Springer) Written for medical students, graduate students and postdocs, this book describes the development of the visual system, the effects of visual deprivation and the mechanisms by which visual deprivation produces its effects.

Menstrual Disorders: A Practical Guide

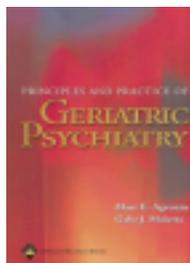
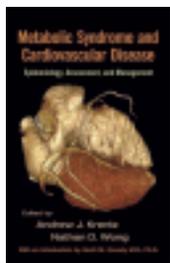
edited by Deborah B. Ehrenthal, M.D., Matthew K. Hoffman, M.D., and Paula J. Adams Hillard, M.D., with contributions by Henry M. Rinder, M.D., associate professor of laboratory medicine (The American College of Physicians) Designed for the primary care clinician, this book is divided into three sections. The first discusses the adolescent patient, the second covers the range of disorders that patients may experience from adolescence through menopause and the third examines the relationship between menstrual disorders and other medical illnesses.

Extreme Prematurity: Practices, Bioethics and the Law

by Geoffrey Miller, M.D., professor of pediatrics and neurology (Cambridge University Press) This book examines issues surrounding the clinical management of extremely premature neonates in the context of modern neonatal intensive care. The text covers the epidemiology of extreme prematurity and patient care practices in different parts of the world; bioethics considerations, including ethical theories, moral principles and quality-of-life issues; national and international guidelines; and medical law in the United States and elsewhere.

Field Guide to Bedside Diagnosis, 2nd ed.

by David S. Smith, M.D., associate clinical professor of medicine (Lippincott Williams & Wilkins) This book enables students and physicians to navigate the path from collecting information on the patient's symptoms and presenting signs to reaching a diagnosis. The guide is organized to parallel the diagnostic reasoning process, providing a differential overview of probable causes, a diagnostic approach for each differential diagnosis, and the specific clinical findings that point to diagnosis.



Metabolic Syndrome and Cardiovascular Disease: Epidemiology, Assessment and Management

edited by Nathan D. Wong, M.P.H. '87, and Andrew J. Krentz, M.D. (Informa Healthcare) This text addresses the epidemiology, diagnosis, assessment and management of patients with metabolic syndrome—focusing on implications for cardiovascular disease risk. With tables, flowcharts and practice guidelines, this resource analyzes recent clinical trials, compares and assesses new and emerging therapies and provides recommendations for improving the assessment and treatment of patients.

Principles and Practice of Geriatric Psychiatry

edited by Marc E. Agronin, M.D. '91, and Gabe J. Maletta, M.D., Ph.D. (Lippincott Williams & Wilkins) This book describes in detail the neurologic and neuropsychiatric patient assessment and the use of all treatment modalities, both psychotherapeutic and pharmacologic, in elderly patients. The contributors discuss the treatment of disorders in all clinical settings: inpatient, outpatient, emergency, primary care, assisted living and long-term care. The book includes case studies and personal accounts by patients and care providers. Appendices provide drug information and list additional resources.

Weight Bias: Nature, Consequences and Remedies

by Kelly D. Brownell, Ph.D., professor of psychology and epidemiology, Rebecca M. Puhl, Ph.D., Marlene B. Schwartz, Ph.D., and Leslie Rudd (The Guilford Press) The authors explore the nature, causes and consequences of weight bias and present a range of approaches to combat it. They discuss topics including the barriers facing obese adults and children in health care, work and school settings; theories on how stigma develops; the impact on self-esteem and health; and strategies for reducing prejudice and bringing about systemic change.

The descriptions above are based on information from the publishers.

SEND NOTICES OF NEW BOOKS TO Cheryl Violante, *Yale Medicine*, 300 George Street, Suite 773, New Haven, CT 06511, or via e-mail to cheryl.violante@yale.edu

A digital treasure trove

James D. Jamieson, M.D., Ph.D., professor of cell biology, knew that he had a piece of history in his closet: lantern slides made by the pioneering cell biologist George E. Palade, M.D., and colleagues. Those images of cells seen through the electron microscope had laid the groundwork for Palade's 1974 Nobel Prize in physiology or medicine. "Palade and his people really formulated, invented and provided the information that started the field of cell biology in the 1940s," said Jamieson, who did his doctoral work at Rockefeller University with Palade and came with him to Yale.

Jamieson knew that his mentor, who was at Yale from 1973 until 1990, wanted the images to be available to students and scientists around the world. And so Jamieson cleaned the 3.25- by 4-inch glass slides, which Palade left at Yale. Jamieson then digitally scanned 191 slides. Arthur R. Belanger, M.S., project manager of academic media and technology, indexed the slides and placed them on the website of the Cushing/Whitney Medical Library.

The Palade slides are among several digitized collections now available on the website. Other collections include engravings of historic figures and oil portraits of Chinese patients with tumors and other deformities from the mid-19th century. The digital collection will expand, said Daniel M. Dollar, M.L.S., associate director of collection development.

Palade's slides helped biologists to relate what they were learning about cell morphology through the electron microscope with what was being discovered about cellular biochemistry through cell fractionation, the process of separating a cell into its distinct parts with a centrifuge.

This holistic understanding of cell function and structure provides the foundation for contemporary understanding of disease processes, because, Jamieson said, "you need to know what's going on in the normal cell before you begin to figure out what's going on in the diseased cell."

The Medical Digital Library can be accessed at <http://www.med.yale.edu/library/subjects/digital.html>. An exhibit by the Yale Medical Historical Library charting the life of pioneering neurosurgeon Harvey Cushing, M.D., is now available online at <http://www.med.yale.edu/library/historical/cushing/>.

—Cathy Shufro

In Circulation focuses on activities at the Cushing/Whitney Medical Library. Send suggestions to Cathy Shufro at cathy.shufro@yale.edu.



MICHAEL LEVY

Physician-assisted suicide is the wrong solution

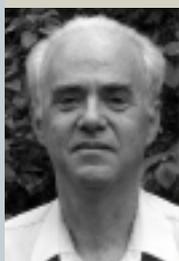
At a time when life is devalued, when people are killed over necklaces or iPods, physician-assisted suicide ill serves patients, physicians and society, said Michael H. Levy, M.D., PH.D., during a talk at internal medicine grand rounds in January.

"If we look at physician-assisted suicide as an act of hastening death," said Levy, vice chair of the Department of Medical Oncology at the Fox Chase Cancer Center in Philadelphia, "then it is an act of harm. ... Do we really need to kill the patient to kill the pain?"

Levy said physician-assisted suicide violates key tenets of medical ethics; erodes trust in health professionals; and diminishes what he called "the miracle of life." It also denies a patient's loved ones the chance to provide care at the end of life. If legitimized, he said, it could force doctors to provide a service they oppose. And, he continued, it could stifle the search for alternate ways to relieve suffering.

"I think the risk to society far outweighs the benefits," Levy said.

—John Curtis



ROBERT STICKGOLD

Is sleep no more than a cure for sleepiness?

In 1989, when scientists kept rats from sleeping, the rats started to die by the 11th day. By the 32nd day, they were all dead. "We are still clueless as to why the rats died," said Robert Stickgold, PH.D., associate professor of psychiatry at Harvard Medical School and an expert on sleep, speaking at internal medicine grand rounds in November. "It happens in rats," he continued. "It happens in humans."

For 2,000 years we have understood other basic drives, such as hunger and sex, he said, but the need for sleep remains a mystery. Among early candidates for its apparent benefits, said Stickgold, were restoration and recovery, energy conservation and avoidance of nocturnal predators. "When you try to parse those out," Stickgold said, "none of those make sense. You end up back at the point that sleep is to cure sleepiness."

Yet more recent studies have confirmed that a good night's sleep confers numerous benefits. Without it, the immune system produces fewer antibodies to fight infection. And it is during sleep that the brain consolidates the day's memories and learning.

"It does matter how much sleep you get," Stickgold said.

—J.C.



SHERWIN NULAND

The teachings of Maimonides and a moral imperative

The 12th-century physician Maimonides, who lived in Spain and Egypt, achieved fame as a rabbi and philosopher yet helped to establish a moral imperative that guides medicine to this day: the obligation to make every effort to heal the patient.

Although best known for his *Guide for the Perplexed*, which proposed ways to reconcile religion and science, the scholar also proposed an alternative to the prevailing Christian view of a doctor's role, said Sherwin B. Nuland, M.D. '55, HS '61, clinical professor of surgery and author of a biography of Maimonides. In a December talk, Nuland told members of the Interdisciplinary Center for Bioethics that Maimonides saw medical care not as a prayer but as "something physical that needs to be done." Healing remained linked to faith, nonetheless, because renewed health would allow the patient to resume his study of God.

As a physician, Maimonides believed that "you are to make any sacrifice other than another human life to save someone you can possibly save," Nuland said. "There is no credit to be given to a physician for doing his work. It is an obligation."

—C.S.



MARK CULLEN

Environment and society: which determines health risks?

A two-story house has peeling paint and no yard. Behind it loom industrial smokestacks. Mark R. Cullen, M.D. '76, HS '79, professor of medicine and of epidemiology and public health, and director of the Yale Occupational and Environmental Medicine Program at the School of Medicine, used a photograph to frame a lecture in March at the School of Forestry & Environmental Studies. Do children in that house face health risks because of toxins from factories and lead from peeling paint or because they live in an overcrowded, high-crime neighborhood with a crummy school and no recreational facilities?

Environmental epidemiologists focus on the physical environment, while social epidemiologists look at patterns of psychological and social stress. Both inquiries, Cullen said, are too narrow. "Neither side explains it all." Historically, however, the two fields haven't shared information. Cullen says researchers need to "deal with their agendas in tandem," because that's the only way to get a full understanding of a population's health status. That knowledge can lead to the creation of such initiatives as more recreational space on the street or tougher air pollution standards, which will better address health issues.

—Jennifer Kaylin

An arrest in New Haven, contraception and the right to privacy

In 1961 a Yale physician joined with Planned Parenthood to challenge a state law banning contraceptives. Their case reached the U.S. Supreme Court and opened the door to the acceptance of contraception.

By Lori Ann Brass



ABOVE On June 7, 1965, Estelle Griswold, left, and Cornelia Jahncke, executive director and president, respectively, of the Planned Parenthood League of Connecticut, celebrated a decision by the U.S. Supreme Court that struck down the state's law banning the use of birth control. That decision paved the way for later decisions, including *Roe v. Wade*, which legalized abortion in the United States.

RIGHT Estelle Griswold and C. Lee Buxton, center, in police headquarters on November 10, 1961. The two were arrested after opening a clinic in New Haven that offered birth control counseling and prescribed contraceptives—violations of an 1879 statute that barred the use of any drug or instrument for preventing conception.



When police raided a Trumbull Street clinic on November 10, 1961, it came as no surprise. The Planned Parenthood League of Connecticut (PPLC) had opened the clinic days earlier to offer birth control counseling and to prescribe contraceptives—deliberate violations of an 1879 statute prohibiting the use of “any drug, medicinal article or instrument for the purpose of preventing conception.”

Estelle Griswold, the feisty executive director of the PPLC, and C. Lee Buxton, M.D., the medical director of the clinic and chair of the Department of Obstetrics and Gynecology at the School of Medicine, were arrested, convicted and fined \$100 each. The PPLC had spent decades lobbying the Connecticut General Assembly to repeal or amend the statute, one of the “Comstock laws” promoted by anti-obscenity crusader Anthony Comstock in the late 19th century.

For 21 years the PPLC had operated only as a transport service, shuttling patients to clinics in Rhode Island and New York, where contraception was legal. In Connecticut married women with private physicians could often obtain birth control information and devices, but poor women, or women without connections, could not. Two previous attempts to challenge the statute, in 1943 and 1961, had been dismissed by the U.S. Supreme Court, in the first case because the doctor involved lacked standing to sue on behalf of patients, and in the second case, also involving Buxton, because the plaintiffs had not been threatened with prosecution.

Police charged Griswold and Buxton with aiding and abetting the commission of a crime—anyone who prescribed and advised women about contraceptives was as culpable as the women who used them. The resulting case, *Griswold v. Connecticut*, had far-reaching consequences for women's health and reproductive rights. “Women and families were moving eagerly to adopt birth control

across the country,” said Susan Lloyd Yolen, vice president of public affairs and communication for Planned Parenthood of Connecticut. “The birth control pill came out in 1960, but Connecticut was a holdout on birth control at that point.”

In 1965 the case reached the U.S. Supreme Court. Thomas Emerson, J.D., dean of the Yale Law School, and Catherine Roraback, J.D. '48, represented the PPLC. On June 7, 1965, the court ruled 7-2 that the Connecticut law violated the constitutional right to marital privacy. “It paved the way for the nearly unanimous acceptance of contraception that now exists in this country,” said Yolen.

“The ruling meant the police had no right to raid your house to look

for contraception,” said Gary L. Gross, M.D. '65, HS '70, an instructor at Harvard Medical School and the medical director of federally funded family planning clinics in Boston. Gross, who worked with Buxton as a student and resident, said that Buxton believed in women's rights, the importance of contraception for all women and providing good health care free from interference.

After *Griswold*, the PPLC opened clinics throughout the state, physicians no longer feared arrest for dispensing contraception. It meant, said Gross, that people could decide the number and spacing of their children.

Griswold also laid the groundwork for later reproductive-rights decisions. In its 1972 decision in *Eisenstadt v. Baird*, the U.S. Supreme Court

extended the right to privacy to individuals, effectively legalizing birth control for unmarried women, said Gross. A year later, in *Roe v. Wade*, the court recognized a woman's right to choose abortion.

“In 1957, the wife of a Yale Law School student couldn't obtain a diaphragm at the student health service,” said Gross. “But when the first women were admitted to Yale College in 1969, the health service provided lectures about birth control and where to obtain it as part of freshmen women's orientation.”

Lori Ann Brass is a freelance writer in Woodbridge, Conn.



NEW HAVEN COLONY HISTORICAL SOCIETY

The fight to legalize birth control had a long history in Connecticut. In 1941 supporters of birth control took a lunch break during a legislative hearing in Hartford.

Simulated cases, real skills

Increasingly, medical schools such as Yale are using standardized patients, lifelike mannequins and virtual reality to teach clinical skills.

By Jennifer Kaylin
Photographs by Frank Poole

High-fidelity human patient simulators, such as Sim-Man at right, talk, breathe and can even “die.” The computerized and programmable polymer figures can simulate just about any condition in the human body. Their vital signs can change to create medical emergencies that allow students to practice procedures such as intubation and order X-rays or CT scans. A new curriculum, which began this year, requires third-year medical students to participate in 24 scenarios over a 12-week surgery clerkship.



In a conference room down the hall from his office, Frederick D. Haeseler, M.D., is talking to three visitors about a patient named Noah Savage.

“Noah was short of breath when he exerted himself, so he stopped taking his daily walks. After his feet began to swell, he was given a prescription for a diuretic called Lasix, and the symptoms got better,” Haeseler says. “But then an echocardiogram revealed that he had severe idiopathic dilated cardiomyopathy, an uncommon, but not rare, heart condition. In this case it’s progressive. Medication can help relieve symptoms, but ultimately Noah would need a heart transplant to survive.”

If Noah, an attractive middle-aged man with a ruddy complexion and bright eyes, appeared remarkably relaxed given the seriousness of his diagnosis, it was for good reason. He doesn’t really have a life-threatening heart condition—he’s a character being portrayed by an actor named Jeff Savage. The three visitors Haeseler was addressing are other actors preparing to begin work at the School of Medicine as standardized patients—actors trained to assume the lives and symptoms of patients in order to help students take medical histories, conduct physical examinations and hone the interpersonal skills necessary to be effective physicians.

Training through simulation—whether by such standardized patients as Savage, by mannequins or by virtual computer technology—has become an increasingly accepted methodology in medical education. Medical schools, including Yale, are devoting significant resources to exposing students to these training opportunities. In addition to Haeseler’s program, Yale now has an array of human-patient simulators, or mannequins, for students to “treat,” as well as a simulation laboratory equipped with computers that allow students to practice everything from suturing techniques to performing a colonoscopy.

Instructors say these simulation tools are useful for both teaching and assessment. Students can practice and make mistakes without harming real patients; these tools can simulate unusual cases students wouldn’t often see in practice; and the tools are ideal for comparative evaluations of clinical skills, because each student faces an identical set of patient challenges.

The use of actors is the oldest of these patient-simulation techniques. Yale’s program, which was launched in 1993 with eight actors, was part of the primary care

clerkship. The early response from students was resoundingly positive, says Haeseler, associate clinical professor of medicine and director of the Yale Standardized Patient Program. “Their only complaint was that it wasn’t offered until the fourth year.” Today, students begin working with standardized patients in the second or third week of medical school in the longitudinal communication skills program directed by Auguste H. Fortin VI, M.D., M.P.H., associate professor of medicine, and taught by a multidisciplinary faculty. Haeseler has trained 30 actors and written 75 scripts that represent a range of medical disorders and psychosocial issues. All are designed for the small-group workshops with standardized patients that occur throughout the four-year medical curriculum. In their first year students learn basic interview skills and advance to more challenging interactions in subsequent years.

Savage, who’s been involved for about a year, is a 1961 Yale College alumnus, antiques dealer and professional actor who most recently appeared in *Our Town* at the Thomaston Opera House in Thomaston, Conn. He has played the same patient about a dozen times, his medical condition growing increasingly dire with each performance. On the day Haeseler described Noah Savage’s illness to the other actors, they were preparing for a workshop on breaking bad news. This scenario required Savage to tackle his most challenging medical school role to date—getting the news that he needs a heart transplant.

“Breaking bad news is one of the most challenging things physicians need to do. It is important for students to learn a structured, patient-centered approach that they can practice without causing discomfort for themselves or their patients,” says Haeseler.

The rehearsal began with Haeseler role-playing a student. Following the model for breaking bad news that Fortin introduces to students just before their sessions with the actors, Haeseler asked Noah some general questions about how he was feeling and what he knew about his illness.

Speaking in a slow soothing voice, he gently told Noah that his heart muscle had weakened and that he would likely need a heart transplant to survive. The news hardly seemed to register. “I’ve heard of those,” Noah said quietly, “but I never thought it would be something I’d ever need.” He appeared dazed, as though he needed to go home, talk with his family and think things through before expressing his feelings.

Afterward, Haeseler said Savage's reaction would provide students with an opportunity to listen, respond empathically to emotion and offer continuing support.

The use of standardized patients, also known as simulated patients, programmed patients, surrogate patients, professional patients and patient instructors, has proven to be such an effective tool for teaching and assessing medical students that the United States Medical Licensing Examination (USMLE) has added a clinical-skills assessment that includes standardized patients. The technique has become so widely accepted that now almost every medical school in the country uses it.

This acceptance could hardly have been predicted, given the early reaction to bringing actors into the classroom. In the early 1960s, when the technique was introduced by Howard S. Barrows, M.D., it was dismissed as maligning the dignity of medical education and being too "Hollywood." Barrows, a neurologist at Montefiore Hospital in the Bronx, N.Y., stumbled onto the technique inadvertently. He used to enlist patients on his floor to be examined by students. One day a patient told him that a student had been so unpleasant to him that in order to get back at the offending student, the patient began inventing symptoms. The incident led to an epiphany for Barrows: why not recruit healthy people to act as patients? Real patients wouldn't be inconvenienced by gruff or incompetent students; students could be exposed to uncommon clinical events; and it would be an ideal assessment tool, because every student would get the same case.

Barrows' timing was fortuitous. At around the same time, medical schools were looking for more precise and less arbitrary ways to evaluate students during their clerkships. Until then students generally received satisfactory or better evaluations, because faculty members almost never directly observed them interacting with patients.

The first standardized patient was developed by Barrows when he was at the University of Southern California. An artist's model played a patient named Patty Dugger, a paraplegic woman with multiple sclerosis. After creating the case, Barrows needed to figure out a way to assess students' interactions with her. Rather than using a one-way mirror or peeking through a curtain, he decided to give the actress a checklist to fill out after each encounter.

Haeseler trains the actors to respond to students' open-ended questions, reflections, summaries and empathic statements that they learn from Fortin's introductory demonstrations. "Facilitative behaviors such as these build trust that in turn helps patients to express themselves and tell a more complete story of illness that includes biological, personal and emotional dimensions," Haeseler says.

Characters are developed using many sources, including literature, the actors' own life experiences and real cases. During a standardized-patient encounter, a student is observed by one faculty member and two other students. What enhances

the educational value, Haeseler says, is that students may call a time-out at any time during the session and freeze the action. This option gives the student a chance to get feedback and advice, or to get some expert information that might be helpful.

"Everyone has a memory of a doctor who didn't seem to care or who didn't explain things well," says Savage, adding that through his work as a standardized patient, he feels he's "helping future doctors acquire skills that are extraordinarily important."

A mannequin with human ailments

Elsewhere on campus, simulated patients of a different sort are being used to help students master other important skills. Last June, Leigh V. Evans, M.D., HS '02, director of health care simulation for the Section of Emergency Medicine in the Department of Surgery, launched a program using high-fidelity human patient simulators for third-year medical students during their surgery rotations. The lifelike polymer figures are computerized and programmable, so they can simulate just about any condition that occurs in the human body.

The simulators can talk and breathe, their vital signs can change and they can even "die," although Evans, an assistant professor in the Section of Emergency Medicine, says she's never made a simulator do that because she worries it would be too traumatic for the students. The major advantage a simulator has over actors is that you can create a medical emergency or practice such procedures as intubation that you wouldn't perform on a real person.

During a recent session, a white male mannequin lay on an examining table surrounded by six students. Evans, who watched through a one-way mirror, used a microphone and a computer to alter the patient's vital signs and talk to the students, either as the patient or as an expert consultant. This type of simulation has advanced significantly, thanks to the work of anesthesiologist David M. Gaba, M.D. '80, at Stanford University. A researcher committed to refining simulator-based teaching techniques, he and his colleagues have developed a program that creates lifelike situations in clinical settings. Gaba's program has been adopted at Yale, Harvard, Penn State, the University of California, San Francisco, and abroad. [See "A Safer OR," *Yale Medicine*, Summer 2003.]

The "patient" in Evans' class was a 47-year-old man with severe abdominal pain and bloating. The students' job was to figure out what was wrong with him and prescribe a course of treatment. As they began asking him questions, he complained of feeling nauseated; then he vomited. When he told the students that he still felt "horrible," they decided to insert a nasogastric tube.

The students then ordered X-rays, which showed that the patient had a large bowel obstruction. When Evans, assuming the role of a consultant, asked what the rectal

exam had revealed, the students realized they'd forgotten to perform one. A CT scan finally revealed the problem: sigmoid volvulus—a twist in the colon that caused everything moving through it to back up. Although this condition can sometimes be treated with a rectal decompression, the patient had already had two similar episodes, so surgery was recommended this time.

Simulators can cost between \$40,000 and \$200,000, says Evans, depending on the sophistication of the software. The current curriculum, which requires third-year students to participate in 24 scenarios over a 12-week block, began this academic year.

“We’re not dependent on what comes through the door, and students can treat much sicker ‘patients,’” says Evans. The simulators are ideal for clinical decision making and developing teamwork skills, she says, but are less effective for teaching physical diagnostic skills, because regardless of the sophistication of their computer programs, they’re still just plastic dolls.

Evans’ students work in groups of six, with a faculty member overseeing the session. During the exercise, participants can call a consultant, talk to a surgeon, order X-rays or request any service that would be available during an emergency. The simulations are videotaped so that participants can review their performances afterward. The Department of Pediatrics now has an infant mannequin, and the Yale New Haven Center for Emergency Preparedness and Disaster Response is also using mannequins to teach students. The next step, says Evans, is to set up a simulation center with a simulated operating room, an intensive care unit, a trauma bed and other hospital settings.

“It’s helpful to be able to see serious cases, unstable cases, and think through everything on your own,” says Kathryn Hogan, M.D., a third-year resident in emergency medicine who led the group that treated the patient with sigmoid volvulus. She says that during the first few scenarios in which she participated, she and the group forgot to ask key questions as they tried to diagnose the patients. But she says they’ve gotten better. “When you learn by doing, you learn fast because it feels like you’re treating a real patient. It’s very dynamic.”

“See one, do one, teach one”—virtually

Another variation on the simulated-patient model—the computer simulator—is now in wide use at the surgical simulation laboratory run by Andrew Duffy, M.D., assistant professor of surgery, director of the surgical simulation center and assistant program director of the surgical residency.

Launched last March, the surgical simulation center resembles a video arcade without all the flashing lights and electronic noises. Several box trainers designed to help students with such skills as performing endoscopic procedures, manipulating remote instruments, developing spatial

During her acting career Kris Montgomery had the starring role in *Evita* in national and international touring companies and performed Off Broadway and in motion pictures with Harrison Ford, Tom Hanks and Meg Ryan. As a standardized patient at the School of Medicine she plays the role of a Manhattan executive whose hip problems stem from a high-stress job. During interviews with medical students, she drops clues to her physical and psychological states, hoping they’ll respond with appropriate questions.



Last March the surgical simulation center opened at the medical school, with computer simulators that allow students and residents to master such skills as performing endoscopic procedures, manipulating remote instruments, developing spatial relationships, hand-eye coordination and suturing. Andrew Duffy, assistant professor of surgery, director of the surgical simulation center and assistant program director of the surgical residency, demonstrates on a simulator that can replicate both the inside of an abdomen and a full colonoscopy procedure. "You can watch yourself zipping around the colon on the video screen. The machine even groans if you've hurt the patient," Duffy says. About 100 surgical, orthopaedic and ob/gyn students and residents use the lab on a regular basis.



relationships, hand-eye coordination and suturing are located in a suite of rooms near Yale-New Haven Hospital, so that residents can stop in and practice in between their duties at the hospital.

One trainer replicates the inside of an abdomen. Another is a full colonoscopy procedure simulator. "You can watch yourself zipping around the colon on the video screen. The machine even groans if you've hurt the patient," Duffy says.

The surgical simulation laboratory grew out of the need to teach students and residents more skills in less time. "With an 80-hour limit imposed on surgical residents' training, and so many new laparoscopic procedures, residents have to learn twice as much in 20 percent less time," Duffy says.

About 100 surgical, orthopaedic and ob/gyn students and residents use the lab on a regular basis. The machines, which came into use in medical schools about five years ago, are now so popular that some of the hand pieces have worn out. "These machines are essential tools," Duffy says. He says the next generation of simulators, which are now in development, will include gall bladder and hernia models.

Duffy contrasts this type of training with his own, when the mantra was "see one, do one, teach one" and the main way in which residents honed their skills was by observing experienced doctors at work. "I vividly remember how bad I was and how quickly the surgeon took over," he says. "We want students to learn and practice on our machines, so that when the time comes to treat real patients, they'll already be proficient." In fact, all residents are now required to complete this training before they assist in laparoscopic and endoscopic procedures on patients.

For laparoscopic surgeons, simulators help them learn how to manipulate instruments in a three-dimensional space while looking at a two-dimensional screen. "Dissection combined with computers helps surgeons look at two dimensions, but 'see' in three," says Lawrence J. Rizzolo, PH.D., associate professor of surgery and of ophthalmology and visual science, and director of medical studies in the anatomy section in the Department of Surgery.

Computer software and patient narratives also help build a clinical correlation between patients and the study of anatomy by transforming the cadaver into a simulated patient. All course activities become centered on clinical problems and procedures. "The software allows us to see internal organs and rotate the images," Rizzolo says. "In our dissection lab, there's a computer at every table. The idea is to make it so the software can't be used without the cadaver and the cadaver can't be used without a computer," says Rizzolo.

Assessing clinical skills

Although it's accepted that clinical skills are central to the practice of medicine, prior to the introduction of standardized patients into the USMLE there was no national approach

for objectively evaluating students' competency in clinical skills. "It was always pointed to as a gap in the medical licensing program," says Gerard F. Dillon, PH.D., associate vice president for the USMLE at the National Board of Medical Examiners. That gap was filled in 2004 when standardized patients were introduced as part of the USMLE system. "To introduce it into the examination program was an enormous step forward," he added.

With this new assessment tool, examiners have been better able to identify students who are deficient in clinical skills. These students, who previously might have flown beneath the radar, now get feedback, and their schools are notified so that they can get help to remedy the deficiency. The other benefit, Dillon says, is that since the USMLE has begun assessing clinical skills, medical schools have put more emphasis on teaching these skills and ensuring that students have mastered them.

As the USMLE assessment program develops, the hope is that it will expand beyond standardized patients to include such other technologies as patient simulators. "With live actors, you can't assess all of the skills that you would like," Dillon says. "Our plan is to introduce some other technologies that will allow an even broader assessment, but first we have to make sure that such technologies are reliable and that their presentations are consistent."

Money is another consideration. At a cost of \$1,000 per assessment, which students pay, Dillon says the USMLE program has a responsibility to consider the expense of any additional assessment tools.

Still, despite the considerable investment and inevitable growing pains that come with the introduction of a new program, it's clear that standardized patients, mannequins and increasingly sophisticated computer trainers are going to become a key methodology in medical education.

"I like it very much. It's a great addition to the pre-clinical education. It gives students the chance to develop the skill of eliciting medical histories and physical findings," says Peter N. Herbert, M.D. '67, HS '69, chief of staff and senior vice president for medical affairs at Yale-New Haven Hospital. Herbert says that unlike real patients, actors are able to objectively assess the student's technique and offer feedback, which he says is "extraordinarily useful."

For example, if a student makes the common mistake of lapsing into med-speak ("Is your child febrile?") rather than "Does your child have a fever?"), a standardized patient will quickly point that out.

"I can only say that I wish there had been standardized patients when I was a medical student," Herbert says. "It would have saved me and my early patients a lot of embarrassment." **YM**

Jennifer Kaylin is a freelance writer in New Haven.



FROM THE POTION TO THE PILL

In traditional Chinese medicine, the herb yarrow is used to treat the common cold, colic, indigestion and toothache.

BY
CHARACTERIZING
AND
QUANTIFYING
THE ACTIVE
INGREDIENTS
IN TRADITIONAL
CHINESE
HERBAL
REMEDIES,
YALE
SCIENTISTS
HOPE TO
IMPROVE
TREATMENT AND
REDUCE TOXICITY
FOR CANCER PATIENTS.



By John Dillon

Illustrations by Mark Gagnon



estern physicians, who demand clinical proof of a drug's efficacy, and proponents of alternative remedies, who point to anecdotal evidence that their products work, have carved out distinct but neighboring territories in the world

of medicine. Although the inhabitants of these territories have often regarded each other with suspicion, their borders have become increasingly porous. According to a 2004 survey by the National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (NIH), 36 percent of Americans 18 or older have tried an alternative remedy. That survey also found that 26 percent of the respondents used alternative treatments based on a recommendation from a mainstream medical practitioner.

This wary and shifting relationship stems in part from differing world views. Practitioners of traditional or alternative medicine take a more holistic view of healing than their mainstream counterparts. And mainstream physicians see a lack of scientific rigor in published evaluations of traditional medicines whose recipes have been handed down over generations. Furthermore, how does a physician calculate a reliable dosage of a medicine that's brewed in a tea and whose chemical makeup depends on how much water and how many leaves are used, where the plants were grown, when they were harvested and how much it rained that season?

Now Yale scientists are attempting to bring traditional Chinese medicine into the mainstream. Working with two companies in New Haven and Taiwan, they have brought precision and consistency to a traditional Chinese remedy for headache, fever and gastrointestinal problems. Clinical trials have shown that the compound reduces the unpleasant effects of chemotherapy. Trials will soon begin to evaluate whether it also enhances the action of the chemotherapy. The researchers' main accomplishment, however, is the development of a platform technology that combines quality control, a robust database, clinical trials and herbal resources to produce plant-based medicines with a biologically consistent result.

"We're in a new frontier," said Yung-Chi "Tommy" Cheng, PH.D., the Henry Bronson Professor of Pharmacology, who is leading efforts at Yale to advance the study of traditional Chinese medicine.

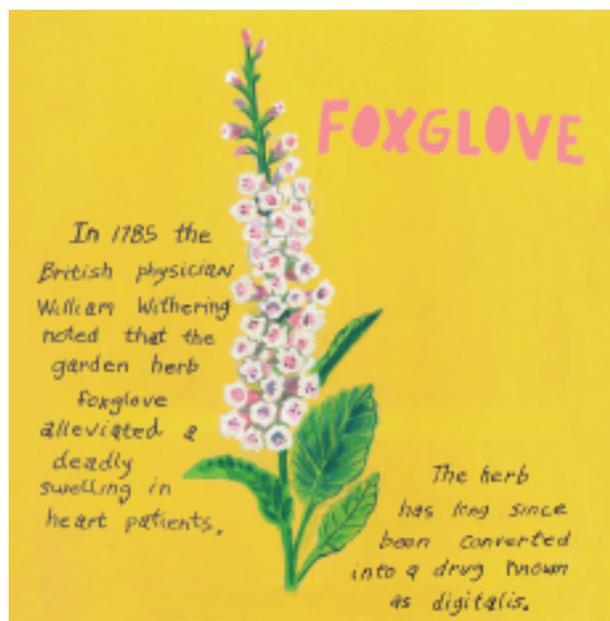
Prehistoric origins of herbal medicine

Most users of herbal remedies point to anecdotal rather than clinical evidence of efficacy—but that evidence, like the botanicals themselves, has firm roots in many countries around the world.

Otzi the Iceman, the 5,300-year-old mummified human discovered in the Italian Alps in 1991, carried his own medicine kit, which contained birch fungus, a natural antibiotic. An autopsy showed that Otzi suffered from intestinal parasites, so the birch may have come in handy to fight the infestation. Birch fungus also could have served as a styptic pencil to close minor cuts.

In the Middle Ages, ergot, a fungus that grows on rye and other food grains, caused ergot poisoning in people who ate bread made from rye, barley or wheat infested with the parasite. Characterized by constriction of blood vessels, ergotism often led to gangrene. It was also marked by convulsions and hallucinations known as Saint Anthony's fire. (The alkaloids in ergot were a key ingredient in the experiments performed by a Swiss chemist that led to the synthesis of LSD.) Ergot was also used in 16th-century Europe to stop postpartum bleeding and to induce abortions; its first recorded use as an oxytocic was 1582.

And also in the 16th century, Western explorers like Sir Walter Raleigh were impressed by the way in which South Americans killed prey—and sometimes Europeans—with arrows poisoned with curare. Curare, which is concocted from several plants, kills by isolating muscle tissue from contact with nerves, eventually paralyzing the victim's respiratory muscles. The powers of curare weren't tamed until 1942, when two physicians converted it into a muscle relaxant that allowed lifesaving procedures to be performed more rapidly and effectively.



The coca leaf has been a chief target in the war on drugs, but it was woven into the fabric of Andean society thousands of years before its illicit use as the raw material of cocaine. To this day, indigenous people in South America chew on the leaf as a stimulant and appetite suppressant, helping them get through a day of hard labor on the mountainsides. Brewed as a tea, coca combats altitude sickness and settles the stomach.

Since the Enlightenment, the healing ability of botanicals has been rooted in hard science: the British physician William Withering, M.D., noted in a seminal 1785 paper that the garden herb foxglove, also known as *digitalis*, alleviated a deadly accumulation of fluid in the lungs and other body tissues—a condition then called dropsy—in patients with congestive heart failure.

Humankind has also been wary of medicinal plants. They tend to trigger a bitter taste on the tongue, long recognized as a poison detector. They also vary in their potential to harm as well as heal. As Withering himself acknowledged, the perils of foxglove were well-known.

Foxglove has long since been converted into a standardized drug known as digoxin, but controversy over its use—including its potential toxicity—continues to this day. But the disputes are based on numerous studies, something that can't be said about many other botanicals with supposed healing properties. The longstanding use of herbal preparations notwithstanding, they have a hard time getting a seat at the table dominated by Western pharmaceuticals, which rely heavily on the clinical trial, largely unheard-of until the 1920s.

Star anise is a staple in Chinese spice cabinets, in part because of its licorice-like flavor and in part because it helps promote healthy digestion. Teas made from it have traditionally been used to treat colicky babies. However, in 2003 the Food and Drug Administration (FDA) issued an advisory to warn consumers against drinking the tea—Chinese star anise was sometimes adulterated with Japanese star anise, a toxic species of the herb. It also provides the key ingredient for the anti-flu drug oseltamivir phosphate, marketed under the name Tamiflu by Roche. When reports of avian flu hit Asia in 2005, Chinese officials reported a run on star anise, both by people who wanted its protective properties and by those who wanted it to flavor their food. Eating the spice offers no protection against flu, however, because the active ingredient, shikimic acid, is obtained only after a laborious extraction process.

For over two millennia herbal treatments have been a mainstay of Chinese medicine, whose techniques also include acupuncture and massage. Among the herbs used are yarrow, to treat the common cold, colic, indigestion and toothache; aloe, which has a laxative effect and is also used to treat wounds and burns; cardamom seeds for infections of the digestive tract as well as nausea and vomiting; and devil's root, for chronic bronchitis. Traditional Chinese medicines are made of a blend of herbs, usually a principal

ingredient and three others intended to reinforce the effects of the principal herb, mitigate its side effects or treat a coexisting disease pattern.

Finding a consistent dosage

Complementary and mainstream medicine “have a different type of approach” to healing, but “eventually, they're going to meet,” said Cheng. “Chinese medicine has been used for years and is still used today.” He knows full well that “mainstream medicine has always been suspicious” of such methods of healing, even if their popularity has risen in Western countries. By 1997, according to the NCCAM, spending on complementary and alternative medicines totaled between \$36 and \$47 billion in the United States alone. By comparison, the major pharmaceutical companies registered \$251.8 billion in sales in 2005, according to the most recent figures from IMS Health, a consulting firm that tracks the drug industry.

In 1999 Yale's Office of Cooperative Research worked with Cheng to found PhytoCeutica, a company devoted to making cancer drugs out of herbs used in traditional Chinese medicine. That this project is connected with a leading research institution at all reflects a major shift in attitude, said James C. Whorton, PH.D., professor of medical history and ethics at the University of Washington School of Medicine in Seattle and the author of *Nature Cures: The History of Alternative Medicine in America*. “It would not have happened 25 or 30 years ago,” he said. “A faculty member wouldn't risk having his name associated with some group that was doing alternative medicine. It was career suicide.”

Cheng also hopes to advance the acceptance of traditional medicines at the international level. In December 2004 he founded the Consortium for the Globalization of Chinese Medicine, which counts as members 61 institutions around the world, including seven from industry. Member institutions include the School of Medicine; the Department of Intramural Research Affairs at the National Health Research Institutes of the NIH; and academic and research institutes in Canada, China, Great Britain, Hong Kong, Singapore, Taiwan and the United States. The consortium's goals are to develop platform technologies for producing Chinese medicines, to facilitate collaboration among institutions and to develop medicines based on Chinese herbal preparations as well as traditional medicines from other countries. “The spirit is to share the technology,” said Cheng, who chairs the consortium. “This is something no company or institution can do by itself.”

The key to success for producing Chinese herbal remedies, aside from showing that they work, is getting a consistent formula to deliver the drug. This concern for consistency is what separates PhytoCeutica from other purveyors of Chinese herbs. The alternative treatment landscape is littered with botanical products that looked like promising

cancer therapies but ultimately failed or were deemed dangerous. When such products are taken in their herbal form or as unregulated supplements, however, the bath water comes with the baby. “With two different preparations, you come up with a different result,” Cheng said. “The chemical composition is going to be different.”

For example, PC-SPES, a widely touted herbal concoction for prostate cancer, was removed from the market after reports that it caused cardiovascular and other problems. “Different formulations were found to have different impurities,” said Edward Chu, M.D., deputy director of the Yale Cancer Center. If the impurities had been removed, it might have worked, he said.

For the past few years PhytoCeutica has been conducting early-stage clinical trials of a traditional Chinese medicine formula that goes by the designation PHY906 and acts as an adjuvant to chemotherapy for cancer. For competitive reasons, the company, which has a patent for PHY906 in the United States and other countries to treat cancer, won't release many details about the herbs used in the compound. Cheng said it is a traditional Chinese medicine derived from four different plants whose therapeutic ingredients work better together than each does alone. Unlike other plant-based drugs with a single active molecule, however, PHY906 is multipronged. “Chinese medicine always claims to have multiple chemicals hitting multiple targets,” explained Cheng, referring to the traditional practice of blending several herbs to produce a single remedy. “There is a possibility this could be a shortcut to look for medicines which have a broad spectrum of usage, and also cover most patients.”

The herbs used to make PHY906 are typically brewed as a tea or put in a blender, according to Chu, who was born in the United States, but whose great-grandfather practiced Chinese herbal medicine. The plants have been used historically to treat headache, fever, swelling and a host of gastrointestinal problems.

Initial Phase I trials involving 17 patients found that PHY906, used in combination with a standard two-drug regimen for colon cancer, caused no adverse effects and appeared to reduce the toxicity of the chemotherapy. The next step of the trial, with 29 patients, is to determine whether PHY906 will enhance the action of the chemotherapy and shrink tumors as it did in animal models, Cheng said. Another trial tested the compound with capecitabine, marketed by Roche under the name Xeloda to treat liver cancer, and again found no adverse effects from PHY906. Data are still being gathered to assess the effects of the traditional formula on quality of life, but initial findings, said Cheng and Chu, are encouraging.

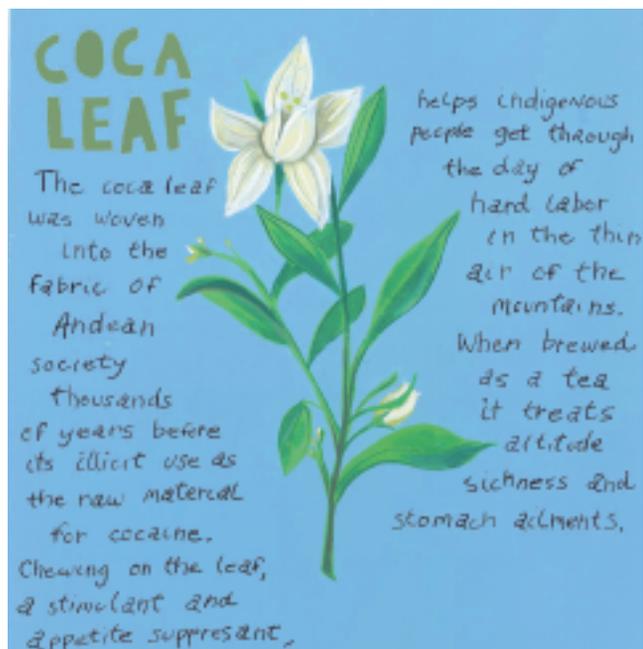
“It seemed like the anti-tumor activity of Xeloda was improved upon the addition of the herb,” said Chu. “In Phase I, patients seemed to tolerate the combination pretty well, and there are some patients who are continuing to

receive treatment for a lot longer than with chemotherapy alone.” In Phase II of that trial, the investigators will see “whether it can cause the tumors to shrink and allow the patients to be living with their cancer for a longer period of time,” Chu said. In addition, a new trial at Yale-New Haven Hospital is testing PHY906 in combination with Xeloda for treatment of pancreatic cancer.

Chu and Cheng still don't know how PHY906 works, but they suspect that it inhibits certain proteins or clears a path to allow cancer drugs to get into cells. “To be honest, as a patient you don't really care how the compound works,” Cheng said. That people have used these herbs for nearly two millennia, and still do in the age of pharmaceutical plenty, makes for a tough-to-ignore case. “A number of our friends who have had cancer and who have taken these herbs have benefited,” Chu said. The point of the research, however, is to “take it out of the mystique and prove in fact that there is real clinical efficacy.”

If proven effective, PHY906 could become the first botanical prescription medicine developed from multiple herbs to be approved for oral administration by the FDA, said Cheng. (The FDA recently approved an unrelated topical application based on herbal medicine for treatment of genital warts, Cheng said.)

While the trial results have looked good so far, this botanical-to-pharmaceutical therapy still faces an uphill battle. “So far, I have not seen any herb go beyond Phase III,” said Lixing Lao, M.D., Ph.D., director of traditional Chinese medicine research at the University of Maryland School of Medicine. Another concern endemic to herbal medicines—and one that has ended trials in the past—is getting a consistently successful formula. “We have standards of chemical identities,” said Peter Goldman, M.D., professor emeritus of



pharmacology at Harvard, who has called for stronger research on medicinal herbs. “How sure are you that what you have from a chemical perspective could actually be reproduced?” he asked. Lao added that the potency of an herb can vary greatly from sample to sample. “Different fields in different seasons may come up with different chemical compositions.”

PhytoCeutica’s work on PHY906 stems from a collaboration with SunTen Phytotech, a Taiwanese herbal medicine company that had manufactured the compound in pill form for years. What’s new is the application of PhytoCeutica’s platform technology, called Phytomics, and quality control methods to develop a standard consistency for the compound. Cheng said PhytoCeutica uses modern bioinformatics, “including chemical and biological fingerprints,” to obtain the same formula each time. “We compared our product with the company’s product that was made previously, not following current good manufacturing practices,” Cheng said. “As far as chemistry and biology are concerned, they are different. The manufacturing practices are a critical element to ensure the product’s consistency.”

The success of PHY906, according to *Nature Cures* author Whorton, depends on whether “they’ve actually identified the compounds present in the crude herbs and isolated that in pure form, the way you’d isolate morphine from opium.” If that works, then PhytoCeutica and its Taiwanese partner can separate from the large pack of herbal medicine companies. Paul Talalay, M.D. ’48, professor of neurology and pharmacology at Johns Hopkins School of Medicine, said that will be necessary because many products make bogus claims, are dangerous or both. A 1994 federal law allows sellers of alternative remedies to make health claims without adhering to the same strict standards as a pharmaceutical drug. The law, the Dietary Supplement Health and Education Act (DSHEA), essentially deregulated the industry—the FDA can’t remove a product until there is overwhelming evidence that it causes harm—and spurred more intense interest in readily available products. DSHEA was “a disaster” that “confuses our ability to handle disease properly,” Talalay said. Everything should undergo the same standards of testing, he said.

The program as developed by Yale may be an excellent model for raising standards, according to Jeanne A. Drisko, M.D., who developed an integrative-medicine program at the University of Kansas and served on an Institute of Medicine committee that wrote a report on alternative medicine. “The only way that we’re going to separate those [remedies] that work from those that don’t is to do the research,” she said. “And it has to be done in a partnership between the conventional practitioner and the complementary and alternative practitioner.” **YM**

John Dillon is a freelance writer in New Haven.

Chinese herbal remedy found to work against kidney disease in mice

The search for a treatment for polycystic kidney disease (PKD), a disorder in which genetic mutations lead to the formation of cysts that impair kidney function, has led a Yale team to a Chinese plant-based medicine used for centuries to treat cancer, inflammation and other conditions. “The active ingredient has been known for 30 years, but nobody knew how it worked,” said Craig M. Crews, PH.D., associate professor of chemistry, of molecular, cellular and developmental biology and of pharmacology. “We wanted to find out how this compound worked.”

Crews and colleagues found that the compound, known as triptolide, binds to a calcium channel encoded by the gene *PKD2* and implicated in polycystic kidney disease. Furthermore, the gene that encodes that channel had been cloned by Stefan Somlo, M.D., FW ’91, the C.N.H. Long Professor of Medicine and professor of genetics. Triptolide is the active ingredient in the traditional Chinese medicine *Lei Gong Teng*, typically brewed as a tea.

In March, Crews and his team, in collaboration with Somlo, reported in the *Proceedings of the National Academy of Sciences* that triptolide reined in the rogue calcium channel in mice and thus appeared to mitigate the symptoms of PKD. “Our research shows that triptolide ... markedly decreases cyst formation in a mouse model of this most common genetic lethal kidney disease,” Crews said.

PKD, Crews said, is the result of a gene mutation that confuses epithelial cells into thinking they’re at an earlier stage of development. As a result they

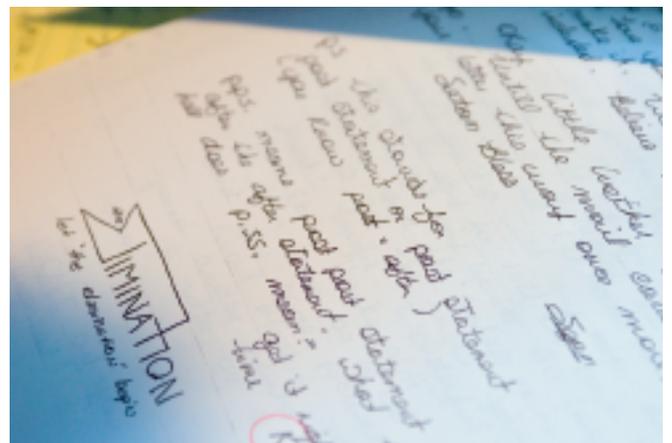
continue to generate tubules that turn into fluid-filled cysts in the kidney. “They accumulate cysts to the point where after 40 or 50 years of life the kidneys are so full of cysts that they lose function,” he said. More than 12 million people worldwide suffer from the disease.

“The next step with triptolide is that we want to see if this may have an effect in humans,” Crews said.



ABOVE As a child growing up during World War II, Dorothy Lewis wondered what happened to shape Adolf Hitler's character. As a psychiatrist, she has studied serial killers and murderers, finding three elements that occur consistently in the most violent offenders: brain dysfunction, child abuse and psychotic thinking, particularly paranoia. The three occurring simultaneously, she believes, are a recipe for violence.

RIGHT Lewis' records include writing samples and drawings from the killers she has studied. The style of these records tells her as much as the substance—marked changes in handwriting can reveal as much as what is written.



A fascination with violence

Dorothy Lewis has spent her career trying to understand serial killers such as John Allen Muhammad and Ted Bundy. Her theory—that all violent offenders share three traits—was once considered outrageous but now influences Supreme Court decisions.

By Colleen Shaddox

Photographs by Terry Dagradi

Dorothy Otnow Lewis, M.D. '63, HS '70, a clinical professor in the Child Study Center, recalls her childhood in New York City during World War II as painful and awkward. As children were choosing up sides for a game, she remembers praying, "Please God, let me be picked second to last, not last." The little girl who was the object of so much teasing at school would once again see her prayers go unanswered.

At home, things were not always easy. She was tangled in an ambiguous relationship with her older sister, who liked to hide in dark closets, jump out and scream, "The green witch will get you!" But at other times, she helped Dorothy with her French homework, keeping her a week ahead of her classmates. A serious, often sad, child, Dorothy was urged by her mother to be more social: "shorten your skirts; be a butterfly." But young Dorothy never felt much like a butterfly. She felt like an outsider, and she credits that feeling of isolation with her lifelong interest in society's pariahs.

Her interest began in kindergarten, when a precocious desire to understand how a human being could be so cruel led her to try to figure out Adolf Hitler. After all, she was horrified when she watched her uncle slaughter a chicken on their farm in New Jersey. In Lewis' memoir, *Guilty by Reason of Insanity: A Psychiatrist Explores the Minds of Killers*, she recalls stories of the Nazi dictator hanging over her childhood as "a source of fascination and fear." She was the only student in her elementary school "who did not rejoice upon hearing of Hitler's suicide. Now I could never know what made him tick. ... I was convinced, even as a child, that Hitler could not have been born that way. Something had to have happened to him. No one could be born that way. I still believe that."

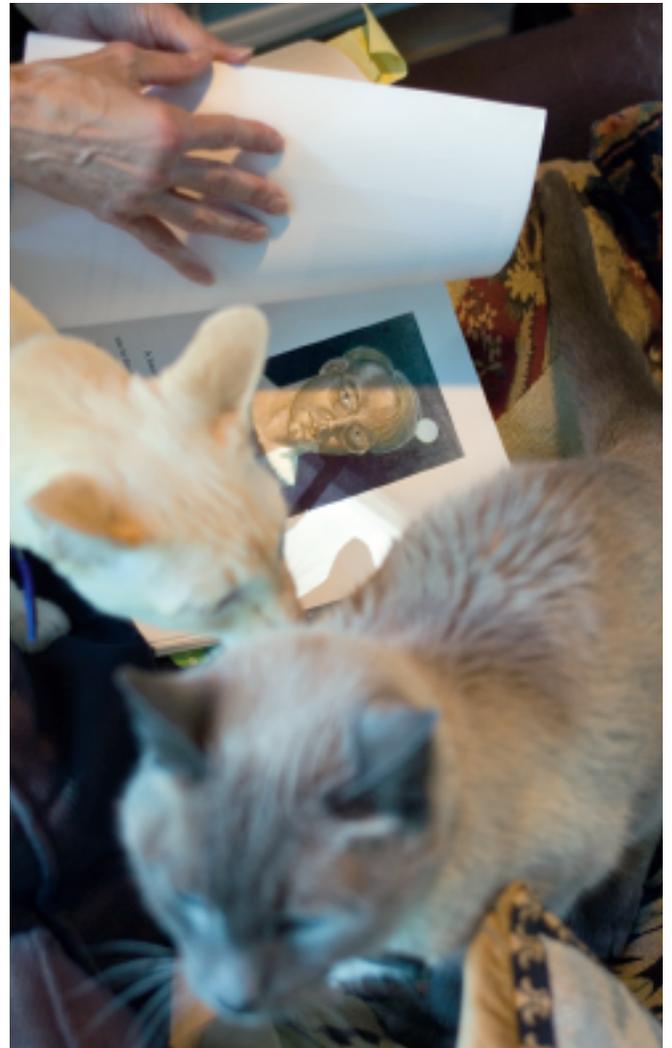
Lewis has spent her career as a psychiatrist studying murderers and searching for scientific explanations for their

behavior. Her work would take her away from her family as she flew to reform schools and prisons around the country to research cases or testify for the defense. It would put her in the company of such notorious murderers as Mark David Chapman, who shot John Lennon; serial killers Ted Bundy and Arthur Shawcross; and in 2005, John Allen Muhammad, the so-called "Beltway Sniper," who examined her fingers and told her she should drink more water. Lewis' work would place her on the stand as a defense witness where prosecutors would do their best to discredit her. It would even put her at odds with the mainstream of her profession as she challenged conventional theories that attribute violent behavior to socioeconomic deprivation and lax discipline.

Her findings, based on psychiatric and neurological evaluations coupled with reviews of medical records, have appeared in such publications as the *American Journal of Psychiatry* and the *Journal of the American Academy of Child and Adolescent Psychiatry*. Three elements, she has found, occur consistently in the most violent offenders: brain dysfunction, child abuse and psychotic thinking, particularly paranoia. When all three occur simultaneously, Lewis believes, they become primary ingredients in a recipe for violence.

Her theories, once considered outrageous, influenced Supreme Court rulings on capital punishment in 1988 and 2005. The outsider has become the expert and even something of a butterfly. "She's very petite, very feminine. The last person in the world you'd expect to be doing this work," said Jonathan H. Pincus, M.D., HS '64, her long-time collaborator, now chief of neurology at the Veterans Administration Medical Center and a member of the Center for the Brain Basis of Cognition at Georgetown University in Washington, D.C.

Lewis believes that child abuse acts in several ways to turn people into violent adults. The abuse itself can cause brain damage that leads to a lack of control. Children also learn an unhealthy model of behavior. "Children do as they see," Lewis said. And the abuse engenders rage that is almost never directed toward the abuser, but is displaced onto others.



In concentrating on violence, Lewis chose, to put it mildly, the road less traveled. Her husband, Melvin Lewis, M.D., HS '59, professor emeritus and senior research scientist in the Yale Child Study Center, frequently ribs her, "Dorothy, with two basic drives why did you have to choose violence?" She has no regrets. "Violence is probably the single most important public health issue anywhere in the world," Lewis said.

A murder with no reason

She is a master at separating the lurid side of her work from her family life. On a snowy afternoon last winter in her comfortable Tudor home in New Haven, a boom box flooded the house with Mozart. Lewis sat on the sofa thumbing through case records.

Her records are full of drawings and writing samples from the murderers she has examined. There are sketches that they made of their own disjointed conceptions of their brains as well as scenes of sexual abuse they remembered from childhood. Lewis often saw as much in the style of their works as in the substance. "See. Here! And here again!" She tapped the pages wherever she saw marked changes in handwriting—clues that the writer may periodically dissociate.

Until 1984, when she recognized her first case of dissociative identity disorder (DID), she questioned the phenomenon's very existence. It is still regarded with skepticism by some psychiatrists.

Once known as multiple personality disorder, DID is marked by two or more personalities coexisting in the same patient. While DID has been listed in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* since 1994, the diagnosis remains controversial—some psychiatrists believe it is the product of therapist suggestion. Nevertheless, Lewis is now asked to lecture about DID internationally—evidence, in her view, that the profession is giving the diagnosis more credence.

As she pored over records of Lee Anne Jameson, the first juvenile murderer Lewis ever evaluated, a small boy bounded into the room and asked, "Grandma, do you have any batteries?" Her grandson, Noah, held up an action figure. Lewis looked up from the book and grinned. She asked him a bit about his day, then directed him to the batteries. When Noah left the room, she returned to the Jameson case without missing a beat.

Lee Anne (a pseudonym to protect the girl's identity) was 13 when she killed her best friend with a paring knife while waiting for a school bus. No one, least of all Lee Anne, could say why. Lewis got involved in the case because she was running a clinic in New Haven's juvenile court at that time. Observing "normal" children in a preschool as a child psychiatry fellow at Yale didn't interest her; she convinced the faculty that her evenings with her daughter, Gillian, then four, gave her ample opportunity to observe normal child

development. She got permission to observe at the juvenile court in New Haven. After witnessing the severe psychopathology in children and families coming through the court and the lack of services available to them, she received a grant from the state of Connecticut in 1971 to open the first court clinic in the state. With psychologist David A. Balla, PH.D., a research associate at the Child Study Center, she published *Delinquency and Psychopathology* in 1976. The book was based on their work with children in the clinic.

One of the first cases Lewis encountered was that of Lee Anne. The girl's medical history was telling. She had made more than 30 visits to Yale-New Haven Hospital. While pregnant with Lee Anne, her mother suffered from syphilis and untreated hypothyroidism, conditions that limited Lee Anne's intelligence. During a difficult delivery, the soft bones of the baby's cranium had been squeezed together and her clavicle broken. The ensuing years saw a string of emergency room visits—cuts, burns, stomach pains and numerous accidents and injuries. Lee Anne was dismissed as a manipulative attention-seeker. No one paid attention to a medical student's note: "she stared off into space and could not be aroused for several seconds. ... Get EEG." Lewis suspected a neurologic problem and consulted Pincus, then also a faculty member at Yale. Pincus found some signs of neurologic problems and ordered an EEG, but it was normal. Nevertheless, Lee Anne's symptoms were consistent with complex partial seizures. She also was paranoid and sometimes heard voices that told her what to do.

Lee Anne displayed the three traits that Lewis and Pincus would see again and again in murderers: brain injury, psychosis and a history of abuse. Their combined testimony was less conclusive than Lewis would have liked. But it was enough to get Lee Anne sent to a treatment center; it was also the start of a partnership that would alter the careers of both doctors, who often see things very differently.

For example, Lewis has long been at odds with the conventional wisdom and often puts more trust in her own observations than in the literature. Pincus, however, has a deep respect for the literature. And when they began their second collaboration, in 1977, Pincus observed that the study was "a waste of time." Lewis was studying the neuropsychiatric characteristics of youths in Long Lane School in Middletown, then Connecticut's detention facility for violent juveniles. The state wanted detailed information about the children who would be housed in a proposed secure wing. Pincus did not believe that violence and neuropathology were linked—he opened one of the classic texts on crime and psychiatric disorders and read a list of factors *not* associated with criminal behavior, including such impairments as schizophrenia and brain damage. Pincus finally agreed to participate in the study after Lewis explained that her grant included a stipend for a neurologist—he needed the extra income. What he found was

staggering. He told Lewis that he had never seen so many neurologically impaired children in one place.

Their collaboration continued when Lewis joined the faculty of New York University (NYU) in 1979 as a professor of psychiatry. She made the move because her Yale appointment as a clinical professor carried no salary. She also maintained a small private practice in addition to her academic work. But when Melvin Lewis was diagnosed with angina, she faced the possibility of becoming the sole breadwinner for a family that now included two children.

"I wanted to work in New Haven, and Yale was the obvious place to begin my job search," Dorothy Lewis wrote in her memoir. "Yale was not interested. Yale had never in its history given a tenured faculty position in psychiatry to a woman psychiatrist; maybe once to a pediatrician, once to an epidemiologist; never to a woman psychiatrist. Yale was not about to break tradition for me." After receiving offers from Columbia, Cornell and NYU, Lewis joined the faculty at NYU, because it had an inpatient adolescent unit and offered access to Bellevue Hospital's prison ward. Lewis secured funding to study prisoners and again convinced Pincus to become the project neurologist.

An interview four years later on the *CBS Morning News* brought her to the attention of a Florida public defender. The lawyer saw Lewis' interview with Diane Sawyer on the subject of children who kill, and thought that the children she described sounded a lot like two of his clients on death row. He asked Lewis and Pincus to come to Starke, Fla., to evaluate his entire death row clientele. The only place to eat was a greasy spoon with an electric sign outside flashing "Burn Bundy Burn," a reference to the serial killer Ted Bundy, due to be executed. Bundy was not on their list of convicts to examine, though Lewis would end up interviewing him many times before his execution in 1989.

Lucky Larson (not his real name) was on their list. Larson was sentenced to die for two separate murders in which he'd hacked victims to death in the course of robberies. The death row inmate's demeanor was remarkably cheerful. Larson explained that he'd adopted an optimistic attitude after a serious car accident he'd had years before the murders. Larson's smile was lopsided, as was his gait. Tests revealed several brain injuries. An MRI showed that his frontal lobes had been injured and could not perform their usual job of controlling impulses emanating from the deeper, more primitive parts of the brain.

Meanwhile Lewis was probing Larson's history for evidence of abuse. Interviews revealed nothing. He had no memory of maltreatment of any kind. Displaying a characteristic of many brain-damaged individuals, he would go off on verbal tangents and then ask, "Where'd I go? What was the question?"

When Larson's brother, Frank, was arrested for molesting his own children, the defense team got important clues

about Lucky's upbringing. Where, Lewis wondered, had Frank learned such behavior? A private investigator working for Lucky Larson's lawyers found social service records documenting that Lucky's mother had begun sexually abusing Lucky when he was six years old. His father, jealous of the relationship, was violent toward the boy. Once Lucky scrambled up a tree to escape his enraged father. The man took an axe and chopped down the tree with Lucky in it.

Larson won a new sentencing hearing, but the jury again condemned him to death. On death row, he talked almost constantly—happy chatter about very little. He would try to snap his fingers—even though his neurological problems made the task impossible—to illustrate how little it all mattered. "The only comfort we could find," Lewis wrote, "was in our knowledge that the very lesions that separated Lucky's frontal lobes from the rest of his brain and caused him to act so ferociously also protected him from appreciating the reality of his situation and kept him in perpetual good spirits."

A scientific explanation for violence

Over the past 25 years Lewis and Pincus have evaluated more than 100 juvenile and adult capital defendants. They are often asked to testify for the defense during the sentencing phase. That atmosphere is emotionally charged, and the scrutiny they receive can be intense.

One of her best-known adversaries is forensic psychiatrist Park Dietz, M.D., M.P.H., Ph.D. Dietz testified for the prosecution in the case of the New York serial killer Arthur Shawcross, for whom Lewis was a defense witness. In addition to being a frequent prosecution expert witness, Dietz also runs Threat Assessment Group, a firm that advises employers on the risk of stalking, product tampering and other forms of violence in their workplace.

Detailed and harsh in his criticism, Dietz has accused Lewis of interpreting "ambiguous symptoms" as psychosis. "I can't escape the theory that Dr. Lewis has some position or a zealotry against the death penalty that influences her findings and judgment," he said.

Lewis, however, insists that she takes no sides on the morality or politics of the death penalty. She offers objective testimony on the mental health of accused killers, most of whom hide their illnesses and childhood traumas because "they'd rather be killed than called crazy. ... I just give you the facts. Then if you decide you want to kill him, you can kill him," she said.

Of course, her strictly clinical explanation for murder does not answer traditional questions of right and wrong. *Fox News* commentator Bill O'Reilly once asked her in a 2002 interview, "But Dr. Lewis, what about evil?"

"Evil is not a scientific term," Lewis answered. "It's a religious term."

In most cases, Lewis sees the defendant executed despite her testimony. But her work has changed the way the

death penalty is applied nationally. Lewis' research on juveniles condemned to death in Texas became part of the record in a 1988 Supreme Court ruling that youths under the age of 16 could not be executed, and in a 2005 Supreme Court ruling that murderers cannot be executed for crimes they committed before the age of 18. (Justice Thurgood Marshall also cited her work in his 1991 dissent from a Supreme Court decision allowing the execution of the brain-damaged Ricky Ray Rector.) Her research cited in the 2005 case found the same three factors she had so often observed—a history of abuse along with psychiatric and neurological problems—and documented how little the courts had considered them.

Her most important contribution, according to Pincus, is establishing the link between child abuse and violent behavior. It would be easy to see how their work together might have made Pincus and Lewis anti-death penalty crusaders, but they avoid association with groups trying to ban capital punishment. Instead they have become zealous about preventing child abuse.

Preventing child abuse

Lewis has retired from NYU but remains a clinical professor in the Department of Psychiatry and in the Child Study Center at Yale. She continues to evaluate violent offenders, conduct research on violence, supervise trainees and see private patients. She is currently studying the moral implications of our knowledge about violence; the origins of the concept of the sociopath; and ethical issues surrounding the “lottery” of life that places some people at greater risk of becoming violent. She is also working with Jennifer S. Bard, J.D. '87, M.P.H., professor of law at Texas Tech University (TTU) School of Law and adjunct associate professor of neuropsychiatry at the TTU School of Medicine, on a study of capital defendants who represent themselves. One of Lewis' major interests continues to be the prevention of child abuse.

Child abuse, says Lewis, acts in several ways. First, the abuse itself can cause brain damage that leads to a lack of control in individuals. It exposes children to an unhealthy model of behavior. “Children do as they see,” she said. The stress resulting from ongoing physical and verbal abuse changes the structure of the brain. And finally, she said, “Abuse engenders rage that is almost never expressed toward the perpetrator of the abuse. That rage is displaced onto others.

“I would give my right arm to get funding to do an early identification and prevention project,” she said. “We could identify kids early whose maladaptive behaviors reflect terrible violence at home.” The goal would be to offer support to parents—parenting education and mental health services—rather than remove children from the troubled home. But she believes that the program would be seen as intruding on families and therefore be a tough sell.

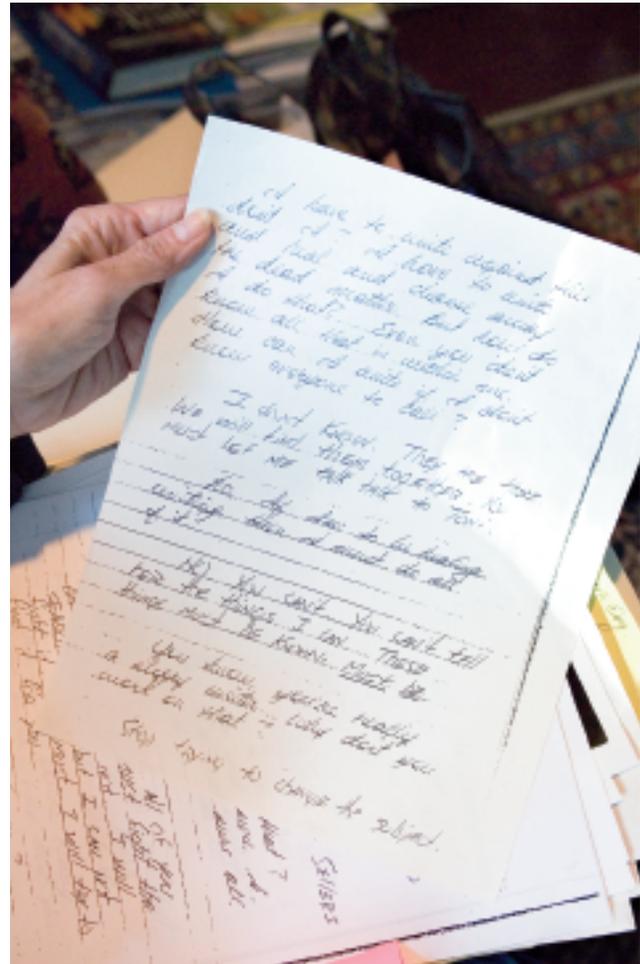
Lewis' childhood curiosity about humanity's dark side launched her on a mission to understand the very people

much of society would prefer to eliminate. Ted Bundy asked to see Lewis the day before his execution and even kissed her goodbye. “Everyone else wants to know what I did,” he explained. “You want to know why.”

If violence is the most serious public health problem in the world, Lewis sees understanding killers as the key to devising a cure. The closest that Lewis comes to condemning the death penalty has less to do with arguments about justice and compassion than a thirst for answers. “How is it,” she asks in her memoir, “that we pour millions of dollars into Bundy books and the like, but are nevertheless willing to sacrifice further knowledge about him and his ilk in the interest of doing away with them?”

At 69, and after decades of study, Dorothy Lewis is no less fascinated by our pariahs than she was at age five. **YM**

Colleen Shaddox is a freelance writer in New Haven.



Among the murderers and serial killers Lewis has studied are Ted Bundy, Mark David Chapman and “Beltway Sniper” John Allen Muhammad. The first murderer she evaluated was a 13-year-old

schoolgirl who killed her best friend for reasons she could not explain.



Edward Chu

New deputy director at Yale Cancer Center

EDWARD CHU, M.D., was named deputy director of Yale Cancer Center (YCC), effective January 1. He succeeds José Costa, M.D., who has filled the post for the past 10 years. Costa will remain on the faculty as a professor of pathology and of medicine, vice chair of the Department of Pathology and director of anatomic pathology in the department. Costa will also remain an active member of YCC.

Chu, who is currently professor of medicine and pharmacology and chief of medical oncology, has held positions of increasing responsibility at the center since 1996. In his new role, Chu will continue to lead the Section of Medical Oncology and will also direct the clinical research initiatives for YCC.

Chu is a graduate of Brown University, where he also received his medical degree and completed his residency training. He completed a fellowship in medical oncology at the National Cancer Institute and served as a tenured senior clinical investigator. He came to Yale in 1996 as chief of medical oncology and director of the VA Connecticut Cancer Center

at the VA Connecticut Healthcare System in West Haven and as co-director of the Developmental Therapeutics Research Program at YCC.

Chu is the author of *Physicians' Cancer Chemotherapy Drug Manual*, a comprehensive review of all major cancer drugs and treatment regimens used in daily clinical practice. The manual, which is now in its seventh edition and is updated annually, is recognized as a leading publication in the field of cancer therapy. Chu is also editor in chief of the journal *Clinical Colorectal Cancer* and chair of the International Colorectal Congress, an annual meeting that brings together leaders in oncology from the United States, Europe and Asia to present and discuss the latest developments in the management and treatment of colorectal cancer.



Michael Cappello

Pediatrician named to research society

A Yale pediatrician is among 27 of the nation's foremost experts in global health who will band together to advocate for greater U.S. investment in global health research. MICHAEL CAPPELLO, M.D., FW '95, professor of pediatrics, microbial pathogenesis, and epidemiology and public health, joined the inaugural class of ambassadors in the Paul G. Rogers Society for Global Health Research in November. The Rogers Society, funded by the Bill and Melinda Gates Foundation, is named for the former congressman from Florida, a champion of health research. Rogers is the current chair emeritus of Research!America, a nonprofit public education and advocacy alliance founded in 1989. Members of the Rogers Society team are leaders in medical and global public health research. The inaugural class of ambassadors will meet with opinion leaders and decision makers at the national level to convey the importance of global health research. Among the ambassadors are two former Yale faculty members, PETER J. HOTEZ, PH.D., M.D., chair of microbiology and tropical medicine at The George Washington University Medical Center, and LEON E. ROSENBERG, M.D., HS '63, professor of molecular biology at Princeton University and a former dean of the School of Medicine.



Gerhard Giebisch

Professor honored with prestigious award

GERHARD H. GIEBISCH, M.D., professor emeritus and senior research scientist in cellular and molecular physiology, received the John P. Peters Award from the American Society of Nephrology at its annual meeting in November. Giebisch, a pioneer in the use of cellular and molecular approaches to elucidate mechanisms of electrolyte pathophysiology, is the first Yale faculty member to receive the Peters Award.

Established in 1983, this annual award is named for one of the fathers of the discipline of nephrology. Peters spent his entire faculty career at Yale, and was chief of the metabolic division in the Department of Medicine from 1922 to 1955.

Giebisch studied kidney functions at the micro level. He considers the kidney one of the body's most complex control organs.



Robert Udelsman



Linda Degutis



Michael Green



Alan Kazdin



Anthony Koleske



Joel Rosenbaum



Thomas Steitz

The Yale Corporation made the following appointments in the Department of Surgery at its December meeting: the chair of the department, **Robert Udelsman**, M.D., M.B.A., was named the William H. Carmalt Professor of Surgery; **John A. Eleftheriades**, M.D. '76, HS '81, FW '83, chief of cardiothoracic surgery, was named the William W.L. Glenn Professor of Cardiothoracic Surgery; and **Ronald R. Salem**, M.D., was named the Lampman Professor of Surgery.

Sidney J. Blatt, PH.D., professor of psychiatry and psychology and chief of the psychology section in the Department of Psychiatry, has received the Mary S. Sigourney Award from the Mary S. Sigourney Award Trust, for distinguished contributions to psychoanalytic theory and research. The Sigourney Award, considered the most distinguished international award for contributions to psychoanalysis, includes a prize of \$50,000. Blatt's research has focused on disruptions of normal psychological development as the core of many psychiatric disorders.

James P. Comer, M.D., the Maurice Falk Professor of Child Psychiatry, is the winner of the 2007 Grawemeyer Award for Education, the University of Louisville announced in November. The award carries a \$200,000 cash prize, the highest in the field of education. Comer established the School Development Program in 1968, a whole-child development program that encourages collaboration among teachers and between schools and their communities.

David C. Cone, M.D., associate professor of surgery (emergency medicine) and epidemiology, was installed as president of the National Association of EMS Physicians (NAEMSP) in January. The NAEMSP promotes excellence in emergency medical services in out-of-hospital settings.

Linda Degutis, M.S.N. '82, DR.PH. '94, associate professor of surgery (emergency medicine) and public health (environmental health sciences), has been named president-elect of the American Public Health Association (APHA). She will begin her term in the fall of 2007. The APHA represents more than 50,000 members in more than 50 occupations within the field of public health. Degutis is the director of the Yale Center for Public Health Preparedness, whose work ensures that front-line workers are prepared to respond to public health emergencies.

Michael Green, M.D., associate professor of medicine, has been selected as a Kimball Scholar by the American Board of Internal Medicine. Green will develop an Internet-based portfolio that allows the board's diplomates to document the characteristics, pursuit and application of their clinical questions, in order to facilitate reflective evidence-based practice.

Alan E. Kazdin, PH.D., the John M. Musser Professor of Psychology, has been named president of the American Psychological Association, the largest association of psychologists worldwide. Kazdin, who also directs the Yale Parenting Center and Child Conduct Clinic, began his leadership of the 150,000-member

organization in January 2007 as president-elect. He will take office as president in 2008.

Anthony Koleske, PH.D., associate professor of molecular biophysics and biochemistry and of neurobiology at the School of Medicine, received the \$500,000 Established Investigator Award from the American Heart Association in January. The award will fund Koleske's research on the mechanisms that allow cells to sense differences in their adhesive environment and respond by redirecting migration.

Richard P. Lifton, PH.D., M.D., Sterling Professor of Genetics, chair of genetics and a Howard Hughes Medical Institute investigator, received the 2006 Robert Tigerstedt Award at the 21st Biennial Scientific Meeting of the International Society of Hypertension in Fukuoka, Japan, in October. Lifton was cited for his "pioneering work on the identification of mutations that cause human hypertension, which has identified the key role of renal salt handling in blood pressure regulation in humans." Lifton was also selected to deliver the first Donald Seldin Lecture at the annual meeting of the American Heart Association in Chicago in November.

Joel Rosenbaum, PH.D., professor of molecular, cellular and developmental biology, and a faculty member since 1967, received the 2006 E.B. Wilson Medal, the American Society for Cell Biology's highest honor

for scientific research in November. The honor recognizes significant advances over a lifetime in the understanding of the assembly, maintenance and function of cilia and flagella, which are fine hair-like cell organelles that extend outward from the cell surface.

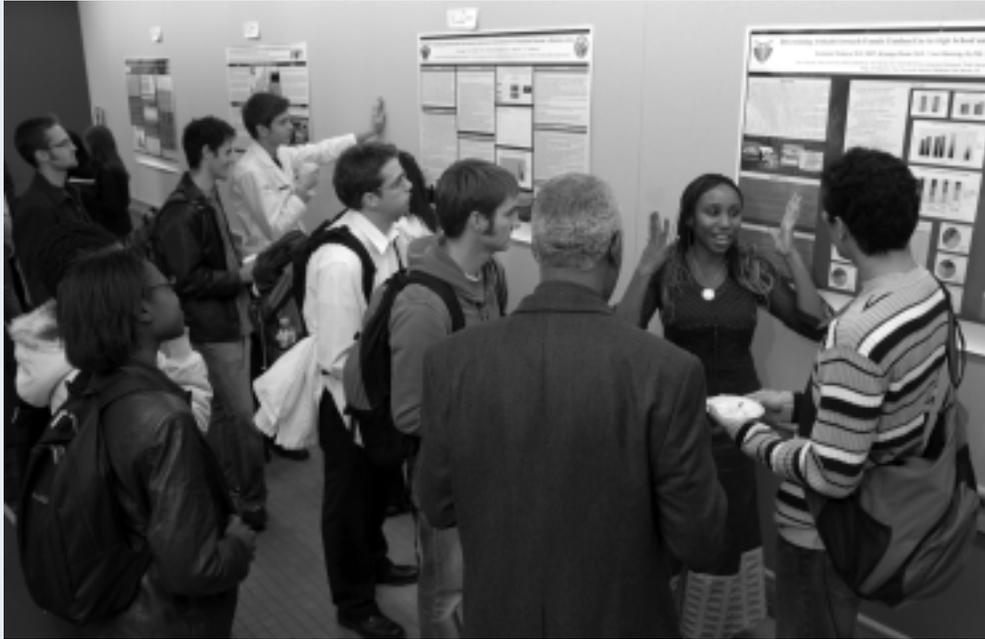
Craig R. Roy, PH.D., associate professor of microbial pathogenesis, has received the 2007 Eli Lilly and Company Research Award from the American Society for Microbiology. This award recognizes fundamental research of unusual merit in microbiology or immunology by an individual on the threshold of his or her career.

Thomas A. Steitz, PH.D., Sterling Professor of Molecular Biophysics and Biochemistry, received the 11th Keio Medical Science Prize on November 1 at Keio University in Tokyo, Japan. Steitz was honored for research that produced the first X-ray crystallographic imaging of the large 50S ribosomal subunit in 2000.

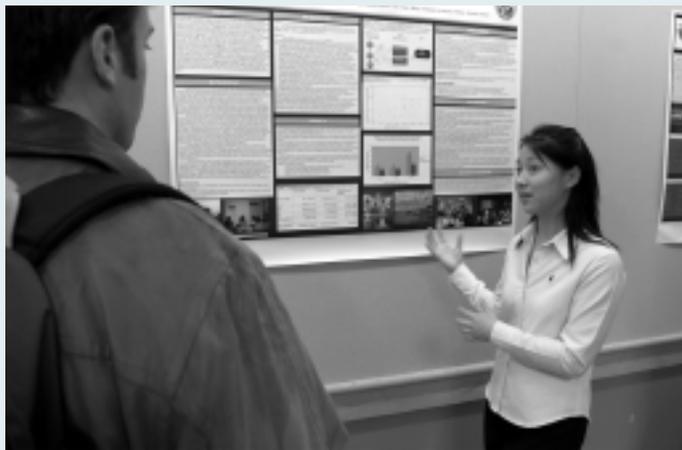
Robert I. White Jr., M.D., professor of diagnostic radiology, received the Leaders in Innovation Award from the Society of Interventional Radiology at the group's annual meeting in Seattle in March. The award recognizes society members who have originated and implemented an idea that has had an advantageous impact on the practice of interventional radiology.

SEND FACULTY NEWS TO

Claire M. Bessinger, *Yale Medicine*, 300 George Street, Suite 773, New Haven, CT 06511, or via e-mail to claire.bessinger@yale.edu



JOHN CURTIS (2)



TOP The 2006 Downs International Health Student Travel Fellows reported on their health research and findings in October, in posters and oral presentations. Ten of the 12 fellows, students in medicine, public health, nursing and the Physician Associate Program, presented posters on their research in Africa, South America and the Caribbean.

ABOVE Jennifer Lee, a second-year medical student, explained her research on sensory phenomena in Tourette syndrome and obsessive-compulsive disorder in Brazil.

Downs fellows report on summer research

HIV/AIDS, trauma of war and genocide are among the topics of last year's presentations.

For Christopher P. McManus, a student at the School of Public Health and the School of Forestry & Environmental Studies, doing research in South Africa's Kwazulu-Natal province meant learning anew what is meant by family. "I didn't even know what a household was," said McManus, noting that polygamy leads to a different definition.

McManus described his research in October at the annual fall symposium of the Committee on International Health. Every year students in nursing, medicine, public health and the Physician Associate Program report on research done the summer before. In 2006 a dozen students undertook research projects in Africa, South America and Jamaica. McManus, one of three students to make an oral presentation, studied the impact of HIV/AIDS on rural households.

"There are a whole bunch of people in these households and everyone does a whole lot of stuff," he said.

"If you remove one member of a household it is very difficult for that household to maintain security." AIDS, he said, tends to affect the most productive family members, and their absence can lead to a food shortage. He found that 42 percent of the households surveyed made up the difference with wild food, such as birds, hare or antelope. Coping strategies included watering down por-

ridge or using pumpkin to stretch it, borrowing food and skipping meals.

Eloise D. Austin, a second-year medical student, described the mental health effects of the Rwandan genocide of 1994 on children. She interviewed 40 orphans and found that their problems included grief, loneliness and frequent memories of traumatic events. According to past studies, “most children had seen the death of a close family member, had witnessed massacres, had been forced to hide, had seen dead bodies or body parts,” she said. Her open-ended interviews suggested that the mental health burden from these traumatic events was still considerable.

Amy L. Glick, a nursing student, examined perceptions of care by patients and providers at a new HIV/AIDS clinic in Togo, in western Africa. In that region she found stigma to be pervasive. Some patients said that people in certain villages or tribes believed that AIDS was caused by sorcery, or that discussing sex education and prevention with young adults would cause promiscuity. And in some hospitals, patients with AIDS described poor care, neglect and insults from staff. The AED-Lidaw Health Clinic, where the research was conducted, is working to combat these negative experiences and provide a positive experience for patients with HIV/AIDS.

Other research topics included sand fly-vectored diseases in Peru, attitudes toward female condom use in Botswana and the willingness of medical and nursing students to treat HIV-positive patients in Sierra Leone.

—John Curtis

Hunger and Homelessness Auction raises \$36,000 for community agencies

The student-run Hunger and Homelessness Auction raised \$36,313 in November for seven community agencies in New Haven, an increase of \$5,000 over the previous year.

This year’s auctioneer was Wade Brubacher, father of first-year student Jake Brubacher. State Attorney General Richard Blumenthal, J.D., made a guest appearance to auction his own donation—lunch in Hartford and a personal tour of the state capitol.

Recipients this year are the Community Health Care Van, HAVEN Free Clinic, Community Soup Kitchen, Domestic Violence Services of Greater New Haven, Immanuel Baptist Shelter, Leeway, Loaves and Fishes and the St. Thomas More Catholic Chapel and Center at Yale University, which runs a soup kitchen.

The fundraising began with a silent auction, from November 13 to 16, followed by a live auction in the Harkness Ballroom on November 16. Offerings included a dinner and wine tasting hosted by Dean Robert J. Alpern, M.D., Ensign Professor of Medicine, with samples from his private collection; lunch with University President Richard C. Levin at Mory’s; weekends in New York, New Hampshire and other choice locations; classic books; stargazing sessions; and lessons in art, athletics, cooking, dance and languages.

Student organizers offered their thanks to faculty. “We owe a lot of our success to their help and generosity,” said Joshua I. Weiner.

—J.C.



TERRY DAGRADI (3)



TOP Wade Brubacher, a professional auctioneer and father of first-year student Jake Brubacher, offered his services to this year’s auction.

MIDDLE Medical student Laura Tom enticed prospective buyers to bid on a gold and diamond necklace before the live auction.

BOTTOM Physician Associate students Melissa Studdard, Tamara Brining, Dan Heacock and Anthony Pazienza perused the list of available items at a reception before the live auction.

Blending the clinical and the statistical

Early in his career, Lee Goldman saw the value of applying epidemiology to clinical practice.

For more than two decades physicians have carried in their pocket copies of the Goldman Index, a list of factors to determine whether a patient undergoing surgery for noncardiac reasons is at risk of a heart attack or another major cardiac complication. The index is named for **Lee Goldman, M.D.** '73, M.P.H. '73, FW '78, who developed it during his medical residency and published it during his cardiology fellowship at Yale by applying techniques derived from epidemiology and clinical practice.

In recent years Goldman has also achieved renown for his leadership of the department of medicine at the University of California, San Francisco (UCSF), which he joined in 1995. In July 2006 Goldman moved to Columbia University's College of Physicians and Surgeons as executive vice president for health and biomedical sciences and dean of the faculties of health sciences and medicine.

Goldman traces his interest in statistics to a class he took during his first semester at the School of Medicine with John D. Thompson, R.N., M.S., the legendary director of the program in hospital administration at the Department of Epidemiology and Public Health. That course convinced Goldman to enroll in Yale's master of public health program, and a study he undertook there cemented his love of numbers and other data. In 1971,

President Richard Nixon was pushing a plan for national health insurance. Goldman surveyed Yale medical students and faculty, deconstructing this bill and competing pieces of legislation to determine how his colleagues should perceive each proposal. Goldman then took his programming textbook to the beach over Labor Day weekend and came back ready to crunch numbers in the giant computers of the day. As the analysis came together, he was hooked. "I ended up publishing five papers out of my thesis," he said, "and kind of got the bug."

He soon began to apply his newfound statistical and programming savvy to studies of cardiac risk. After an internship and residency at UCSF and a second residency at Massachusetts General Hospital, Goldman became a cardiology fellow at Yale. As his fellowship ended, Goldman said, his interest in epidemiology propelled him toward nontraditional applications of cardiology. "Cardiology divisions weren't really interested in me, and I didn't really want to run an echo [cardiogram] lab," he said.

In the division of general internal medicine at Harvard's Peter Bent Brigham (now Brigham and Women's) Hospital, where he stayed for almost two decades, Goldman continued to focus on combining epidemiology with clinical care in cardiology. "Most of my work used the same kinds of methods an epidemiologist used, but applied it to patients we actually touched," he said, describing his efforts to determine risk factors for heart attacks after surgery and among patients who came to emergency rooms with chest pain. "There were

Lee Goldman, executive vice president for health and biomedical sciences at Columbia University's College of Physicians and Surgeons, is known for his work in combining epidemiology with clinical care in cardiology.



CHARLES MANLEY

so many factors to consider that clinicians did not have a way of determining which ones were the best predictors of a patient's risk," he said. "The concept was always to gather comprehensive data and to whittle it down to what might be important."

One of Goldman's most enduring contributions was the Goldman Index. "It was the first systematic approach to that question," said Lawrence S. Cohen, M.D., HS '65, special advisor to the dean. "It has remained a benchmark for the care of patients that are undergoing noncardiac surgery, and it has stood the test of time over three decades."

Goldman and his colleagues also started one of the first chest pain evaluation units at Harvard. Today, these are common at many hospitals nationwide. And Goldman developed the Coronary Heart Disease Policy Model, which sets priorities for preventing and treating heart disease. At Harvard, he also co-developed the Program in Clinical Effectiveness, which has trained

David Kupfer's meeting with a mentor in his second year of medical school set him on a path toward his career in psychiatry.

over 1,000 young physicians in the basics of clinical research.

"He really has been a pioneer," said Harlan M. Krumholz, M.D., M.Sc., the Harold J. Hines Jr. Professor of Medicine and professor of epidemiology and public health, and of investigative medicine, one of Goldman's advisees at Yale. "He was one of the first people to develop large observational studies that drew knowledge from the real world and could be fed back into practice."

After becoming the chair of medicine at UCSF, Goldman and his colleague Robert M. Wachter, M.D., in 1996 coined the term *hospitalist* for inpatient physicians, a concept that quickly produced a major movement in medicine. (Goldman and Wachter started the first hospitalist program in the country at UCSF.) With inpatient care changing rapidly, they argued, office-based doctors simply do not have time to monitor their hospital patients the necessary three or four times a day. Establishing a separate specialty of hospital medicine, they argued, would increase hospital efficiency and benefit patients. "The board is about to recognize it as a distinct discipline," he said, referring to the American Board of Internal Medicine, which certifies subspecialties in internal medicine.

"Columbia is fortunate," said his former advisee Krumholz, recalling his mentor's seemingly limitless capacity to inspire students and colleagues. "When he walked into a room, the energy would just increase, the quality of conversation would go up. I think a whole generation of people was drawn to research because of their association with him."

—Alla Katsnelson

From sleepless nights and a study of narcolepsy to chairing a leading program

When most lights in the dormitory went out, **David Kupfer's** stayed on. A history and economics major at Yale College, Kupfer, M.D. '65, couldn't understand why his peers needed so much sleep. At the time, he didn't realize sleep would influence his career—that he would become a leader in sleep, depression and bipolar disorder research—and that observing two cases of narcolepsy would set him on this path.

While in medical school and still undecided about a specialty, Kupfer saw two patients at Yale-New Haven Hospital (YNHH) who suffered from an extreme exhaustion called cataplexy that results in a complete loss of muscle control. Both were also diagnosed with narcolepsy.

Seeing these two patients solidified Kupfer's decision to study sleep, but two encounters with a Yale professor molded his career. As a second-year student he met Thomas Detre, M.D., then chief of psychiatry at YNHH, whose interests included recurrent depression, violence and aggression in children, biologic aspects of mental disorders and the budding fields of psychobiology and psychopharmacology. At a time when there was little understanding of mental diseases, Detre felt that understanding the body could lead to better treatment of mental illness.

During Kupfer's third year, a last-minute trade with a classmate led to a chance reunion with Detre and solidified Kupfer's decision to pursue



psychiatry. The night before beginning his psychiatry rotation at the VA hospital in West Haven, Kupfer agreed to switch rotations with a classmate who wanted to work at the VA. Kupfer was back at YNHH with Detre. They soon realized they had a lot in common—both were high-energy and stayed up late. Detre expected diligence and Kupfer delivered.

"Some people have considered [Detre] a tough taskmaster because he was so persistent. I found him loyal and supportive and clever. He gave me freedom," Kupfer said.

After medical school, Kupfer trained at the National Institute of Mental Health (NIMH), then returned to Yale in 1969 as an NIMH investigator and assistant professor of psychiatry. Kupfer's career was blossoming at Yale, but Detre asked him to join him at the University of Pittsburgh and its Western Psychiatric Institute and Clinic (WPIIC), which Detre felt he could transform to better treat patients with mental illness. In 1973, Kupfer went to Pitt as an associate profes-

sor of psychiatry and director of research. In 1983, he became director of the WPIC and chair of the Department of Psychiatry when Detre became senior vice chancellor for health sciences. In 1994, further cementing the connection between these remarkable colleagues, Kupfer was named the first Thomas Detre Professor of Psychiatry.

Finally retired from his 23-year career as vice chancellor, Detre now serves as a professor emeritus of psychiatry and is teaching a course to residents on psychiatric diagnosis.

He sits on the boards of two software companies in Pittsburgh and is also on the scientific advisory board of PsychoGenics, a New York-based company that tests neurological drugs.

At Pitt, Kupfer stressed the importance of determining the biological underpinnings of psychiatric disease and led a research revolution by earning a number of NIMH grants for research on sleep disturbances, depression and bipolar disorder. The number of faculty and beds increased, along with the reputation of Pitt's psychiatry program. "From 1983 to 1993 the department went from Number 4 to Number 1 in federal research funding," Detre explained.

With his wife, Ellen Frank, PH.D., Kupfer co-directs the Bipolar Disorder Center for Pennsylvanians, created with a \$5 million grant from the commonwealth. He is principal investigator of several studies, including one on the pharmacogenetics of bipolar disease.

"You're going to laugh when I say this—writing is very difficult for me," he said. He has written 800 articles,

books and book chapters. His latest book, written for a general audience with Helena Chmura Kraemer, PH.D., and Karen Kraemer Lowe, M.S., is titled *To Your Health: How to Understand What Research Tells Us About Risk*, and stresses the importance, throughout medicine, of designing more rigorous clinical trials and clearly defining the results. As a case in point Kupfer cites media reports of studies that appeared to show a high risk of suicide among young children on antidepressants. According to Kupfer, many of the studies poorly defined the risk.

Kupfer hopes that someday more physicians will value the relationship between mental and physical illnesses. Research has shown that depression, for example, makes people more susceptible to other illnesses, like diabetes. Kupfer feels that many doctors treat the diabetes rather than exploring the link between the depression and diabetes. He hopes this paradigm changes soon—patients who receive poor mental health treatment face serious health risks, just like patients who receive the wrong medical care.

It might keep Kupfer up at night, but that's when he does his best work.

—Meghan Holohan

A rebel with "medicine in his veins" becomes a scientific researcher in India

When **Manohar V.N. Shirodkar**, MED '54, M.D., initially rebelled against a family tradition and rejected medical practice, his father, a famed gynecologist in Mumbai, India, despaired. The young Shirodkar knew he had "medicine in his veins"—his father had developed the Shirodkar stitch, which is still used to treat cervical incompetence. But Shirodkar wasn't interested in being a clinician.

Shirodkar, however, found something more exciting—the viral causes of illness. When he learned that his grandmother had died of cervical cancer, Shirodkar was hooked. How did she get sick? Why would she have cancer when others do not? Today, the medical community knows that some types of the human papilloma virus can cause cervical cancer, but at that time the young man simply knew that one way to understand illness was to study oncogenic viruses.

To his father's delight, Shirodkar begged to study medicine in the United States. After he completed his undergraduate work at Johns Hopkins University, he headed to the Yale School of Medicine in 1950. His clinical studies were interrupted when Shirodkar learned his wife was pregnant. The couple returned to Mumbai, where their daughters, Renée and Diane, were born. With a growing family, Shirodkar didn't have the funds to complete medical school. He accepted a position at Johns Hopkins' school of public health, which gave him a stipend to pursue an S.C.D.

Manohar Shirodkar has spent his career, in India and the United States, studying oncogenic viruses.



COURTESY OF MANOHAR SHIRODKAR

His detour from a traditional medical education gave Shirodkar the opportunity he wanted. (He finished his M.B.B.S. in 1970 at the Seth G.S. Medical College in Mumbai.) And throughout a career filled with many twists and turns, his drive to understand viruses remains constant.

As a graduate student at Hopkins in 1958, Shirodkar began investigating the Rous sarcoma virus in chickens, the first virus discovered to cause a solid cancer. His research took him from Hopkins to the Virus Research Center of the Rockefeller Foundation in Pune, India, where he completed his doctoral thesis. In 1978 he found that West Nile virus, and later, rabies, blocked the Rous-produced sarcoma, and that the underlying mediator was not interferon, but his newly discovered anti-sarcoma, antiviral protein, called plasma factor. His research findings appeared in *The Journal of Immunology* in December 1965, the *Journal of General Virology* in 1973, *The Indian Journal of Medical Research* in 1978 and the *Indian Journal of Experimental Biology* in October 2006.

“The most gratifying aspect of my career,” Shirodkar said, “is the fact that I have been a perpetual student—quite literally—and have been able to pursue, with some success, ... the search for scientific truth.”

As a young man, Shirodkar turned away from a career as a clinician, yet he always admired his father. In 1976, Shirodkar and his wife, Sudha, founded the Dr. V.N. Shirodkar Memorial Research Foundation, an organization that embodies the dreams of both Shirodkar and his father. The organization screens underprivileged women for cervical cancer and investigates novel antiviral biological agents to treat virus diseases.

—M.H.

Familiar Faces

Do you have a colleague who is making a difference in medicine or public health or has followed an unusual path since leaving Yale? We'd like to hear about alumni of the School of Medicine, School of Public Health, Physician Associate Program and the medical school's doctoral, fellowship and residency programs. Drop us a line at yym@yale.edu or write to Faces, Yale Medicine, 300 George Street, Suite 773, New Haven, CT 06511.

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1940s

Morris A. Wessel, M.D. '43, has retired from the Clifford Beers Clinic, the oldest outpatient behavioral health clinic in the United States, after 35 years of service as a pediatrician and advocate for children and families. The clinic announced that their new national trauma center will now be named the Morris Wessel Child and Family Trauma Center of the Clifford Beers Clinic. Wessel cared for generations of New Haven children as a pediatrician in practice from 1951 until his retirement in 1993.

1950s

Harry C. Miller, M.D. '54, writes to say, "In September 2006, Kari and I moved from Great Falls, Va., where we'd lived for 33 years, to a new home in Keswick, Va. It's a lovely spot in a lovely development called Glenmore. Nice golf course, nice neighbors, lots of kids, six miles from Charlottesville. Gorgeous views of the Blue Ridge." Miller still participates in urology conferences at the University of Virginia in Charlottesville.

Mary W. Schley, M.D. '52, received an honorary doctor of humane letters degree from Columbus State University in Georgia, honoring her 45 years of professional work in Columbus as well as her volunteer work in organizations devoted to education, health care and the performing arts.

1960s

The Tufts-New England Medical Center's (NEMC) Division of Nephrology celebrated the 70th birthday of **John T. Harrington**, M.D. '62, in January and noted his contributions to the medical center, Tufts University School of Medicine and the field of nephrology. Harrington began his association with NEMC in 1965 as a nephrology fellow, subsequently serving as director of the dialysis unit and chief of the division of general internal medicine. In 1996 he was appointed dean of Tufts University School of Medicine, a position he held until 2002. As dean emeritus, Harrington currently serves as a senior nephrologist and professor of medicine. The celebration also featured the inaugural "Dr. John T. Harrington Medical Grand Rounds," and the announcement of the creation of an endowed fund in nephrology in Harrington's name as well as the naming of the Dr. John T. Harrington Conference Room in the Division of Nephrology.

Marc E. Lippman, M.D. '68, a pioneering breast cancer researcher, has been named chair of the Department of Medicine at the University of Miami Miller School of Medicine. Lippman currently chairs the Department of Internal Medicine at the University of Michigan. He was previously director of the cancer research center at Georgetown University and spent 18 years as a senior investigator with the National Cancer Institute. Lippman, who started in Miami on May 1, has five patents and author credit on more than 600 articles, chapters and books. Lippman is currently studying

biological markers that could predict which breast tumors will respond to hormone therapy. He will continue to see patients and, with his new post, will also chair the Department of Medicine at Jackson Memorial Hospital.

John E. Mayer Jr., M.D. '68, a senior associate in cardiovascular surgery at the Children's Hospital in Boston and a professor of surgery at Harvard Medical School, was elected president of the Society of Thoracic Surgeons (STS) at its annual membership meeting on February 5. Mayer has been involved with STS throughout his career, his principal interests being issues in government relations and public affairs.

1970s

C. Gene Cayten, M.D., M.P.H. '72, senior associate dean and professor of surgery at New York Medical College, received the Physician Achievement Award in September from Our Lady of Mercy Medical Center in the Bronx, N.Y. Cayten is the author of more than 100 publications and 36 book chapters and has been chair of surgery at the medical center for 23 years.

Robert B. Diasio, M.D. '71, began serving as director of the Mayo Clinic Cancer Center in September. He will also oversee cancer center activities at the branches of the Mayo Clinic in Scottsdale, Ariz., and in Jacksonville, Fla. Diasio was previously a profes-

sor of medicine, pharmacology and toxicology at the University of Alabama School of Medicine in Birmingham. He plans to continue his pharmacogenomic research, which focuses on maximizing the effectiveness of chemotherapy through new genetic diagnostic methods.

Edward C. Halperin, M.D. '79, vice dean of the Duke University School of Medicine, assumed the deanship of the University of Louisville's School of Medicine in November. Halperin is also the Ford Foundation Professor of Medical Education and a professor of radiation oncology and pediatrics at the medical school, as well as a professor of history in the university's College of Arts and Sciences.

Ralph I. Horwitz, M.D., FW '77, the Arthur Bloomfield Professor and the chair of the Department of Medicine at Stanford University, is one of seven people named as members of the National Institute of Health's Advisory Committee to the Director. The committee has advised the director on policy and planning issues for more than 40 years. The seven new members join 13 current committee members.

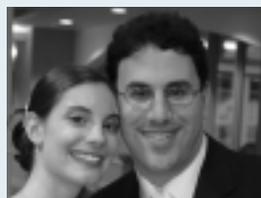
Tom Smith, M.D. '79, and **Joann Bodurtha**, M.D. '79 (married in 1982), report that their daughter Anna has enrolled in Yale College in the Class of 2010. The Thomas Palliative Care Program at Virginia Commonwealth University (VCU), which Smith directs, won the American Hospital Association's Circle of Life award for the best palliative care program in 2005 and the International Association for Hospice and Palliative Care's



Rock Positano



Andrew Steele



Alexandra Block and Curtis Weiss

University Award for the best academic program in 2006. Smith is a professor of medicine at the VCU Massey Cancer Center in Richmond. Bodurtha is professor of human genetics, pediatrics and obstetrics-gynecology at VCU, and has been named interim chair of the Department of Human Genetics. Both have active RO1-funded research programs as well as busy clinical practices—important now that they are empty nesters.

Eliot Sorel, M.D., FW '75, co-chaired the Pan American Health Organization Forum on Bioethics, Public Health and Health Policy at the World Congress of Public Health in Rio de Janeiro in August. As part of that forum, he also presented "Modernising Health Systems, a 21st-Century Essential Prerogative." Last May he served as a senior advisor to the Center for Strategic and International Studies in Washington, on "Modernising Health Care Systems in Central and Eastern Europe."

1980s

Robert L. Levin, M.D. '89, and Karen Shaevel Gumer, M.S., C.R.N.P., were married in September in Washington, Levin is a medical officer in the Division of Psychiatry Products of the U.S. Food and Drug Administration. Gumer is a family nurse practitioner in Rockville, Md.

William A. Petit Jr., M.D., FW '88, was installed as president of the Hartford County Medical Association in Cheshire, Conn., in November. He was also cited by *Connecticut Magazine* as one of the state's top physicians for women.

Rock G. Positano, D.P.M., M.S.C., M.P.H. '89, was named director last fall of the Joe DiMaggio Sports Foot and Ankle Center at the Hospital for Special Surgery in New York City. The center is dedicated to nonsurgical management of foot and ankle problems as well as athletic injuries. Positano also writes the Tuesday health column for the *New York Post*.

Andrew Steele, M.D. '86, M.P.H., has received a master's degree in health informatics from the Royal College of Surgeons in Edinburgh, Scotland.

1990s

Duane A. Bryan, M.D. '96, and Sarah E. O'Loughlin, R.N., were married in November at the Brooklyn Botanic Garden in New York. Bryan is a cardiologist and partner in Advanced Cardiovascular Care, a group practice in Valley Cottage, N.Y. O'Loughlin is a nurse anesthesiologist with Northeastern Anesthesia Services in Mt. Kisco, N.Y.

Brian "Ari" Cole, M.D., M.P.H. '95, has recently started his second master's-degree program at Harvard's Kennedy School of Government. He hopes to serve as a diplomat, perhaps in Scandinavia. Last fall he was also cross-registered at Harvard Law School "to better understand the problems between lawyers and physicians." Cole practices medicine in Hawaii, Pennsylvania, Massachusetts and New York. He considers Prague and Stockholm his favorite European cities for vacation and work.

Benjamin R. Doolittle, M.D. '97, M.Div. '97, HS '02, assistant professor of medicine (general medicine) and pediatrics at the School of Medicine, was one of 53 nominees for the 2006 Association of American Medical Colleges Humanism in Medicine Award. The nomination by medical students is recognition of a candidate as a positive and caring role model. Five characteristics are considered: mentoring skills, compassion and sensitivity, collaboration, community service activity and observance of professional ethics.

Rommel Nobay, M.P.H. '99, was married on January 20 in Stamford, Conn., to Frances Wu. Nobay is an associate director of information technology at Genzyme, a biotech company. Wu is an account director in the direct marketing unit of the McCann Worldgroup, an international advertising agency headquartered in New York City.

2000s

Aaryn Cohen Oleson, M.P.H. '00, and her husband, Matthew, announce the birth of their first child, Wyatt Samuel, on August 16. She is the pharmacovigilance consultant at the University of North Carolina in Chapel Hill and a doctoral candidate in pharmacoepidemiology. He is receiving his doctorate in physical therapy from Duke University.

Peter J. Mason, M.D., HS '00, M.P.H., has joined the Wisconsin Heart and Vascular Institute in Madison. A cardiac and vascular interventionist, Mason received his medical degree from the University of Massachusetts School of Medicine, where he

was inducted into the Alpha Omega Alpha honor society. He completed his internal medicine internship and residency at Yale-New Haven Hospital, and fellowships in cardiovascular epidemiology and peripheral vascular medicine and intervention at Brigham and Women's Hospital in Boston. He also completed fellowships in cardiovascular medicine and interventional cardiology at Boston Medical Center. Mason earned a public health degree at Harvard University School of Public Health.

Peter M. Petrillo, PA '02, was married to Bridget Nester in Falmouth, Mass., in September. Petrillo is a physician's assistant at the Hospital of St. Raphael in New Haven. Nester is a nurse anesthetist in New Haven.

Curtis Weiss, M.D. '05, was married to Alexandra Block, J.D. '04, in Westbrook, Conn., on August 27. Weiss is a resident in internal medicine at Yale-New Haven Hospital. Block is an associate in a New Haven law firm.

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Richard N. Abbott, M.D. '43, died on January 26 in Tilton, N.H. He was 88. Born in Lewiston, Maine, Abbott lived in Gilmanton, N.H., after his retirement in 1987. He completed his internship and residencies at New Haven Hospital, Boston Children's Hospital and the Boston Floating Hospital. Abbott was a captain in the Army Medical Corps during World War II, and served in the Philippine Islands and in the Army of the Occupation in Japan. He was the first pediatrician in Natick, Mass., where he practiced for more than 45 years. During that time he served as the school physician for elementary schools in Natick and Wellesley.

George R. Barnes Jr., M.D. '47, HS '50, died on October 22 in Tacoma, Wash., following a short illness. He was 84. After a pediatrics residency, Barnes served in the U.S. Army for five years. He subsequently entered academic medicine, teaching pediatrics at the University of Iowa. An interest in diagnostic medicine led to a second residency in radiology. In 1967 he joined a private practice in Tacoma, practicing radiology. Upon his retirement he joined the faculty at the University of Arizona Medical School in Tucson.

Arnold M. Baskin, M.D., HS '57, assistant clinical professor of surgery and a sponsor of a lectureship in the Humanities in Medicine at Yale, died on January 9. He was 79. Baskin received his medical degree from Albany Medical College and completed his internship and residency at Yale-New Haven Hospital (YNHH), where he trained in general surgery and urology. He entered private practice after completing

his residency, and he founded the urology practice in New Haven and surrounding areas now known as the Urology Center. Baskin participated in YNHH's Recovered Medical Equipment for the Developing World program, which collects and distributes unused surgical supplies for distribution to hospitals in the developing world.

Francis L. Black, PH.D., professor emeritus of epidemiology (microbiology), an expert in the biochemistry of viruses and the third scientist to use the measles vaccine in humans, died on January 27. He was 81. Black was born in Taipei, Taiwan, one of four children of medical missionaries. After receiving his PH.D. in biochemistry from the University of California, Berkeley, Black completed a research fellowship at the Rockefeller Foundation Laboratories and a postdoctoral fellowship under Joseph L. Melnick, PH.D. '39, a founder of modern virology, at the School of Medicine. Black went on to become a virologist at the Laboratory of Hygiene in Ottawa. In 1955, he returned to Yale to the departments of microbiology and epidemiology and public health, where he remained for 41 years.

Maurice L. Bogdonoff, M.D. '52, died on January 15 in Wheaton, Ill., of complications from esophageal cancer. He was 80. Born in Chicago in 1926, Bogdonoff grew up in Connecticut. He took two years off from Tufts University to serve in the U.S. Navy in the Philippines during World War II. After graduating from the School of Medicine with top honors, he spent his entire 35-year career at Rush University Medical

Center in Chicago, where he was a professor of radiology and internal medicine. Bogdonoff was also a consultant for the Department of Energy's Argonne National Laboratory outside Chicago and the U.S. Army's Gorgas Hospital in the Panama Canal Zone. He retired and moved to Maine in 1988 when macular degeneration began to affect his eyesight; nonetheless, he was a guest lecturer in nuclear power engineering at the Maine Maritime Academy in Castine. He traveled the world, riding yaks along the Silk Route in Asia, visiting Tibetan monasteries and sleeping under the stars on the deck of a barge in Indonesia.

James M. Cary, M.D., HS '51, died on February 8 in Simsbury, Conn. He was 85. Cary received his medical degree from Case Western Reserve University. During the Korean War he served as a captain in the U.S. Army in Alaska and in a Forward Army Hospital Unit. After his military service he came to Yale to complete a residency in orthopaedic medicine. He then began an orthopaedic surgery practice in Waterbury, Conn. In 1969 he became the assistant medical director and director of education at the Newington Children's Hospital, where he remained until his retirement in 1983. He enjoyed auto racing and was the racetrack physician at Lime Rock Park in Lakeville, Conn., in the late 1950s and early 1960s.

Norton G. Chaucer, M.D., M.P.H. '51, died on January 17 in Milford, Conn. He was 90. Chaucer graduated from Yale College in 1937 and received his medical degree from Columbia University in 1941. During World War II he served in

the U.S. Navy at several hospitals. After the war he became health director for Fairfield, Conn., and later served as health director for Hartford and West Hartford, Conn.

Henry M. Gewin, M.D., HS '51, died on February 1 in Mobile, Ala. He was 85. A 1945 graduate of Vanderbilt University School of Medicine, Gewin completed his internship at Yale. He then moved to Tuscaloosa, Ala., where he was a U.S. Army medical officer. Upon leaving the Army, he returned to Yale to complete his training. At Yale he was a chief resident and instructor in medicine. In 1951 he moved to Mobile to begin practice at the Diagnostic & Medical Clinic, where he remained until his retirement in 1994. He was chair of the Mobile County Board of Health and served as president of the medical staffs of several local hospitals. Gewin was a fellow of the American College of Physicians, the specialty society for physicians in internal medicine and related subspecialties.

Dennis Gilbert, M.P.H. '83, died on December 8 in Roseville, Ill. He was 54. Gilbert was a professor at Eastern Illinois University and author of the textbook *Book on Health*.

Herbert Goldenring, M.D., former associate clinical professor of pediatrics and director of the Newborn Nursery at Yale-New Haven Hospital, died on January 24, 2006. He was 84. Goldenring received his medical degree from New York University and trained in pediatrics before serving as a general medical officer in Korea. He set up practice in Branford in 1954, the first pediatrician in private practice on the shoreline.

He cared for thousands of children in his practice before retiring to academia in 1990. He retired from Yale in 2000.

Edward H. Hon, M.D., HS '55, died on November 6 at his home in Bradbury, Calif. He was 89. Hon worked with Orvan Hess, M.D., to invent electronic fetal heart rate monitoring at Yale in the 1960s. Born in China to Australian parents in 1917, he grew up in Australia and came to the United States in 1945 to attend Loma Linda Medical School, then known as the College of Medical Evangelists of the Seventh-Day Adventist Church. Hon completed his residency in obstetrics and gynecology at Yale, hoping to return to China later as a medical missionary. After publishing a landmark paper with Hess on fetal electrocardiography in the journal *Science* in 1957, Hon wrote more than 150 scholarly papers and received numerous awards, including the Distinguished Service Award of the American College of Obstetricians and Gynecologists and the 1999 Order of Australia Gold Medal.

Francis J. Kalamán, M.D., M.P.H. '68, died on January 25 in Palm City, Fla. He was 93. Kalamán came to the United States from Hungary at the age of 8. During World War II he was a physician in the medical corps of the U.S. Army and received the Bronze Star for setting up and commanding two hospitals on different fronts. In 1947 he began a private practice in Norwalk, Conn., where many of his patients came from the city's Hungarian community. He served as health director for the city and physician for the police department.

Aaron B. Lerner, M.D., PH.D., the founding chair of Yale's Department of Dermatology and an internationally renowned scientist, died on February 3. He was 87. Lerner, who was born in Minneapolis and received his graduate and professional degrees from the University of Minnesota, was one of the world's leading authorities on skin pigmentation. He guided dermatology at Yale from its inception in 1956 as a small new section within the Department of Internal Medicine to its later status as a free-standing department in 1971. Lerner was the first dermatologist elected to the National Academy of Sciences. He is well-known for his 1958 discovery of melatonin, a hormone secreted by the pineal gland that regulates circadian rhythms, and for his work with melanocyte-stimulating hormone, which he completed with colleagues at Yale and elsewhere. Previously he and a fellow graduate student, G. Robert Greenberg, PH.D., had isolated the first monoclonal antibody, known as cryoglobulin. Lerner was a pioneering "translational scientist," tightly coupling scientific insights with clinical advances.

F. Eugene Martin, M.D. '41, died on December 16 in Dayville, Conn. He was 90. During World War II Martin was a flight surgeon and lieutenant commander in the U.S. Navy. He practiced medicine in New Jersey and Pennsylvania after his discharge from the military in 1947. In 1961 he became chief medical officer at the Mansfield Training School, an institution for the mentally retarded in Mansfield, Conn. Martin retired in 1975.

Ernest L. Sarason, M.D. '39, died on November 28 in Syracuse, N.Y. He was 92. Sarason completed his internship and residency at Mt. Sinai Hospital in New York City and served during World War II as a major in the U.S. Army. Upon his return to Syracuse he practiced surgery. He was best known in his community as a donor and fundraiser for hospitals, charities, museums and the Syracuse Symphony Orchestra. For his contributions to the community he received numerous awards, including the President's Citizenship Award from the Medical Society of the State of New York.

Lewis S. Solomon, M.D. '67, died of a brain tumor on January 31 in Santa Rosa, Calif. He was 65. Solomon worked in Sonoma County for almost three decades as a pulmonologist and critical care physician. After graduating from the University of California, Los Angeles, in 1963, he was a research student there and later received a research fellowship under Willard F. Libby, PH.D., who won the 1960 Nobel Prize in chemistry for the use of carbon-14 to date archaeological artifacts. After medical school Solomon served in the U.S. Air Force and was a researcher in the Armed Forces Radiobiology Research Institute in Bethesda, Md. In 1976 he moved to Santa Rosa to join a medical practice.

Mattie L. Wade, R.N., M.P.H. '59, died on November 30 in Atlanta. She was 94. Wade was a private-duty nurse in South Carolina and Florida before she moved to Atlanta to work as a public health nurse. After receiving her public health degree from Yale she became the assistant to the director of public health nursing

in Fulton County, Ga. She later became the county's director of public health nursing.

William J. Waskowitz, M.D. '57, died of congestive heart failure in Kensington, Conn., on December 4. He was 75. Born in New Britain, Conn., Waskowitz followed in his father's footsteps to Yale College as well as the School of Medicine. He completed a residency in orthopaedic surgery at the University of Oklahoma, and then returned to his home in New Britain to join his father's practice as a sports physician and orthopaedist. He cared for children with hemophilia at Newington Children's Hospital, as well as treating high school and college athletes. He was given the Moyer Award, the top honor of the National Athletic Trainers' Association, for his work in sports medicine in the 1980s. An expert in treating knee injuries, Waskowitz pioneered the use of arthroscopy at New Britain General Hospital, where he was chief of orthopaedic surgery. He collected piano sheet music from the early 1900s and played the piano regularly, particularly the music of Porter, Gershwin and New Orleans jazz composers.

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TERRY DAGRADI

Research in Iran yields clue to heart disease

In 1998 Arya Mani, M.D., HS '97, FW '01, assistant professor of medicine (cardiology), returned to his native Iran to embark on a research project that linked modern genomics with his country's patterns of intermarriage [See "Journey of the Heart," *Yale Medicine*, Spring 2004]. Working with Richard P. Lifton, M.D., PH.D., chair of genetics, Mani sought a genetic component to heart disease. He also believed that genetic mutations would be more prevalent in families where relatives intermarried.

Although their initial research focused on patent ductus arteriosus (PDA), in March the journal *Science* published Mani and Lifton's research on metabolic disease, also involving coronary and carotid arteries. They identified a rare defect in a single gene that causes metabolic syndrome—a cluster of risk factors that include high LDL cholesterol, low HDL cholesterol, high triglycerides, hypertension and diabetes—and early heart disease. The paper relied on a study of an Iranian family with high rates of coronary artery disease (CAD). Among 58 blood relatives, 28 were diagnosed with early CAD—before the age of 50 for men and 55 for women—and 23 of the 28 died at young ages. Relatives without CAD died at an average age of 81.

Mani and Lifton traced the mutation to a section of chromosome 12. There they found a mutation in a gene called LRP6. One change in an amino acid altered the activity of the protein encoded by the gene, which acts in the Wnt signaling pathway, a network of proteins that is involved in development and is altered in certain malignant tumors.

"The main finding is the role of Wnt signaling in development of metabolic syndrome and CAD; that is where science has to focus on now to understand the basic molecular mechanism of the disease," Mani said.

"We expect that studies of the Wnt signaling pathway in patients with early CAD and metabolic syndrome will provide new insight into the basic biology of disease causation and allow new approaches to disease prevention," Lifton said.

—John Curtis



New Integrated Course in Basic Neurology

—*Alumni Bulletin*
October 1957

"The extensive growth of knowledge concerning the nervous system resulting from work in the fields of anatomy, physiology, psychology, biochemistry and pharmacology in recent years is causing many medical schools to re-evaluate the organization of basic science courses related to the nervous system. This problem has been under discussion at Yale for several years, and this winter an integrated program in the teaching of neuroanatomy and neurophysiology will begin with the initiation of a first-year course, 'Introduction to the Nervous System.'

"This course will be presented jointly by the Departments of Anatomy and Physiology with the cooperation of the Sections of Neurology and Neurosurgery. The program will consist of lectures, demonstrations, laboratory exercises, conferences and correlation clinics covering the basic structure and function of the nervous system. In addition to the presentation of fundamental concepts of normal morphology and activity, the program will endeavor to introduce the first-year medical students to the use of quantitative analytical methods and the rudiments of experimental design through laboratory experiments applied to the nervous system."



Yale Enters a Cooperative Research Agreement With Bristol-Myers for Development of Anticancer Drugs

—*Yale Medicine*
Fall / Winter 1982

"Bristol-Myers Company and Yale University have entered into a \$3 million cooperative research agreement to facilitate the production and availability of new anticancer drugs.

"The agreement brings the investigative talents of Yale medical scientists, who are recognized leaders in cancer chemotherapy research, together with the research and developmental resources of Bristol-Myers Company, a major producer and distributor worldwide of anticancer agents. Through ongoing technical and scientific interaction, they will seek to employ the unique resources and skills of university- and industry-based approaches to development and production of new effective and safe drugs for the diagnosis and treatment of neoplastic diseases. ...

"Yale is one of very few research institutions in the world where scientists involved in the development of a new anticancer drug work together from the first experiments at the laboratory bench through to treating patients in the clinic. They played a leading role in the development of several important drugs, and in addition, they have been conducting research to increase the effectiveness and reduce the toxic side effects of a number of drugs which have been used with some success, by revising the scheduling of their administration, and by utilizing them in combination."

YALE RESEARCHERS CITED AMONG TOP 10

Among the top 10 scientific breakthroughs of 2006, the journal *Science* has noted the work of two faculty members and a Yale alumnus for their research on the genetics of macular degeneration, the capacity of stem cells to copy themselves and the decoding of the Neanderthal genome.

The journal cited genomic studies of age-related macular degeneration (AMD) led by Josephine J. Hoh, PH.D., associate professor of epidemiology and of ophthalmology and visual science, along with other studies as representing significant progress against the disease, the most common cause of blindness in people over the age of 50. In 2005, Hoh and colleagues linked a variant of a gene on chromosome 1 with the milder dry form of AMD. Last year a group led by Hoh identified a single change in a gene on chromosome 10 that leads to a much greater risk of developing the more aggressive wet form of the disease. [See “Yale Scientist Finds Two Genetic Anomalies Linked to Macular Degeneration,” page 11.]

Haifan Lin, PH.D., professor of cell biology and director of the Yale Stem Cell Center, was one of four scientists who contributed to breakthroughs in the understanding of small RNA molecules known as Piwi-interacting RNAs, or piRNAs. Lin’s lab first discovered Piwi/Argonaute genes, which are essential for the self-renewal of stem cells, in 1998. But it was not understood what role these genes play in stem cell division until last year, when Lin’s group showed that Piwi/Argonaute proteins bind to piRNAs.

Alumnus Jonathan Rothberg, PH.D. ’91, founded and chairs 454 Life Sciences, a Branford, Conn., company that created technology for the rapid sequencing of genomes. Two of the labs on the top 10 list used this technology, and Lin is using it in his work. Rothberg and collaborators in Europe analyzed DNA from a 38,000-year-old Neanderthal fossil and found that the difference between the human and Neanderthal genomes is just one base pair in 2,000.

—Jill Max



The journal *Science* cited two Yale medical school faculty members and a Yale alumnus among the scientists behind the top 10 breakthroughs of 2006.

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