Yale Medicine

winter 2007

Water is life

A LETTER FROM NIGER

WINTER 2007

CONTENTS

ON THE COVER
Takat and Aminata, Tuareg girls from Camp Tantigellay Teckniwen, fetch water from a marsh contaminated with animal and human waste, and load it into a bag on a donkey. Water flows only a few months of the year in the Azawak plains of Niger in western Africa. During the dry season inhabitants spend most days in search of water.

BACKGROUND
Aminata, a Tuareg girl, fetches water from a marsh.

Photographs by Ariane Kirtley

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New state stem cell fund awards $7 million to Yale investigators

As *Yale Medicine* was in production, Yale scientists received $7 million in grants from the State of Connecticut Stem Cell Research Advisory Committee in November to study aspects of stem cell biology. The grants were the first awarded from the $100 million fund established by the state last year to promote stem cell research outside the restrictions of federal funding. The state also awarded grants totaling $12 million to investigators at the University of Connecticut and $900,000 to scientists at Wesleyan University. The total allocated for 21 research projects was $19.78 million. A state advisory panel awarded the grants after reviewing 70 applications. (See related story, page 7.)

The lion's share of the Yale funding went to Michael P. Snyder, PH.D., professor of molecular, cellular and developmental biology, to investigate the neural differentiation of human embryonic stem cells. He received $3.8 million.

Haifan Lin, PH.D., director of the Yale Stem Cell Program, received $2.5 million to support a human embryonic stem cell core facility. The University of Connecticut received a similar amount for its core facilities as well. Diane S. Krause, M.D., PH.D., associate professor of laboratory medicine and pathology and co-director of Yale's stem cell program, received $856,653 to study a leukemia gene using human embryonic stem cells.

Yingqun Joan Huang, M.D., PH.D., assistant professor of obstetrics, gynecology and reproductive sciences, received $200,000 to study the Fragile X mental retardation protein in early human neural development. Eleni A. Markakis, PH.D., assistant professor of psychiatry, received $184,407 to direct the isolation of neuronal stem cells from human embryonic stem cell lines. And Erik Shapiro, PH.D., assistant professor of diagnostic radiology, received $199,975 for using magnetic resonance imaging to study the directed migration of endogenous neural progenitor cells.

"With this first allotment of money, Connecticut becomes a national leader in the area of stem cell research," said Gov. M. Jodi Rell in a statement announcing the grants. "We have proven ourselves able to provide a place where such research can be done safely, ethically and effectively, in addition to providing investment dollars for the growth of the bioscience industry in Connecticut and making an investment intended to improve the health of generations to come."

Five other states—California, New Jersey, Maryland, Missouri and Illinois—have decided to fund stem cell research.

"After careful consideration and review by both an international panel of experts and this committee, we are confident that Connecticut is investing in stem cell research projects that will yield significant scientific findings in the long term," said J. Robert Galvin, M.D., M.P.H., chair of the state's Stem Cell Research Advisory Committee and Commissioner of Public Health.

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Water, a jumping gene and Paul Beeson

This past spring we heard from Ariane Kirtley, M.P.H. '04, who grew up in Africa and returned there after her graduation. Our cover story—her account in words and photographs—describes the life of the Tuareg and Woodabe inhabitants of the Azawak, the remote and drought-stricken plains in Niger where life is a constant search for water. But Kirtley is not content with simply documenting living conditions there—she has also formed a foundation to help build wells in the region and save not only lives but a pastoral way of life as well.

Closer to home, Tian Xu, PH.D., professor and vice chair of genetics, has found a faster and cheaper way of making knockout mice. It involves a transposon, a "jumping gene" from a moth that can be inserted into the mouse genome, and a complex process that allows the laws of genetics to run their course with a little tweaking from human hands. This first transposon to be effectively used in mammals allows scientists to knock out known genes and discover others previously unknown. Freelance writer Pat McCaffrey spent some time with Xu to learn how he hopes to use his technology to help scientists find the causes of disease on a grand scale.

Last August we learned of the passing of Paul B. Beeson, M.D., who served as chair of internal medicine from 1952 to 1965. During his tenure he hired new faculty, inspired his staff and residents and built the department into one of the best in the country. Renowned internationally as both a scientist and clinician, Beeson made fundamental contributions to the understanding of fevers and infectious diseases. Richard Rapport, M.D., author of *Physician: The Life of Paul Beeson*, has graciously allowed us to excerpt sections of his biography that deal with Beeson's time at Yale.

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SECOND OPINION BY SIDNEY HARRIS

LASSE SKARBÖVIK

New funding paradigms reshape research

Despite a tougher climate for NIH dollars, school gets its largest grant ever as part of Roadmap initiative.

Flat funding and a new research paradigm have turned federal funding of medical research on its head. After the recent doubling of the budget of the National Institutes of Health (NIH), funding has leveled off, resulting in a net decrease thanks to inflation. And the NIH is shifting the remaining dollars away from lone investigators to multidisciplinary teams of scientists.

Both trends are being felt at the School of Medicine. In October the school received its largest NIH research grant ever, a $57.3-million Clinical and Translational Science Award (CTSA), a new grant designed to encourage interdisciplinary research and the rapid movement of laboratory findings into human studies.

The award, one of 12 made around the country, will "transform how clinical and translational research is conducted," said NIH Director Elias A. Zerhouni, M.D.

The CTSA fits in with the NIH Roadmap for Medical Research, which calls for reshaping clinical research to accelerate medical discovery. It also fits in with the medical school's own planning, said Dean Robert J. Alpern, M.D., Ensign Professor of Medicine.

"A strategic planning initiative we launched in 2004 identified clinical research as a top priority and established the Yale Center for Clinical Investigation (YCCI), a focal point for translational research," Alpern said. "The YCCI's structure, which builds on Yale's strengths in education, basic science and community-based research, is virtually identical to the vision put forth by the NIH in this new program."

"With the CTSA grant we will be able to train many more clinical investigators, known as YCCI Scholars, who will be well-equipped to assemble the expert interdisciplinary teams they need to do top-quality translational research," said Robert S. Sherwin, M.D., YCCI director and principal investigator on the CTSA grant.

Meanwhile, scientists at Yale and other universities are finding grants harder to acquire. Over the last two years, said Carolyn W. Slayman, PH.D., deputy dean for academic and scientific affairs, Yale's success rate has fallen, in line with national trends, but it is still above the national average.

"Some labs might have to cut back on the number of people in the lab, making it more difficult to complete projects," said Lynn Cooley, PH.D., professor of genetics and cell biology and director of the Combined Program in the Biological and Biomedical Sciences. "Students and postdocs in training contribute enormously to research excellence in their labs. Both valuable research and the pipeline of new research talent are threatened by these budget cuts."

Slayman said the medical school's Grants and Contracts Office, working with the development staff and with the Office of Cooperative Research, is providing information on alternative funding, including nonfederal granting agencies, foundations and corporations. She said these efforts have met with some success—direct grant dollars to Yale researchers increased by 5.9 percent last year.

"We are working closely with department chairs and program directors to provide as much help as possible to faculty members who run into difficulty with grant support," Slayman said.

—*Pem McNerney* and *John Curtis*

University hopes to build on success in campaign for "Yale Tomorrow"

Nearly a decade after the close of its last major fund-raising campaign, Yale has begun a five-year drive to raise $3 billion, a major portion of which will be directed toward science and medicine.

At the public launch of the "Yale Tomorrow" campaign on September 30, President Richard C. Levin announced that donors have already committed $1.3 billion in gifts and pledges during its quiet phase, which began in mid-2004.

The public campaign kicked off with a day of presentations by noted faculty and alumni—including medical school professors Irwin M. Braverman, M.D. '55; HS '59, FW '62; Christopher K. Breuer, M.D.; Carolyn M. Mazure, PH.D.; Milissa A. McKee, M.D.; R. Lawrence Moss, M.D.; W. Mark Saltzman, PH.D.; Bennett A. Shaywitz, M.D.; Sally E. Shaywitz, M.D.; and Tian Xu, PH.D.—followed by a multimedia program narrated by actor Sam Waterston, a 1962 Yale College alumnus, and a gala dinner in University Commons.

The campaign is organized around four major priority areas: "Yale College," "The Arts," "The Sciences" and "The World." In the sciences Yale will seek support for programs focused on translating basic science insights into clinically relevant work. Among the priorities are programs in neural degeneration and repair, stem cell biology, translational immunology, functional genomics and clinical investigation. The ultimate goal is to find new and better methods of diagnosing and treating illness, said medical school Dean Robert J. Alpern, M.D., Ensign Professor of Medicine.

According to Inge Reichenbach, Yale's vice president for development, the campaign has set specific goals for the medical school, including the establishment of new endowed professorships, financial aid for students, new buildings for research and clinical care, technology resources, educational innovation and support for the cancer hospital addition to Yale-New Haven Hospital.

The drive comes at a time when the university is enjoying record growth in its endowment, which grew from $5.8 billion in 1997, at the conclusion of the university's "... and for Yale" campaign, to $18 billion for the fiscal year ending June 30. During that same nine-year period, the medical school's endowment has risen from $446.6 million to $1.5 billion. The university has an operating budget of $1.67 billion for 2006-2007, of which $676 million is expected to come from the endowment.

But the size of the endowment, second only to Harvard's $29 billion nest egg, does not mean the university has all the resources it needs to grow in new directions, according to campaign leaders. "To expand Yale beyond its current scale and scope, to build the Yale of tomorrow, we will need new financial resources," said President Levin. "Above all, we need to complete the transformation of Yale from a local to a regional to a national to an international university."

Yale's wealth is an issue that fund-raising staff must address directly with potential donors, said Jancy Houck, M.A., who became the university's associate vice president for development and director of medical development and alumni affairs on September 18. Income from the current endowment was committed to specific items at the time of the original gift decades or more ago, she said. "It takes new resources to do new things," said Houck.

The same is true with grant dollars that come from the federal government, foundations and corporations, she added. For example, the $57.3-million Clinical and Translational Science Award (CTSA) that the medical school received in October (see related story), the largest grant ever received by the school, also presents an opportunity to engage donors in conversations about the medical school's future.

"This support from the National Institutes of Health doesn't take away from our need for philanthropy, because grants are very, very specific. You have to use the funding in the exact manner outlined in the proposal," said Houck. "The philanthropy that we would be looking for would be for items that are not included in a big grant, where people could really leverage their gift, knowing that there is a certain amount of activity that is going to take place already."

—Michael Fitzsousa

Years after gas attack, the horror lingers in an Iranian town, EPH alumna finds

After every bombing, people in Sardasht, a small town at the foot of Iran's Zagros Mountains, ran outside to help the injured. On June 28, 1987, they rushed into a world that smelled of garlic. The air burned like acid. Bodies were covered with blisters. Children were crying, beyond comfort. When the blindness came, the villagers had no reason to expect that it would be temporary. For many, it was not.

FARAHNAZ FALAHATI

After an interview in Rabat, a Kurdish town in Iran that endured high-intensity warfare during the Iran-Iraq war, Farnoosh Hashemian, right, posed with some of the women she interviewed.

The physical effects of chemical weapons like the mustard gas that fell on this Iranian town during the 1980-1988 war between Iran and Iraq are well-documented: burns, respiratory problems and temporary or permanent blindness. A new Yale study now sheds light on the psychiatric effects. Farnoosh Hashemian, M.P.H. '05, a research associate in the Department of Epidemiology and Public Health (EPH), has documented severe and long-term mental health problems in Sardasht residents who survived a chemical attack. Her data were so compelling that the Iranian government made a psychologist, a scarce resource in the country, available to the 4,000 chemical-attack survivors in Sardasht.

Hashemian's team published their findings in the August 2 issue of *JAMA: The Journal of the American Medical Association*. They collected data in three Kurdish towns in rural Iran: one was bombed 10 times; another was bombed 75 times; and a third, Sardasht, was bombed 60 times and also was attacked with chemical weapons. Hashemian did not anticipate the magnitude of distress she found in Sardasht— 59 percent of those exposed to chemical weapons had experienced post-traumatic stress disorder, and 33 percent were still suffering from the disorder. She found that 65 percent had major anxiety symptoms and 41 percent had severe depressive symptoms.

Growing up in Tehran during the war, Hashemian knew that Saddam Hussein had gassed civilians and Iranian troops. "Will he gas Tehran?" the adults whispered. Believing a chemical attack on the Iranian capital was imminent, her family fled the city, eventually settling in Canada.

Three years ago Hashemian returned to Iran as an EPH student on a Downs International Health Student Travel Fellowship. Although the program usually sends students to countries unfamiliar to them, Hashemian convinced the review committee that rural Kurdish areas would constitute a new culture for a woman raised in fast-paced Tehran. Her parents in Canada were a harder sell. The border region in northern Iran is known for smugglers and land mines. "They were very worried, but now they are proud of me," she said.

Hashemian collected data along with Farahnaz Falahati, M.D., a physician with the Janbazan Medical and Engineering Research Center, the Iranian equivalent of the Veterans Administration. The women stayed in spartan quarters with no showers or kitchen. But Hashemian said their main challenge was hearing the dreadful and grim stories.

Survivors reported nightmares, inability to work and relationships broken under the weight of stress. They believed another attack would come at any moment. Their fear was heightened during Hashemian's visit because the United States had just invaded Iraq. Many villagers expected that Saddam would gas them again in retaliation for the U.S. attack. Despite their fearfulness, they invited the researchers into their small houses, offered them special meals and willingly told their stories.

"They felt that they had been forgotten," Hashemian explained, and she agrees. The international community was silent during and after the attacks, she said.

Hashemian would like to see her work used by international organizations seeking to eradicate chemical weapons. By documenting the suffering of civilians—who account for most war casualties—Hashemian said, public health professionals can raise discussions of war and peace above the realm of politics. "War is a serious public health issue."

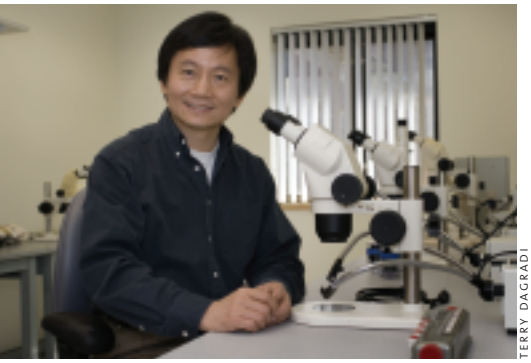
—*Colleen Shaddox*

Stem cell program gets under way at Yale with arrival of cell biologist

One of the nation's leading stem cell biologists arrived at Yale last summer to lead a new program that will explore the unique properties and therapeutic potential of these cells. Haifan Lin, PH.D., and Associate Director Diane S. Krause, M.D., PH.D., an associate professor of laboratory medicine and pathology and an expert on bone marrow stem cells, will lead the new Yale Stem Cell Program (YSCP). They will oversee a group of a half-dozen scientists and an administrative and technical staff devoted to research on human embryonic and adult stem cells, as well as stem cells in the mouse, fruit fly and roundworm.

The new center comes as the State of Connecticut has allocated $20 million for the Connecticut Stem Cell Research Grants Program, making it one of three states to fund this research. The YSCP has applied for funding from the state program and its applications were still under review this fall.

Stem cells, which can differentiate into many of the myriad cell types that form the body's tissues and organs, have been much in the news as a potentially powerful treatment for diabetes, Parkinson's disease, heart disease, spinal cord injury and other serious illnesses. The program will provide a scientific hub for more than 30 faculty members across the medical school and university who work on stem cell-related topics. Over the next few years, the YSCP will recruit four additional faculty members.



TERRY DAGRADI

Haifan Lin is leading a new scientific center for faculty working on stem cell-related projects.

Three core research facilities are now being put in place: a human embryonic stem cell culture laboratory directed by Lin and Krause; a cell sorting center directed by Mark J. Shlomchik, M.D., PH.D., professor of laboratory medicine and immunobiology; and a confocal microscopy laboratory directed by Michael H. Nathanson, M.D., PH.D., professor of medicine and cell biology. The YSCP will eventually occupy one floor of the Amistad Building on the southern edge of the medical school campus, which is now under construction and slated for occupancy next year.

Lin comes to Yale from Duke University, where he was co-founder and co-director of the Stem Cell Research Program. He received his undergraduate degree from Fudan University in Shanghai, China, and his PH.D. from Cornell University in 1990. He completed his postdoctoral training at the Carnegie Institution of Washington before joining the Department of Cell Biology at Duke University Medical Center in 1994.

Through his discovery of stem cells in the ovary of the fruit fly and his establishment of these cells as a research tool, Lin obtained direct evidence for the century-old hypothesis of asymmetric division as the means by which stem cells can both self-renew and produce daughter cells with the ability to differentiate into many distinct cell types. Lin has also discovered key genes that regulate stem cell division.

"Haifan Lin is a pre-eminent scientist whose research on the most basic mechanisms of stem cell biology has had a tremendous impact on the field," said Dean Robert J. Alpern, M.D., Ensign Professor of Medicine. "He has the broad perspective needed to lead this exciting new effort at Yale."

—Peter Farley

et cetera . . .

YALE LICENSES AIDS DRUG

Yale University concluded in June a license agreement granting Oncolys BioPharma of Tokyo exclusive rights to develop a new compound to treat HIV. Yale has also applied for a patent for the compound, Ed4T. Preclinical studies have already begun, and Oncolys BioPharma hopes to begin Phase I/II clinical trials in 2008.

Ed4T is a thymidine analogue that blocks reverse transcriptase, an essential enzyme for viral replication. The compound was discovered and developed jointly by researchers in Japan and Yung-Chi Cheng, PH.D., the Henry Bronson Professor of Pharmacology at Yale.

Pharmacological studies have shown that Ed4T has more potent anti-HIV activity than existing nucleoside-analogue reverse transcriptase inhibitors (NRTIs) and is active against viruses that are resistant to the existing NRTI and non-NRTI drugs. Further, Ed4T does not affect DNA synthesis in mitochondria, a toxic side effect of some nucleotide analogues. These findings suggested that Ed4T might offer unique therapeutic advantages over existing anti-HIV drugs.

—John Curtis

NEW MR SYSTEM AT YALE

Yale will receive a $2 million High-End Instrumentation (HEI) grant from the National Center for Research Resources (NCRR) to buy a 7-Tesla human magnetic resonance (MR) system that will facilitate ultra-high resolution studies of diabetes, epilepsy, psychiatric disease and learning disorders. The NCRR makes one-time awards to support the purchase of sophisticated instruments costing more than $750,000 to advance biomedical research and increase knowledge of the underlying causes of human disease. Douglas L. Rothman, PH.D., professor of diagnostic radiology and biomedical engineering, will oversee the MR system, a shared resource for several investigators funded by the National Institutes of Health. Yale has recruited two new faculty members to develop new methods of biochemical image-guided neurosurgery using the system.

—J.C.

Consistency lacking in transfer of patient data

Many hospitals don't have protocols for passing patient information among doctors, Yale study finds.

No matter how swift the runners, a relay race is lost if they don't pass the baton properly. A new Yale study finds that patient care is a baton at increasing risk of being dropped because too many internal medicine residency programs lack systems for transmitting patient information from shift to shift.

Communication failure is one of the chief causes of medical errors, studies have found, and the transfer of care is a weak link in the chain. But the Yale study, published in the *Archives of Internal Medicine* in June, finds that many hospitals lack an established protocol for passing on patient information, even though transfers, also known as sign-outs, are becoming more common as residents work fewer hours.

"Communication is not something that the layman thinks is a problem," said Leora I. Horwitz, M.D., a postdoctoral fellow in internal medicine and the study's lead author. However, patients are now under the care of more doctors, due to limits on residents' workweeks. Transfers "happen routinely and have the potential for catastrophe," she said.

Hospitals should have a standardized system each time a doctor hands off a patient to another doctor, Horwitz said.

Horwitz's team investigated the sign-out practices at 202 internal medicine residency programs in the United States and the impact of the reduced workweek on patient transfer protocols. Patient transfers, they found, rose 11 percent—to an average of twice daily in a four-day hospital stay—since the regulations took effect in 2003.

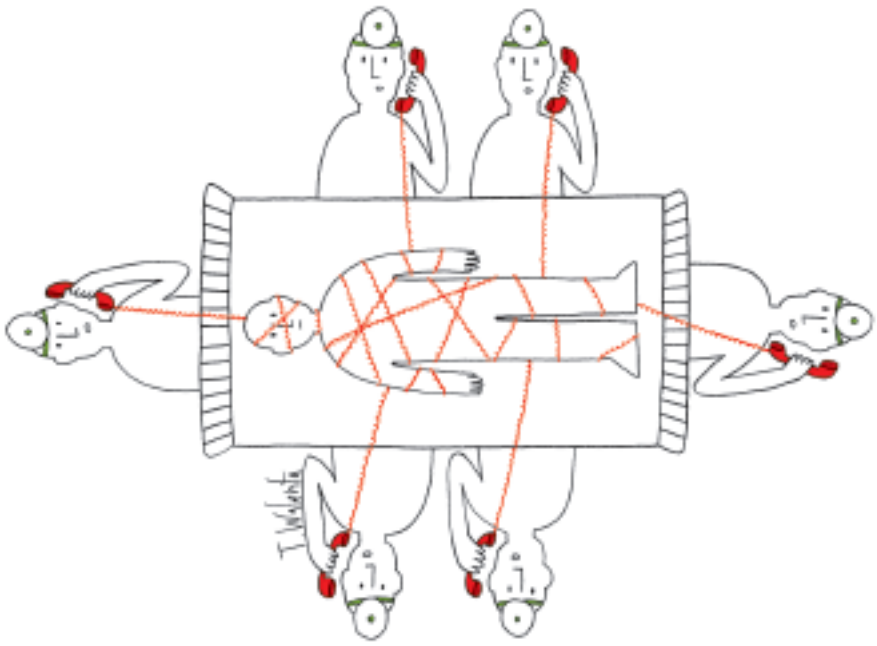
The procedures for those handoffs varied widely, though. Fifty-five percent of the programs didn't require doctors to pass on key patient information in both oral and written form, which Horwitz said would curtail the risk for errors. In six of 10 programs, nurses were not informed that a transfer had occurred, and in many programs no workshops or lectures on sign-out skills were offered. In 34 percent of the cases, the handoff was left to interns alone. And fewer than a fifth of the programs used a Web-based program, or forwarded pager messages in the transfer process.

"If you're the primary doctor, you're much less likely to make a preventable error than if you're covering that person just for a day and you don't know that [patient] well," Horwitz said. An oral transfer allows the new doctor to ask questions or give "readback"—like a pilot would give to an air traffic controller. Written information can be referred to later if needed.

The sign-out can differ from hospital to hospital, but it needs to be consistent within the health care organization, said Paul M. Schyve, M.D., senior vice president of the Joint Commission on Accreditation of Healthcare Organizations, which made sign-outs one of its chief patient safety goals for 2006. "A standardized approach makes it easy for people to ask and respond to questions," he said.

The survey didn't examine whether the various approaches to sign-outs actually prevent medical errors, especially in light of the shorter workweek. "There's a lot of anxiety around work-hour limitations in terms of whether they increase discontinuity enough that it overwhelms the benefits of physicians being rested," Horwitz said. Future studies will decide "whether that's clinically significant or not."

—John Dillon



New forum offers a place for doctors and nurses to discuss issues of patient care

On a Thursday afternoon last fall, 23 physicians, nurses and social workers at Yale-New Haven Hospital (YNHH) met to discuss a case that made everyone uncomfortable: a patient with colon cancer suffered serious and eventually fatal complications following surgery, and the patient's daughter refused to leave her side or her room during the two-month hospital stay. The daughter would not allow staff to communicate directly with her mother and slept much of the day in the hospital room, denying access to nurses even when they attempted to administer medications or other care.

The discussion was part of the Schwartz Center Rounds, a program that creates a forum for caregivers to discuss complex emotional and social issues involved in caring for patients. In 1995, Kenneth B. Schwartz, a health care attorney in Boston, was dying of lung cancer. He was fortunate to receive not just top-notch medical care, but also an attention to his comfort and quality of life that made his illness easier to cope with for himself and his family. Shortly before his death, he established the Kenneth B. Schwartz Center, a nonprofit organization that has been helping caregivers provide compassionate care to their patients since 1997. The Schwartz Center Rounds now operate in approximately 100 hospitals in 25 states; the program was brought to the Yale Cancer Center last February as part of a larger effort to increase the focus on supportive care for patients with severe illness.

TERRY DAGRADI

Health care professionals at YNHH can discuss complex issues of patient care during Schwartz Center Rounds, a national program.

"It's a unique forum for talking about difficult and challenging situations in a nonmedical fashion," said Kenneth D. Miller, M.D., assistant professor of medicine (medical oncology), director of supportive care programs at the Center and the rounds leader for the program. Open to all YNHH staff, the rounds take place once a month and feature a presentation by a medical team followed by a group discussion.

Past topics of the Schwartz Center Rounds have included obtaining informed consent from mentally ill patients; keeping hope alive; and what to do when the patient, doctor and family are not on the same page. "We're trying to develop a broader view on how different patients, and different families cope with really difficult situations that may be different than what we might have chosen for ourselves or what we think we'd choose," Miller said.

According to Marjorie Stanzler, director of programs for the Schwartz Center, the ability of caregivers to voice their concerns in a safe environment translates into new insights into caring for patients, an appreciation of the problems faced by colleagues in other disciplines and the realization that they are not alone in dealing with troublesome circumstances.

—Jill Max

et cetera . . .

STROKE, HEART ATTACK AND FIRING

Losing a job just as retirement approaches more than doubles the chances of a heart attack or stroke, according to a Yale study published in *Occupational and Environmental Medicine* in June.

For over 10 years researchers observed more than 4,000 people who were between the ages of 51 and 61 when the study began in 1992. During that period 582 lost their jobs. An earlier six-year study of the same people had suggested a higher risk of stroke, but didn't make a definitive link between job loss and heart attacks. "With longer follow-up ... on heart attack and stroke events we were able to better assess the association between employment separation and the medical outcomes," said William T. Gallo, PH.D., the lead author and an associate research scientist in the Department of Epidemiology and Public Health.

"We do a lot of downsizing in our country and older individuals are often affected," said co-author Elizabeth H. Bradley, M.B.A., PH.D., professor of public health. "We need to recognize not only the economic consequences, but also the health consequences."

—John Curtis

KIDNEY PATIENTS LEFT OUT OF TRIALS

Although at high risk for cardiovascular death, patients with chronic kidney disease (CKD) are frequently left out of cardiovascular trials, School of Medicine researchers reported in the September 20 issue of *JAMA: The Journal of the American Medical Association*.

The researchers' review of 153 clinical trials published between 1985 and 2005 found that patients with kidney disease were excluded from 56 percent of the trials and were more likely to be excluded from multicenter trials. Cardiovascular death is the leading cause of death in patients with CKD.

"Inclusion and reporting of kidney disease patients in cardiovascular trials must improve," said senior investigator Chirag Parikh, M.D., assistant professor in the Section of Nephrology. "Alternatively, we need to design separate trials for cardiovascular treatment exclusively in CKD patients."

—J.C.

An early start for the thinking brain

Yale scientists discover predecessor cells that pave the way for the cerebral cortex.

The cerebral cortex, a layer of cells just a few millimeters thick on the outermost surface of the brain, is largely what makes humans noble in reason and infinite in faculties. New research from the School of Medicine shows that developing embryos, in their haste to become quintessentially human, generate the first neurons of the cortex only 31 days after fertilization—much earlier than previously thought.

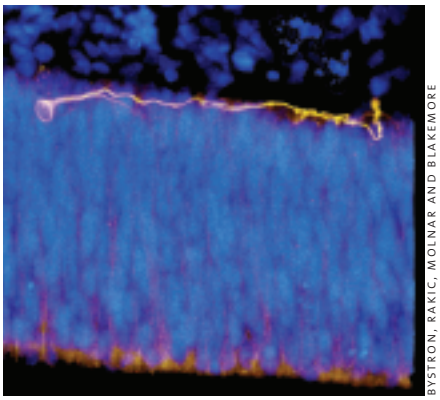
The cerebral cortex is an evolutionary marvel. Its distinctive convoluted shape arose because the size of the cortex expanded disproportionately in relation to the rest of the brain during evolution. The 20 billion neurons packed within the cortex's smooth gray folds account for about 40 percent of the brain's weight, and the connections among them are largely responsible for the functions considered unique to humans, such as memory, thought, perceptual awareness, language, intellect and consciousness.

Using precise cellular markers, Pasko Rakic, M.D., PH.D., the Dorys McConnell Duberg Professor of Neurobiology and professor of neurology, and chair of neurobiology and colleagues have discovered "predecessor" neurons that first appear in human embryos before the neural tube, the precursor of the central nervous system, has completely closed and before eyes, arms and legs begin to bud. According to Rakic, these predecessors could well be one type of neural stem cell of the "thinking brain."

Until recently, researchers thought that all cortical neurons arose within a rudimentary cortical nexus and then migrated radially, like spokes jutting out from an axle, into place. However, Rakic's findings show that the predecessor neurons arise from basal layers within the developing brain and then travel through inner cell layers to reach the cortex. The precocious cells generate long extensions that pull them to different locations as the brain develops. These extensions may also act as scaffolds to guide late-blooming cortical neurons to their proper locations.

In the July issue of *Nature Neuroscience*, the researchers wrote that studying how predecessor cells help to wire the billions of neurons of the adult human cortex may provide new insights into how humans differ from more primitive species and may shed light on the causes of mental illness. "Unraveling the early development of this complex structure," the team wrote, "might provide the key to understanding both the mechanisms underlying its expansion during evolution and the pathogenesis of many cognitive disorders." Rakic added, "If we want to repair the human brain, we have to know how the human cortex develops; we have to know the timing, the sequence and the type of cells involved."

Rakic said that the next goal is to determine which genes are switched on in predecessor cells to control early cortex development. If the predecessors are indeed neural stem cells, identifying the genes responsible for early cortex formation could provide insight into ways to generate new cortical neurons to repair brain injury. The team also plans to identify the source of predecessor cells by performing experiments in nonhuman primates that will enable them to visualize neuron migration using modern microscopy techniques.



BYSTRON, RAKIC, MOLNAR AND BLAKEMORE

Yale scientists have identified the first neurons (the golden area in the image) in the embryonic human cerebral cortex, which appear only 31 days after fertilization. This is much earlier than previously thought, and the discovery of these predecessor cells in the part of the brain responsible for such human attributes as memory, language and intellect may provide insights into mental illness.

These findings will bring researchers one step closer to understanding the developmental mechanisms responsible for creating the thinking brain. "I am fascinated with the idea that I use my cortex to look at the cortex itself to determine what makes it possible for me to think," said Rakic.

The project, supported by the Kavli Institute for Neuroscience at Yale, involves collaborations with societies in England and Russia.

—*Kara A. Nyberg*

Lacking an enzyme linked to diabetes and obesity, mice stay slim on a high-carb diet

Even on a "supersize" diet, mice bred to lack a certain enzyme remained more svelte than mice with the enzyme, according to a study by Yale scientists in the July 2006 issue of the journal *Cell Metabolism*. Moreover, in a finding that surprised the research team, the mice's blood sugar levels remained under control.

The study's senior author cautioned against premature talk of an elixir that prevents diabetes or does away with the need for exercise. "The long-term goal, I think, would be to figure out how this enzyme is working under normal circumstances," said Anton M. Bennett, PH.D., associate professor of pharmacology. "But I think we're a long ways away from this as an obesity target."

Bennett's laboratory studies mitogen-activated protein kinase phosphatases (MKPs), important players that have been implicated in numerous cellular functions such as cell growth and cell survival. For a better understanding of these enzymes, mice were bred to lack one of them, MKP-1. "There was no preconceived hypothesis that it would necessarily be involved in regulating body mass," Bennett explained.

At first there appeared to be no obvious differences between the mice lacking MKP-1 and the control mice. "If you looked in the cage and had the mice side by side, they would be indistinguishable," Bennett said. Both groups ate a typical chow diet—"the equivalent of three squares a day." Soon, the knockout mice showed that they were less likely to put on the ounces.

"Then we put them on a McDonald's 'supersize' equivalent, where 55 percent of the calories was from carbohydrates," he continued. "The differences in weight were extremely pronounced." The mice without the enzyme were, on average, 15 to 20 percent leaner than the control group. "The enzyme seems to act as a brake on how fast you burn energy. When you remove that enzyme, energy expenditure seems to go up dramatically."

The mice without the enzyme were also better able to control their glucose levels. Because they were leaner, they also should have exhibited signs of increased insulin sensitivity. "But it was normal," Bennett said. "That was somewhat of an unexpected result." The knockout mice also were less likely to show signs of metabolic syndrome, a constellation of risk factors for heart disease and diabetes. One of the hallmarks of metabolic syndrome is a fatty liver, and the mice without the enzyme were resistant to that symptom.

While the study shows that MKP-1 "may contribute to obesity and diabetes," it is far from certain whether turning it off will prevent or ameliorate those conditions. There is also concern about the overall effect of turning off the enzyme in the body. Bennett said studies have found knockout mice to be more susceptible to infection.

"That's not a good thing," he said. "Everything is connected."

—John Dillon

EINAT PELED

et cetera . . .

SMOKING AND NICOTINE RECEPTORS

Smokers may have a hard time quitting because their brains have significantly more nicotine receptors than those of nonsmokers, according to a study by Yale researchers published in August in the *Journal of Neuroscience*. The study, funded by the National Institute of Drug Abuse, is believed to be the first to offer direct evidence in living smokers that the numbers of the most common nicotine brain receptors are higher during early abstinence from smoking.

"Nicotine craving is an important factor associated with relapse," said Julie K. Staley, PH.D., associate professor of psychiatry and diagnostic radiology and lead author of the study. "This study paves the way for determining whether medications normalize the number of receptors and why some smokers, such as women and those with neuropsychiatric disorders, have more difficulty quitting smoking."

Staley said the team used SPECT imaging to see how the nicotine receptors adapt in response to the repeated stimulation of smoking a cigarette.

—John Curtis

TESTOSTERONE VS. NERVE CELLS

A study by Yale scientists has shown that a high level of testosterone—such as that caused by the use of steroids—can lead to the death of brain cells. "Next time a muscle-bound guy in a sports car cuts you off on the highway," said senior author Barbara E. Ehrlich, PH.D., professor of pharmacology and cellular and molecular physiology, "don't get mad, just take a deep breath and realize that it might not be his fault."

Previous studies have shown that large doses of steroids can cause hyperexcitability, an aggressive nature and suicidal tendencies, which could mean alterations in neuronal function caused by the steroids. "In the present study we have demonstrated for the first time that the treatment of neuroblastoma cells with elevated concentrations of testosterone for relatively short periods, six to 12 hours, induces a decrease in cell viability by activation of a cell death program," said Ehrlich, whose study appeared in the *Journal of Biological Chemistry* in September.

—J.C.

Bruce Wexler's new book explores neural processes and how they influence psychological and social processes.

Culture and the brain

A new book explores the links between neural networks, feelings and culture.


JOHN CURTIS

Bruce E. Wexler, M.D., professor of psychiatry, believes that understanding how our brains work can illuminate human experiences small and large—from why our favorite letters in the alphabet are those in our own names to why we must struggle to adjust when a loved one dies. In his new book, *Brain and Culture: Neurobiology, Ideology, and Social Change*, he summarizes contemporary research into the brain and how it explains why we resist the unfamiliar and the alien—whether it's a colorful tattoo on our teenager's biceps or the rhetoric of those who insist theirs is the only true religion.

"The aim of this book is to look at what we know about neural processes to see if that can increase our understanding of the psychological and social processes that rest upon this neurobiological platform," said Wexler, a clinician and researcher at the Connecticut Mental Health Center. "Our appreciation of the neurobiology can help us to understand—and eventually deal with—both psychological and social issues."

The connections between neurons that create networks derive not only from our genes but also from sensory input when we're young. And human neural networks remain plastic into the third decade of life, much longer than those of any other animal.

The less flexible adult human brain strives to see the world in a way that "agrees with internal structures." That's why physicians evaluating a sick patient may choose a common diagnosis even when the patient's problems don't quite fit. "We complete perceptions in keeping with our expectations, and those expectations are based on past experience, but not necessarily on the facts at hand," Wexler observed.

It is the comfort of the familiar that motivates some immigrants to settle in ethnic enclaves, Chinatowns and Little Pakistans that recreate their former homes. The generation gap is especially poignant for immigrants, whose children are shaped by a very different world from the one in which they grew up. And for all parents, the world changes from generation to generation. "Most children in the world today are raised almost entirely in human-made environments," Wexler said. Because each new generation has different brains from those of their parents, they in turn raise their children differently—leading to what Wexler calls "transgenerational shaping of brain function." But the generation gap discomfits all parents, because children loom large in parental neural networks.

"We don't like our children to turn into foreigners, because our children are so richly represented within us," said Wexler. Similarly, we have trouble adapting when a loved one dies, because that person occupied a central place in our neural networks. "It's a very arduous task to restructure, and it takes adults about a year."

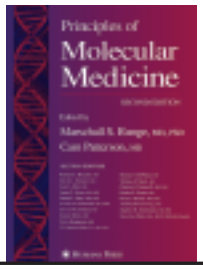
What he calls "the neurobiological antagonism to difference" can help explain violent cultural clashes: genocide in Armenia, Germany and Bosnia; massacre in Rwanda; Christians warring against Muslim "infidels;" and Muslims attacking Western "infidels."

Understanding our resistance to differences can point the way to reconciliation. Wexler now spends most of his spare time working for a nonprofit group he started called A Different Future. Its aim is to "amplify the voices" of Arabs and Israelis advocating peace—delivering a message of mutual respect that will embed itself into the neural networks of young Israelis and Palestinians.

Wexler admits that even his own neural networks may balk at the unfamiliar. On a trip though Ohio he saw a building that looked out of place. He remembers thinking, "What is a *mosque* doing here?"

—*Cathy Shufro*

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



Play Ball with Me!
by Lynn Reiser, M.D. '70, clinical professor of psychiatry (Alfred A. Knopf) This interactive picture book of guessing games introduces young readers to various ballgames through the recognition of simple objects.

Social Structures, Aging, and Self-Regulation in the Elderly
with contributions by Becca R. Levy, PH.D., associate professor of epidemiology and psychology; edited by K. Warner Schaie, PH.D., and Laura L. Carstensen (Springer Publishing Company) Contributors to this book explore how societal contexts influence aging and how self-regulation at the most basic levels of functioning influences the physical health and economic circumstances of people as they age.

Principles of Molecular Medicine, 2nd ed.
with contributions by Jean Bolognia, M.D. '66, professor and vice chair of clinical affairs (dermatology), Daniel Goldstein, PH.D., assistant professor of medicine (cardiology), and Stephen M. Strittmatter, M.D., the Vincent Coates Professor of Neurology and professor of neurobiology (Humana Press) This volume contains new sections on genetics, oncology and metabolic and infectious diseases. The authors discuss the latest findings about links between genetic mutations and diseases; genomic approaches to a variety of diseases; the potential of stem cells to regenerate muscle, heart and neural cell populations; and advances in the understanding of the biology of such previously untreatable neurodegenerative diseases as Huntington's.

Aglow in the Dark: The Revolutionary Science of Biofluorescence
by Vincent A. Pieribone, PH.D., associate professor of cellular and molecular physiology and neurobiology, and David F. Gruber (Belknap Press) This book describes the human fascination with bioluminescence, or "living light." It follows the path to one of the groundbreaking discoveries of the 20th century—green fluorescent protein, the glowing compound that has revolutionized molecular biology.

DNA Vaccines: Methods and Protocols, 2nd ed.
by W. Mark Saltzman, PH.D., the Goizueta Foundation Professor of Chemical and Biomedical Engineering and professor of cellular and molecular physiology, Janet L. Brandsma, PH.D., associate professor of comparative medicine and pathology, and Hong Shen, PH.D. (Humana Press) This five-part volume contains state-of-the-art information about DNA vaccine technology. Part I contains DNA vaccine design protocols, focusing on methods that achieve optimal expression in host cells. Part II presents methods for DNA delivery. Part III discusses methods for enhancing the potency of DNA vaccines. Part IV describes several key areas of application in the field, including allergy, avoidance of autoimmunity, and neonate and infant vaccine response. The book concludes with a review of protocols for vaccine production and purification, and quality control methods.

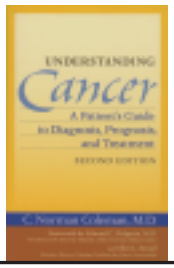
College Life 102: The No-Bull Guide to a Great Freshman Year
by Andrew G. Kadar, M.D. '73 (iUniverse) The author offers advice to newly arrived college students on how to succeed both inside and outside the classroom. Tips include how to dodge the stress of deadlines, enroll in classes after they're officially filled, avoid the "freshman 15" and get better grades by studying smarter rather than harder. The book also provides information about nutrition, illegal drugs, contraception and tattoos and piercings.

Immunology of Pregnancy
by Gil Mor, M.D., associate professor of obstetrics, gynecology and reproductive sciences (Springer) This text reviews current knowledge about the role of the immune system during pregnancy and the interactions between the maternal immune system and the placenta. Mor analyzes studies related to the immunology of implantation and provides a practical approach for the application of basic reproductive immunology research to such pregnancy complications as pre-eclampsia and preterm labor.

"Shrink": On Becoming a Psychotherapist
by Louis B. Fierman, M.D., associate clinical professor of psychiatry (Blue Dolphin Publishing) Fierman, now retired, recounts his "only-in-America" journey as the son of uneducated immigrant parents and how, with their support, he pursued a career as a maverick psychiatrist and psychotherapist at Yale and elsewhere.

Hematology: Basic Principles and Practice, 4th ed.
by Edward J. Benz Jr., M.D., FW '79, Ronald Hoffman, M.D., Sanford J. Shattil, M.D., Bruce Furie, M.D., Harvey J. Cohen, M.D., PH.D., Leslie E. Silberstein, M.D., and Philip McGlave, M.D. (Churchill Livingstone) This book covers the basic scientific foundations and clinical aspects of hematology. It provides practitioners with comprehensive and up-to-date information on hematology that reflects the rapid change in the molecular and cellular areas of the specialty.

The Profession of Ophthalmology: Practice Management, Ethics and Advocacy
edited by David W. Parke II, M.D., associate clinical professor of ophthalmology and visual science (American Academy of Ophthalmology). This three-part volume contains blueprints for business skills to develop and manage successful practices; a review of ophthalmology's Code of Ethics and real-life case studies illustrating ethical behavior in ophthalmic-related situations; and a discussion of the importance of advocating on behalf of patients and the profession, and principles and methods for doing so.



Travel and Tropical Medicine: Infectious Disease Clinics of North America
by Frank J. Bia, M.D., professor of medicine and laboratory medicine, and David R. Hill, M.D. (Saunders) Topics covered in this guide include new vaccines against yellow fever and Japanese encephalitis, the current prevention of malaria and treatment of such common syndromes as traveler's diarrhea and cutaneous leishmaniasis. Other chapters address pretravel screening of high-risk travelers, problems associated with airline travel, sexual tourism and the interactions between HIV infection and tropical diseases.

Understanding Cancer: A Patient's Guide to Diagnosis, Prognosis, and Treatment, 2nd ed.
by C. Norman Coleman, M.D. '70 (Johns Hopkins University Press) This book describes new treatments that target specific types of cancer and explains how to gather and interpret information when making decisions about treatments. It also provides guidance for preparing for visits to doctors and the hospital. Topics include biomarkers, novel imaging techniques, molecular signatures and profiling and molecular-targeted therapy. Some of these therapies are currently available only through clinical trials, and the author includes a detailed discussion of what is involved in participating in such trials.

Kelley's Textbook on Rheumatology, 7th ed.
by Clement B. Sledge, M.D. '55, Edward D. Harris Jr., M.D., Ralph C. Budd, M.D., Gary S. Firestein, M.D., Mark C. Genovese, M.D., John S. Sergent, M.D., and Shaun Ruddy, M.D. (Saunders) This book provides encyclopedic coverage not only of the etiology and pathogenesis of rheumatic diseases, but also of the biology of the normal joint, immune and inflammatory responses, evaluation of the patient and diagnostic tests and procedures. The book includes a bound-in DVD with chapter-by-chapter multiple-choice questions for board review.

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

Blogging saves doctors time

With all the information on the Web already, why would anyone want to add to the volume by reading blogs? To save time, according to librarians at Yale's Cushing/Whitney Medical Library.

Yale reference librarian Charles J. Greenberg, M.L.S., M.ED., for example, maintains a blog for surgeons at http://surgery-update.blogspot.com. "Surgeons don't have time to look at all the journals," said Greenberg, the library's coordinator of curriculum and research support. He describes his blog as "the equivalent of a newsstand for information on certain emerging surgical topics." Greenberg assembles his "newsstand" by combing 30 leading medical and surgical journals each month and posting entries on surgical news two or three times a week.

Greenberg's blog can be reached from the home page of the medical library, which maintains its own blog (http://elibrary.med.yale.edu/blog/) to inform visitors of library news. Postings include descriptions of two newly acquired electronic databases offered by the library, one containing 1,800 online journals (The ScienceDirect Freedom Collection), and the other listing drug eruptions and interactions.

The library website lists links to two other blogs by Yale medical librarians. Education services librarian Jan Glover, M.L.S., uses hers to dispense advice about doing online research (http://janstips.blogspot.com/). Glover posts research tips and entries that highlight databases. "Someone might not know a database existed, and it might be perfect for their topic," she said.

Janene Batten, M.L.S., reference librarian for the School of Nursing, started a blog about 18 months ago that focuses on items of interest to nurses (http://ysnlibrary.blogspot.com/), and she posts something new several times a week.

Blogging took off during the run-up to the 2004 general election, said Web Services Librarian Hongbin Liu, M.L.S., who coordinates the library's blogs. With blogs, said Liu, "everybody can be a freelance journalist." Liu uses Technorati, a blog search engine, to monitor the growth of blogs. As of October there were 56.4 million blogs worldwide, not counting some of those that are written in languages other than English. Blogging, says Liu, is here to stay.

—*Cathy Shufro*

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

ARTHUR CAPLAN

Changing the ethical culture of pharma

The last five years, said Arthur Caplan, PH.D., have seen the demonization of the pharmaceutical industry. Conflicts of interest, censored scientists, flawed drugs and devices placed on the market and the failure to protect subjects of clinical trials have been "flat-out ethical disasters," said Caplan, chair of the Department of Medical Ethics at the University of Pennsylvania School of Medicine.

Nevertheless, he told an audience at the School of Management in September, this demonization is irresponsible. "The pharmaceutical industry is not the tobacco industry," he said. "The pharmaceutical industry produces medicines that relieve pain, save lives and cure patients. The pharmaceutical industry does do a lot of good."

How, he asked, can the industry change its ethical culture? He called for mandatory registries of all clinical trials that would make data—and reports of adverse events—public. Epidemiology, he said, must trump marketing. He also called for tougher Food and Drug Administration monitoring of Phase IV, when drugs are in the marketplace.

"I think pharmaceuticals need to commit to the scientific foundations of the industry," he said.

—John Curtis

ROBERTO JOHANSSON

An ongoing disaster stemming from neglect

For Roberto Johansson, M.D., PH.D., Hurricane Katrina was a disaster that didn't have to happen. During a talk at the Department of Epidemiology and Public Health in October, he described what he saw in his hometown of New Orleans. "Roads were out. Telephone lines were out. The fire department broke down. EMS totally broke down. The hospitals were marginal at best," he said.

But a long history of neglect—of the levees, of the city's schools and of the city's poor—compounded the problem, he said. And the order to evacuate came late. "Many of the people who stayed couldn't get out because they were medically disabled or poor," he said, noting that doctors, nurses and other health care workers stayed on their jobs.

Disasters, he said, follow five stages. First comes knowledge of a possible disaster, followed by a warning phase. Then comes impact. In the rescue phase first responders try to save lives, and those outside the strike zone mobilize to help. The recovery phase, in which New Orleans finds itself, tries to keep survivors at a functioning level.

"Katrina," he said, "is a story that must not be forgotten."

—J.C.

KENNETH LUDMERER

Tracing the history of medical education

In the mid-19th century, medical schools were faculty-owned, for-profit operations that churned out doctors after just a few months of lectures.

With the Flexner Report of 1910, medical educators realized that medical schools should be integral parts of universities, said Kenneth M. Ludmerer, M.D., professor of medicine and history at Washington University in St. Louis, in his address at the 30th Annual Yale Affiliated Hospitals Symposium in November.

By the 1920s, medical schools had become academic centers that emphasized research and clinical care. The fee-for-service era of the 1960s to 1980s also afforded rich learning opportunities because hospital stays were longer. But that learning environment has been threatened by managed care, with its emphasis on seeing as many patients as possible.

Today, Ludmerer sees a need for a social contract that funds and values medical education and research, while medical schools teach and practice cost-effective medicine. Despite the faults of the current system, Ludmerer said he wouldn't trade today's problems for those of a century ago. "It's better to have problems financing treatment for Alzheimer's disease and cancer than to watch children die of diphtheria," he said.

—Jill Max

ROBERT SAPOLSKY

Baboons, humans and stress: the cost of being an SOB

Baboons in Africa's Serengeti Plain spend just three hours a day finding food, said Robert Sapolsky, PH.D. "That leaves nine hours of daylight for them to be really crappy to the other baboons," Sapolsky said, adding that such behavior carries a cost. "Physiologically, it's very expensive to be a bastard all day long."

In his keynote talk at a symposium in October sponsored by the Department of Psychiatry, Sapolsky, a professor of biological sciences and neurology and neurological sciences at Stanford University, described how chronic stress—in humans as well as baboons—can cause or contribute to physical and mental afflictions ranging from heart disease, ulcers and memory loss to infertility and even diminished growth. "If stress goes on too long, it becomes pathogenic," he said.

But Sapolsky, who studies the relationship between personality and stress-related disease in wild baboons, found cause for optimism. Male baboons have "pungent individualistic personalities," he said. Some handle stress well; others don't. There is compelling evidence that the same is true for humans. "If some baboons see the watering hole as half full, so can we," he said.

—Jennifer Kaylin

BOTTOM In the United States the Spanish influenza pandemic of 1918 struck 28 percent of the population, killing 675,000 and depressing the average life span by 10 years. In Kansas, Camp Funston, built during World War I as a training camp, also served as an emergency hospital during the epidemic.

BELOW When Milton Winternitz came to Yale as chair of pathology in 1917, he brought with him a commitment to the U.S. Army to study the poison gases being used in the war. During the pandemic the Army Laboratory School at Yale, which studied human pathology, autopsied flu victims in New Haven.

Yale's Army Medical Laboratory and the 1918 Influenza Pandemic

Studies undertaken during World War I led to breakthroughs in chemotherapy, providing a new understanding of the pathology of the deadly influenza virus.

By Jennifer Kaylin

CUSHING/WHITNEY MEDICAL HISTORICAL LIBRARY

The two facilities established at Yale during World War I for training lab technicians for fieldwork and for studying the effects of poison gas were in existence for only three years, but during that brief period they created a legacy of teaching and patient care that is still relevant to students at the School of Medicine and to health practitioners around the world.

"In the early 20th century, Yale wasn't a leader. There was no full-time faculty, and the teaching was mostly rote memorization followed by an apprenticeship," said Michael Kashgarian, M.D. '58, HS '63, professor of pathology and molecular, cellular and developmental biology.

That changed in 1917, when Milton C. Winternitz, M.D., became chair of Yale's Department of Pathology. Winternitz brought with him the conviction that the study of medicine needed to be supported by science. He also brought a commitment to the U.S. Army that he would investigate the pathology of the poison gases that were being used in the Great War.

The Army set up the Medical Division of the Chemical Warfare Service at Yale and the Army Laboratory School at Yale, both to be overseen by Winternitz. The first facility focused on experimental animal pathology. Using dogs as experimental subjects, researchers counted red and white blood cells and examined the organs after the dogs were repeatedly exposed to poison gases. They described how these chemicals kill cells, and they made the significant observation that nitrogen mustard is particularly lethal to lymphoid tissues. Researchers at the second facility concentrated on human pathology, examining in autopsy the lungs of patients who had been exposed to mustard gas. Together, the two facilities provided the ideal setting for Winternitz to introduce his new scientifically based pedagogy.

In the midst of their work on gases used in war, researchers were hit with a new challenge: the influenza pandemic. In the autumn of 1918, this acute respiratory infection made its first appearance on the New England coast.

"Terrible as has been the war, the cost of life and distress ... has been infinitesimal compared to the havoc caused by the late epidemic of influenza," reads a passage from the New Haven Health Department's 1918 annual report. From October through December of that year, the department recorded 777 deaths from influenza and its complications.

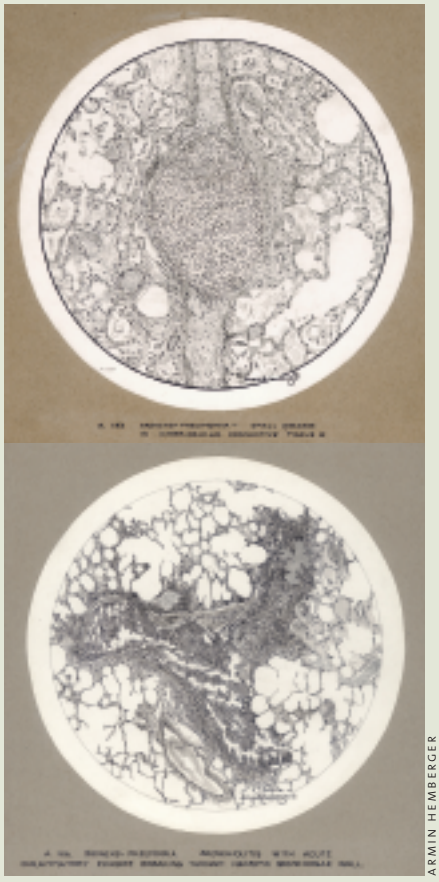
"People were healthy in the morning and dead by nightfall," said Martin E. Gordon, M.D. '46, clinical professor of medicine and chair of the board of trustees of the Cushing/Whitney Medical Library Associates.

The Army Laboratory School at Yale, located in the Brady Laboratory and one of several such schools around the country, was also set up to train laboratory technicians in bacteriology and pathology before dispatching them to medical field units. After the flu outbreak, the Laboratory School assumed the task of performing autopsies of the victims. They found that the pathology produced by influenza pneumonia closely resembled that produced by the inhalation of certain types of poison gas. Illustrators made a series of watercolors and drawings of the characteristic lesions. These pictures were part of an exhibit produced by Gordon called "The Flu and You: Old and New Threats" that appeared in conjunction with a lecture last spring by Harvey Fineberg, M.D., president of the Institute of Medicine of the National Academies of Science.

The work of both the poison gas and influenza researchers is also preserved in three monographs: *The Pathology of War Gas Poisoning, Lethal War Gases—Physiology* and *Experimental Treatment and Pathology of Influenza*. By the standards of the time, Kashgarian said, the biochemical and pathological observations presented in these volumes were state of the art, but even by today's standards, they provide a "strong basis" for additional studies. "Given the tools they had, the information they present is very complete and thorough," said Kashgarian.

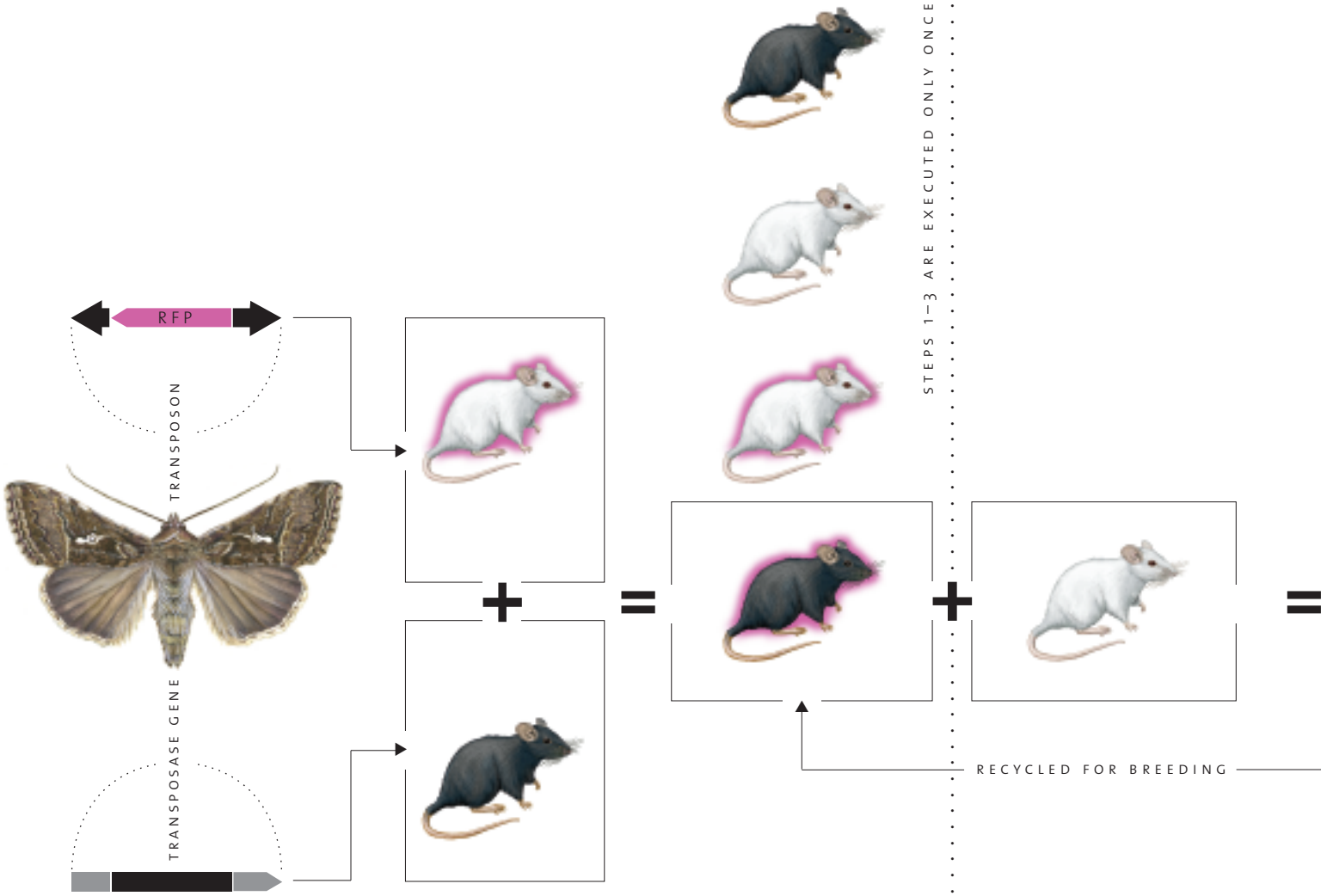
One observation stands out—the researchers noticed that lymphatic and bone marrow tissue are destroyed by mustard gas. The therapeutic potential of this observation wasn't explored until years later, but eventually researchers found that nitrogen mustard, derived from the family of chemicals used in battle, caused tumors in mice to shrink. Human trials were equally encouraging and paved the way for treating cancer with chemicals.

Jennifer Kaylin is a contributing editor of *Yale Medicine* and a freelance writer in New Haven.



ARMIN HEMBERGER

Studies of the pathology of the 1918 influenza pandemic in New Haven yielded three publications, and illustrations of diseased tissue by Armin Hemberger. His images appeared in *Experimental Treatment and Pathology of Influenza*, which counted Winternitz as one of its authors.



FROM A MOTH, A TOOL TO DECODE GENE FUNCTION IN MAMMALS

Transposons are snippets of DNA that are also known as jumping genes because they move around a genome. Their movements are random, but they typically insert themselves into other genes and disrupt their functions, causing a mutation. For more than 50 years scientists have been looking for a transposon that can efficiently work in mammals. Tian Xu has modified a transposon from the cabbage looper moth and uses this transposon system to mutate genes in mice and discover their functions. The process is described below.

1

The *piggyBac* transposon, found in the cabbage looper moth, is split into two modified DNA plasmids. One, the transposon lacking the gene that expresses the jumping enzyme transposase, carries a red fluorescent protein (RFP) marker. The other is the modified transposase gene, plus a gene that causes a mouse's coat to turn black.

2

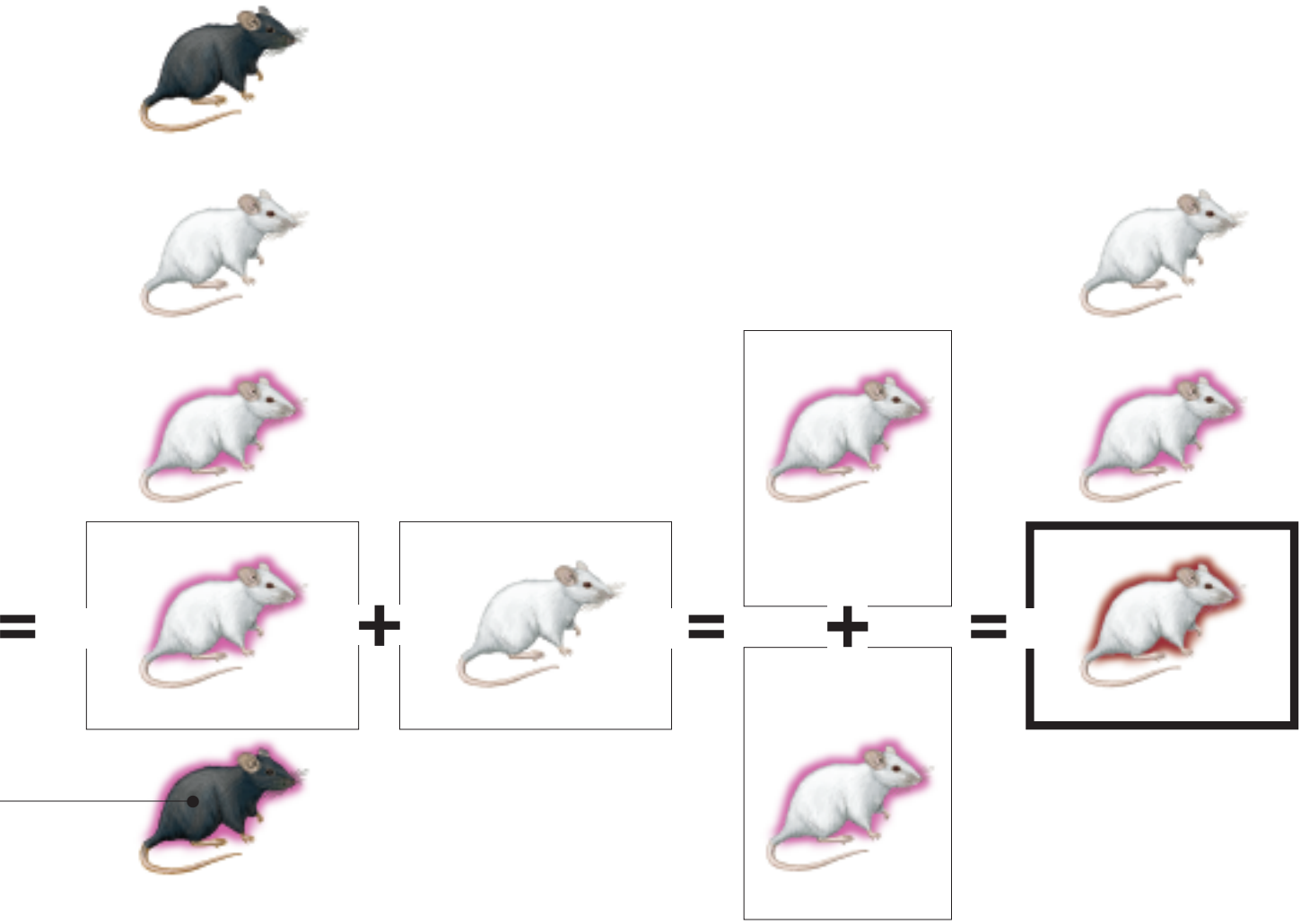
Each plasmid is injected into a different mouse embryo. As the mice grow, their appearance reflects their genetic status—mice that carry the transposon gene glow pink under ultraviolet light; black mice carry transposase, the jumping enzyme. A black mouse and pink mouse are bred.

3

Some of their offspring—identified by a black coat and a pink glow—carry both the transposon and transposase and have actively jumping genes.

4

These mice are bred with normal mice.



Little mouse, big science

How fruit fly geneticist Tian Xu is transforming the mouse into a genetics workhorse to reveal the causes of human disease.

Story begins on page 20

5

Some of their offspring will inherit a mutation but not the jumping enzyme. Without the enzyme, the transposon remains in place, and polymerase chain reaction will reveal which gene has been disrupted. Other offspring will inherit both the mutation and the jumping enzyme and can be bred with normal mice, as in step 4, to produce mice with different mutations.

6

Mutant mice are bred with normal mice to produce offspring that have the same stable mutation.

7

Mice, each carrying one copy of the same mutation, are bred. The breeding of these two heterozygous mice will produce a homozygous mouse with identical copies of the same gene mutation.

8

The offspring with two copies of the same mutation can be identified by a red glow because they also carry two copies of the RFP gene. If a defect results, researchers can discern the function of that gene by the consequences of the mutation. Xu's goal is to determine the cause of single-gene diseases by doing this type of analysis for each of the 20,000 mouse genes that have not been analyzed.

ILLUSTRATIONS BY EMILY DAMSTRA / DIAGRAM BY DAPHNE GEISMAR

by Pat McCaffrey

Sitting in a standard-issue clear plastic cage among hundreds of other white laboratory mice, the *piggyBac* mouse looks absolutely ordinary, not a bit like an animal poised to turn human genetics research on its head. But when Tian Xu, PH.D., professor of genetics, switches on an ultraviolet lamp, the mouse emits a faint pink glow—an aura that holds the secret of its transformative power. If Xu, professor and vice chair of genetics and the mouse's inventor, has his way, he will breed up to a million more pink animals. Those animals, he says, will reveal the causes—and in some cases the cures—for myriad human diseases.

What is *piggyBac's* secret? Xu knows, because he engineered the mouse to carry a small piece of moth DNA, a "jumping gene" called the *piggyBac* transposon, which in turn carries a genetic marker to turn the mouse pink for easy identification. The jumping gene makes the mouse a mutant factory: when the animal breeds, the transposon causes random genetic mutations in the mouse's offspring—one gene per mouse is disabled. Compared to current methods for making experimental mice, known as knockouts, using *piggyBac* is 100 times quicker and cheaper.

Xu eventually plans to produce 100,000 new strains of mice with missing genes. Among them, he expects to find a knockout for the majority of the estimated 25,000 to 30,000 genes in the mouse genome. More than 99 percent of mouse genes have direct equivalents in humans, and so these mice will provide the first glimpse of the functions of many of our genes, most of which remain mysterious half a decade after the human genome project first cataloged their existence.

TERRY DAGRADI

Tian Xu has found a method of making knockout mice that is faster and far less expensive than conventional technology.

From China to Yale

Tian Xu came to New York City from China in 1983, a 21-year-old refugee from the Cultural Revolution pursuing graduate work in genetics at City College. After six months of living on a partial teaching assistant's stipend in an abandoned building in Harlem, he received an offer he couldn't refuse: a full scholarship to Yale. He was soon in New Haven, studying the development of the fruit fly *Drosophila melanogaster* with cell biologist Spyros Artavanis-Tsakonas, PH.D.

His good fortune did not impress his mother in China.

"It was the first time she'd heard from me in six months, because I couldn't afford to call home. But this was big news." When Xu's mom asked what he intended to study, Xu replied, "I'm gonna work on flies, Mom." After a very long silence, his mother spoke: "Son, we have a lot of flies right here in our hometown."

For a geneticist, fruit flies are a model organism for figuring out what genes, and the proteins they encode, actually do. The ability to produce hundreds, even thousands, of mutant flies quickly by using chemicals, radiation or even transposons lets researchers look for traits they are interested in, such as slow growth or crippled wings.

This kind of large-scale mutagenic analysis, called a forward genetic screen, has been a staple of fly research for decades. And at his lab in Yale's genetics department Xu has used the technique to unravel the biochemical pathways involved in cancer cell growth and metastasis in *Drosophila*.

Forward genetic screens have played a pivotal role in our understanding of modern biology in lower organisms, including bacteria, yeast, flies, worms, plants and zebrafish. But the lack of comparable genetic screens in mammals has impaired our ability to understand many aspects of human biology and disease. Xu felt that his fly work could only begin to approximate human disease because of the wide evolutionary distance between the two organisms. Moving his research closer to humans meant moving to the mouse.

Are you a mouse or a man?

Like humans, mice are mammals, with similar anatomy, physiology and developmental stages. They breed rapidly and can be inbred to produce large numbers of identical animals. Their care and feeding are more complicated and costly than that required for fruit flies, but as higher animals go, they are small and inexpensive.

For years, the obstacle to genetic studies in mice was a lack of tools for mutating genes en masse for forward genetic screening. Starting in 1981 with Frank H. Ruddle, PH.D., Sterling Professor of Molecular, Cellular and Developmental Biology at Yale, researchers developed genetic engineering methods that allowed them to add and subtract genes from mice, and these methods revolutionized the use of mice for targeted genetic research.

Today, researchers can selectively mutate mouse genes at will. Typically, they use genetically altered embryonic stem cells to create embryos, which mature and pass the altered genes on to their offspring. The process is investigator-driven—scientists decide which genes to add or eliminate. From choosing a gene and designing a piece of DNA to disrupt it, to creating embryonic stem cells and injecting the cells into embryos to produce mice, to breeding out the final mutants, each new knockout is a custom product that takes a year and approximately $100,000 to bring to life. But the goal of large-scale systematic mutations in the mouse genome has remained elusive. Efforts to use chemical mutagens or viruses to disrupt large numbers of genes have been abandoned as too expensive and unpredictable.

Xu had a different idea. He wanted to create mutant mice as easily as he had made mutant fruit flies. He didn't want one or two or even 10 mouse mutants—he wanted a complete collection, one mouse strain for each gene, that would allow him and scientists around the world to discover the roles of genes in human disease. "I thought if we could do the kind of work in mammals that we do in flies, that would be tremendous."

For that, he needed a new tool.

Finding *piggyBac*

Based on his experience with *Drosophila*, Xu believed a transposon could do the trick for wide-scale mutagenesis in mice. Transposons, also known as jumping genes, were first described in corn in the 1950s by Barbara McClintock, PH.D., who won the 1983 Nobel Prize in physiology or medicine for her discovery that the varied colors of Indian corn kernels arise from the disruption of pigmentation genes by transposons.

Mere snippets of genetic material, transposons insert themselves at random in the middle of the long DNA molecules that make up chromosomes. If they happen to land in the middle of a gene, the sequence becomes hopelessly garbled and the gene becomes nonfunctional. Over the course of evolution, transposons have remained active in plants and insects, presumably because they generate genetic diversity. For reasons that aren't entirely understood, the abundant transposons in mammalian genomes (they make up as much as 40 percent of human DNA) have been "disabled," perhaps to protect organisms from unwanted mutations. Despite decades of efforts by many researchers, no one had succeeded in discovering or engineering an efficient transposon in mammals.

Xu imagined using transposons like buckshot to pepper the mouse genome, where they would randomly insert themselves into genes and generate large numbers of mice with uniquely altered outward characteristics, or phenotypes. "People said I was crazy," Xu recalls. "They said, you've never trained in mouse genetics. You've never even touched a mouse."

Xu didn't give up his day job; he kept his lab pushing ahead with its regular *Drosophila* work. On the side, though, he continued to search for the elusive transposon. In 1996

he applied for funding from the Howard Hughes Medical Institute, a foundation known for supporting risky but promising ventures. With its support, over the last eight years he has tested a succession of transposons and viruses from plants, insects and wherever he could find them.

Finally, he tried a strange-looking transposon known as *piggyBac*, found in the cabbage looper moth. It was different from anything else he had seen, and it was so exotic Xu figured it might work. *PiggyBac* had been discovered several years earlier by Malcolm Fraser, PH.D., at the University of Notre Dame in Indiana, and it had already been shown to suppress gene activity in insects.

After engineering the *piggyBac* transposon to adapt it for mammalian cells, Xu found that it worked, and Xu's mutant mice were featured on the cover of the journal *Cell* on August 12, 2005. "We don't know why this one works while others don't," Xu said at the time, "It just works. We have a magical tool now." Xu and colleagues further engineered a red fluorescent protein gene from jellyfish, which they added to the transposon, allowing them to identify visually which mouse carries a mutation and which is a mutant.

Mutants-R-Us

With quick and easy generation and recognition of mutants, the mammalian *piggyBac* transposon system is ideal for the large-scale project Xu envisioned. Besting the standard time requirement of one year per mutant mouse, within months the researchers had created 460 unique mutant mice.

Among the first batch of 95 mutants they examined in depth were mice with tusks, mice with neurodegeneration, mice that could not sense pain, mice that turn only leftward, mice that don't grow and mice with bad manners. Then there were the sterile mice, and mice never even born because their defects were lethal early in development. In each case, these afflicted mice will lead the researchers to single genes critical for growth and development, autoimmune disease, social behavior, spinal cord defects and neurodegeneration.

"This is only looking at the first 95—imagine if we mutate every gene and look through them all, what we will find," Xu says. The hit-or-miss nature of *piggyBac* mutations gives researchers a decided advantage over knockouts produced using embryonic stem (ES) cells, he says. *PiggyBac* allows scientists to study genes they didn't even know existed. "We don't pick which genes to get rid of. We just make the mutants randomly and let the animals tell us which ones are important. This is a critical difference, because scientists are not that smart that they always pick the right gene to knock out."

Richard P. Lifton, M.D., PH.D., chair and Sterling Professor of Genetics, an expert on hypertension genes and a Howard Hughes Medical Institute investigator, agrees. Lifton says, "That's the power of forward genetic screens. They allow us to find genes that affect these phenotypes that up to now we've had no idea about at all."

So unlike the ES cell method, which focuses exclusively on known genes, the unbiased approach of transposon-based mutagenesis can open up exploration of the entire genome, including areas of the genome previously dismissed as "junk" DNA.

Time for a new mouse

Xu's development of the *piggyBac* mouse came as the drawbacks of the knockout technique were holding back mouse genetics, despite international support for a centralized program to knock out every gene in the mouse. First, the process of producing knockout mice via ES cell engineering is slow and expensive. According to the National Institutes of Health (NIH), about 11,000 mouse knockouts have been generated since the late 1980s, but that number is less impressive than it seems. Many genes have been knocked out more than once by different labs—one gene was knocked out independently at least 28 times. Of the estimated 25,000 mouse genes, only about 4,000 have been published, and studies of those genes have been limited to specific areas.

And not all mouse mutants are available to all researchers. Given the time and resources invested in making knockouts, some researchers want to keep their own mice close to home, impeding the sharing of reagents and increasing the chances for redundancy and waste.

To solve some of these shortcomings, the NIH has set aside $50 million to establish a central repository for 10,000 mutant ES cell lines. The lines, which will be produced over the next five years, will be freely available to all researchers, who can request the ES cells and then use them to produce their own knockout mice in their labs. A parallel effort, using different strains of mice and creating a different type of knockout, is being started by an international consortium that includes Canada and several European countries.

Xu thinks that the key is to produce mutant animals that will reveal defects and diseases. Producing mutant animals from ES cells is a long process. The *piggyBac* mouse system can reach the goal faster and cheaper because it produces mutant animals in a highly efficient and cost-effective fashion, and allows rapid identification of mutants for analysis. His plan is to produce up to 100,000 mutant strains, each of which carries a single transposon mapped to a known site. A bank of frozen *piggyBac* mutant embryos would then be generated for distribution to researchers around the world. The resource would enable researchers in all fields of medicine to study the genes regulating the disorders they encounter, Xu says.

Going with *piggyBac* for genome-wide mutagenesis has other advantages, too. Transposons may be the only way to generate mutants in dozens of strains of mice for which

ES cell cultures are not available. There are more than 200 breeds of mice used by researchers, each with its own personality. Some are preferred by immunologists, while others are better for neurological studies. To move a mutation between strains takes two or three years, which might be skipped altogether by utilizing transposon technology. Transposons could theoretically be used in other species, too, like the rat.

From Yale back to China

To produce the million mice it will take to find 100,000 mutants, Xu and the School of Medicine have embarked on a joint research project with his alma mater, Fudan University in Shanghai. The mutagenesis of the mice will be done at Fudan, where Xu and his colleagues have set up a state-of-the-art mouse facility and production lab supported by Chinese government funds. Researchers in China have produced the first 500 mutants already, including the 460 Xu's team produced. But finishing the job will require much more funding, and Xu is on the stump for that now.

He has applied for NIH funding for the research at Fudan, to produce 500 more mouse mutants in a pilot project. Xu wants to demonstrate that *piggyBac* can work in a different strain of mouse, and specifically in the strain that was selected for the NIH ES cell-based knockout project. One way or another, the mutants will all be made within five years, according to Xu. "We hope that our project will be supported by the NIH so that the mutants will be available to the scientific community throughout the world as soon as possible."

Making the mutants is just the first step of Xu's plan, and not even the most ambitious part. Once the mutants are created, the real work begins. Every one of the million mutant mice will need a thorough physical exam. The project, which Xu envisions carrying out at Yale, calls for a full workup for each mouse, and could include a CT scan, blood work and measures of immune, kidney, lung and cardiovascular function, as well as of behavior. Not all the mice will appear sick—many will seem perfectly normal until researchers take a closer look.

"Now, researchers generate their own mutant mice and study only the processes they are interested in," Xu explains. "For example, they make one or a few mutations and look for hypertension. If they see hypertension, that's great. But if they do not see hypertension, that's the end of the story, and they will most likely abandon the mice. But those mice could easily have diabetes, a very significant piece of information that would be totally missed. Furthermore, researchers working on different diseases and biological processes are now repeatedly mutating the same genes in ES cells and/or taking the same ES cell line to repeatedly produce the same mutant mice. There is a significant waste of resources."

The centralized and comprehensive phenotyping will allow researchers to choose only the genes of interest for in-depth mechanistic studies and ensures that the mice rapidly make their way into the labs of experts who can best utilize them to discover new treatments for disease. Right now, Yale scientists are defining a scientifically solid and practical panel of phenotyping procedures that will cover the widest possible range of diseases.

They believe their integrated approach will provide the biggest return on the *piggyBac* investment. They plan to make their results—and their mice—freely available to researchers all over the world. Xu wants to see all data posted on the Web, where interested scientists can troll for new genes for their favorite disease, then order off-the-shelf mice for their experiments.

Besides having an impact on the most common major diseases, the mouse studies will advance research into orphan diseases—neglected conditions affecting so few people that they do not attract interest from for-profit drug companies. "There are about 6,000 orphan diseases. While each one affects only a small part of the population, all together they affect many people. We have a solution to the problem of lack of interest, because by the process of systematically mutating every gene and screening through our mice, we will identify many of the genes that are responsible for these diseases," says Xu.

Ultimately, Xu hopes to create more than just mice.

"I want to make Yale the premier international center for human disease studies. The aim is to set up a center, based on these mice, which will attract researchers from all over the world. Each one can focus on a disease, and identify the causes of that disease right here. Then, they will move on to develop a career studying the mechanism of each disease and finding a cure," Xu says. "When I came to the United States 23 years ago, I had $50 to my name. Yale gave me a research fellowship and changed my life. Now, we have a chance with these mice to cultivate a new generation of physician-scientists, who will mushroom out to solve disease and help millions of patients. That would really be my dream come true." **YM**

Pat McCaffrey is a freelance writer in Boston.

A LETTER FROM NIGER

Water is life

The 500,000 inhabitants of the Azawak plains of Niger wage a daily struggle to find enough water for their basic needs. Through her photographs, an alumna of epidemiology and public health hopes to draw attention to their plight and improve their lives.

Text and photographs by Ariane Kirtley, M.P.H. '04

In the Tuareg camp of Tchintaloukan, 18-year-old Againakou gives her 10-month-old son, Agoubouley, a drink of marsh water. Such water can be deadly—10 of 120 children in another camp visited by author Ariane Kirtley died of diarrheal diseases caused by drinking the water.

When I threw a pebble into Mohammed and Gonda's well, I heard a faint thump, not the splashing of water. "How deep is it?" I asked. Two hundred feet, I was told, and no sign of water.

For six years Mohammed and Gonda's families from neighboring villages and camps in the Azawak plains of the Republic of Niger pooled their resources to dig an adobe well. Then they abandoned their efforts. There was no more money to dig deeper or to line the well with cement—the adobe well threatened to cave in. Even if the families had had the resources, it would take six more years to reach water. In the Azawak the first water table typically lies 430 feet underground, and renewable aquifers are at 700 to 1,400 feet. Because the people of the Azawak cannot afford pumps and pipes, there are few sources of water, and none are permanent or reliable because they dry up from overuse.

Finding water occupies the lives of the 500,000 members of the Tuareg and Woodabe Fulani ethnic groups who make their homes in the plains' 200,000 square kilometers. Most of the year there is no water. During the rainy season from July through September, the pastures turn green, the animals grow fat, milk is plentiful and water overflows from marshes that reappear after nine months of drought. The water, fouled by animal and human waste, may be darker than coffee and dirtier than a New York City mud puddle, but people drink and bathe to their hearts' content. Dysentery and diarrhea soon follow.

Most of the inhabitants of Niger's Azawak plains belong to the Tuareg and Fulani ethnic groups. Pastoralists, they graze livestock, driving them as far as 350 miles in search of water. Author Ariane Kirtley describes the region as a "rich and diverse land of extremes: extreme kindness, extreme heat, extreme beauty and extreme challenges."

When the marshes dry up, people travel by foot or donkey to find water. Prevented by local populations from settling near the few sources of water that exist on the outskirts of the territory, they repeat their search every day. The men travel up to 350 miles south seeking water for their livestock, and the search for water becomes a daily chore for women and children. Children as young as 9 or 10 may travel—with temperatures topping 100 degrees—10 to 17 miles to the nearest well, only to wait for hours for their turn to fetch water. Often their turn comes too late, as the other people and their livestock sharing the well have left it dry. The children may stay at the marsh as long as three days while the water is replenished.

Water consumption in these plains, less than a gallon and a half per person per day, is well below the World Health Organization's recommendation of 6.5 gallons. During the dry season, water is reserved for drinking and cooking—personal washing awaits the return of the rains. In the Azawak almost half the children die before their fifth birthday.

Despite the hardships, people stay in the Azawak. It is their traditional home, but on a practical level, they have no place to go. Their numbers are too large for relocation, and moving elsewhere could lead to strife with other ethnic groups.

Finding water

Although I spent the first 10 years of my life in Africa, I had never seen an area as poor as the Azawak. With my brother

While in the Azawak, Kirtley stayed with families in their homesteads, camps and villages. In January 2006, during a Muslim festival, she posed with children of Tantigellay Teckniwen, a Tuareg camp.




and our *National Geographic* journalist parents, I lived among the nomadic Bozo fishermen in Mali, the Ibadite Muslims of central Algeria, the animist Gueré "panther men" of western Ivory Coast and the Inadan Tuareg artisans of Niger's Aïr Mountains in the Sahara Desert.

I studied public health at Yale and for my internship returned to Niger to work on a hygiene and sanitation program with CARE. After graduating in 2004, I went back to Niger as a Fulbright Scholar to build upon my work with CARE. My Fulbright research revealed significant variations in knowledge, attitudes, behaviors and resources relating to health and nutrition among seven ethnic groups living in rural Niger. (For example, of 700 men I interviewed in the Azawak, only three had heard of AIDS, and all three believed it resulted from women having sex with dogs.) With this information I created a database that allows health organizations to tailor their programs to their target populations' unique needs and attributes.

During my Fulbright research I discovered the Azawak. My research assistant, Moustapha, whose family had abandoned the plains during the drought of 1974, persuaded me to visit his homeland. Little did I know that my visit in September 2005, which was to last only a month, would consume me professionally ever since. I spent October and November 2005 attempting to interest humanitarian organizations in the Azawak. With a team of Nigerien employees from a large international humanitarian agency, we wrote a proposal to fund a water and food program. It was rejected because the Azawak is "too vast and remote"—the organization did not want to risk its employees in a region without water.

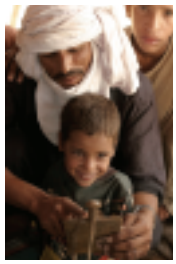
Realizing that I had to take the first step if humanitarian aid is to reach the Azawak, I have founded Amman Imman, which means "water is life" in Tamachek, the Tuareg language. Amman Imman has been raising money since February 2006, with a goal of $280,000 for a pilot program to build two borehole wells, each of which could provide water for 25,000 people. With more funding, we hope to sink even more such wells. Once water is available, humanitarian organizations may safely send workers to improve the lives of one of the most vulnerable populations on earth. (More information about the project is available at www.waterforniger.org.)

The people of the Azawak

Most people of the Azawak are pastoral nomads of the Tuareg and Woodabe Fulani ethnic groups. The Tuaregs of the Azawak have retained a nomadic existence, herding cattle, camels, goats and sheep, and living in tents of red-dyed goat hide in camps of 50 to 150 people. During the rainy season, they move every three to four days in search of pastures. In the dry season they move often within their "home territories," land occupied by their families for generations.

Gonda and Mohammed spent six years trying to dig a well, with money raised from their Tuareg families and neighbors. They abandoned their efforts over a lack of money and worries that the well would collapse.

Throughout her travels in the Azawak, Kirtley captured images of daily life and portraits of the Woodabe and Tuareg peoples.



The Woodabe are nomadic cattle herders who live in camps of one or two families and move frequently to greener pastures. Their homesteads consist of a traditional wooden bed (covered with a plastic sheet when threatened by rain or sun) and a wooden table covered with 20 to 30 calabashes—bottle gourds hollowed out and dried for use as containers. Only a few of these calabashes hold grain or milk—the rest are on display as a sign of the woman's wealth.

Sedentary villages grow more common as drought takes its toll on livestock. Without animals for their livelihood, the nomads settle into villages of between 100 and 300 people and try to survive through subsistence agriculture, mostly growing millet and sorghum. But even they abandon their villages to search for water during the harshest months of the dry season.

Hospitality and hope

Sadouan was the first to greet me as my research assistant, Moustapha, and I arrived at our Tuareg host camp in September 2005. She invited me to her tent, prepared a traditional bed of large wooden poles and woven mats, and gave me a mosquito net and elaborate leather pillows for armrests.

Late into the night her relatives came bearing bowls of camel milk. Sitting on a pillow and sipping the frothy liquid, with Moustapha as my interpreter, I had a conversation with Sadouan's husband, Alhassan. The camp and its herds, he said, had recently returned from salt licks in the north. He lamented losing 80 percent of his herd to drought that year. "Around 100 of my camels died because they didn't have enough food and water. When we ourselves had no more food, we also had to eat some of them. I sold others to buy millet for Sadouan and the kids," he said. "Ten years ago, only the poorest families in our camp owned fewer than 300 animals. With only 20 animals left, what can I count on to survive? Maybe if I grow enough millet this year, we'll have enough to eat."

After putting her children to bed, Sadouan gently ran her fingers through my hair. "Why haven't you braided your hair?" she asked, implying that she would never leave her hair uncovered and unbraided. "If you want, I can wash it with ochre, and give you the festivity braids."

A wild harvest to fill empty bellies

The sun was setting as I arrived in the Tuareg village of Intatolen to greetings from men and women returning from a day planting millet. Two women waved me over to their thatched hut to share their supper of wild squash and a grain I didn't recognize. After several minutes of silence, I introduced myself and asked their names. They giggled. I had committed *senti* by speaking while eating. A faux pas in Tuareg tradition, *senti* is nonetheless covertly appreciated as a sign that the food was so good that it made your mind wander from matters of etiquette.

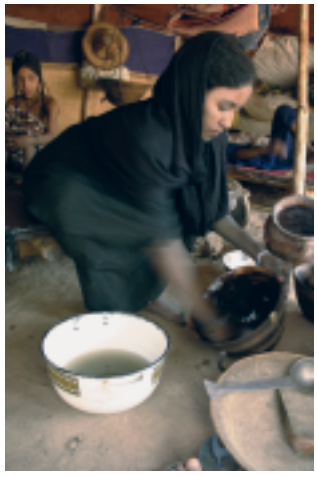
"We would have liked to serve you meat, but all our animals have died," said Issibit, the elder of the two co-

RIGHT Tackawel, a Tuareg woman who lives in a sedentary village called Intatolen, pounded grain in September 2005. Many inhabitants of the Azawak are turning to raising grain instead of livestock in order to feed their families.

FAR RIGHT Muddy marsh water is all that's available for drinking, bathing, cleaning and washing dishes. In September 2005 in Tantigellay Teckniwen, a Tuareg woman, Zeinabou, washed her bowls.

OPPOSITE LEFT The Woodabe, a subgroup of the Fulani ethnic group, move their camps of one or two families every two or three days. Their homesteads include a wooden bed, which they cover with a plastic sheet when it rains or the sun is too harsh.

OPPOSITE RIGHT In the region of Inagar in January 2005, a Woodabe Fulani family moved camp with their belongings carried on donkeys.






wives, after dinner. "We ran out of rice a few weeks ago, and so now we are eating wild grains until they too run out. And the *lacada*, we are *very embarrassed* to have served you the wild zucchini, but we have nothing else to eat."

I later learned that eating wild grains and vegetables is a sign of famine—they are eaten only when every other food source has run out. My research revealed that 71 percent of the households that I interviewed went from eating one or two meals a day supplemented with milk to one or no meals a day, sometimes supplemented with far less milk. And 91 percent reported resorting to eating wild grains, squash and bitter berries.

From school to Guerwuls

Fada, about 14, adorned with charm talismans, a round feather-topped hat and a Tuareg saber, came bouncing toward me as I struggled through prickly burrs. "Hey, follow me, I'll show you where it's best to step," he said. "Come to my camp. It's just over that dune." Two hours and about 2,000 prickly burrs later, with a herd of long-horned cows following, we arrived at his home: a wooden bed and a table covered with calabashes.

The camp was deserted. "Oh, I forgot—everyone has left to prepare for the Guerwul tomorrow." I had heard of Guerwuls, beauty competitions held by the Woodabe people, a subgroup of the Fulani. "Can you come?" Fada asked.

I asked Fada about life as a herder. Had he ever been to school? At first he laughed and then answered that the Fulani reject formal education because they believe that schools steal their children away from their pastoral lifestyle. A child who attends school is considered dead because he or she no longer understands magic or the art of herding.

This is how Fada's uncle, Ali, came to go to school 35 years ago. French colonists demanded that his grandfather, the chief of his camp, send the children to school in Tchintabaradène, the capital of the Azawak. He sent only his own grandchildren to their "death," Ali among them. Ali ran away and hid in the bush for three weeks, traveling by foot through unknown prairies. When he reached his camp, the white men were waiting. He ran away five more times before accepting his fate. Ali never returned to life as a herder. Instead, he traveled to Morocco and France to obtain a degree in sustainable agriculture. Ali now works on crop productivity projects for a nonprofit organization in southern Niger.

After I refreshed myself with a bowl of curdled cow milk and promised to see Fada at the Guerwul, he said, "I'd like to go to school someday and become like my Uncle Ali. Maybe when I have children, there will be schools in the Azawak for them to attend." **YM**

Ariane Kirtley, M.P.H. '04, grew up in Africa and has founded the nonprofit organization Amman Imman to build permanent water sources in the Azawak region of Niger.


Infectious disease, internal medicine and Paul Beeson

During his 13 years as chair, Paul Beeson made internal medicine at Yale one of the best departments in the country. He is remembered for his skill in the laboratory, his compassion for patients and his nurturing of students and residents.

by Richard Rapport, M.D.

Paul B. Beeson, M.D., former chair of internal medicine at Yale and an internationally renowned physician and scientist, died on August 14 in Exeter, N.H., at the age of 97.

Beeson held leadership posts at major academic medical centers, was an editor of two major textbooks on internal medicine, advanced the study of fever and infection and was a member of the National Academy of Sciences. Among the honors he received was the Kober Medal, the highest award given by the Association of American Physicians. In 1973, Queen Elizabeth II named him an Honorary Knight Commander of the Most Excellent Order of the British Empire, a rare honor for an American, in recognition of his service as the Nuffield Professor of Medicine at Oxford University.

While at Yale Beeson conducted groundbreaking research, transformed the Department of Internal Medicine into a national model and cemented his own reputation in medicine. "When he came it was a relatively small department," recalled Arthur Ebbert Jr., M.D., professor emeritus of medicine, who was hired by Beeson as an instructor in 1953. "He apparently had a mandate to expand the department and to encourage patient referrals from around the state. Before he came and reorganized the department, if doctors had a patient they wanted advice on, the patient went to New York or Boston."

Beeson the scientist was the first to identify proteins in white blood cells now recognized as cytokines, signaling compounds used for intercellular communications, that also play a role in the body's response to infections. With one of his residents, Robert G. Petersdorf, M.D. '52, HS '58, Beeson subsequently wrote a paper on patients with persistent fevers of 101 degrees or more. Published in the journal *Medicine* in 1961, the article is considered a "landmark," said Lawrence S. Cohen, M.D., HS '65, the Ebenezer K. Hunt Professor of Medicine and Special Advisor to the Dean. Cohen, an intern and resident under Beeson, told *The New York Times* that the paper is "as relevant in 2006 as in 1961, in pointing out causes that were not obvious and teaching clinicians what they should be thinking about in making a differential diagnosis."

Beeson grew up in Anchorage, Alaska, where his father, John Beeson, M.D., was a general practitioner and surgeon for the Alaskan Railway. When he was 19, Paul Beeson followed his older brother to McGill University, where both received their medical degrees. After an internship at the University of Pennsylvania, Beeson joined his father and brother in practice in Ohio. The lure of research drew him to Rockefeller University, and he subsequently took appointments at some of the most prestigious academic and medical centers in the country.

He came to Yale in 1952 from Emory University. When he left New Haven 13 years later to become the Nuffield Professor of Medicine at Oxford, internal medicine at Yale was regarded as the premier department in the country. In 1981, the Paul B. Beeson Professorship in Internal Medicine was established at Yale, endowed by a former colleague,

Paul Beeson was widely regarded as a scientist and a caring physician, teacher and mentor.

Elisha Atkins, M.D., and his wife, Elizabeth. In 1996, the School of Medicine named its medical service in Beeson's honor.

In this article adapted from *Physician: The Life of Paul Beeson* (Barricade Books, 2001), author Richard Rapport, M.D., describes Beeson's tenure at Yale.

Beeson sat behind a glass-topped desk, rolling a letter opener around in his fingers, while the patients admitted during the night were presented to him by the residents. Laboratory tests had become more sophisticated since Beeson's own house officer days, but history and physical examination remained central to the process of diagnosis. The impact of technological innovation was slight, in spite of cardiac catheterization and even early angiography. Laboratory values, X-ray results and physical examination were expected to be reported efficiently by the sleep-deprived residents. Long-windedness was abbreviated by an impatient tapping of the letter opener. The house staff soon learned that, while their new chair didn't like mistakes, he tolerated them as a function of learning. What he could not tolerate was thoughtlessness. When it was uncovered that a patient had been treated unkindly or misused, as happened the day a resident referred to a homeless, alcoholic patient as "a 35-year-old bum," the letter opener snapped unhappily to the desk and the room quieted while the offending resident searched in vain for an escape. This happened rarely, a testimony to both residents and chief, but when it did occur it was remembered for the life of the perpetrator.

Teaching on the wards

Tuesdays and Thursdays, after morning report, Beeson left his office with the residents and students assigned to his service, walked past the Fitkin Amphitheater and climbed upstairs to the wards where he consulted for two hours—all year long. Beeson approached the bedsides of the patients, who were exposed on all sides and confronted by a crowd of people they barely knew, and immediately sat down. He had come to believe, possibly from his practice experience in Ohio, that standing by a patient's bedside places the doctor in a position of dominance that makes many ill people want to be somewhere else. He wished to place them at ease and so he reduced the distance between them by sitting unhurriedly, an act that suggested interest in each patient, rather than the disease being discussed. As the resident presented the history, physical examination, laboratory and X-ray findings, a task that sometimes took a while, Beeson said nothing. He allowed the younger doctors to discuss the problem themselves, develop a differential diagnosis, and argue about what made one possibility more likely than another. If speculations behind the curtains drawn around the bed grew too

outrageous, Beeson gently guided the discussion back toward reason. Sometimes he said nothing at all, or simply agreed with the diagnosis and what was being proposed to manage the illness. Occasionally he differed altogether, as in the case of a third-year medical student admitted late one night in 1953.

The student was Sherwin B. Nuland, M.D. '55, HS '61, later a Yale surgeon and gifted writer, who had been brought to the emergency room with a very high fever and, the admitting resident thought, an enlarged spleen. The temperature elevation alone wasn't a great worry, but Nuland was clearly sick, and a spleen that can be palpated expands the possibilities in several nasty directions. Because they didn't know what was the matter with him, the residents did what they often did then (and now)—they gave him antibiotics and started to work up the fever. Nuland later noted, "I was evaluated from one end of myself to the other, carrying a diagnosis of either mononucleosis or hepatitis—no one being sure which. After about three days like this the Professor came to make rounds, examined me briefly, looked at his retinue and pronounced, 'This boy had a strep throat a few days ago, but he's fine now. He can be discharged.' I don't suppose this is a major triumph diagnosed by Dr. Beeson, but what impressed me most was the gentleness with which he treated his residents when he had shown them to be in error, and his certainty."

A growing faculty and more specialists

The tendency toward subspecialization had begun, and the Department of Medicine was forced to add faculty members with more focused interests than only general internal medicine. While recognizing this requirement, Beeson was reluctant to abandon his lifelong view that internists should be generalists. But by 1954, this position, learned from both his father and Soma Weiss, M.D., the legendary Harvard physician and mentor, was difficult to defend, and new fellowship-trained faculty members were hired. With support from Vernon W. Lippard, M.D. '29, dean of the medical school, Beeson and the Yale department were now in a position to recruit from the best talent available.

As the department added more faculty, it also grew in other dimensions. Space was always an issue (one cardiologist's lab was in a remodeled coat closet off the Fitkin Amphitheater), and was relieved only slightly when the West Haven Veterans Hospital opened. The private Memorial Unit was constructed, allowing department attending staff to admit insured private patients and residents an opportunity to care for them, as well as for the nonpaying patients admitted to the Grace-New Haven Hospital. All of the faculty, with the exception of the dean, were entirely indifferent to the funding sources for the care of any of these sick people. The faculty and house staff were paid a salary by the medical school; this income was not linked to nor influenced by months spent attending on the wards, number of patients seen or procedures performed, number of research papers published nor volume of work done as measured by any other scale. Patients were admitted through the clinics, emergency room or privately, and they were taken care of by the same attending physicians and the same house staff regardless of their type of insurance—or its lack.

Such administrative issues always impose on the time of a department chair, and Beeson expected them. What he did not necessarily expect was the growing line of petitioners that never seemed to shrink outside his office door.

Beeson still ran the entire department with only a secretary. Of course, the tasks were far beyond those of a routine secretarial job. His secretary, Betsy Winters, who would later have an award, the Betsy Winters House Staff Award, named in her honor, was responsible not only for scheduling appointments, phone calls, typing and mimeographing—the general business of running the office—but also for managing grant applications to the National Institutes of Health (NIH), intern and resident applications and medical student evaluations and monitoring the queue outside Beeson's door. Whenever people showed up, regardless of their rank, Winters found a way to coax a few more minutes out of the chair's schedule for them.

TERRY DAGRADI

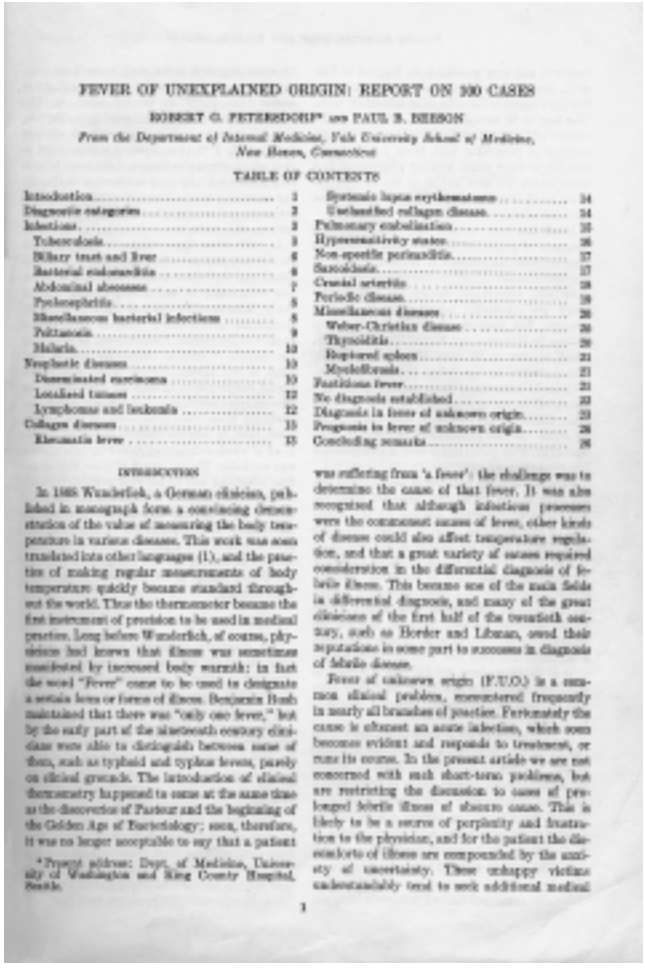
OPPOSITE In 1952, his first year as chair, Paul Beeson posed with the faculty in front of the Sterling Hall of Medicine. Beeson is fifth from left in the front row. To his immediate left is nephrologist John Peters, who made significant contributions to the study of renal disease.

ABOVE In May 2003, Paul Beeson was reunited with nine of his former residents when he came to Yale for the unveiling of his portrait, which hangs in the Fitkin Amphitheater.

A caring mentor

Dedication to the careers of students, residents and faculty is a labor-intensive activity. The students, who often entered medical school with no idea about what clinical medicine really involved, were sometimes overwhelmed when they found out. Patients admitted to teaching centers in the late 1950s were often so sick they could not be cared for in a community hospital, and the mortality rate was as high as 10 percent on the Yale medicine wards. These patients were hospitalized for long periods, and the house staff and students developed relationships with them not available in today's technology-rich day-surgery and outpatient environment.

An intern from 1958 remembers his young female patient with meningitis being treated with the new technique of injecting intrathecal penicillin, the drug infused into spinal fluid through a lumbar puncture needle in order to achieve high concentration at the site of infection. This was a procedure advocated by Beeson, who recommended that, even though she was improving, the spinal taps be continued until the patient was completely without fever. An arithmetical error was made by the nurse preparing the infusion, and instead of 10,000 units of penicillin, the intern pushed in 1 million. The patient convulsed and died. The intern, who had been taking care of the young woman since her admission, also collapsed. Beeson was called by someone still left standing, and immediately came to the ward, gathered both nurse and intern and took them into an empty room. After the tears slowed and a little calm had been restored, he explained to the two young people that errors are certain to be made in the care of the desperately ill, and that everyone involved in their care assumes part of the responsibility for what happens on the wards—the triumph and the loss. By involving himself in the accident, and reminding them that it was he who chose the treatment, Beeson comforted the nurse and intern at least a little, and helped them to know that they were supported. Next, they told the family exactly what had happened. There was no lawsuit.



FEVER OF UNEXPLAINED ORIGIN: REPORT ON 100 CASES

ROBERT G. PETERSDORF AND PAUL B. BEESON

From the Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

TABLE OF CONTENTS

INTRODUCTION

In 1868 Wunderlich, a German clinician, published in monograph form a convincing demonstration of the value of measuring the body temperature in various diseases. This work was soon translated into other languages (1), and the practice of making regular measurements of body temperature quickly became standard throughout the world. Thus the thermometer became the first instrument of precision to be used in medical practice. Long before Wunderlich, of course, physicians had known that illness was sometimes manifested by increased body warmth: in fact the word "fever" came to be used to designate a certain form or forms of illness. Benjamin Rush maintained that there was "only one fever," but by the early part of the nineteenth century clinicians were able to distinguish between some of them, such as typhoid and typhus fevers, purely on clinical grounds. The introduction of clinical thermometry happened to come at the same time as the discoveries of Pasteur and the beginning of the Golden Age of Bacteriology; soon, therefore, it was no longer acceptable to say that a patient was suffering from 'a fever': the challenge was to determine the cause of that fever. It was also recognized that although infectious processes were the commonest causes of fever, other kinds of disease could also affect temperature regulation, and that a great variety of causes required consideration in the differential diagnosis of febrile illness. This became one of the main fields in differential diagnosis, and many of the great clinicians of the first half of the twentieth century, such as Horder and Libman, owed their reputations in some part to successes in diagnosis of febrile disease.

Fever of unknown origin (F.U.O.) is a common clinical problem, encountered frequently in nearly all branches of practice. Fortunately the cause is often not an acute infection, which soon becomes evident and responds to treatment, or runs its course. In the present article we are not concerned with such short-term problems, but are restricting the discussion to cases of prolonged febrile illness of obscure cause. This is likely to be a source of perplexity and frustration to the physician, and for the patient the discomforts of illness are compounded by the anxiety of uncertainty. These unhappy victims understandably tend to seek additional medical

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In 1961 Beeson and Robert Petersdorf, his chief resident, published their landmark paper on Fever in the journal *Medicine*. (See sidebar on opposite page.)

In the first rank of internal medicine

By 1960, the administration of a major department of medicine such as Yale's had become much more than the chair and one secretary could manage. A business manager was added to the staff and took over fiscal responsibility for the department, as well as management of the growing volumes of reports that the NIH and other funding agencies expected. Even this increased manpower did little to allow Beeson the freedom for laboratory research and unhurried individual meetings with students he had so valued at Emory and during his first years at Yale. He became a clever and capable administrator, but never the kind of merciless program director consumed by competition for money, faculty and patients.

The Department of Medicine had joined the first rank, competing with Harvard, Johns Hopkins and Columbia. A 1964 article about Yale in *Newsweek* describing the medical school as "good, if not outstanding," brought this quietly outraged response from John Bowers, M.D., who had been dean at two medical schools, member of the Atomic Bomb Casualty Commission and later president of the Macy Foundation: "The medical school at Yale has consistently ranked as one of the top schools in the country, with an excellent faculty and students. ... Recently a distinguished colleague at a New York medical school told me the Department of Medicine at Yale was unquestionably the most outstanding in the country—and neither he nor I are sons of Old Eli."

Beeson's students make their mark

While the department expanded both in depth and scope, some people left, of course. The vast majority of Beeson-trained academics found careers in the best medical schools in the country; 27 went on to hold major administrative positions at other universities. All of these academic physicians

continued to train their own students and house staff in the image of their teacher, valuing patient care, instruction of house staff and clinical research above their own advancement.

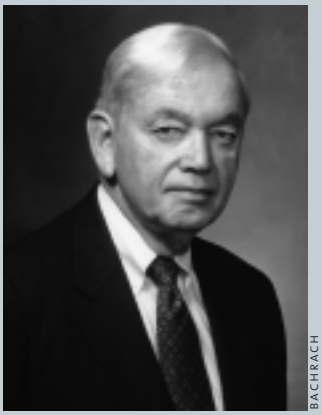
As the success and size of the department continued to grow, so did Beeson's own prestige, both at Yale and nationally. This was not the result of self-promotion, but happened as a natural function of his unassuming manner and what Lewis Landsberg, M.D. '64, HS '70, and the rest of the house staff called the "Beeson mystique."

"What was it, we wondered, that contributed to the aura of greatness that surrounded this man? When Beeson walked into a room everybody stood up. His very presence imbued the Department of Medicine at Yale with an organic unity that was felt by third-year clerks and full professors alike. No one wanted to appear unworthy in behavior, demeanor or medical knowledge in the eyes of Dr. Beeson," Landsberg recalled in a letter.

At Yale, Beeson continued to take morning report himself in his office at 8 o'clock, he still attended on the wards throughout the year and he gave the introductory lecture to the third-year medical students annually as they began their clinical training. At this lecture, a gravely ill person was chosen from among the hospitalized patients and brought to the Fitkin Amphitheater. As students who had studied only basic sciences, these 24-year-olds about to enter the wards for the first time had little understanding of the disease being presented. Neither was it their professor's intent to teach them details of that specific illness or class of diseases as he carefully and slowly interviewed and then examined the patient on those fall afternoons. What a comfort it was to these bewildered students when they were then told:

"As your acquaintance with clinical teachers grows, you will observe that although each of them has special knowledge and experience in some area of clinical medicine, they make no pretense of knowing it all. You will also find that clinicians frequently disagree, and that each of them comes to wrong conclusions from time to time. ... Biochemists and pharmacologists have 'hard' facts to propound. We, on the other hand, deal with such commodities as pain and nausea. We must accept any kind of problem. We cannot insist on working with inbred strains of people, we cannot control the environment from which they come, we know that their recollection of past events is faulty and we cannot reduce them to subcellular fractions to determine what is going on. ... We live, therefore, in an atmosphere of doubt and uncertainty, and make our decisions and take our actions on the basis of probabilities. ... So these are some precepts you must consider: Give each patient enough of your time. Sit down; listen; ask thoughtful questions; examine carefully. ... Be appropriately critical of what you read or hear. ... Follow the example set by William Osler: 'Do the kind thing and do it first.'" **YM**

Richard Rapport, M.D., is a neurosurgeon in Seattle.



BACHRACH

As head of the Association of American Medical Colleges, Robert Petersdorf believed that medicine had become too specialized and tried to increase the number of primary care physicians entering general internal medicine and family practice.

Alumnus Robert Petersdorf, former AAMC president, dies in Seattle at 80

While this issue of *Yale Medicine* was in production, we learned of the passing of ROBERT G. PETERSDORF, M.D. '52, HS '58, former president of the Association of American Medical Colleges (AAMC), as well as chair of the University of Washington Department of Medicine, dean of the School of Medicine at the University of California, San Diego, and president of Brigham and Women's Hospital in Boston. It seemed fitting to remember him on the same pages as Paul B. Beeson, M.D., former chair of internal medicine, who mentored Petersdorf early in his career.

The two met in 1952, when Beeson had just begun his tenure as chair and Petersdorf was in his last year of medical school. In 1996, when Petersdorf accepted the Kober Medal from the Association of American Physicians, he remembered what Beeson had told him that day: "The secret to success in [academic medicine is] to get one's hands dirty in the laboratory."

Five years after they met, when Petersdorf was chief resident, Beeson asked him to begin working on a paper describing 100 patients who had been ill for more than three weeks, had episodic fever of more than 101 degrees and had remained undiagnosed after one week in the hospital. This work was published under both their names in the journal *Medicine* in 1961 as "Fever of Unexplained Origin," an article that remains one of the most frequently cited papers in medical literature.

Petersdorf went on to lead premier medical centers and departments around the country, as well as several medical organizations. He died on September 29 in Seattle of complications of strokes at the age of 80. Colleagues remembered him as a mentor to young physicians and as one of the foremost infectious disease experts in the United States.

As AAMC president from 1986 to 1994, Petersdorf sought to improve the nation's system of medical education through efforts to increase the number of primary-care physicians, strengthen efforts to enroll underrepresented minorities, support the role of teaching hospitals, encourage academic physicians to devote more time to teaching and advocate for limits on the demands of residency training. He also succeeded in improving communication between medical educators and Congress, in an era when national health policies and budgets increasingly affected medical schools and their teaching hospitals.

Richard Flavell

Jack Elias

Fred Volkmar

James Tsai

Brian Smith

Immunobiologist named to IOM

RICHARD A. FLAVELL, PH.D., Sterling Professor of Immunobiology, and chair of immunobiology was named to the Institute of Medicine (IOM) in October. The IOM was established by the National Academy of Sciences and is recognized as a national resource for independent, scientifically informed analysis and recommendations on issues related to human health. Election to the institute recognizes people who have made significant contributions to the advancement of the medical sciences, health care and public health and is considered one of the highest honors in the fields of medicine and health.

Dean Robert J. Alpern, M.D., Ensign Professor of Medicine, said, "Richard's research is outstanding, clearly placing him among the best immunologists in the world. This is combined with a talent for leadership that has allowed him to cultivate an immunology program that is unsurpassed anywhere. His wisdom and experience should prove valuable to the Institute of Medicine."

Flavell's research primarily concerns the molecular basis of T cell differentiation in the immune system. His research team has used genomic approaches to identify the genes that are selectively expressed in T cell lineages, and has used gene targeting, transgenic mice and retroviral technology to elucidate the function of these genes and their target sequences.

Flavell, a Howard Hughes Medical Institute investigator, studies effector mechanisms of programmed cell death using mice lacking caspases and investigates the molecular and cellular basis for autoimmune disease.

New chairs named at School of Medicine

Several new appointments at the medical school were announced last summer and fall, with new leadership in the Department of Internal Medicine, the Child Study Center, the Department of Ophthalmology and Visual Science and the Department of Laboratory Medicine.

JACK A. ELIAS, M.D., the Waldemar Von Zedtwitz Professor of Medicine and chief of the Section of Pulmonary and Critical Care Medicine, was named chair of the Department of Internal Medicine, effective October 1. Elias, a leading authority on the molecular basis of asthma and other lung disorders, will lead the school's largest department, with 351 full-time faculty, $83 million in research funding and $45 million in clinical activity. Elias, who came to Yale in 1990, is the author of more than 160 original journal articles and 200 abstracts. He is also a co-editor of the fourth (2007) edition of the leading textbook in the field, *Fishman's Pulmonary Diseases and Disorders*. His research focuses on the cellular and molecular biology of the lung and processes related to both injury and repair of lung tissue. Elias has studied asthma, emphysema, pulmonary fibrosis, respiratory syncytial virus infection and acute lung injury.

Elias succeeds David L. Coleman, M.D., HS '80, former interim chair, who left Yale to become chair of medicine at Boston University.

FRED R. VOLKMAR, M.D., a leader in the field of autism research, was named director of the Child Study Center and chief of the Department of Child Psychiatry at Yale-New Haven Hospital for a three-year term, effective July 1, 2006. The center is a national and international leader in the field of children's mental health. Its programs in early childhood development, childhood trauma, Tourette syndrome, obsessive-compulsive disorder, mental retardation, autism and other pervasive developmental disorders are national models. Volkmar, the Irving B. Harris Professor in the Child Study Center and professor of child psychiatry, pediatrics and psychology, came to Yale as a fellow in 1980 and joined the medical school faculty two years later.

An editor of the *Handbook of Autism and Pervasive Developmental Disorders* (3rd ed., 2005), Volkmar was the primary author of the autism section of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV), published in 1994. This month he became editor of the *Journal of Autism and Developmental Disorders*, the field's oldest academic journal. Volkmar has also made major contributions to the 2001 monograph, *Educating Children With Autism*, written for the Committee on Educational Interventions for Children with Autism of the National Research Council. He succeeds Alan E. Kazdin, PH.D., who had served as director since 2002.

JAMES C. TSAI, M.D., M.B.A., was named chair of the Department of Ophthalmology and Visual Science, effective October 1. Tsai was associate professor of ophthalmology and director of the glaucoma division at the Edward S. Harkness Eye Institute of the Columbia University College of Physicians and Surgeons. He succeeds M. Bruce Shields, M.D., who had served as chair since 1996.

Tsai's goal for the department is to make it an internationally recognized leader in patient care, vision research and medical education. He plans to recruit clinicians and basic scientists with a focus on translational studies.

His investigations have concentrated on three areas related to glaucoma: the search for molecules with the potential to protect the optic nerve from damage directly without lowering intraocular pressure, the evaluation of surgical outcomes in glaucoma patients and the development of advanced techniques of vision testing.

Tsai is a fellow of the American Academy of Ophthalmology, the American College of Surgeons and the Royal Society of Medicine in the United Kingdom.

BRIAN R. SMITH, M.D., has been named chair of the Department of Laboratory Medicine and chief of laboratory medicine at Yale-New Haven Hospital. His three-year term began on July 1. Smith has served on the Yale faculty since 1989. His research interests in basic and translational science center on the biology of the inflammation-coagulation interface. Since 1997, Smith has served as vice chair of the department, which is a major center for research, patient care and teaching in laboratory medicine. The department has one of the few National Institutes of Health research training grants in transfusion medicine and hematopathology. The department performs nearly 5 million clinical tests each year.

Smith succeeds Peter I. Jatlow, M.D., HS '65, who had headed the department since 1984.


Tarek Fahmy and Erin Lavik


Michelle Bell


Sven-Eric Jordt


Myron Genel


Andres Martin


Annette Molinaro

Three Yale School of Medicine researchers investigating schizophrenia, depression and Tourette syndrome recently received Distinguished Investigator Awards from the National Alliance for Research on Schizophrenia and Depression. The one-year grants are intended to encourage study of areas of neuropsychiatric research that present special opportunities for discovery.

Angus C. Nairn, PH.D., professor of psychiatry and pharmacology, is studying brain-derived neurotrophic factor, which has been implicated in several psychiatric disorders, including schizophrenia and depression.

Paul J. Lombroso, M.D., the Elizabeth Mears and House Jameson Professor of Child Psychiatry in the Child Study Center, will use an animal model to investigate the molecular events associated with Tourette syndrome, a childhood disorder characterized by repetitive movements and vocalizations.

John H. Krystal, M.D., the Robert L. McNeil Jr. Professor of Clinical Pharmacology and professor of psychiatry, will use functional magnetic resonance imaging to collect pilot data on 20 healthy human subjects to determine whether certain brain receptors are related to the cognitive deficits in schizophrenia.

Two assistant professors have received Wallace H. Coulter Foundation Early Career Translational Research Awards in Biomedical Engineering. **Erin Lavik**, SC.D., was granted the award for developing, in collaboration with scientists at the University of Iowa, a long-term delivery system for medications to lower intraocular pressure in glaucoma patients. **Tarek Fahmy**, PH.D., in collaboration with Joseph Craft, M.D., professor of medicine and immunobiology, developed a platform technology that promises to detect, through magnetic resonance imaging, cells that cause autoimmune disease, and to deliver drugs to those cells.

Two Yale environmental scientists were among eight who will share $3.6 million in grants from the National Institute of Environmental Health Sciences. The Outstanding New Environmental Scientist Award supports early-career scientists who make long-term commitments to environmental health research.

Michelle L. Bell, PH.D., assistant professor of environmental health and of epidemiology and public health, will study the relationship between outdoor concentrations of ozone and the incidence of respiratory disease and death in exposed populations. **Sven-Eric Jordt**, PH.D., assistant professor of pharmacology, will study the ways in which airborne pollutants interact with sensory nerve cells to cause eye, nose and throat irritation.

Jonathan S. Bogan, M.D., assistant professor of medicine (endocrinology), has been named one of five Distinguished Young Scholars in Medical Research for 2006 by the W. M. Keck Foundation. Bogan studies the way in which insulin triggers cells to take up glucose from the blood.

Myron Genel, M.D., professor emeritus of pediatrics and past chair of the Association of American Medical Colleges' Council of Academic Societies, was appointed in July to the Health and Human Services Secretary's Advisory Committee on Human Research Protections. The 11-member committee meets three times a year to provide recommendations to the secretary on the responsible conduct of research involving human subjects.

Andres S. Martin, M.D., M.P.H. '02, has been named editor of the *Journal of the American Academy of Child and Adolescent Psychiatry*, effective January 2008. Martin, an associate professor of child psychiatry and psychiatry in the Yale Child Study Center, is also the medical director of the Children's Psychiatric Inpatient Service at Yale-New Haven Children's Hospital.

Annette M. Molinaro, PH.D., assistant professor of public health (biostatistics), was awarded a three-year, $500,000 grant by the National Cancer Institute in July to develop statistical methods for searching large sets of genomic, epidemiologic and pathological data for variables that predict cancer outcomes.

Marvin Moser, M.D., clinical professor of medicine, was honored for "Outstanding Contributions to the Advancement and Promotion of Scientific Research and Clinical Investigations Into Blood Pressure Related to Cardiovascular Health" at the annual meeting in May of the American Society of Hypertension in New York.

Barry L. Zaret, M.D., the Robert W. Berliner Professor of Medicine, received the Distinguished Service Award of the American Society of Nuclear Cardiology at its annual meeting in Montreal in September. The award was based on Zaret's contributions to the field of nuclear cardiology and his 10-year term as the founding editor in chief of the *Journal of Nuclear Cardiology*.

Heping Zhang, PH.D., professor of biostatistics in the Department of Epidemiology and Public Health, was named a fellow of the Institute of Mathematical Statistics at their annual meeting in Rio de Janeiro in August.

Hongyu Zhao, PH.D., the Ira V. Hiscock Associate Professor of Public Health, has been elected a fellow of the American Statistical Association, a scientific and educational society established to promote excellence in the application of statistics.

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

Beyond the white coat: training great doctors

The deputy dean of education discusses outstanding physicians and what they must be able to say to their patients.

In his welcoming speech to 100 members of the Class of 2010 at the White Coat Ceremony on August 29, Richard Belitsky, M.D., reminisced about his own introduction to medical school. His role models, he said, were the television doctors of his youth. "I wanted to be smart like Dr. Casey. I wanted to be compassionate like Dr. Welby. I wanted to be good-looking like Dr. Kildare," he said, provoking laughs from the audience.

Turning serious, Belitsky, the deputy dean for education and associate professor of psychiatry, acknowledged that the students have much to learn. "But so much of what you need to be really good doctors, you already know," he said.

Belitsky went on to list the qualities he believes are essential to being a good doctor. "Becoming a great doctor begins not with what you know, but who you are. Being someone's doctor is about a relationship. That relationship is built on trust," he said. "Being a great doctor begins not with what you have to say, but your ability to listen."

He concluded with what doctors need to be able to say. "First, 'I'm sorry,'" he said. "Things go wrong. Sometimes it's your fault. Sometimes it's nobody's fault. ... Things go wrong. Sometimes the most healing thing that you can do is to acknowledge that by saying 'I'm sorry.'"

The other things doctors need to know how to say include "'I don't know,'" he said. "Being great doctors doesn't mean you have to know everything. You can't. What is the main thing you need to know? The limits of what you know. You can't just say 'I don't know.' Something else has to happen. 'I don't know ... yet. But I will find out.'"

—John Curtis

TERRY DAGRADI (3)

ABOVE Jonathan Belman, Marie Bewley, Adriana Blakaj and Gregory Blanton watch as their classmates don white coats.

TOP RIGHT Deputy Dean Richard Belitsky welcomes students and parents at a reception after the ceremony.

BOTTOM RIGHT The Class of 2010 gathers in the rotunda of the Cushing/Whitney Medical Library for a group photo.

"You are the guardians of your profession," speaker tells new Physician Associates

Twenty-nine students in the Physician Associate Class of 2006 received their degrees at Commencement in September, entering a profession that has grown from small beginnings in the 1960s to more than 60,000 practitioners with their own national and specialty organizations. In his address, Commencement speaker Jerome P. Kassirer, M.D., noted advances in the profession but sounded a note of caution for all health care practitioners, including physician assistants. They face challenges, he said, over conflicts of interest, the influence of the pharmaceutical industry and ethical standards not designed for what he called a "market-driven" health care system.

"What is the antidote to all of these threats? How do we respond as individuals?" asked Kassirer, editor in chief emeritus of the *New England Journal of Medicine*. "The only antidote I know for these threats is professionalism."

He defined professionalism as a combination of technical competence, a commitment to self-improvement and a requirement to use knowledge and competence in the best interests of patients. "You alone," he said, "are the guardians of your profession."

Dean Robert J. Alpern, M.D., Ensign Professor of Medicine, then presented a challenge to the new physician associates.

"I challenge you to strive to be great. There will be many times in your careers when you will make a choice, when you strive to be your best or just try to get by. I hope you will strive to be the best," he said. "You can be smart. You can be hard-working. But you have to care for your patients."

Student awards went to Maura Brennick, M.M.SC., PA '06, who received the Academic Achievement Award, Anne Flitner, M.M.SC., PA '06, who received the Clinical Excellence Award, and Scott McKay, M.M.SC., PA '06, who was given the Dean's Humanitarian Award for his work with the Student-Run Free Clinic.

The Didactic Instruction Award for dedication and excellence in the classroom went to Kalpana Gupta, M.D., M.P.H., assistant professor of medicine (infectious diseases). The Clinical Instructor Award, for a clinical rotation site that provides exemplary clinical teaching, was given to two preceptors in geriatric medicine, Chandrika Kumar, M.D., of Harborside Healthcare Arden House in Hamden, Conn., and assistant clinical professor at Yale Geriatric Services, and Gerard Kerins, M.D., section chief of geriatric medicine at the Hospital of Saint Raphael. The Jack Cole Society Award, for significant contributors who support the physician associate profession, was given to Claire Hull, PA-C, a former academic coordinator of the program who is now at Oregon Health & Science University.

—*J.C.*

JOHN CURTIS (3)

TOP Jerome Kassirer, former editor in chief of the *New England Journal of Medicine*, urged graduates to use professionalism to confront the challenges facing health care practitioners.

MIDDLE Rebecca Pooley, Catherine Rabbitt and Anne Flitner pose for a photo before the Commencement ceremony.

BOTTOM Kolby Vaughan, with his daughter, receives his diploma from Dean Robert Alpern.


ALESSANDRO BIANCHI/REUTERS

Juan Lubroth believes avian flu's real threat to humans is its ability to disrupt people's livelihoods and deny them a source of food.

Avian influenza—it's strictly for the birds

A Yale alumnus who investigates animal diseases for the UN believes a human pandemic is unlikely.

Sitting in his Rome office, gazing at cypress trees and terra cotta rooftops, **Juan Lubroth**, D.V.M., M.PHIL. '92, PH.D. '95, sighs when he hears the words "avian influenza pandemic"—not because he foresees the demise of the human race in a terrifying display of sickness and death, but because he believes that such concerns currently have little merit.

"After over two years of looking at avian influenza, I do not see an imminent pandemic occurring in humans. Yes, we have had a little over 100 deaths in humans attributed to this virus, but this pales in comparison with deaths from other pathogens in humans, such as HIV, tuberculosis and childhood diarrhea," Lubroth said during an interview last spring. And he should know. As the senior officer and head of the Emergency Prevention System (EMPRES) livestock component at the Food and Agriculture Organization of the United Nations since 2002, Lubroth and his team have contained numerous avian influenza outbreaks. From their analysis of the viral sequence, they don't believe we are any closer to a human pandemic.

"Avian influenza needs to be put into perspective. Today, I have an epidemic in poultry, and people's livelihoods and source of protein are at stake. That is my battle right now—in poultry," Lubroth said. To shore up this form of food security, he and his team are trying to teach poultry handlers how to improve their hygienic practices in order to reduce the spread of avian influenza among chickens and, in turn, among humans. These responsibilities fall under Lubroth's mandate to track the international animal trade and ensure that food products are safe and free from such infectious agents as those that cause foot-and-mouth disease, swine fever, Rift Valley fever and avian influenza, among others. Lubroth jokes that he lives in Alitalia—Italy's national airline—given his frequent travels to Thailand, Egypt, Turkey, Vietnam and China.

As a veterinarian, Lubroth is the self-described "black sheep" in a family of architects—his father, grandfather, one of his two brothers, his sister, an uncle and a cousin are all architects. Even his only child, 28-year-old Gregorio, is in his third year at the Yale School of Architecture master's program. Yet during his childhood in Madrid, Lubroth found himself drawn to a different calling. His family's large verdant garden, full of animals, formed a pastoral oasis amidst the high-rises of the bustling city. Born the youngest of four children in 1957, it fell to him to clean up after the family's dogs, cats, chickens and ducks. Lubroth demonstrated an aptitude for caring for animals, and when he was 12 he began volunteering at a local veterinary clinic. As he matured, Lubroth increasingly appreciated the relationship between human health and animal health, and he felt that investigating that link represented an ideal strategy for improving the lives of individuals in developing countries.

To further his education and escape the political unrest in Spain during the transition from the dictatorship of Francisco Franco to democratic rule, Lubroth accepted a scholarship at Whitman College in Walla Walla, Wash., where he studied biology and played on the college's soccer team. At the University of Georgia he earned a master's degree in medical microbiology

and worked as a wildlife biologist. While there he met his wife of 24 years, Adriana, a native of Colombia, at a concert by the B-52's. As he puts it, Lubroth married both Adriana and her young son, Gregorio. Lubroth stayed on at the university to earn his veterinary degree, fulfilling a longtime dream.

Since then, Lubroth's professional pursuits have led him far and wide: to New York to study foreign animal diseases, to Mexico City to prevent foot-and-mouth disease and to Brazil for more studies of foot-and-mouth. Before his appointment to EMPRES, which is based in Rome, Lubroth headed the Reagents and Vaccine Section and Diagnostic Services Section at the Plum Island Animal Disease Center of the U.S. Department of Agriculture in New York. During his travels and many jobs, Lubroth picked up a second master's degree along with a PH.D. from Yale's Department of Epidemiology and Public Health, where he focused his interests in infectious diseases, specifically foot-and-mouth disease.

Through it all, Lubroth's mission has remained the same: "It is my passion to work with developing countries to help with their strife by providing better health, both in animals and in humans." Although his nonstop travel limits his time with his wife and prevents him from weeding through the stacks of articles and files cluttering his office, Lubroth is delighted with his position. "I feel that there is only one medicine, there is only one health. Whether it is environmental or wildlife or livestock, we are dealing with the same world," he said.

—*Kara A. Nyberg*

A road trip in Latin America and a lifelong interest in a debilitating endemic disease

In 1966 a young Harvard graduate with a B.A. in Romance languages and literature set out on a three-month drive through Mexico and Central America. The part-time interpreter for the U.S. Department of State never imagined that his road trip would lead to a career in medical science.

"The culture was fascinating, the poverty oppressive, and I got hooked on Latin America," recalled **Louis V. Kirchhoff**, M.D. '77, M.P.H. '77. In 1967, determined to use his fluency in Spanish and Portuguese to improve lives, Kirchhoff, the son of a Chicago insurance agent, became the lone Peace Corps volunteer in drought-prone Apodi, a Brazilian town without running water, electricity or paved streets.

Kirchhoff set out to demonstrate that vegetables could be grown out of season—a project that would require irrigation. He rented 2.5 acres of land, then organized sharecropper families to build an irrigation system. That led to year-round crops—and income. By the early 1970s, Apodi, in the northeastern state of Rio Grande do Norte, was nicknamed the "Tomato Capital" of the westernmost region.

Despite the agricultural improvements, Kirchhoff recognized that the sharecroppers of Apodi had few options. "They had no access to education, better jobs or even birth control information," he said. Health care consisted of two pharmacists dispensing informal diagnoses and prescription drugs.

"Everyone had parasites, so I got a book on them," recalled Kirchhoff. That's when he learned about Chagas disease, a major cause of morbidity and death in Latin America that is associated with poverty and a semi-arid climate. The Chagas parasite (*Trypanosoma cruzi*) is transmitted when infected reduviid bugs (also known as triatomine or kissing bugs for their habit of attacking the face) gorge themselves on blood drawn from sleeping people and deposit parasite-laden feces near the site of the bite wound. The parasites enter the wound when the victim scratches the bite. Chagas causes debilitating, sometimes fatal, cardiac and gastrointestinal manifestations in 10 to 30 percent of those who have it, even decades after transmission.

Convinced that infectious diseases were the biggest health problem in poor tropical regions, Kirchhoff left Brazil with a reawakened childhood career goal. His Russian-born mother had always urged him to become a doctor, one of her own criteria for success in America. He returned to school and took undergraduate as well as graduate science and epidemiology courses only to discover—at 26—rampant age discrimination at most medical schools. Fortunately,

REX BAVOUSETT

Louis Kirchhoff has spent his career studying Chagas disease and recently developed an assay for screening the U.S. blood supply for the debilitating disease.

Yale admitted Kirchhoff to its M.D./M.P.H. program.

In 1976 he found himself back in Brazil because his thesis advisor, Alfred Evans, M.D., was studying links between Epstein-Barr virus (EBV) and tumors in Brazil. After a lengthy initial interview, Evans asked, "You don't happen to speak Portuguese, do you?"

Kirchhoff spent four months in São Paulo studying a possible Hodgkin lymphoma-EBV link. Collecting and organizing data solidified Kirchhoff's love of research and earned him Yale's Harold Lamport Biomedical Research Prize at graduation.

After a residency in internal medicine at Michigan and a four-year fellowship at the National Institutes of Health's National Institute of Allergy and Infectious Diseases, in 1985 he became an assistant professor at the University of Iowa College of Medicine and began studying Chagas genetics and diagnostics. Between 12 and 14 million people (including about 100,000 residents of the United States) harbor the Chagas parasite; about 25,000 die annually, typically of premature heart disease. Asymptomatic in 70 to 90 percent of cases, Chagas is easily transmitted by blood transfusion. Kirchhoff wanted to develop an accurate seriodiagnostic tool to avoid transmission of the parasite by transfusion.

His appointment in 1990 as associate professor of internal medicine, infectious diseases and epidemiology at the University of Iowa brought him nearer to his goal. "Getting tenure brought more freedom to explore less traditional avenues of academic research, in technology transfer and commercialization," said Kirchhoff. He had already developed a radioimmune precipitation assay, still the gold standard for confirmatory testing, yet slow and complicated to use. With co-inventor Keiko Otsu, he employed recombinant DNA technology to develop chimeric antigens as the basis of a test that is accurate and easy to use.

Last year the company he founded in 1998, Goldfinch Diagnostics, signed a licensing agreement with Abbott Laboratories to use the chimeric antigens as the basis of an automated assay for screening the United States blood supply for Chagas. The assay may eventually be marketed in Latin America as well. And in September Kirchhoff received a national Tibbetts Award for the development of the chimeric antigens.

Settled in Iowa City, Kirchhoff, who is divorced, continues to attend on internal medicine and infectious disease services. His children, Alicia, 29, and Aaron, 26, are both artists. Kirchhoff's favorite pursuits include foreign films, National Public Radio and jogging. (In June, he ran his sixth marathon—in Argentina.)

"I get an enormous sense of accomplishment thinking about what my technology may do," Kirchhoff reflected. "When the automated assay comes to market, it will be very satisfying that I could have an original idea, bang away at it in my lab for 10 years and finally be able to more effectively protect transfusion recipients. I will be delighted."

—*Carol Milano*

Sharing a home, a family and science—two alumni try to make a difference

Jonathan and Bonnie Rothberg share not only a home and family but also a passion for probing the mysteries of the human genome. Together and separately, they attempt both to untangle genetic differences among individuals that can affect disease and to develop novel treatments that target disease at the genetic and molecular levels.

In 1993, when many scientists were trying to decipher the human genome, **Jonathan Rothberg**, PH.D. '91, had a vision: to mine the genome for drug targets. He founded CuraGen, a company that uses information systems, automation and robotics to develop drugs that target specific genes. In the company's early years, Jonathan would bring home sets of newly generated differential gene expression (DGE) profiling data sets and ask his wife, **Bonnie Gould Rothberg**, M.D. '94, M.P.H. '05, to apply her medical background to make sense of the data. By January 1997, midway through her internal medicine residency at Yale-New Haven Hospital and with Jordana, the first of their three children, still an infant, she decided to place her clinical training on hold and assume a full-time position designing and analyzing DGE data. So she joined Jonathan at CuraGen, where she developed a pharmacogenomics program to understand the mechanisms that underlie differing responses to drugs. CuraGen developed five drugs (all in preclinical and clinical development) for treating cancer, the adverse effects of chemotherapy, kidney inflammation and type 2 diabetes.

Bonnie Gould-Rothberg and Jonathan Rothberg share an interest in science and medicine, which they advance through their companies and foundation.

JOHN CURTIS

As CuraGen grew, so did the Rothberg family. The birth of their second child, Noah, in 1999, led Jonathan to start another company. Noah turned blue the night he was born and the doctors had no idea what was wrong. "I wished I could just read off his genome," said Jonathan. "I had a computer magazine with me and I thought that since the computer guys have been able to make things a million times faster and a million times cheaper by putting them on a chip, why not the genome?" Noah quickly turned a healthy pink, but nonetheless Jonathan created a new company, 454 Life Sciences, to pursue his vision of sequencing genomes.

454 Life Sciences is also attempting to reconstruct the genome of Neanderthals, an evolutionary predecessor and possibly a subspecies of modern *Homo sapiens*. "The wonderful thing about the Neanderthal project is that we may uncover the molecular basis for the mind," Jonathan said. Since the genetic difference between modern humans and Neanderthals is only one-twentieth of 1 percent and the main distinction between the two species is largely cognitive, it's possible that just a handful of genes are involved in human brain function.

But that's not the Rothbergs' only project. In 2002, Jonathan formed The Rothberg Institute for Childhood Diseases, a nonprofit organization dedicated to finding a cure for tuberous sclerosis, a genetic disorder that causes benign tumors to grow in the brain and other vital organs throughout the body, as well as cures for other orphan diseases of childhood. With three children under the age of five, Bonnie joined the institute as director of clinical development. Although her medical degree served her well, she felt that she needed formal training in clinical research design and analysis to conduct large-scale clinical research. While earning an M.P.H. at Yale, she rediscovered genomics as a subdiscipline of molecular epidemiology and is now pursuing a doctorate in chronic disease epidemiology. She is working with David L. Rimm, M.D., HS '91, PH.D., associate professor of pathology, using tissue microarrays to find proteins that could serve as prognostic markers for the speed of growth in melanoma tumors. Her work has also come full circle: at CuraGen she participated in the discovery of a drug for melanoma, a disease that she is now studying at Yale, where the drug is currently being tested.

With 25 U.S. patents, work featured on the covers of *Cell*, *Science* and *Nature* and election to the National Academy of Engineering in 2004, Jonathan has moved on to his next project, which he calls the culmination of his life observations. "If you walk into a lab, it's very inefficient," he said. "So I decided that instead of just miniaturizing gene sequencing, why not create a general-purpose machine very much like a computer but that would move chemicals or lab components around?" In 2004, he founded RainDance Technologies to develop a system for testing, profiling or sorting samples used in chemistry, molecular biology and biochemistry on disposable chips. The company expects to ship its first machine, which it calls the Personal Laboratory System, or PLS, in 2007.

Although Jonathan and Bonnie are both fascinated by science, it wasn't their shared academic interests that brought them together. The two met at a party in 1993, but only began dating three months later when Bonnie found an opening in her on-call schedule. They were married in 1995. Jonathan acknowledges that hundreds of dedicated people have helped him turn his groundbreaking ideas into commercial successes. But he recognizes that his most important partnership, in life and in work, is with Bonnie.

—*Jill Max*

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 ymm@yale.edu or write to Faces, *Yale Medicine*, 300 George Street, Suite 773, New Haven, CT 06511.

Aaron Beck

Elizabeth Blackburn

Joseph Gall

Three Yale alumni received Lasker Awards in September for outstanding research in medicine. For 61 years the Albert Lasker Medical Research Awards, among the most coveted in science, have honored scientists, physicians and public servants who have made major advances in the understanding, diagnosis, prevention, treatment and cure of many of the great crippling and killing diseases of the 20th and 21st centuries.

This year's recipients include **Aaron T. Beck**, M.D. '46, who on September 17 received the 2006 Albert Lasker Award for Clinical Medical Research, "for the development of cognitive therapy, which has transformed the understanding and treatment of many psychiatric conditions, including depression, suicidal behavior, generalized anxiety, panic attacks and eating disorders."

Beck is university professor emeritus of psychiatry at the University of Pennsylvania, where he joined the faculty in 1954. His initial research dealt with the psychoanalytic theories of depression, but he subsequently developed a different theoretical-clinical approach that he called cognitive therapy. Since 1959 he has directed research into the psychopathology of depression, suicide, anxiety disorders, panic disorders, alcoholism, drug abuse and personality disorders, as well as the application of cognitive therapy to these disorders. His most recent work has focused on reducing the number of suicide attempts among chronic attempters and patients diagnosed with borderline personality disorder.

The two other Yale alumni to receive Lasker awards were colleagues here in the 1970s.

Elizabeth H. Blackburn, PH.D., FW '77, SC.D.H. '91, the Morris Herzstein Professor of Biology and Physiology in the Department of Biochemistry and Biophysics at the University of California, San Francisco, shared in the Albert Lasker Award for Basic Medical Research. She won the award, along with Carol W. Greider, PH.D., of Johns Hopkins, and Jack W. Szostak, PH.D., of Harvard, for the prediction and discovery of telomerase, an enzyme that contains RNA and synthesizes the ends of chromosomes, protecting them and maintaining the integrity of the genome. Blackburn began her research in this area while she was a postdoctoral fellow at Yale.

Blackburn earned her doctorate from the University of Cambridge in England in 1975 and did her postdoctoral work at Yale from 1975 to 1977 in molecular and cellular biology in the laboratory of another 2006 Lasker honoree, **Joseph G. Gall**, PH.D. '52.

"As a postdoctoral fellow in my lab at Yale," Gall recalled, "Liz identified the short DNA sequence that defines the telomeres, or ends of chromosomes. Later when she and her student, Carol Greider, found the enzyme (telomerase) that adds these sequences to chromosomes, everyone knew immediately that they had made a monumental discovery. Since then, the importance of their discovery has only grown."

Among other honors and awards, Blackburn was named California Scientist of the Year in 1999, elected President of the American Society for Cell Biology for the year 1998 and served as a board member of the Genetics Society of America (2000-2002). Dr. Blackburn is an elected fellow of the American Academy of Arts and Sciences (1991), the Royal Society of London (1992), the American Academy of Microbiology (1993) and the American Association for the Advancement of Science (2000). She was elected Foreign Associate of the National Academy of Sciences in 1993, and was elected as a member of the Institute of Medicine in 2000.

Gall received the Albert Lasker Award for Special Achievement in Medical Science, "for a distinguished 57-year career—as a founder of modern cell biology and the field of chromosome structure and function; bold experimentalist; inventor of *in situ* hybridization; and early champion of women in science." Gall, now at the Carnegie Institution (Department of Embryology at Baltimore), ranks among the most distinguished cell biologists in the history of the discipline.

Among Gall's awards are the 2004 Society for Developmental Biology Lifetime Achievement Award and the 1996 American Association for the Advancement of Science Mentor Award for Lifetime Achievement. In 1988 he received the Wilbur Lucius Cross Medal, the highest honor bestowed by the Yale Graduate School on exceptionally distinguished alumni.

1950s

Eiji Yanagisawa, M.D., HS '59, clinical professor of otolaryngology, received the Presidential Citation from the American Laryngological, Rhinological and Otological Society at its 109th annual meeting in Chicago in May. The award was given in recognition of his contributions to otolaryngology and head and neck surgery.

1970s

Deborah Rose, M.P.H. '77, PH.D. '89, has been selected by the Association of Yale Alumni (AYA) to receive the Yale Medal, the highest award presented by the AYA and conferred in recognition of outstanding service to the university. Since its inception in 1952, the Yale Medal has been presented to 257 individuals, all of whom not only showed extraordinary devotion to the ideals of the university, but also demonstrated their support of Yale through extensive and exemplary voluntary service on behalf of Yale as a whole or one of its many schools, institutes or programs. Rose has served her class as secretary, class council member and reunion chair. Her dedication extends beyond her class to many areas of the university and the surrounding community, including the Sterling Memorial Library, Jonathan Edwards College and the new Rose Center that houses both the Yale Police Department and the Dixwell Community Center.

Kate Lally and Antony Chu

Alejandro Necochea and Lauren Smith

Vicki Shi and Edward Poon

She initiated computerization of the branch libraries of the New Haven Free Public Library. A longtime supporter of Yale's initiatives to help revitalize the city of New Haven, Rose has worked since her earliest days at Yale with community outreach programs through Dwight Hall, the Yale-affiliated student-run public service organization.

Robert E. Steele, M.P.H. '71, PH.D. '75, president of the Association of Yale Alumni in Public Health (AYAPH), has received the 2006 Nathan Hale Award for his efforts in establishing a Nathan Hale Scholarship in 2006, which is being named the Association of Yale Alumni in Public Health Board Scholarship. The scholarship will be awarded to a student in the Department of Epidemiology and Public Health (EPH). Steele has made fundraising one of the top priorities of the AYAPH board. During his presidency Steele has ensured that the EPH Alumni Fund reaches its goal by writing letters, calling alumni, negotiating with major donors and contributing his own funds.

1980s

Christiane Nockels Fabbri, PA-C '84, received a doctorate in history from the Graduate School of Arts and Sciences in May 2006. Her dissertation, a survey of medieval and early modern treatises on the plague, analyzes continuity and change in plague medicine from 1348 to 1599. Fabbri was associate director of the Yale Physician Associate Program from 1991 to 2000, and was voted Distinguished Alumna in 2004. She currently practices family medicine in West Haven, Conn., and continues her research on early modern health care. She and her husband, Remo Fabbri Jr., M.D. '64, look forward to hearing from any alumni visitors when in town.

Justin O. Schechter, M.D., HS '85, assistant clinical professor of psychiatry, has been appointed by Gov. M. Jodi Rell to serve on the Psychiatric Security Review Board (PSRB) in the state of Connecticut. The PSRB is a state agency to which the Superior Court commits persons who are found not guilty of a crime by reason of mental disease or mental defect. The PSRB reviews the status of acquittees through an administrative hearing process and orders the level of supervision and treatment for the acquittee considered necessary to protect the public. Schechter, who has a special interest in forensic psychiatry, has also been appointed an associate fellow of Silliman College.

1990s

Jonathan N. Grauer, M.D. '97, was married in August to **Jane S. Merkel**, PH.D. '00, in New Haven. Grauer is a director of the orthopaedic spine service and an assistant professor of orthopaedics and rehabilitation at the School of Medicine. Merkel is director of chemical genomics at the Center for Genomics and Proteomics at Yale.

Joanne N. Quinones, M.D. '98, **Bryon P. Wenrich**, PA '98, and big sister Elena Sofia proudly announce the arrival of William Carlos Wenrich-Quinones, born December 29, 2005. Quinones is an attending physician in maternal-fetal medicine at Lehigh Valley Hospital in Allentown, Pa., and Wenrich is a cardiothoracic surgery physician assistant at Lankenau Hospital in Wynnewood, Pa. Yale classmates can reach the Wenrich-Quinones clan at jqwenrich@yahoo.com.

2000s

Kate M. Lally, M.D. '02, and **Antony F. Chu**, M.D. '02, were married in July in Bedford, N.H. Lally is an internist at a group practice in Radnor, Pa. Chu is a cardiology fellow at the University of Pennsylvania. Both were Howard Hughes Medical Institute fellows. Lally studied melanoma at the National Institutes of Health and Chu did work in vascular biology at Yale.

Stephanie M. Marticello, M.P.H. '04, was married in June to Christopher M. Poulin in Thomaston, Conn. Marticello works as an epidemiologist with the state Department of Public Health.

Alejandro J. Necochea, M.D. '04, was married on July 1 to Lauren B. Smith, M.P.A., in Philadelphia. Necochea is a third-year resident in internal medicine at the Hospital of the University of Pennsylvania. Smith is a policy analyst fellow with joint appointments at the Robert Wood Johnson Foundation in Princeton, N.J., and the Center for Health and Wellbeing at Princeton University. The two met in Lima, Peru, Necochea's hometown, when he was on leave from medical school to study tuberculosis in shantytowns and she was there on a Fulbright scholarship, studying microfinance, the provision of small loans to women entrepreneurs.

Rahul Rajkumar, J.D. '06, M.D. '06, was married in May to Usha-Kiran Ghia, J.D., in Cincinnati. Rajkumar recently began an internship in internal medicine at Brigham and Women's Hospital in Boston. Ghia began clerking in October for a Federal District Court judge in Boston.

Vicki Shi, M.P.H. '00, manager in strategic marketing for Johnson & Johnson's pharmaceuticals division in New Jersey, was married in August to Edward Poon, M.D., a radiologist also based in New Jersey. Fellow EPH grads who attended included **Sobin Chang**, M.P.H. '97, **Nicole Durbin**, M.P.H. '00, **Scott Durbin**, M.P.H. '99, and **Greg Kruse**, M.P.H. '01.

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John L. Binder, M.P.H. '85, a colonel in the U.S. Air Force, died on September 7 following a battle with cancer. He was 49. A resident of Yorktown, Va., Binder served 21 years in the Air Force, most recently as chief of the Expeditionary Medical Operations Division, Headquarters Air Combat Command at Langley Air Force Base in Hampton, Va. His duties included directing functions for medical readiness operations, providing medical forces and support to planners throughout the world. His career took him all over the world and he served in Korea, Turkey, Germany, Hawaii and the continental United States. As an executive officer at Ramstein Air Base in Germany, Binder was instrumental in the November 1991 repatriation of Terry Waite and Thomas Sutherland, who had been hostages in Beirut in the late 1980s and early 1990s. Colonel Binder recently received the Legion of Merit Medal signifying meritorious and distinguished service.

Charles R. Cavanagh Jr., M.D. '47, died on May 6 In Spokane, Wash. He was 83. Cavanagh served in the Navy Reserve while in medical school and in the Air Force, where he was chief of surgery at Fairchild Air Force Base in Washington. After his military service he formed the Spokane Surgical Group.

William L. Donegan, M.D. '59, died on July 17. He was 73. An academic and athletic standout in high school in Florida, Donegan earned scholarships to Exeter Academy, Yale University and the School of Medicine. He completed his residency at Barnes Hospital-Washington University School of Medicine in St. Louis. At Ellis Fischel State Cancer Hospital in Columbia, Mo., he developed his expertise in surgical oncology. In 1974 he joined the faculty of the Medical College of Wisconsin, where he spent the next 29 years.

Richard K. Friedlander, M.D. '47, died on June 3 in Geyersville, Calif. He was 82. After serving as house physician at the American Hospital in Paris, Friedlander went to San Francisco to train as a psychiatrist at the Langley Porter Neuropsychiatric Institute at the University of California, San Francisco (UCSF). He also worked in emergency psychiatric services at San Francisco General Hospital and the student health service at UCSF. He retired in 1983.

Howard H. "Howdy" Groskloss, M.D. '35, died on July 15 at VNA Hospice House in Vero Beach, Fla. He was 100. While at the School of Medicine, Groskloss also played professional baseball for the Pittsburgh Pirates, from 1930 to 1932. He practiced gynecology for more than 25 years and during World War II he was a Navy flight surgeon.

Terry L. Hatmaker, M.P.H. '74, died on July 30 in High Point, N.C. He was 59. Born in LaFollette, Tenn., Hatmaker grew up in Oregon. He worked at the Center for Life Cycle Analysis (LCA) at Oak Ridge National Laboratory in Tennessee, helping to develop an LCA system for the U.S. Department of Energy (DOE) to assist in making decisions about decontamination at various DOE sites. The LCA system is intended to minimize risks to human health and added insults to the environment.

Jay G. Hayden II, M.D. '66, died on May 20 after a struggle with pulmonary fibrosis. He was 66. An anesthesiologist, Hayden served in the U.S. Air Force at Andrews Air Force Base, then worked at the Lahey Clinic in Massachusetts. In 1982 he moved to Maine and worked at the Maine Medical Center's Spectrum Medical Group.

Gueh-Djen (Edith) Hsiung, PH.D., an internationally recognized virologist and professor emeritus in the Department of Laboratory Medicine, died of cancer on August 20, at Connecticut Hospice in Branford. She was 87. Hsiung was a pioneer in the field of diagnostic virology and known for the techniques she invented to detect and characterize viruses. She authored a landmark textbook, established laboratories and trained generations of new professionals in the field, even into her early 80s. She was also known for her development of animal models to study the pathogenesis and treatment of viral infections. Hsiung was born in Hupei, China, and graduated with a degree in biology from Ginling College in Chengdu in 1942. During World War II she tested bacterial and viral vaccines for use in animals at the Ministry of Public Health in Lanzhou. After the war, she came to the United States and obtained her doctorate in microbiology from Michigan State University in 1951. She applied for admission to medical school at Yale but was told she was too old. Instead she was offered a postdoctoral fellowship in 1953, working under Joseph L. Melnick, PH.D. '39, on poliovirus and related enteroviruses. She joined the faculty the next year and, aside from a two-year sojourn at New York University, spent her entire professional career at Yale.

John K. Joe, M.D., HS '00, assistant professor of otolaryngology, died suddenly on August 8. He was 36. Joe came to Yale in 1995 as an intern in the Department of Surgery and completed his residency in otolaryngology in 2000. After a fellowship at Memorial Sloan-Kettering Cancer Center and an assistant professorship at the Medical University of South Carolina, Joe returned to Yale in 2003 to join the faculty of the Section of Otolaryngology in the Department of Surgery. He rapidly established himself as a premier head and neck surgeon and developed one of the largest head and neck surgical oncology practices on the East Coast. He specialized in treating patients with advanced and complex cancers and offered the highest level of technical and compassionate care.

Frederick F. Krauskopf, M.D. '44, died on August 7 in Florida. He was 87. Born in Germany, Krauskopf came to the United States when he was 5. After a residency at Jackson Memorial Hospital in Miami, he served in a U.S. Medical Corps M.A.S.H. unit in Korea. He subsequently served as chief of surgery at Fort McClellan, Ala., and at the Walter Reed Army Hospital in Washington. He also served as chief of surgery and deputy commander of the Medical Center of the European Theater in Landstuhl, Germany. After serving as chief of surgery at Martin Army Hospital at Fort Benning, he retired to private practice in Stuart, Fla.

Victor A. Machcinski Sr., M.D. '47, died of cancer in West Chatham, Mass., on May 11. He was 82. Machcinski interned at Grace-New Haven Community Hospital and completed a surgical residency at New Britain Hospital. He served in Korea with the U.S. Army Medical Corps and was awarded the Bronze Star. A fellow of the American College of Surgeons, he practiced at Danbury Hospital for 31 years.

Ralph G. Maurer, M.D. '67, died on May 12. He was 62. Maurer served as a major in the Medical Corps, U.S. Air Force Reserve, at the School of Aerospace Medicine in San Antonio. For the last 26 years he was on the faculty at the University of Florida College of Medicine, where he was an associate professor of psychiatry and director of the Center for Autism and Related Disabilities.

Iwao M. Moriyama, M.P.H. '34, PH.D. '37, died on June 10 in Cheverly, Md., of complications from injuries sustained in a fall. He was 97. In 1940 Moriyama joined the U.S. Public Health Service in Washington, where he worked for more than 30 years. He served on the National Committee on Vital and Health Statistics and the World Health Organization's Expert Panel on Health Statistics. During his retirement he spent three years studying health risks from radiation exposure in Hiroshima, Japan.

Richard M. Peters, M.D. '45, died of metastatic melanoma on September 1 at his home in Palo Alto, Calif. He was 84. Peters was born in New Haven, the son of John P. Peters, M.D., a distinguished professor of medicine at the School of Medicine. After graduating, Peters served as a medical officer in the Army, and in 1952 he became assistant professor of surgery and head of cardiothoracic surgery at the University of North Carolina at Chapel Hill. In 1954 he was instrumental in opening the first intensive care unit in the United States for postsurgical patients at North Carolina Memorial Hospital. Eight months later it became the first desegregated ward in the hospital, a precedent that led to the eventual desegregation of the entire hospital. In 1963 Peters' research on pulmonary mechanics led him to recognize the need to use computer and physiology methodologies to collect and analyze pulmonary mechanics and work done on the lungs. He also established a postgraduate curriculum in bioengineering, one of the first of its kind in the country. In 1961 he was elected to the Chapel Hill School Board and was instrumental in desegregating the city's public schools, making it the first totally desegregated school system in the South. In 1969, Peters became head of the division of cardiothoracic surgery and bioengineering at the new University of California, San Diego, School of Medicine. Throughout his career, Peters was very interested in the teaching of medical students, residents and fellows. He served as head of the examination committee for the American Board of Thoracic Surgery and developed the automated system for construction of the written examination. He published 250 articles and a book on respiratory mechanics; was senior editor of five textbooks, including a comprehensive text on cardiothoracic surgery published in China; and was a contributing author to books on pulmonary mechanics, fluid management and thoracic surgery.

Hannah C. Russell, R.N., M.P.H. '60, died on September 13 in Avon, Conn. She was 95. Russell worked as an operating room nurse at Columbia Presbyterian Hospital in New York. She also worked at the Visiting Nurse Association in New Haven. She was an assistant professor of nursing at the University of Bridgeport and a Red Cross instructor during World War II. She was on the Planning and Zoning Commission in Orange, Conn., and served as a state representative in the Connecticut legislature.

Bradford Simmons, M.D. '39, died on July 13 at Marin General Hospital in California. He was 94. An athlete, Simmons played football, rowed crew and was a heavyweight boxer. During World War II he was a Navy flight surgeon, and after the war he practiced at Southern Pacific Hospital, Marin General Hospital and San Quentin Prison. After retiring he served on the ship *Hope* in Brazil, at a Quaker hospital in Kenya, at a hospital in Samoa and on the Navajo Indian Reservation at Shiprock, N.M.

Charles A. Slanetz Jr., M.D. '57, died on June 12 in Locust Valley, N.Y. For 41 years Slanetz practiced general surgery in Glen Cove, N.Y. He also had staff positions at North Shore Hospital and at the University Hospital at Stony Brook, N.Y. His research on colon cancer was published in several journals.

Lester J. Wallman, M.D. '38, died on July 23 in Burlington, Vt., where he lived and practiced medicine since 1947. Wallman was born in New York City and received his undergraduate and medical degrees from Yale. He trained in pathology in Sweden, in general surgery in Delaware and in neurology and neurosurgery in Connecticut. After leaving the U.S. Army in 1946 as a captain, Wallman completed his neurosurgery training in Vermont. He joined the faculty of the University of Vermont in 1948. Wallman was named professor emeritus in 1992. He wrote a chapter in the university's bicentennial history and established the Beaumont Medical History Lecture Series. He also served as chair of the Vermont State Board of Health and on many civic boards, including that of the Vermont chapter of the American Red Cross.

Paul B. Beeson, M.D., and **Robert G. Petersdorf**, M.D. '52, HS '58, are remembered on pages 30–35.

SEND OBITUARY NOTICES TO
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JOHN CURTIS

Ovarian cancer screening to reach patients

Physicians refer to epithelial ovarian cancer as "the silent killer." With few early symptoms, the disease often goes undetected until it has spread to other parts of the body and it's too late for curative treatment. It ranks as the deadliest of all gynecological cancers, claiming approximately three of every four women in the United States diagnosed with the disease. Now a scientific team led by Gil Mor, M.D., PH.D., associate professor of obstetrics, gynecology and reproductive sciences, has found a way to detect the disease in its earliest stages, and has teamed with biopharmaceutical companies to transfer this technology from the bench to the bedside.

In May 2005, Mor and colleagues, in an article in the *Proceedings of the National Academy of Sciences*, showed that abnormal concentrations of four cancer-related proteins—leptin, prolactin, osteopontin and insulin-like growth factor II—in blood samples could indicate the presence of epithelial ovarian cancer with 95 percent accuracy and 95 percent specificity. [See "Biomarkers Warn of a 'Silent Killer'," Autumn 2005.]

Since then they have added two other protein markers and the accuracy rate has risen to 98 percent and the specificity rate to greater than 99.6 percent. This means that only 20 of every 1,000 women screened will be mistakenly diagnosed as being cancer-free, while only four of every 1,000 screenings will yield false positives.

Now the research team is pursuing partnerships with biotech companies throughout the world to develop this technology commercially. Yale recently signed a licensing agreement with SurExam Life Science & Technology Co., a Chinese company founded in part by scientists trained at Yale, and negotiations are under way to license the technology to a new diagnostic company in Israel.

Mor predicts that the test will be available in the United States early this year, following the completion of a pivotal Phase II trial being conducted by the National Cancer Institute in partnership with Laboratory Corporation of America. He hopes that his blood screen will be routinely used to detect epithelial ovarian cancer. "At the beginning, we thought this test may be appropriate only for women at high risk, but we now see this test as becoming a more routine diagnostic for screening," he said.

—Kara A. Nyberg

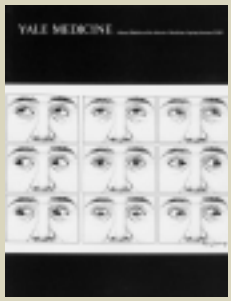
Yale Receives Top Ford Foundation Grant

—Alumni Bulletin

May 1957

"A record-setting grant of $3,600,000 to the Yale School of Medicine from the Ford Foundation was announced in March as part of the Foundation's program to strengthen instruction in the nation's private medical schools. The Ford Foundation is making awards totaling $90,000,000 to the nation's 45 private medical schools. The money is to be held as invested endowment for at least 10 years. The income from endowment may be used for instructional purposes but not for construction or research needs. After the 10-year period, Yale and the other recipient medical schools are free to use the principal sum as well as endowment income. ...

"Dean [Vernon W.] Lippard, in commenting on the Ford Foundation award, said: 'This is the largest gift ever received by the Yale School of Medicine. Its importance is not related to its size alone but rather to the fact that it is designated for unrestricted endowment. The income will be used in support of the basic operation of the school and improvement of its educational program. Yale will be forever grateful to the Ford Foundation.' "



"The Move" Into New Patient Care Facility

—Yale Medicine

Spring/Summer 1982

"The first patients moved into the Yale-New Haven Hospital's new seven-story patient-care facility on April 21, culminating nearly 20 years of planning and three years of construction. The enormous task of moving patients, staff and equipment from the outmoded New Haven Unit and parts of the Memorial Unit was launched amid balloons, flowers and a spirit of festivity in the pristine, attractive new facility. ...

"The $73 million project replaces outdated facilities located across the street in the New Haven Unit with a modern, comfortable and integrated patient-care area. The project also includes renovation of the childbirth facilities in the Memorial Unit.

"The building has enabled the Hospital to consolidate the departments of radiology, pediatrics, the operating rooms, admitting and discharge offices and the cafeterias. The new emergency room located on the first floor has doubled in size. Patient rooms on floors five through seven have been designed with privacy and comfort in mind."

"A SURGERY TO PREVENT HIV"

Since Kyeen Mesesan, an M.D./PH.D. candidate at the School of Medicine, began her dissertation project in South Africa in 2003, she has received accolades and invitations to present at conferences. But nothing was quite like the 16th International AIDS Conference in Toronto in August, where she presented a paper on adult male circumcision programs and HIV.

"I had an idea it would be a bit contentious," said Mesesan. "We're talking about a surgery to prevent HIV." Indeed, activists at the conference raised pointed questions about genital mutilation, race and gender. But the idea has gained currency as the notion of a single magic bullet against AIDS gives way to multiple measures to prevent HIV infection.

Circumcision was not originally part of Mesesan's research—she was exploring a hypothetical question. "What does a country like South Africa do 10 years from now if a partially effective vaccine comes out—say 30 percent effective—and they have to decide whether they're going to use it on their population?" she asked. Mesesan put this question in the context of other risk factors, such as sexual behavior and condom use. "Although in most scenarios such a low-efficacy vaccine would be beneficial, in some scenarios you could actually make the epidemic worse."

Her research took a detour in July 2005 when, in a study in South Africa, French researchers linked male circumcision to a 61 percent reduction in female-to-male transmission of the virus. Mesesan took that number and, applying statistical modeling techniques, estimated that in the township of Soweto, a five-year prevention program that boosted the current 35 percent circumcision rate by 10 percent would prevent 53,000 infections.

"While even a low-efficacy HIV vaccine may be decades away, circumcision is effective and the technology is available immediately," Mesesan stated. In December trials in Kenya and Uganda showed that circumcision reduced the risk of AIDS from heterosexual sex by half.

—John Curtis

JOHN CURTIS

Kyeen Mesesan used statistical modeling to determine how many new HIV infections adult male circumcision could prevent in a township in South Africa.

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2002	5th

Yale School of Medicine Alumni Reunion Weekend

Reminisce with classmates.
See what's new.
Stroll down Cedar Street.
Reconnect.

Classes ending in 2 and 7 will be holding special celebrations this year.
All alumni are welcome to attend Alumni Reunion Weekend.
To learn more about this year's program, please call (203) 436-8551
or visit ourwebsite at http://info.med.yale.edu/ayam