


yale medicine

spring 2002



reinventing surgery



ON THE COVER

Robert Udelsman's arrival at Yale last June as chair has focused major attention on the Department of Surgery. Recruited from Johns Hopkins, where he helped develop new techniques for thyroid and parathyroid surgery and made laparoscopic adrenalectomy standard, Udelsman has set his sights on making the department one of the world's leaders. Page 16

Cover photograph by
Sean Kernan

SPRING 2002

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This season on the Web
info.med.yale.edu/yymm

Explore the following topics in greater depth by visiting our website and selecting EXTRAS:

- Surf the Janeway and Medzhitov lab websites and learn more about innate immunity. Pay a virtual visit to the Howard Hughes Medical Institute.
 - Visit the AYAM and learn about Reunion 2002 (and view photos from 2001 reunions). See which of your classmates are coming to Alumni Reunion Weekend on June 6 to 8.
 - View additional photos from the second-year show, *O Doctor, Where Art Thou?* and recent alumni events.
- On the website, readers can submit class notes or a change of address, check the alumni events calendar, arrange for a lifelong Yale e-mail alias through the virtual Yale Station and search our electronic archive.

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ANOTHER LESSON FROM ANTHRAX

Yale Medicine's roundtable on bioterrorism was an encouraging take on a very discouraging subject ("Lessons from Anthrax," Winter 2002). It was particularly heartening because so much care has gone into thinking about how to deal with the possibility of great tragedy.

The big issue that those interviewed skirted, however, was the politics of coercion in public health policy. This is an old issue within public health, certainly. But it becomes much more salient as discussions proceed about mass vaccination for diseases such as smallpox and anthrax, either before or during an epidemic.

Under what circumstances would it be permissible for the federal or state governments to require vaccination for such diseases? Right now, most public health authorities are advocating only "ring vaccination" in case of an outbreak of smallpox. And even Anthony Fauci has eloquently written in a recent issue of *The New England Journal of Medicine* that the formulation of smallpox vaccination policy must proceed through democratic dialogue.

But how will we balance the often-competing values of democracy and authority, coercion and informed consent, in the midst of a bioterror crisis?

One thing is certain: we need to begin to reflect on these matters now, not during such an episode. The time to begin is now, and our discussions must include ordinary citizens as well as public health elites.

ROBERT JOHNSTON
ASSOCIATE PROFESSOR OF HISTORY

A SLIGHT FOR SORE EYES?

Apropos of the letter from John Mahoney, M.D. '00, in the Winter 2002 issue, I'm gratified that he, as a young person, pointed out the difficulty of reading the small print in the magazine. The magazine itself is very attractive, but we needed a magnifying glass to read much of it. Also, in our age group many of us have painful arthritis in the hands, and the stiff cover as well as stiff binding and stiffer (than in old format) pages make it hard to turn the pages. Miserere nobis....

Thanks.

LAURA NEVILLE, M.D. '46
JOHN NEVILLE, M.D. '46
COTUIT, MASS.

Amen, amen and amen to John Mahoney's comments regarding the size of the print in *Yale Medicine*. On the other side, thank you for using adequate contrast between the print and the colored background.

EDNA MAY KLUTAS, M.P.H. '57
NEWVILLE, PENN.

GOOD NEWS, BAD NEWS

We found ourselves on the receiving end of a brief flood of opinions this spring from readers who found our new typeface too small. "Your format is great—it will win awards, but not from your senior readers. One needs a magnifying glass to read it," wrote George R. Barnes, M.D. '47, HS '50, of Tucson, Ariz., one of a half-dozen readers who weighed in on the topic.

Dr. Barnes was right on both counts. In April, Yale Medicine won the silver medal for best magazine and bronze medal for Visual Design in Print from the 23,500-member Council on Advancement in Support of Education. The category in which we were judged was special-interest magazines, which includes entries from graduate and professional schools nationally. These honors follow the Award of Excellence granted last November by the Association of American Medical Colleges, the group's highest level of recognition. But regardless of these glories, it is also true that Yale Medicine is hard to read for many in our audience. To address this, we are tuning up the type for better legibility in time for the Summer issue.

HOW TO REACH US

Yale Medicine welcomes news and commentary. Please send letters to the editor and news items to *Yale Medicine*, P.O. Box 7612, New Haven, CT 06519-0612, or via electronic mail to yymm@yale.edu, and include a daytime telephone number. Submissions may be edited for length, style and content.

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FROM THE EDITOR**Feedback mechanism**

Two years ago, the spring issue of *Yale Medicine* included a feature story on an initiative by Dean David A. Kessler, M.D., to review the curriculum and examine the larger questions surrounding medical education at the start of the 21st century. The magazine also featured an interview with the school's new education dean, Herbert S. Chase Jr., M.D., and a collection of alumni essays titled "Eight Decades of the Yale System." Several issues earlier we had invited alumni to reminisce about what the Yale System meant to them and to their generation. The response we received was overwhelming, as was the obvious affection nearly every alumnus and alumna appears to have for the Yale System.

This past February, a new generation of Yale scholars brought the topic into focus once again with a statement and petition, mailed to alumni, seeking to prevent proposed changes to the second-year testing format. The nine medical students who circulated the petition felt that requiring certain qualifying exams was incongruous with the Yale System, conceived in the 1920s by then-Dean Milton C. Winternitz, M.D. His vision was to give students freedom to pursue knowledge in a graduate-school-like environment by eschewing grades, class rankings and required exams in favor of close mentoring relationships between students and faculty and the completion of a thesis based on original research.

The proposed second-year qualifiers have since been dropped, but not before the issue elicited a huge response from alumni. From their mailing to more than 4,000 addresses, the students received well over 400 replies, many echoing Stanford oncologist William M. Rogoway, M.D. '61, who wrote: "The freedom to chart one's own course with support and encouragement along the way (and few inhibiting rules) is a model for a professional career."

As a course director at Columbia P&S in the mid-1990s, Chase lobbied for the abolishment of grades for the first- and second-year courses, and he came to New Haven excited about Yale's emphasis on intellectual independence. He thinks there are other, more serious threats to the Yale System: the incursion of managed care into teaching time, class sizes that are too large, an overstuffed schedule and incapacitating student debt. In response, the faculty has increased the number of small-group discussions and reduced class hours and the total number of qualifying exams. Chase is working on ways to boost financial aid and the rewards for teaching.

Following our initial coverage in 2000, we planned to revisit this topic as it evolved and will do so in depth in an upcoming issue. The intense interest of both current students and alumni reinforces the view that the Yale System is not only central to the experience of Yale medical students but also that it is here to stay.

Michael Fitzsosa

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JOHN CURTIS

Pete Kenyon survived longer than any other American—three years—on a device that replaced the diseased left side of his heart. After a successful heart transplant in January, Kenyon, shown with his wife, Kathy, returned to the medical center for a checkup in February.

WAITING FOR A HEART, BROKER BEATS THE ODDS

A Connecticut man sets record for survival on heart pump and receives a gift of life.

In his 63 years Robert “Pete” Kenyon has been a Navy officer, an amateur race car driver and, most recently, a reinsurance broker. As someone who makes his living assessing risk, he surely knew the odds as he reached a difficult milestone last year. In August, he became the longest-surviving recipient in the United States of a mechanical pump that replaced the diseased left side of his heart.

At that point he had lived three years on the pump, the outer limits of the manufacturer’s warranty. Novacor’s left ventricular assist system (LVAS) remained in place because none of more than a dozen hearts offered to Kenyon from the organ sharing network had been immunologically compatible.

“We were getting increasingly concerned communications from the engineers at Novacor,” said John A. Elefteriades, M.D. ’76, Hs ’83, who implanted the device. By October Kenyon’s physicians decided the pump should be replaced. “The machine was making a lot of abnormal noises, and it was misfiring,” Kenyon said.

He prevailed upon the doctors to wait until the Christmas holidays, when his chances of getting a new heart would increase. On New Year’s Eve, Kenyon went into the operating room, where an expected problem turned out to be even worse than imagined. “The LVAS had been in such a long time that the body’s fibrous tissue had virtually encased it,” Elefteriades said. The device

was replaced with an identical, semi-permanent pump.

In a fateful turn of events, another donor heart became available 36 hours later—and this time it matched. Despite having just undergone the ordeal of surgery to implant the new LVAS, Kenyon seized the opportunity. “Dr. Elefteriades felt I was strong enough to undergo surgery, so off we went,” Kenyon said.

From the moment of the donor’s death, a deadline loomed. For the transplant to succeed, the donated heart had to be pumping in the recipient’s chest within four hours. Fortunately, the surgeons had freed the three-year-old LVAS from his tissue the day before. “I do not think we could have gotten everything out fast enough for the heart to be viable,” Elefteriades said.

Three more surgeries followed the heart transplant. A lung infection had to be treated, a pacemaker was installed and Kenyon’s gall bladder had to be removed.

After recuperating from five surgeries in the space of a few weeks, Kenyon is back at work part time, telecommuting from his home office in Darien. “I usually get tossed out of bed at nine o’clock in the morning,” he said with a grin at his wife, Kathy, during an interview in February. “I go down the hall to my office and do my office work. My wife doesn’t like me sitting there for hours at the computer. She wants me up and around. I’m trying to walk as much as possible. I’ll take a nap and read. My appetite is coming back but I can’t eat the quantities of food that I used to.”

He plans to return to a childhood sport learned on frozen ponds—ice hockey. The man whose heart now beats inside Kenyon’s chest was a 30-year-old hockey coach from the Boston area who died of a brain aneurysm. “I want to thank the donor’s family for giving me the gift of life,” Kenyon said.

EVEN AFTER HIS DEATH, A SKEPTIC INSPIRES A LEGION OF SCHOLARS

Alvan R. Feinstein, M.D., HS '54, joked in his 400th scholarly article that he hoped to continue writing until he faced "the ultimate rejection, by adverse pathophysiology." When Feinstein did die in October—at age 75, while participating in the Gairdner Foundation conference in Toronto—his former student, Peter A. Singer, M.D., M.P.H., found himself taking Feinstein's place on the podium. Instead of listening to Feinstein speak, Singer delivered a eulogy.

The first part of Singer's tribute was what one might expect: He described Feinstein's leadership in establishing the field of clinical epidemiology, in which researchers use scientific principles to study decisions about patient care—what one colleague called "conducting research at the bedside." And he spoke of Feinstein's "pattern of challenging orthodoxy." But then Singer did something unusual: he quoted a comment Feinstein had written on a manuscript that Singer sent him.

"I don't think your writing is actually bad," Feinstein wrote to Singer, the Sun Life chair in bioethics at the University of Toronto. "After you fixed the tone and removed most of the sociobabble in this manuscript, the paper could be understood despite its prolixity, verbosity, and subadequate inter- and intrasentence structure."

That Singer would affectionately recall the man who offered such criticism reflects Feinstein's mystique: he had almost impossibly high standards and never minced words, yet his students deeply valued his guidance. Many of those students were young physicians

Feinstein supervised as founding director of the Robert Wood Johnson Clinical Scholars Program at Yale, which since 1974 has provided two years of post-residency training in research.

Although Singer now studies bioethics rather than the clinical epidemiology in which he immersed himself as a clinical scholar from 1988 to 1990, he says he uses what Feinstein taught him every day. "He didn't teach us only clinical epidemiology. He taught us how to think," said Singer in an interview. He said Feinstein also imparted to students "a fundamental irreverence for scientific authority and established beliefs. ... He was one of the giants of 20th-century American science. It was really an honor to be able to learn from him."

The core values that Feinstein established for the clinical scholars program will endure, said Ralph I. Horwitz, M.D., a program scholar from 1975 to 1977 and now chair of internal medicine at the School of Medicine. The scholars—four to five are admitted each year—will continue to study quantitative methods in depth, to think critically not only about methodology but also about the merit of research questions themselves, and to work closely with faculty mentors, said Horwitz, co-director of the program with Harlan M. Krumholz, M.D.

Second-year scholar Thomas M. Morgan, M.D., said that he and fellow scholars learn to recognize hidden assumptions underlying research and to find limitations to methodology. "They want us to be able to think critically about the techniques used rather than just to be able to plug numbers into a computer and get results," said Morgan. "We deconstruct research and try to build it up from the rubble." He said the scholars are taught to evaluate whether a question is even worth studying. "The difference between good research and great research, as defined by the mentors of this program, is determined by the quality of the question."

The clinical scholars program is at a crossroads now: Yale faces unprecedented competition in seeking renewed

funding for the 28-year-old program, because The Robert Wood Johnson Foundation will reduce training sites from seven to four beginning in 2005. To win a grant, Yale must successfully argue that its program not only ranks among the best four programs but also outflanks new competitors from top-ranked schools. Lewis Sandy, M.D., the foundation's executive vice president, said it decided to fund fewer sites for two reasons. First, although the clinical scholars program was unique in 1974, other fellowships now provide similar training. Second, the foundation hopes that through consolidation it can provide more in-depth training in clinical epidemiology and health services research, with an option to extend the fellowship for as long as six years.

Whatever the future of Yale's program, Singer believes that Feinstein's model for rigorous research and his "unswerving devotion" to training his students will have a lasting effect. More than 100 clinical scholars studied with Feinstein. Those men and women, said Singer, compose Alvan Feinstein's "living legacy."



Alvan Feinstein (right) plays guitar during a performance of the Beatles song "Let It Be" at Commencement in 1991, accompanied by Robert Gifford, then dean of students. They had previously performed their rendition at the Class of 1991's second-year show.

YALE GROUP LAUNCHES NEW EFFORT TO UNDERSTAND WHY ORGAN TRANSPLANTS FAIL

By 11 a.m., Yinong Wang, M.D., is performing his fifth transplant procedure of the day. Each one is the same, and not what you would expect: Prepare a snippet of blood vessel from a donor patient and slip it into the aorta of the anesthetized recipient. Suture and close. Repeat.

Though Wang is indeed a surgeon, it would be misleading to call these recipients patients. They are mice. The delicate suturing is part of a long-term study to determine why coronary arteries narrow over time and become blocked. By using so-called severe combined immunodeficiency (SCID) mice that have been bred without the genes necessary to create T and B cells, the study's designers are able to introduce immune cells from one human and see how they interact with the blood vessels of another. A week after the microsurgery, the study team will introduce T cells and macrophages from the second human into the mouse's circulation, then watch for signs of inflammation in the transplanted artery. It's a model that mimics the real-life battle that occurs after the transplantation of a heart, kidney or liver and which can speed the rejection of the organ. Wang, along with George Tellides, M.D., HS '93, Marc I. Lorber, M.D., and Jordan S. Pober, M.D. '77, PH.D. '76, HS '78, is interested in seeing how the cytokine interferon gamma may affect that interaction.

The SCID-mouse model for inflammation is one way Yale scientists are exploring common ground between the basic science of the vessel walls and the clinical problems of organ transplantation. Their efforts were formalized at the medical school in 2000 with the establishment of the Interdepartmental Program in Vascular Biology and Transplantation (vBT), a working group of 24 scientists and physicians in 10 departments.

"Our goal is not to become the world's largest transplant program but

to change the ways that transplantation is being done," said Pober, the program's director.

vBT has succeeded in attracting new support from the NIH in the form of a \$6.4 million program project grant, and is embarking on a collaboration with Cambridge University funded by Britain's Medical Research Council. The Interdisciplinary Program in Clinical Transplantation (IPCT), the vBT's companion program, also received \$2.5 million last year in the first round of funding from the Yale-New Haven Medical Center's new Clinical Program Development Fund. More than a dozen visiting scientists have presented their work in the program's seminar series.

The science in this area is promising, and that's a good thing. With long waiting lists for organ transplants (4,323 people died last year waiting for a heart, lung, kidney, liver, intestine or pancreas) and a shortage of donors, transplant physicians are eager to find new ways of protecting those scarce organs that are available.

The new generation of immunosuppressive drugs that emerged during the past decade has greatly reduced the threat of acute rejection immediately following a transplant. Solving the problems of chronic rejection, which leads to the failure of transplanted organs within the first year, is the next step in the effort to reduce demand and stretch supply. Creating a new source of organs through the creation of engineered pig organs, or xenografts, is another. Yale scientists are working in both areas, as well as searching for ways to create artificial tissues or synthetic skin to improve graft viability.

Applying the rapidly unfolding science of immunology to clinical problems will make a huge difference, said Lorber, director of the IPCT. "Most organs that fail do so not because of the failure of immunosuppression in the early post-transplant period. Rather they fail over a period of months to years from the process of chronic rejection," said Lorber. "We believe that understanding this process may dramatically

improve the long-term outlook." Toward that end, the group's research is focused on the possibility that chronic rejection may result from an attack by the immune system on the blood vessels, Lorber added. The same process that causes coronary artery disease and heart attacks may be similar to the events leading to chronic organ rejection.

Hence, the group's interest in SCID mice and the "vascular remodeling" they've observed in the studies of transplanted vessels. After doing more than 100 of the procedures, they reported last May in *Nature* that interferon gamma actually contributed to a thickening of the vessel wall and sped the division of smooth muscle cells, contrary to the conventional wisdom. Both factors contribute to the narrowing of the arteries that supply blood to transplanted organs.

For Tellides, chief of cardiac surgery at the Veterans Administration hospital in West Haven, the finding is an important step. "By knowing which molecules exacerbate vascular disease, we can improve diagnosis and eventually treatment," he said. "Right now we can only bypass the blockages."



Surgeon Marc Lorber (left) accepts a kidney from colleague Amy Friedman during a transplant procedure at Yale-New Haven Hospital. The medical school and hospital have launched new programs to speed the translation of scientific knowledge to benefit transplant recipients.

ALCOHOL AND THE BRAIN

Since the 1950s, when Yale scientist E.M.Jellinek pioneered the notion that alcoholism is a disease, investigators have discovered links between certain genes and problem drinking. Now, with a \$9 million grant from the National Institute on Alcohol Abuse and Alcoholism,investigators at Yale, the University of Texas and Columbia University will explore the biochemistry of a brain circuit that appears to make some people more likely to become alcoholics; they will also look for ways to apply that knowledge to the treatment of the disease. “With new imaging tools to look at brain chemicals, and molecular genetics studies, we now have an opportunity to observe broad clinical implications from molecular neuroscience,”said John H. Krystal, M.D. ’84, HS ’88, the Albert E. Kent Professor of Psychiatry. Krystal, the principal investigator on the five-year grant,said it will fund the new Center for Translational Neuroscience of Alcoholism at Yale.



JOEL NAKAMURA

et cetera

CLEAR GUIDANCE ON CONFLICTS

Since the Bayh-Dole Act of 1980, technology transfer has brought thousands of academic inventions to the private sector. For almost as long, universities have struggled with the conflicts of interest that could arise if investigators held a financial stake in the outcome of their research. When an Association of American Medical Colleges task force issued guidelines on conflicts of interest in December, it all but ruled out participation by scientists who might profit from the research. The panel, which included Yale Vice President and General Counsel Dorothy K. Robinson, urged institutions to presume that individuals with a financial interest in a clinical study may not conduct it and to enforce that view through close scrutiny of research proposals. “Transparency,” the task force members agreed, “must be the watchword.”

COMMUNITY MINDED

Libraries at the School of Medicine have teamed up with the New Haven Free Public Library to offer health information to the public. Located at the main public library on Elm Street and three branches throughout New Haven, the Consumer Health Information Center (CHIC) will provide workstations with computers, consumer health books and access to health resources on the Web. The partners in the CHIC are the public library, the School of Medicine, the Harvey Cushing/John Hay Whitney Medical Library and the Epidemiology and Public Health Library. A \$43,885 grant from the National Network of Libraries of Medicine will fund the program for 18 months.

SIGN OF COMPASSION

Emotions have a legitimate place in the practice of medicine, according to Associate Dean for Student Affairs Nancy R. Angoff, M.P.H. ’81, M.D. ’90, HS ’93. Writing in *JAMA: The Journal of the American Medical Association* last fall, Angoff reported that of 182 Yale students surveyed, 133 said they had cried at least once during their first year of clinical rotations. Thirty had been on the verge of crying and only 19 said they didn’t cry even once. In her *JAMA* essay, “Crying in the Curriculum,” Angoff wrote that “medical educators who fail to look for or listen to stories of crying may be missing an opportunity to have an impact on students’ emotional [development as doctors]. ... We should let [students] know that not only is it normal and okay, but it may be a sign of a valuable capacity for compassion.”

WAR AND ITS IMPACT ON AMERICAN HEALTH

For veterans who witnessed combat, there's more to look for than PTSD, new analysis of health outcomes finds.

For American society, the war in Vietnam was unlike any other. It spawned widespread protests, a questioning of the nation's role in the world and, in the medical field, a new diagnosis. Society, as well as medicine, recognized that soldiers could not go from fire-fight to firefight without psychological consequences. What had once gone by the names "shell shock" and "combat fatigue" got a new name. Post-traumatic stress disorder (PTSD) was what happened to people who had fought for their lives and seen their

comrades die. But it was just one of the many consequences of surviving battle.

Years after soldiers came home, the ghosts of combat haunted them in the form of not only PTSD but also divorce, depression, drug and alcohol abuse and domestic violence. These lingering effects of combat have affected society as well as individual soldiers, according to epidemiologist Holly G. Prigerson, PH.D., FW '91. How, she asked, do the experiences of combat veterans burden society as a whole? "No one had looked at societal outcomes," said Prigerson, an associate professor of psychiatry and of epidemiology and public health.

Using as her database interviews with about 2,500 men between the ages of 18 and 54 from the 1992 National Comorbidity Survey, which examined psychiatric

disorders in the United States, Prigerson focused on the roughly 7 percent who had seen combat, mostly in Vietnam. "How are these vets doing now?" Prigerson asked. "The answer is, not very well. And these are not just the vulnerable few." Prigerson noted that the survey did not single out men who reported problems stemming from combat. "They just asked: 'Did you witness combat?'"

The numbers of respondents with psychiatric problems and other adverse outcomes, Prigerson found, were "really huge. We were struck by the magnitude of the effects this long after combat." And men who avoided developing PTSD were not off the hook: decades later, even without suffering from PTSD, combat veterans were significantly more likely than noncombatants to lose jobs, to divorce and to abuse drugs or alcohol. "Our findings," said Prigerson, "have important implications for the thousands of Americans now involved in military strikes against Afghanistan. Depending on what the soldiers there see and do, their lives may be disrupted for longer than they may anticipate."

Prigerson's analysis showed that a significant portion of societal problems

FIRST THE STUD, THEN THE SEQUELA

At last, the news that horrified parents everywhere have been waiting for: piercing certain parts of one's anatomy might not be so healthy. Last year, Yale physicians Richard A. Martinello, M.D., and Elizabeth L. Cooney, M.D., linked a young woman's brain infection to the tongue-piercing she received a month earlier. "The bacteria that caused the abscess in this patient were those typically found in people's mouths," said Martinello. A few days after the piercing, the patient's tongue was swollen and tender and produced a foul-tasting discharge. The symptoms cleared up after she removed the jewelry, but a month later she presented with headaches, fever, nausea and vomiting, and a CT scan showed an abnormality in her brain. Six weeks of treatment with intravenous antibiotics led to a full recovery. The physicians presented the case at the annual meeting of the Infectious Disease Society of America in October.



HENRIK DRESCHER

could be linked to combat exposure. In the year preceding the survey, combat veterans accounted for 7.4 percent of major depression nationally, 8 percent of substance abuse and 27.8 percent of PTSD. They accounted for 21 percent of current spouse abuse, 8.9 percent of unemployment and 7.8 percent of current divorce or separation.

Compared to other men in the study, a combat veteran was six times as likely to be suffering from PTSD, more than twice as likely to be suffering from recent major depression or substance abuse and more than twice as likely to be separated, divorced or unemployed. The likelihood that he had lost a job in the past year was almost triple the norm and that he'd abused his spouse, more than quadruple.

Combat veterans, Prigerson said, "have assumed huge risks. Recognizing what the outcomes of war are likely to be can help policy makers determine how to help them reintegrate into society as civilians." When a veteran does not show signs of PTSD, she said, "The assumption shouldn't be that everything's well and good."

Results of Prigerson's study appeared



AP/WIDE WORLD PHOTOS

in the January issue of the *American Journal of Public Health*. Co-investigators were Paul K. Maciejewski, PH.D., associate research scientist in psychiatry, and Robert A. Rosenheck, M.D., HS '77, professor of psychiatry and of epidemiology and public health.

Exposure to combat scenes such as this, near Hue, South Vietnam, in 1968, increases the chances of psychological problems and other adverse outcomes later in life. "Our findings," said principal investigator Holly Prigerson, "have important implications for the thousands of Americans now involved in military strikes against Afghanistan."

et cetera

NO LAUGHING MATTER

A new study suggests there might be something to the notion, first proposed by physicians in ancient Greece, that seasonal mood swings are caused by "humors." According to Yale investigators, patients with seasonal affective disorder (SAD) have lower nocturnal levels of the bile pigment bilirubin. The study is the first scientific investigation of circadian levels of bilirubin in the blood of people with depression. Psychiatrist Dan A. Oren, M.D. '84, HS '88, and colleagues found that nighttime bilirubin levels were lower in nine patients with SAD, compared to a group of seven healthy volunteers. The patient group's levels of bilirubin increased after exposure to a light source, a standard therapy for the disorder. The article was published in the March 1 issue of the journal *Biological Psychiatry*.

COCAINE VACCINE ADVANCES

Scientists at Yale are exploring a new method to help cocaine users stay clean and sober. A vaccine that produces antibodies that dull the cocaine high has been found safe in a phase I clinical trial, according to a report in the January 15 issue of the journal *Vaccine*. The vaccine, TA-CD, is recommended for people who are already trying to kick the habit. "We found that the vaccine is safe and that there is no significant toxicity," said principal investigator Thomas R. Kosten, M.D., HS '81, professor of psychiatry, who is testing the vaccine for Xenova Group plc. of Cambridge, England, which owns and is developing the compound. Subjects who received the highest dosages also produced the most euphoria-depressing antibodies.

A BOOST FROM NICOTINE

Why do so many patients with schizophrenia smoke? It may be because nicotine improves one aspect of cognitive function and helps compensate for other brain impairment associated with schizophrenia. "This is one of only a few studies to suggest that nicotine has a beneficial effect on spatial working memory, which is known to be impaired in schizophrenic patients," said principal investigator Tony P. George, M.D., who published findings in the journal *Neuropsychopharmacology* in January. Smokers without schizophrenia did not show an improvement in spatial working memory, and in fact, nonschizophrenic smokers had an impairment of this cognitive function, which improved when they quit smoking.

A LIVELY DEBATE ABOUT THE BRAIN'S CAPACITY FOR RENEWAL

Two competing views of neurogenesis are played out in the pages of *Science*.

Neurogenesis, an arcane and complex issue, has leaped out of scientific journals and conferences in the last few years to land in the pages of newspapers and magazines, including *Newsweek* and *The New Yorker*.

The source of this growing interest is an ongoing debate over the brain's ability to generate new neurons in the cortex. Pasko Rakic, M.D., Ph.D., the Doris McConnell DuBerg Professor of Neuroscience and chair of the Department of Neurobiology, believes that the neocortex of primates, including humans, gets

its lifetime share of neurons during development and shortly after birth.

Elizabeth Gould, Ph.D., a professor of psychology at Princeton, has published studies asserting that primates generate neurons in the neocortex well into adulthood.

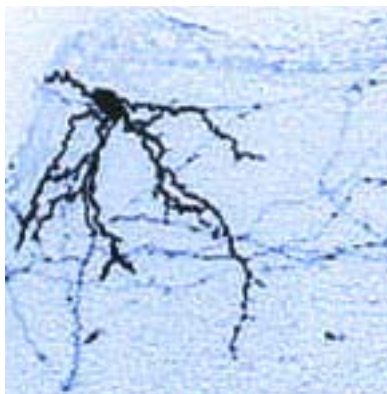
The two camps have reached such different conclusions using largely the same experimental design, but with variations in their techniques and criteria for identifying new cells. Each publication on the topic rekindles the debate.

Rakic fired the latest salvo in the December 7 issue of *Science* when, with colleague David R. Kornack, Ph.D., his former postdoc who is now at the University of Rochester, he reported that Gould had indeed found new cells in the neocortex. They simply weren't neurons. Instead, reports Rakic, Gould

mistook glial and endothelial cells for neurons.

"Our study shows that neurons of the cerebral cortex are created in a precise sequence during restricted periods of development before birth and during the neonatal period," Rakic said. "Therefore we have to live our entire lives with the cortical neurons we are born with."

With a preponderance of evidence in its favor, this view has dominated study of the brain since the 1980s, when Rakic published his findings after conducting lengthy studies of macaque monkeys. Subsequent studies with new labeling techniques found evidence of neurogenesis in other parts of the mammalian brain—the hippocampus and the olfactory bulb. But neurogenesis in the neocortex remains a controversial topic.



T. GRUDT ET AL.

A LINK FROM SLEEP TO PAIN

A neuropeptide whose absence may be a factor in sudden sleep attacks also appears to modulate pain. A team that included Anthony N. van den Pol, Ph.D., professor of neurosurgery at Yale, and colleagues at the University of North Carolina, found that hypocretin neurons provide a biochemical link from the hypothalamus—which regulates eating, drinking, sleeping, waking, body temperature, chemical balances, heart rate, hormones, sex and emotions—to the spinal cord. "We found that most cells in a region of the spinal cord responsible for detecting pain (pictured at left) show a significant physiological response to the peptide hypocretin-2," said van den Pol, a co-author of the study published in the January issue of the *Journal of Physiology*. New drugs related to hypocretin, which plays a role in narcolepsy, could help in the treatment of pain.

Gould insists she has found new neurons in the cortex. Like Rakic, she used the thymidine analog BrdU, along with other markers that would stain new cells. And she said she has factored in the possibility of false positives. When viewed through a confocal microscope and rotated, she said, it's clear that the cells she found are neurons. Rakic counters that BrdU labeling, although essential to identify new cells, is not by itself sufficient evidence. "Incorporation of BrdU may also occur during DNA repair, cell degeneration and during cell death," he said. And large and multiple injections of BrdU may also induce DNA synthesis, he said.

"There are lots of reasons there could be a discrepancy in the findings," Gould said. "We don't go about it in the same way. Our histological techniques differ. Our animals could have different experiences." Stress, for example, limits production of neurons, while a stimulating environment encourages it, she said.

It is also unclear what function, if any, the new neurons may have in the neocortex. Gould notes that the cortex, which is associated with higher func-

tions, is very large. The number of new neurons she has found is so small relative to the total number that their impact may be minimal. Indeed, she said, the generation of new neurons might be a vestige of a developmental process that was never turned off.

But what Gould sees as a very small number is, to Rakic, "staggering." To accommodate these new neurons, Rakic said, the brain would have to grow or kill off existing neurons. Rakic said he has found evidence of neither.

He also believes that neurogenesis in the neocortex makes no functional or evolutionary sense. Early in their evolution humans traded the ability to grow new neurons, as seen in fish, amphibians and reptiles, for the ability to retain memory in existing neurons, he said. "We use neurons to store our life experiences and if we change neurons every season like male canaries do, then we would lose a lot of our life experiences," Rakic said. "Neurogenesis in the neocortex could eliminate crucial, learned cognitive functions and long-term memories. We have to learn how to preserve our neurons during disease and natural aging."



JOHN CURTIS

Experiments by Pasko Rakic more than a quarter-century ago laid the foundation for current thinking about the brain's ability to grow new neurons.

et cetera

BLEACH, WATER AND HIV

Although proven effective in preventing the spread of HIV, needle exchange programs remain unfunded by the federal government, largely for political reasons. Yale scientists, whose earlier work was fundamental in proving the efficacy of needle exchange, reported recently that in a worst-case scenario in which sterile syringes are not available, rinsing syringes with a bleach solution or even plain water can provide effective protection against infection. "We found that for the type of syringe usually used by drug injectors, a solution of bleach and nine parts water disinfects the syringe if the solution is drawn in and squirted back out twice," said Robert Heimer, PH.D., associate professor of epidemiology and pharmacology and principal investigator of the

study, published in the December issue of the *Journal of Acquired Immune Deficiency Syndromes: JAIDS*. "We found that rinsing three times with clean water reduced the likelihood of recovering live virus by 99 percent." While not absolutely protective against HIV, Heimer said, "these measures reinforce the adage that prevention is never perfect and never ending."

COCAINE AND THE FETUS

When pregnant women use cocaine, their offspring may suffer permanent harm to an area of the brain that governs short-term memory, leading to learning impairments and symptoms resembling attention deficit disorder. According to two recent animal studies by Yale scientists Bret A. Morrow, PH.D., John D. Elsworth, PH.D., and Robert H. Roth, PH.D., the effects are manifest in the prefrontal cortex. "Children exposed to cocaine in the womb may have a problem inhibiting excitable neurons in the part of the brain that helps control attention and memory," said Morrow, associate research scientist, associate clinical professor and lead author of both studies, published in February and March in the journals *Behavioral Brain Research* and *Neuropsychopharmacology*, respectively.



Accessible Connecticut: A Guide to Recreation for Children with Disabilities and Their Families

by Nora Ellen Groce, PH.D., associate professor of public health and anthropology, Lawrence C. Kaplan, M.D., and Josiah David Kaplan

Yale University Press (New Haven) 2001

This guide helps parents of children with disabilities plan family outings in Connecticut that are stimulating and fun. Intended for parents of youngsters who use wheelchairs or who have visual, hearing or mental impairments, the book presents places throughout the state that are easily accessible and reasonably priced and that require little or no prior planning. For each place or activity the authors list location, directions, phone numbers, Web information, hours, admission fees, a brief description and an assessment of accessibility by type of disability.

Joining the Club: A History of Jews and Yale, revised edition

by Dan A. Oren, M.D. '84, HS '88, associate professor of psychiatry

Yale University Press (New Haven) 2001

Using archival records and interviews, Oren, a Yale graduate now at the medical school, has produced a thoroughly researched account of the Jewish experience at Yale from the first Jewish graduate in 1809 to the present. Not only does he chronicle the history

of Jews at Yale, but he compares it with the experiences of other minorities at Yale as well as the saga of Jews at other elite schools. The discriminatory quota system and other problems that Jews in American higher education faced during much of the 20th century are well documented.

An Elementary Textbook of Ayurveda: Medicine with a Six Thousand Year Old Tradition

by Frank John Ninivaggi, M.D., assistant clinical professor in the Child Study Center

International Universities Press Inc. (Madison, Conn.) 2001

The author presents the first scholarly description of the origins, development and theories of Ayurveda (Sanskrit for life wisdom), a traditional Hindu system of medicine. One of the oldest extant organized bodies of medical knowledge, Ayurveda is emerging as a leader in the field of complementary medicine. The concept of the person as a biopsychospiritual, integrated field, who is in responsive, dynamic interaction with other persons as well as with nature, is introduced, and its implications for health and disease are explored.

On the Other Side: African Americans Tell of Healing

by Alita Anderson, M.D. '01

Westminster John Knox Press (Louisville, Ky.) 2001

On the Other Side is a collection of oral narratives and original artwork by the author that presents the story of a diverse group of speakers who have one thing in common—a profound experience

with the power of healing. The narratives are woven together with the verses of African-American spirituals that punctuate each story.

How to Keep Your Husband Alive: An Empowerment Guide for Women Who Care about Their Man's Health

by Siegfried J. Kra, M.D., associate clinical professor of medicine

Lebhar-Friedman Books (New York) 2002

In a new approach to men's health, Kra explores the manner in which women can help to prolong the life span of their mate. Kra encourages women to develop simple communication techniques for nudging their man to seek medical attention when warning signs such as fatigue, weight gain or loss and changes in breathing patterns and alcohol use are evident. In clear and direct language, Kra offers a guide for women to the appropriate questions to ask and the relevant tests to request once their mate has scheduled that first appointment.

Primer on International Health

by Robert W. Buckingham, M.D., DR.P.H. '78

Benjamin Cummings (San Francisco) 2000

This book addresses the process of sharing knowledge of international health among colleagues and students, a process that

becomes more important as commerce and international travel accelerate both the globalization of human life and the pace of human and disease interactions. Buckingham and his co-contributors cover issues including global environmental health, primary care, malnutrition, maternal and child health, comparative national health care systems, epidemiology and the future of international health.

Ground Beetles of Connecticut (Coleoptera: Carabidae, excluding Cicindelini): An Annotated Checklist

by William L. Krinsky, M.D. '71, and Michael K. Oliver, PH.D. '84

Connecticut Department of Environmental Protection (Hartford, Conn.) 2001

With the information presented in this book on their occurrence and distribution, carabids become the best-known beetle family in Connecticut in terms of species-level distribution and historical records. The diversity of habitats in which carabids occur and the large number of species that exist provide the basis for the use of this group of beetles as a significant indicator of changes in the environment.

The descriptions above are based on information from the publishers.

SEND NOTICES OF NEW BOOKS TO Cheryl Violante, *Yale Medicine*, P.O. Box 7612, New Haven, CT 06519-0612, or via e-mail to cheryl.violante@yale.edu.



JOHN CURTIS

MICHAEL BLISS Immersing himself in Cushing's "harem"

Out of earshot, the women who worked for Harvey W. Cushing, M.D., referred to themselves as "the harem." The "chief," said Cushing biographer Michael Bliss, Ph.D., would not have been amused.

In a talk in the Historical Library of the Cushing/Whitney Medical Library in February, Bliss, a historian at the University of Toronto and biographer of William Osler, said Cushing enjoyed a decidedly professional relationship with his female staff and was less than tender as a boss. He paid the women who worked as secretaries, histologist and photographer low wages and worked them long and irregular hours. He dictated up to 10,000 words a day, expected a high level of performance and seldom thanked anyone. Yet he also offered perks such as coveted football tickets, invitations to his home and even trips to Europe.

The most devoted of his assistants was Madeline Stanton, who followed him from Harvard to Yale, where she became director of the Historical Library. In one of her journal entries, Stanton wrote, "I shall be miserable, I am sure, if I ever have to work with anyone else." Bliss's biography of Cushing is due out in 2006.



ROBERT NUSSBAUM

ROBERT L. NUSSBAUM In genomics, the end of the beginning?

At the very least, the Human Genome Project was a technical and scientific challenge; it's no simple matter to sequence 3 billion pairs of DNA, as the project's public consortium set out to do in 1990. But the solution to the puzzle was in many ways not a technical one, Robert L. Nussbaum, M.D., said in a visit to the medical school in January. "It became very clear early on that this project was never going to work unless everyone did just a few things over and over again, really, really well," said Nussbaum, chief of the genetic disease research branch at the National Human Genome Research Institute. "It was the introduction of management and organizational techniques from outside of science that probably made the biggest difference." Nussbaum said a debate is now brewing within the institute on whether to declare the project over next April, an even 50 years after Watson and Crick's description of the double-helix structure of DNA, by which time it is believed the final sequence will be assembled. "Should we declare it complete in 2003 and pack up and go home? Some say yes," he said. "The others take the more Churchillian view that this is neither the end, nor the beginning of the end, but rather the end of the beginning—that we have now launched a whole new field called genomic science, and let's get started."



MICHAEL MARSLAND

MARY STARKE HARPER Nurse warns against repeating Tuskegee abuses

The last living health care provider involved in the infamous Tuskegee experiment, which followed African-American men with syphilis for 40 years while withholding treatment from a fraction of the cohort, warns that the American public needs to remain alert to comparable abuses that still exist. "I'm concerned that this is still going on," said Mary Starke Harper, R.N., Ph.D., a student nurse during the research at the Tuskegee Institute in Alabama. She spoke of her experiences on February 18 as part of the Black History Month commemoration at the School of Nursing. Harper, 82, known nationally and internationally as a patient-care advocate and research consultant in geriatric psychiatry, said that neither she nor the two registered nurses with whom she worked at the time knew which patients were in the experimental control group. The study became a symbol of racism in medicine, ethical misconduct in human research and government abuse of the vulnerable, and led to the National Research Act of 1974.

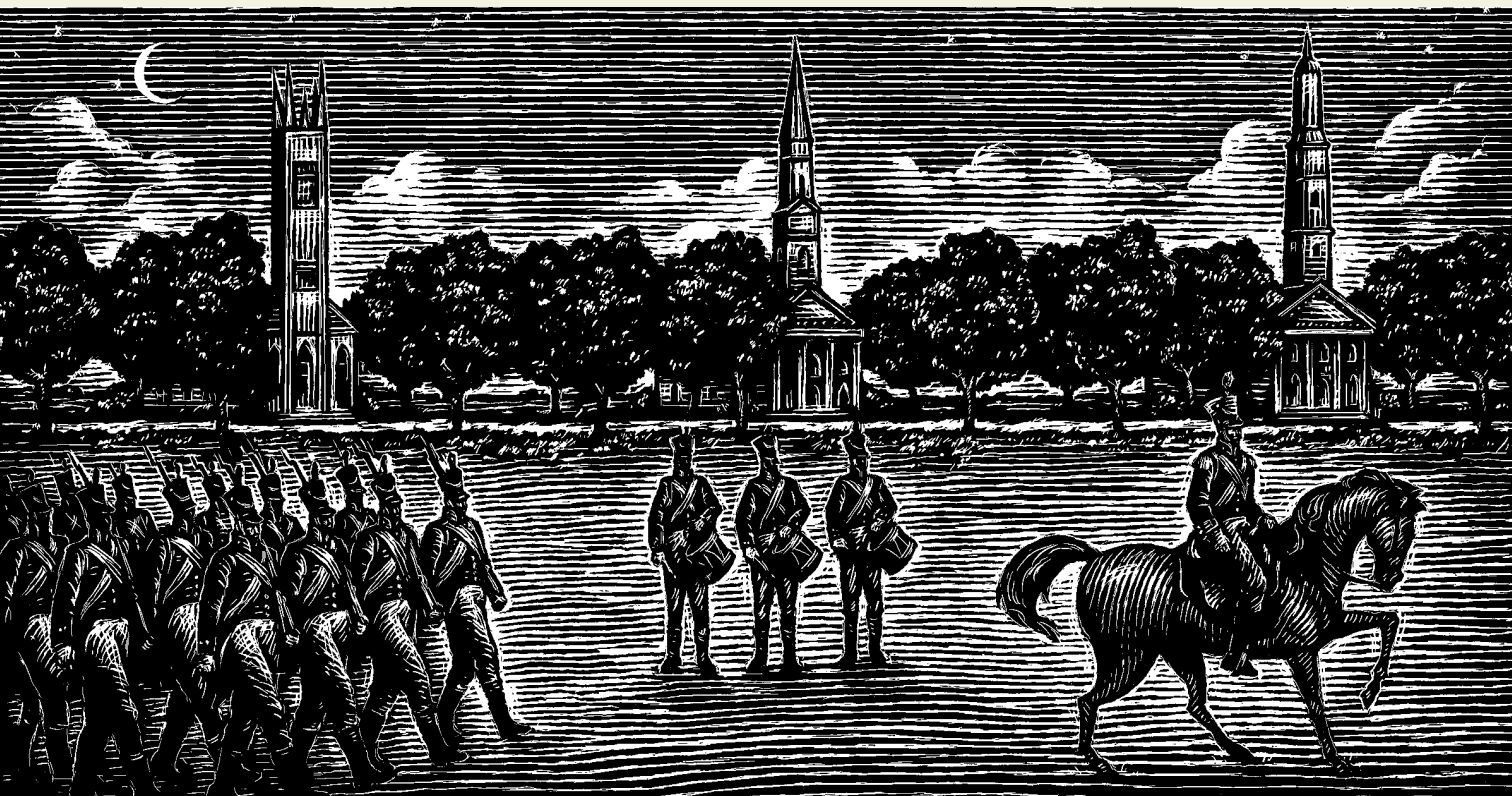


JOHN CURTIS

ZHANGLIANG CHEN The world's biggest country, and biggest market

If you wanted to find one place with some of the thorniest issues confronting biotechnology, you'd need look no further than China. With more than a fifth of the world's people living inside its borders, China has an enormous market for food and drugs, as well as an emerging biotech industry and venture capitalists. And it faces serious problems as it applies biotechnology to agriculture and pharmaceuticals.

The country's pharmaceutical industry lacks original discoveries in its portfolio and, said Zhangliang Chen, Ph.D., director of China's National Laboratory of Protein Engineering and Plant Genetic Engineering, "You have 20 companies producing the same drug." In a talk in December sponsored by the Peking-Yale Joint Center for Plant Molecular Genetics and Agro-biotechnology, Chen said China is also producing genetically modified foods—which he believes to be the most efficient way to produce food in poor countries, despite controversy over their safety. "If we use organic agriculture in China," he said, "many people are going to die because of starvation."



Anatomy of an insurrection

Grave robbing wasn't something a Yale man did in the early 19th century—unless he was in medical school.

By Rachel Engers

Illustration by Ken Perkins

Early on the morning of January 12, 1824, Jonathan Knight, Yale's first professor of anatomy and physiology, received a startling piece of news. During the night, a body had been snatched from a fresh grave in the West Haven burying ground and the incensed townspeople were pointing fingers at the college.

Some suspicion of the medical students was justified. Grave robbing by anatomists was still common in America at the beginning of the 19th century—for contrary to the practice in Europe, there was no legal way to obtain cadavers for medical study. One reason was the deeply ingrained prejudice against the work of anatomists. The inhabitants of New Haven “were the direct inheritors of a flourishing Puritan tradition that naturally fostered strong religious feelings,” wrote Yale historian Hannibal Hamlin in his account of the incident.

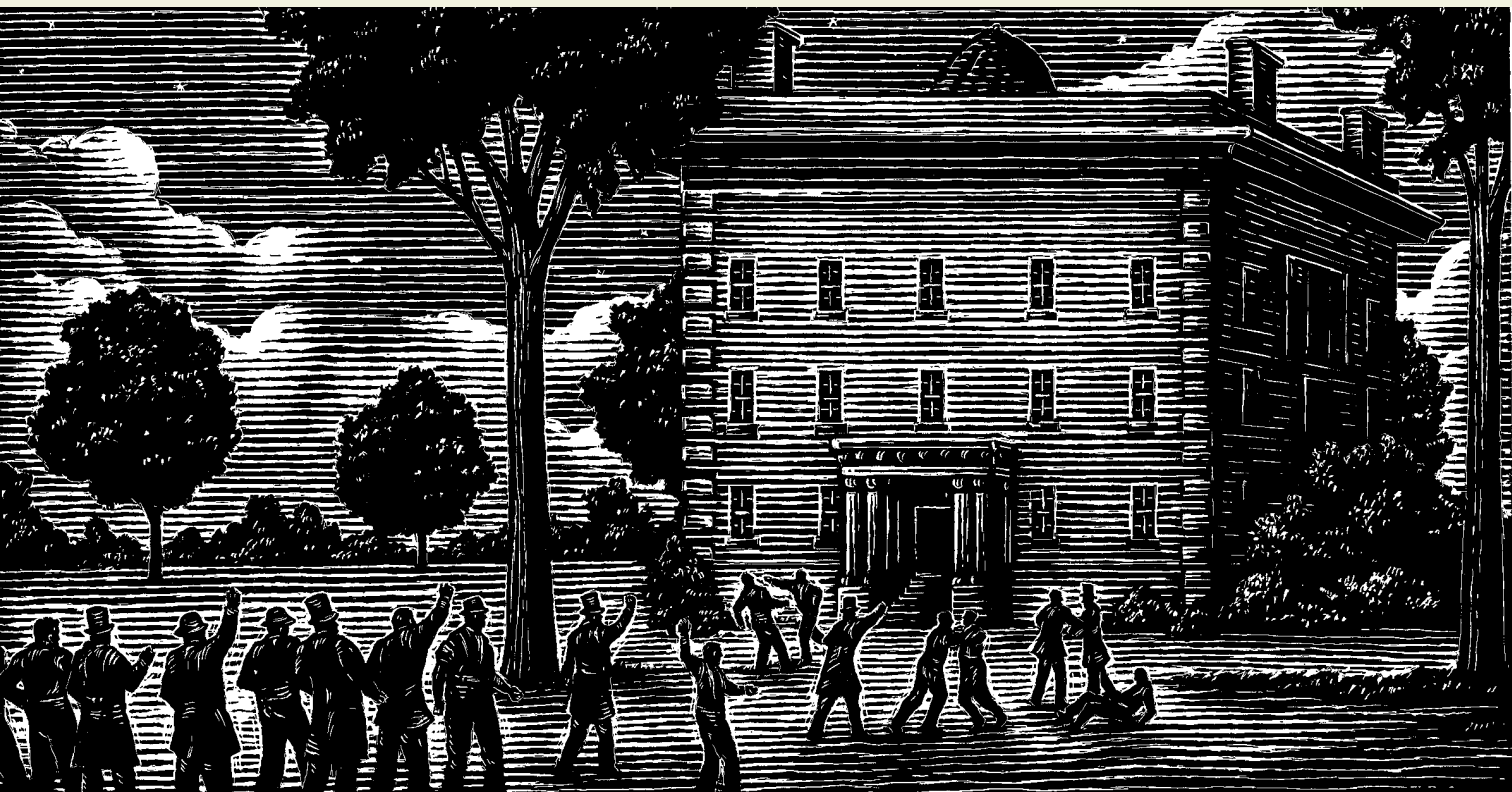
“Their respect for the sanctity of the sepulcher bordered on superstition. The Doctor of Physic was held in high esteem; but the dissection of a cadaver by the surgeon or anatomist was, in general, considered a nefarious and unmentionable business.”

A search began for the missing body of Bathsheba Smith, “a respectable young female of nineteen” and the daughter of a local farmer. The West Haven borough constable, Erastus Osborn, was dispatched immediately to the college. His account of discovering the corpse in the medical school building at Grove and College streets appears in a letter to his father, quoted below with its irregular spelling intact:

“We came to a place in the pavement (the Cellar being paved with large flat stones) which lookd generally like the bottom of the Cellar throughout, but

appeard to have a trifle of fresh dirt lying scatterd about ... I scratchd with the end of my walking stick and the more I examin'd the more suspicion was created. We soon found the earth appeard fresher between the stones & finally took up a large flat stone where we discovered a white bundle, apparently a bundle of cloathes. We examin'd it & found a human body doubled up in a heap entirely coverd up with grave cloathes. We took it out and it was immediately known to be the body of the young woman we were searching for.”

Not since the British invaded New Haven in 1779 had the townspeople been so incensed. Elizabeth H. Thomson wrote in her unfinished history of the School of Medicine. The scandal stirred up such a ferocious anger that a mob of some 600 men armed with pistols, clubs and daggers stormed the



On the night of January 12, 1824, the Governor's footguard, armed with bayonets, swords and rifles, assembled on the New Haven Green, ready to quell a furious mob assaulting the medical school, which was then located on Grove Street. Earlier that day, a body missing

from the West Haven burying ground had been found in a medical school building at Grove and College streets. With no legal means of acquiring cadavers for the study of anatomy, medical students of the era sometimes resorted to grave robbing. A Yale medical assistant was

scapegoated, paid a fine of \$300 and served nine months in jail. A subsequent act of the state legislature made the bodies of those who died in prison or were executed available "to be used for the purpose of advancing medical science."

college at nightfall. The authorities read the state's Riot Act several times, but the crowd kept pelting the building with stones and shouting "tear down the college" and "death to the students." Those inside feared the mob would batter down the walls. Justus D. Wilcox, a medical student who witnessed the attacks, gave this account of the escalating attacks in a letter: "[At nearly midnight] the Governor's foot guards were called out. They assembled on the green, each man provided with sword and bayoneted gun, with ball and cartridge; they marched at quick step to the Medical college inspired [by] fife and drum which beat the reveille, and sounded the notes of war."

During the investigation, sensational newspaper headlines ("Another Grave Plundered!") fanned the fury and gossips spun some outlandish tales about

the medical school. In later years, one rumor held that the institution had been purposely sited near the Grove Street cemetery so that bodies could be easily stolen, and some even speculated that an underground tunnel linked the basement of the building and the graveyard. But in 1824, that cemetery was as yet unbuilt.

While the New Haven dissection riots of 1824 are certainly a strange chapter in the history of the medical school, Yale was by no means alone. Despite epidemics of cholera, smallpox and other diseases, the general public had little appreciation for the work of anatomists. In fact there were violent attacks at medical institutions around the country, including the deaths of seven people in the New York "Doctor's Mob" of 1788 and riots at Wiesenthal's School in Baltimore.

A Yale medical assistant named Ephraim Colborn was scapegoated for the plundering of Bathsheba Smith's grave. Although there were no witnesses against him, he was found guilty of the crime, fined \$300 and sentenced to nine months in jail. Soon thereafter, Connecticut passed an act that established more severe penalties for grave robbing and made it legal for the bodies of those dying in prison and those capitally punished "to be used for the purpose of advancing medical science." This landmark legislation, well ahead of that in other states and preceding the Warburton Anatomy Act of 1832 in England by eight years, helped bring about progress in medical teaching both at Yale and in Connecticut.

RACHEL ENGERS is a writer in Bedford, N.Y.
KEN PERKINS is an artist in Broomfield, Colo.

Reinventing *surgery*

Surgery Chair Robert Udelsman looks up from the operating table during a procedure at Yale-New Haven Hospital in late February. At Johns Hopkins,

where he was chief of endocrine surgery, Udelsman pioneered minimally invasive techniques for removing the thyroid and parathyroid.



Robert Udelsman left one of the busiest medical centers on the planet to lead Yale's Department of Surgery out of its doldrums and into national prominence. He's a man on a mission.

By Cathy Shufro

Photographs by Gale Zucker



Third-year medical student Jennifer Schutzman was acing the middle-of-surgery quiz administered by Robert Udelsman, M.D., M.B.A. She had already correctly described the three causes of primary hyperthyroidism, listed the three veins and two arteries that supply blood to the thyroid gland, and named the two main vocal cord nerves near it—all while holding a retractor steady on either side of a small opening in the patient's neck. As Udelsman and third-year resident Steven Williams, M.D., probed and cut their way toward the patient's diseased thyroid, Udelsman threw his medical student a curve: What famous 20th-century opera singer had undergone thyroid surgery with disastrous results?

Schutzman was silent.

"Amelita Galli-Curci," Udelsman told her. "In 1935, the story goes, Dr. Arnold Kegel removed a goiter, and in a single day, two careers were forever changed."

Schutzman knew her anatomy well enough to understand what Udelsman implied: the surgeon had cut an important nerve controlling the vocal cords. By cutting the nerve, the surgeon had damaged both Galli-Curci's voice and his own reputation. That was the nerve that Udelsman and Williams were painstakingly protecting during this thyroidectomy.

In telling the story, which he'd heard from his mentor 20 years before, Udelsman was continuing the tradition of passing on knowledge to a new generation of surgeons. Yale's new chief of surgery is always teaching. In the operating room, he



peppers residents with questions, coaching them as they cut and telling them stories that teach anatomy. When another surgeon steps into the OR to say hello, Udelsman explains his minimally invasive approach to parathyroid surgery, in which the parathyroid gland is removed while the patient is awake. (It's an innovation that allows the patient to go home the same day, leaves a scar on the neck that's only an inch long and cuts hospital fees in half.) Outside the operating room, Udelsman remains a teacher—presenting cases at the standing-room-only grand rounds in Hope 216 (attendance is mandatory), painstakingly describing to patients what will happen during surgery and explaining to house staff why white coats are required in the lunch line (scrubs are unprofessional). In all of this, Udelsman is perhaps even more intense and focused than your average intense and focused surgeon.

It's nothing new for a department chair to guide young surgeons and to help senior staff keep current. But Udelsman is on a mission. In his soft-spoken, persistent way, he is determined to help transform surgery at Yale. He aims to help make Yale, long known as a research powerhouse, into one of the world's top clinical centers as well. Udelsman came to New Haven last June to head a department that, despite a distinguished past and many strengths, does not have a national reputation and hasn't turned a profit for several years. Recruited from Johns Hopkins, where he helped develop the new tech-



TO Udelsman listens to a colleague while waiting for a fax in the small office that serves as the hub of the operating suite at Yale-New Haven. The day's schedule is posted on the board to his left. He's determined to make the OR run as smoothly as possible; time wasted due

to inefficiencies is a drag on the system and an obstacle to good patient care. **ABOVE** After removing a diseased thyroid, Udelsman sketches the anatomy and makes notes about the case. **OPPOSITE** He reports on the outcome of the surgery to the patient's husband in the waiting room.



niques for parathyroid surgery and made laparoscopic adrenalectomy standard, Udelsman says he wants Yale to become the kind of innovative and profitable surgical center that he left behind in Baltimore.

“The Mayo Clinic, Johns Hopkins, the Cleveland Clinic. That’s the level we want to play at,” says Udelsman. “I do not view our referral base as southern Connecticut. Our referral base is the world.”

“IF MRS. JONES CAN’T PARK ... ”

Udelsman believes Yale will draw patients from far away if they hear that it is simply the best in certain specialties. Udelsman [pronounced YOU-delsman] is still getting to know a department with 300 employees in 13 sections running the gamut from trauma to transplantation, otolaryngology to urology. He already has a few ideas for what Yale’s areas of surgical excellence should be: kidney transplantation and perhaps surgical oncology and heart surgery. “You don’t have to be great at everything. You have to be spectacular at some things. It doesn’t even matter what they are,” he says. He will strengthen research that complements key surgical subspecialties, though research is already strong; Yale surgery ranks seventh in the nation in funding from the National Institutes of Health.

The breast center Udelsman imagines exemplifies the kind of comprehensive care he wants Yale to provide. It would offer diagnostic and therapeutic radiology, surgery, chemotherapy

and counseling, all in one place—and *fast*. “In a typical scenario, a woman has an abnormal mammogram, and she thinks she has breast cancer and that she’s going to be dead in three years. What women want is service, and they want that service in 24 hours or less. It can’t be you’re called [about an abnormality] and two weeks later, you get an appointment.”

Udelsman is determined to make sensitivity to the patient’s experience central to the jobs of medical center staff—the first priority for nurses, facilities planners, doctors and custodians alike. He tells the galling story of a woman who drove hours to reach New Haven for a scheduled appointment and was told to return the next week because the doctor wasn’t there. Inconvenient parking and shabby buildings convey a similar message, says Udelsman. “You can be as empathetic as you want, but if Mrs. Jones can’t park, then she can’t come to the clinic and the whole system breaks down. If there’s dirt in the hallways at the medical center and no one cleans it, the message is, we don’t care. If the phone is answered by voice mail, we don’t care.”

Ralph I. Horwitz, M.D., HS ’77, says Udelsman’s focus on patients is right on target. “We have not made quality of clinical care a strong-enough focus of the institution,” says Horwitz, chair of the Department of Internal Medicine and head of the search committee that nominated Udelsman. “I think Rob is going to focus the attention of the entire medical center on clinical care.”

Udelsman also contends that clinical medicine at Yale won't thrive until the medical school and Yale-New Haven Hospital cement a partnership that is truly based on a common vision. "They are not," he said, "competing institutions."

His chief of cardiothoracic surgery, John A. Eleftheriades, M.D. '76, HS '83, said in December that he had already seen dramatic changes in Udelsman's first months as chair. "The department is already revitalized by his arrival. It's palpable in many different ways. He clearly has great determination, energy and insight, and I think everyone feels that. The weekly grand rounds is revitalized, there's active recruitment to fill needs the department has had for a long time and there's a general sense of energy and direction and forward momentum. I think that's all new," said Eleftheriades, an expert on aneurysms and cardiac arrhythmias who has spent his career at Yale. "I can feel that Rob is committed with every fiber of his body to making this the best academic department that he possibly can. He's very savvy in terms of the finances of running a department. In this era, that's critically important, because all the fat has been trimmed from reimbursements."

Eleftheriades reads Udelsman correctly where finance is concerned. Udelsman thinks constantly about efficiency, schooling those around him to understand an operating room as a profit center. "We're a nonprofit organization, but that doesn't mean we don't have to be profitable," he says. "At the end of the day, if we can't balance our books—if we're spending more than we're taking in—we're going to have to close the doors."

Udelsman even campaigns for fiscal efficiency on the fly. He had just completed a thyroidectomy one morning when he was told that his patient could not be moved to the recovery room; it was filled with overflow patients from intensive care.



ABOVE AND OPPOSITE Preparing for surgery and making the first incision, Udelsman is in his element: "Surgery is fun. You get to fix things. It's a technical tour de force. If you ask surgeons what the best part of their day is, it's when they're in the OR."

Udelsman quietly fumed. With the operating room now serving temporarily as a recovery room, the next case could not begin. Doctors, nurses and technicians were being paid to mark time. Patients anxiously awaiting surgery would wait longer. As he headed up the hall to visit three patients—two in line for surgery and one recovering—Udelsman buttonholed the nursing director for perioperative services. Had she informed anyone of the bottleneck? Yes, the associate medical director. Had she also written to the hospital's chief of staff? No, she hadn't. Udelsman asked her to write to him about the wasted time.

As he walked briskly away down the hall, Udelsman turned back and called to her: "I want so many letters on his desk, he goes nuts!"

Until a few years ago, high finance for Udelsman had been limited to buying a house and car. Then he went back to school at night, earning a master's degree in business administration and another in business in medicine at Hopkins. "I don't want some administrator running circles around me, someone who has no concept of what it is to be a surgeon running the show." Udelsman now knows enough about profit-loss statements, spreadsheets and business plans to guide a department with an annual budget of \$40 million.

Efficient billing is so important—"the blood of our system"—that Udelsman wants same-day billing. "I want a billing and collections person right in the OR," he joked. In one sense, he means that literally: he invited clerks from billing to gown up and witness surgery "so they can experience the magic of what we do."

Pat Napoletano watched Udelsman and a resident operate. "We deal with pieces of paper. We don't deal with the patients," she said, adding that what struck her most about her experience in the OR was "seeing the enjoyment they get out of helping someone."

That is precisely how Udelsman views surgery. "Surgery is fun. You get to fix things. It's a technical tour de force. If you ask surgeons what the best part of their day is, it's when they're in the OR, by far. ... There are few things in medicine where we can so dramatically change a person's life. Diabetes gets a little better or a little worse, hypertension gets a little better or a little worse. In surgery, in a half-hour or an hour interval, a patient comes out a different person than they went in."

"IF YOU CAN'T CUT, YOU'RE NOT PART OF THE GROUP"

The evolution from surgical acolyte to priest is gradual, says Udelsman. When young surgeons face a decision, they ask themselves, "What would so-and-so have done in this situation?" For every surgeon, there eventually comes a day when "there's no one to ask. There's no one better at this than you. That is a maturational moment when you really are on your own." Now that he is a mentor himself, Udelsman trains surgeons in part by quizzing his assistants, by telling stories, "by teaching them the tricks." Udelsman hopes that the surgeons he and his colleagues train "will always hear our voices."



He schedules two days a week in the operating room and wants to increase it to three, both because he enjoys surgery and because his reputation depends on it. “As a chairman, it’s very important for me to operate. I’m in the trenches like everyone else. My colleagues, the nurses, the medical students—everybody is testing my skills every day. If you can’t cut, you’re not part of the group.”

Eleftheriades made a similar observation: “If a chairman is simply an administrator, he doesn’t gain the respect that he does if he is up there at the plate along with the faculty he’s leading. Rob is not only up there, but he is an extremely accomplished, respected and experienced clinical surgeon.”

Udelsman is fascinated by what he calls “the operating culture. It’s very much a ‘captain-of-the-ship,’ military model.” Surgeons may feel frustrated when they find they can’t recreate this system outside of the hospital. “When a surgeon goes home to their family, they want structure,” says Udelsman. He says his wife, Nikki Joan Holbrook, PH.D., a distinguished cell biologist at the medical school, will jokingly call his bluff when he tries to apply the surgical model at home in Woodbridge. “My wife certainly has said, ‘I’m not your scrub tech! Forget it!’”

He brings his life as a surgeon home. “I never let go of the hospital. I carry the hospital with me.” His children—eight-year-old daughter Kelly and sons Andrew, 13, and Brooks, 14—have a general idea of what’s going on at the hospital. One of the boys will answer the phone and tell his father, “Oh no, so-and-so’s got another calcium problem.” Last Halloween, Udelsman had to cut short trick-or-treating to return to the hospital for an emergency, to the disappointment of a small witch.

In surgery things do go wrong. Surgeons have a long tradition of gathering to examine their failures, a weekly morbidity and mortality meeting that “has almost religious

connotations. ... We publicly discuss our worst problems. It takes on an almost confessional aspect. We take our failures very seriously. People do die. You have to ask: Was that a preventable death or not?”

Udelsman moderated when about 40 physicians met for the general surgery morbidity and mortality meeting in Fitkin Amphitheater recently. Residents reported on problems with patients: one who developed a postoperative clot in his heart, another whose hand was mysteriously burned during surgery. For each case discussed, the doctors proposed various ways the complications might have been handled. Udelsman orchestrated the exchanges, occasionally complimenting a resident, repeatedly asking leading questions: Why is it that using a gastrograffin enema may be therapeutic as well as diagnostic? What treatment is available for an obstructed gall bladder in a patient too weak for surgery?

Udelsman talked about a close call with his own patient, who had developed a rare bleed following removal of cancerous lymph nodes. A few hours after surgery, the man’s neck had swelled, a sign of internal bleeding that could block his airway. Udelsman rushed the patient back to the OR and found the source of the bleed. The patient recovered.

“WHY YOU, I DON’T KNOW”

The most intense and exhausting work of Udelsman’s week is clinic. Patients referred to Udelsman usually have complicated cases. He reviews their histories, explains illnesses, describes surgeries, confers with family members and reassures patients. He leans forward, one foot tapping, while the clock ticks. He pretty much keeps to his schedule, doing a biopsy, calling a colleague in another hospital, scrutinizing MRI films, seeing one patient after another ushered in—and out—by Patricia I. Donovan, R.N., who came with Udelsman from Hopkins to be the department’s manager of patient care and quality assurance.

Among the patients at a recent clinic, the last faced the most serious illness. The man, a musician in his 30s, hadn’t expected to be back; Udelsman had removed one lobe of his thyroid three weeks before in what is usually a curative procedure. But the pathologist had diagnosed medullary cancer, a rare thyroid cancer that spreads quickly. Udelsman felt sure that it had invaded the man’s lymph nodes. When last tested, the man’s tumor marker was at 97; a normal reading is below 3.

“It’s such a rare disease that many endocrinologists haven’t seen a case,” Udelsman told the fit, dark-haired man who had come to the clinic with his wife and 4-year-old son. “Why you, I don’t know.”

He would need a central and lateral neck dissection to remove the rest of his thyroid and 20 to 50 lymph nodes that Udelsman believed contain tumors the size of specks of pepper. Surgery would take all day. “This operation is 10-fold what you had before,” Udelsman told him.

Two factors complicated the case. Udelsman explained that it was possible that this cancer was genetic. If testing showed



Udelsman compares Yale’s clinical mission to those of the Mayo Clinic, Johns Hopkins and the Cleveland Clinic and aspires to raise the medical center’s profile to the same level. “I do not view our referral base as Southern Connecticut,” he says. “Our referral base is the world.”

During a meeting with architects in February, Udelsman insists that space for newly recruited faculty members be ready by the start of the next academic year on July 1. The \$40 million department has to run like a business, he says: "We're a nonprofit

organization, but that doesn't mean we don't have to be profitable. At the end of the day, if we can't balance our books—if we're spending more than we're taking in—we're going to have to close the doors."



that it was, then each of the man's four children would have a 50-50 chance of developing the cancer and would need preventive thyroidectomies. And the man is a professional singer. As did Galli-Curci, he faces surgery, again, that will put his voice at risk. Udelsman told him the chance of damage to his voice was 2 percent. "I expect you to do great. But let me give you the picture. This is serious business. You can have big problems" if the cancer spreads, he told the man. His wife listened silently.

The man was upbeat, well informed from research on the Internet. "I'm still in a good place about it," he said. "I am not in any kind of denial, but I'm not going to accept that this is going to take me down."

"I'm not saying it's going to take you, but you've got some hurdles to jump," Udelsman replied. "Our goal is to keep you alive for a long, long time."

**"IF IT COMES BACK MALIGNANT,
THEN WE'VE DONE A REALLY GOOD THING"**

It's a Tuesday, the first of Udelsman's two days in the OR. His first case is a parathyroidectomy, removal of one of the (usually) four raisin-sized endocrine glands on or near the thyroid. The parathyroid glands are intimately involved with the hormone that regulates calcium metabolism. Udelsman is talking to his patient—who is awake.

"Barbers and surgeons were in the same field back in England," Udelsman tells the patient, a retired business executive in his 60s, as he shaves his upper chest. The man has a parathyroid adenoma, probably not cancerous, but causing him problems with calcium levels that leave him weak and up at night urinating. Udelsman will use the minimally invasive technique.

As Udelsman and Chief Resident Rabab F. Hashim, M.D., begin working through an opening in the man's neck the size of a half dollar, Udelsman explains to Hashim: "This is very unusual. Most people would put this patient to sleep."

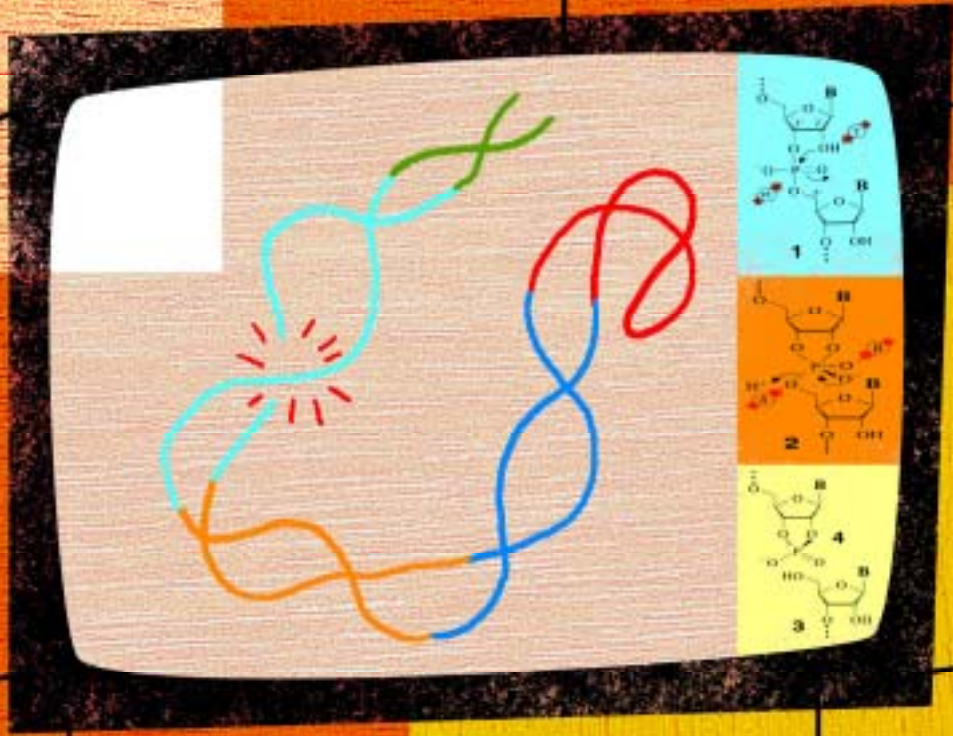
He teaches Hashim about the benefits of this minimally invasive technique for parathyroid surgery. By keeping the patient awake, sedated a bit and injected in the neck with local anesthesia, Udelsman tells her, they gain two things: they can ask the patient to speak from time to time, a method of checking whether the surgery is affecting the recurrent nerve crucial for speech; and they minimize the effects of anesthesia for the patient, reducing risk and speeding recovery so that the patient can go home the same day. (In this case, the patient will go to a hotel. He and his wife drove up from Maryland for the surgery because they heard that Udelsman is "the best.")

The man's parathyroid is hard to find, and the surgery is taking longer than the anticipated hour. "We're getting there," Udelsman tells both Hashim and the patient. "It's a very posterior parathyroid. You see that little mother now?" he asks Hashim. "That's what we're after. It's a very tricky one."

Udelsman shows Hashim that the parathyroid is enlarged. "It's a little bit more stuck [to the thyroid lobe] than I like to see," he tells her. He can't tell for sure where the parathyroid ends and the thyroid begins, which might indicate that the parathyroid is cancerous. Statistically, the chance of malignancy is only 1 percent, but Udelsman tells Hashim that they will remove the thyroid lobe as well, to be sure the parathyroid is completely out. (With the rest of his thyroid intact, the patient will feel no effects of losing a lobe.)

"In my heart of hearts, I think it will prove to be benign," Udelsman tells Hashim, "but the time to make the call is in

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Putting evolution to use

From the landscape of an ancient “RNA world” springs an idea that could lead to the creation of ultrasensitive biosensors based on molecular switches. Marc Wortman talks to biology professor Ron Breaker about the potential of so-called RNA switches.



Biosensors exploit the natural tendency of proteins to recognize and react to other molecules. Ron Breaker theorized that the RNA in proteins could be isolated and serve as a “switch” that targets specific molecules. The central image at left represents a binary RNA switch as it goes through the chemical machinations necessary to recognize a molecule—it must bind to two different molecules before the ribozyme can cleave. Biosensors could be used to diagnose patients, monitor for bioterror weapons and detect metabolites in clinical samples, contaminants in food or pollutants in water.

Illustrations by James Yang



Ronald Breaker

When Ronald R. Breaker, PH.D., associate professor of molecular, cellular and developmental biology, wanted to develop a high-tech tool for detecting everything from infectious agents like HIV in the blood to contaminants such as arsenic in water, he figured that the place to start was about 3.5 billion years ago, when life began.

Some have theorized that RNA, the active component in genes, and not DNA, the genetic library, composed the first life forms. Based on that theory, Breaker supposed that RNA would have needed to act like a simple switch when it came into contact with another molecule, sending out signals in order to control metabolism. He and his team put that evolutionary theory to work in a test tube to “back-engineer” RNA-based molecular switches. As he reported in a paper published in *Nature Biotechnology* in April 2001, the switches worked. In fact, they worked so well that some believe they could be key to one day developing small, easy-to-use biosensors for detecting everything from tumor cells to toxic chemicals.

RNA molecular switches could be used to construct a kind of dashboard panel to detect when sought-after molecules are present. Such biosensors might be developed to detect contaminants in food, pollutants in water, metabolites in clinical samples or biological-warfare agents on the battlefield.

Yale licensed the RNA molecular-switch technology to a Cambridge, Mass., biotechnology company that Breaker helped found, Archemix Inc., which is developing possible commercial applications of the biosensor technology. In his own laboratory, he is continuing to explore the science behind molecular switches. Contributing Editor Marc Wortman asked Breaker to explain how biosensors work and to discuss the challenges of developing the technology.

What is a biosensor?

A biosensor is a device that uses biological molecules (usually proteins) to detect chemicals or other biological molecules. Each of our cells holds a complex mixture of chemical compounds, and all of these compounds are created and used in a highly orchestrated fashion. To do this, our cells mostly use intricately folded proteins to selectively recognize many of these compounds and to make use of them in very specific ways. Scientists found that they could remove one or more of these proteins from their natural setting and use them as biological components of sensor devices.

Perhaps the best-known target for a biosensor is glucose. For many diabetics, frequent monitoring of the concentration of glucose in their blood is necessary. However, glucose is only one

type of molecule within the very complex mixture of chemical and biological compounds present in blood. One way to “see” glucose in this vast sea of other compounds is to use an enzyme called glucose oxidase. This enzyme can identify glucose among all the other compounds and cause it to react with oxygen to produce hydrogen peroxide. Then a second enzyme called catalase destroys hydrogen peroxide in a process that can be monitored electronically. Higher levels of glucose in a drop of blood will give higher electronic signals, and thus one can determine precisely how much glucose is present.

How difficult is it to detect the presence of a potentially harmful biological agent, such as anthrax or *Salmonella*, in the water or air or on the surface of things?

Detecting infectious agents such as anthrax, *Salmonella*, or HIV is very difficult, particularly if the contamination is low and if you want the results fast. The challenge largely centers on the number of targets you want to see. Glucose concentrations are typically measured in “millimolar” units, which means that there are more than a billion trillion glucose molecules in a pint of blood. There are so many glucose molecules that it is quite easy to detect and accurately measure them. However, HIV concentrations could be present in “zeptomolar” units, where only a few hundred virus particles might be present but still able to cause disease. Biological agents such as bacteria and viruses can make billions of copies from a single infectious particle. There might be only a few HIV particles in a pint of blood, but they need to be detected in order to ensure that donated blood is safe for transfusion.

What are the usual methods?

Detection of biological infections has routinely been achieved by growing cultures from samples taken from patients, or by looking for the production of antibodies.

More recently, scientists have exploited two technologies—enzyme-linked immunosorbent assays (ELISA) and polymerase chain reaction (PCR)—to expand the power of biosensors and bioanalytical methods.

Sometimes natural proteins are not available for a particular target; interestingly, the immune systems of animals can be used to produce new antibodies that selectively bind to new targets of interest. These antibodies are typically used in ELISA tests.

More recently, PCR tests have become commonplace. These tests rely on the power of DNA-making enzymes (DNA polymerase) to selectively amplify genetic fragments of infectious agents such as anthrax and HIV. DNA fragments of just a few

Biosensor technology of this advanced type could be used to diagnose patients in a doctor's office, help discover new treatments for disease, detect industrial contaminations and even aid in monitoring for chemical or biological attacks.

infectious particles in a sample are used in PCR to make billions of copies, which can then be observed by any one of several different methods.

What are the problems or limitations of those current methods?

Speed, shelf life, and cost are of significant concern with all existing methods. ELISA and PCR assays take time to run and are usually labor intensive. Automation of some aspects of these tests can reduce the time needed to set up and interpret multiple tests, but the biochemical processes themselves also take time. Antibodies and many other proteins are notoriously unstable, and most biosensor kits have a shelf life that is measured in months—far too short to be of use to most consumers. Finally, proteins can be expensive to produce and store, which drives up the cost of making most biosensors.

Given concerns about bioterrorism, what efforts are under way in your laboratory and elsewhere to develop better biosensors?

Several science funding agencies had embarked on efforts to accelerate biosensor development even before recent events brought attention to bioterrorism. I think that this was a recognition that improvements were needed in detection technology, and also that recent advances in biological research indeed make possible great advances in biosensor sophistication.

Our laboratory took a rather unusual path to enter the area of biosensor research. We were testing a theory of how life began some 3.5 billion years ago. It is believed that an “RNA world” once existed, where all enzymes and other molecular components of primitive cells were made of ribonucleic acid, or RNA. Although this entire way of life has long since become extinct, we can perhaps use evolution in a test tube to recreate many of these long-lost RNA molecules. Through these efforts, we invented RNA switches that can be used as biosensor elements. For example, we have made many types of RNAs that self-destruct only when they come in contact with a specific target molecule. We recently assembled these on a prototype RNA biochip that can be used to detect toxic metals such as cobalt, drug compounds such as theophylline and natural compounds such as cyclic AMP and cyclic GMP.

What types of applications could they have?

We expect that this new type of biological switch will be used to make next-generation biosensor devices that detect a variety of chemical and biological agents in a single assay. Scientists have recently developed “gene chips” that can be used to see thousands of genes on one miniature platform. We imagine

similar platforms that see genes, metabolites, drugs, toxins, biohazards and any other targets of interest all in a single assay.

Biosensor technology of this advanced type could be used to diagnose patients in a doctor's office, help discover new treatments for disease, detect industrial contaminations and even aid in monitoring for chemical or biological attacks.

Are RNA molecules stable enough to serve as biosensor elements?

Nature has chosen DNA to store genetic information because each link in the chain is extraordinarily stable. In contrast, each link in RNA's chain is about 100,000 times more likely to break. If this occurs in one of our switches (which are about 100 links in size), then its function is likely to be destroyed. Fortunately, RNA is sufficiently stable to provide a shelf life of several years. After immobilization, the RNA array can be stored for long periods of time simply by letting the surface air dry and storing it at room temperature. Of course this is assuming that the RNA is not being digested by contaminating enzymes. Even the oils covering our skin carry enzymes that can degrade RNA very rapidly. Again, we are fortunate because chemists have created many modified RNA links that resist destruction by nucleases. In other words, the science to create modified RNA switches that resist attack by chemicals and enzymes is already well developed.

Will we eventually have low-cost, easy-to-use biosensors in our homes and workplaces?

Without question. Glucose tests and pregnancy tests have already become routinely self-administered. If the technology continues to advance, I imagine that home diagnostic tests for diseases such as cancer and viral infections might become the first line of defense for health care.

What might they look like and how would they be used?

Perhaps not surprisingly, we need to look at our science fiction stories to give us some sense of the possibilities. Although biosensors of the near future might look more like home pregnancy tests than a tricorder from *Star Trek*, I think that handheld biosensor devices that can detect thousands of important targets are being envisioned by many in the field. They will contain some sophisticated electronics and some savvy computer algorithms for interpreting various signals and perhaps for giving courses of action to the user. But at their core, they are likely to contain an advanced form of biochip that is engineered to recognize and report the presence of thousands of targets. **VM**

MARC WORTMAN is a contributing editor of *Yale Medicine*.

JAMES YANG is an illustrator in New York City.



The *toll* road

In science, an idea can lie dormant for a century and then enjoy a fantastic rebirth. That's what happened when Charlie Janeway proposed a theory about human immunity in 1989 that captured the imagination of Ruslan Medzhitov.

By Trisha Gura

Photographs by Frank Poole

In so much of science and medicine, breakthroughs begin simply as questions. A provocative one came by chance in January 1989 to Charles A. Janeway Jr., M.D., an immunologist and Yale professor. Although the question—about the initial trigger for the body's immune response—inspired an unorthodox idea, the story might well have ended there had Janeway's speculative answer not been noticed half a world away.

Janeway did write a paper about his idea—a theory about how a little-studied arm of the immune system alerts the body's T and B cells to the presence of an invader—but the 1989 paper drew little immediate interest. Three years later an impoverished graduate student in Moscow stumbled upon it and was galvanized. Launching the kind of quixotic adventure that could have been scripted by Hollywood, the young biochemist followed a circuitous route to Janeway's lab. There, the novice with no lab experience and the veteran scientist collaborated on research that has broken open an important and useful field within immunology. Together, Janeway and Ruslan M. Medzhitov, Ph.D., have elevated Janeway's theory from obscurity to cutting-edge prominence.

Charlie Janeway wasn't supposed to have been an immunologist in the first place; as a young man, he seemed destined to fulfill a family tradition of practicing medicine. But during his second year at Harvard Medical School in 1964, Janeway began to realize that, in his words, "the evidence for treating patients the way we were was flimsy." Rather than admit that they had

Yale professor and Howard Hughes Medical Institute investigator Charles A. Janeway Jr. in his office in Lauder Hall. Janeway had planned to become a physician but switched his focus to the basic sciences underlying immunology.

no effective treatment for a malady, physicians would prescribe something anyway. It bothered Janeway to hear patients thanking their doctors for unproven therapies.

His skepticism prompted a break from his medical studies and a two-year excursion into basic research from 1965 to 1967, first in the lab of immunologist Hugh O. McDevitt, M.D., at Harvard for a summer and then with John H. Humphrey, M.D., at the National Institute for Medical Research at Mill Hill in London for two years. When a more focused and critical Janeway returned from England for his last two years of medical school and a year of internship at the Peter Bent Brigham Hospital in Boston in 1969-1970, he couldn't accustom himself to prescribing treatments with so little information to go on. "Clinical medicine" he said, "was rotting my soul."

Janeway countered this disillusionment by working for the next five years at the National Institute of Allergy and Infectious Diseases under the tutelage of immunologist William E. Paul, M.D., chief of the Laboratory of Immunology. In 1977, he came to Yale as an assistant professor in the Department of Pathology's immunology division. During the 15 years of research that followed, Janeway gained insights into how T cells originate, develop and then become activated to pick off specific fragments of specific invaders.

Indeed, the key to T-cell action is specificity. Janeway has been at the forefront of efforts to understand how each of the millions of T cells formed in our bone marrow and later launched into our circulation has the capacity to respond to one, and only one, unique invader or insult. That pairing of T cell and target takes several days to happen, from the ill person's first feelings of malaise to the moment when the body has amassed its cellular troops and molecular weaponry. But the delay is necessary, pregnant with potential. Meanwhile, a second immune player, the B cell, produces antibodies, and these two protagonists coordinate an entire arm of human immunity known as the adaptive immune system.

During the 1980s, when the world of immunology revolved around problems of adaptive immunity, there was a basic question that no one gave much thought to: during the initial delay period, how are T and B cells first alerted that an intruder has invaded the body?

That was the question first posed to Janeway by his wife and colleague, immunologist H. Kim Bottomly, PH.D., professor of immunobiology, dermatology and molecular, cellular and developmental biology. The couple attended a Keystone Symposia meeting in Steamboat Springs, Colo., in January 1989, and were bantering as usual. "He and I would argue in the car all the time and then we'd forget what we said," Bottomly recalls.

"But," she adds, "this time we brought a notebook."

THE PATTERN RECOGNITION HYPOTHESIS

Janeway offered this answer to her question: the alert signal given to T and B cells must come from another arm of the immune system, the one long referred to as innate immunity. Given only a page or two in medical texts, innate immunity

is provided by skin, mucous and other epithelial barriers. It had been proposed that some unknown biochemical component combines with those simple barriers to act as a first line of defense against everyday assaults. Just cut a finger, and the tender redness that develops will demonstrate the workings of the body's inflammatory process, a function of innate immunity.

As he jotted down Bottomly's question and its provocations, Janeway began to muse on that long-ignored system. The field of innate immunity had languished in the years since Ilya I. Mechnikov had proposed his revolutionary cell-based theory of immunity in 1883. With subsequent discoveries in the 1940s about the powerful roles of T and B cells in allergic reactions, graft rejection and microbial attack, researchers had relegated innate immunity to a footnote. In fact, Janeway wrote his own terse section about it in his book, *Immunobiology*, now in its fifth edition.

Janeway began considering the links between the innate immune system and the adaptive system he'd studied over the years. Perhaps innate immunity worked as the intelligence network to tip off the adaptive system, he thought. Perhaps cells within or near the skin, mucous membranes and intestinal lining bore molecules on their surfaces that could recognize some general aspect of microbes and signal the adaptive immune system that a foreigner had breached security.

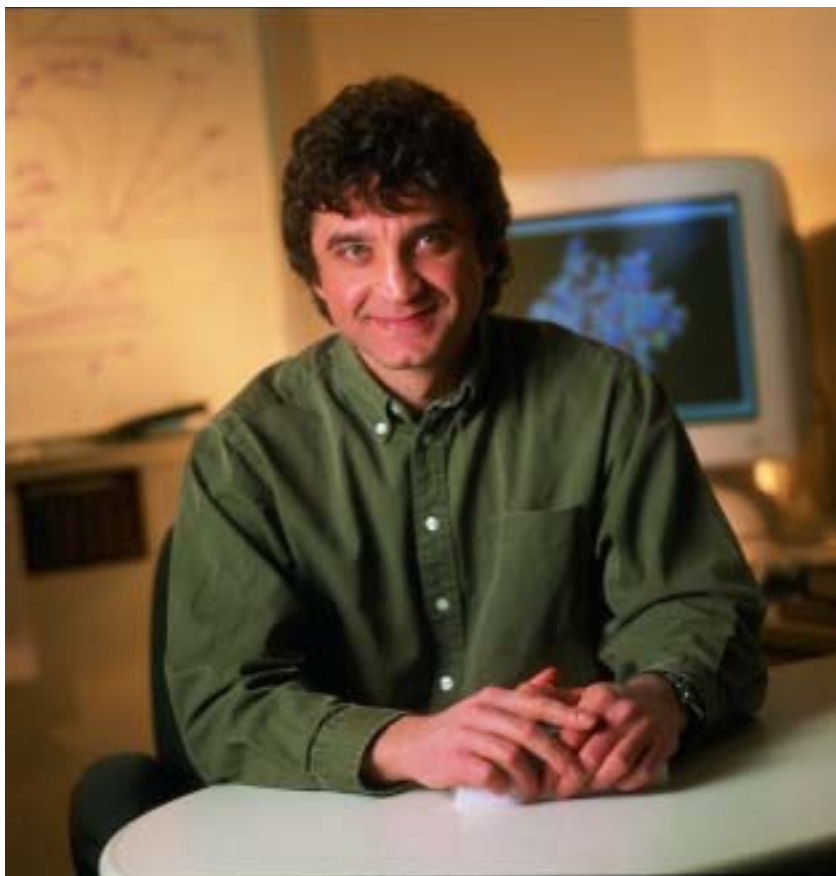
Janeway came up with an idea, which he dubbed the "Pattern Recognition Hypothesis." It goes like this: classes of germs carry molecular patterns, either anchored on their surfaces or secreted from their insides. All multicellular organisms have pattern recognition receptors that can signal, only in vertebrates, the adaptive immune system. Of course, the microbial molecules that carry the patterns would have to be critical to the pathogen in some way; otherwise it would have evolved a way to do without those molecular patterns centuries ago.

"I couldn't let go of the idea," recalls Janeway. In June 1989, he attended a meeting on quantitative biology in Cold Spring Harbor, N.Y., an event at which invited researchers have a chance to discuss ideas in an intimate setting. After the meeting, the immunologist laid out some of the ideas he'd begun developing at Keystone in a paper entitled "Approaching the Asymptote? Revolution and Evolution in Immunology," published as a chapter in the *Cold Spring Harbor Symposia* later the same year.

According to Janeway, that paper was "pretty much ignored" by the scientific community. But it intrigued an eager young student at Moscow University who stumbled across it. That student was Ruslan Medzhitov.

NARY A REAGENT IN SIGHT

Born in 1966 in Tashkent, Uzbekistan, Medzhitov made his way to graduate school in biochemistry at Moscow University in 1990, a time when the Soviet Union was breaking up and science in Russia was in deep trouble. As funding dried up, biochemistry labs lay bare of a single reagent. Entire departments operated on monthly budgets of \$20. In fact, only the



Ruslan Medzhitov



Charles Janeway and Kim Bottomly

In the fall of 1992, [Medzhitov] laid his hands on Janeway's paper and found his calling. [He] wanted to study immunology, and he wanted to do so with Charles Janeway. ...

Janeway had no idea of what to make of this unknown student who was writing to him. Recalls Bottomly, "Charlie told me, 'I've got this fabulously bright guy from Russia who wants to work in my lab.'" Not surprisingly, Bottomly was skeptical.

OPPOSITE The wall of photographs in Janeway's office tells the story of his personal and professional relationships, many of which are intertwined. The portrait of his father, Charles A. Janeway (top row, center), was painted on his retirement

after many years as chief of pediatrics at Boston Children's Hospital. Below that is a photograph of Janeway's colleague Richard K. Gershon, and to his right, the late John Humphrey, Janeway's mentor in London. The third photo down

from the top left shows Janeway and his wife, immunobiology professor Kim Bottomly, on their wedding day in March 1977. Their daughters Katherine Anne and Hannah Heath are pictured above and below, respectively.

Academy of Natural Sciences carried the journals *Science* and *Nature*, and its lone copy of each made its rounds through every lab before landing, worn and barely legible, on the shelves of the academy's decaying library. Due to politics between the university and the academy, university students were unilaterally denied access to the library. But Medzhитov, by wit, resourcefulness and charm, managed to get in. "I sweet-talked the librarians," he says.

Indeed, in the fall of 1992, the graduate student laid his hands on Janeway's paper and found his calling. Medzhитov wanted to study immunology, and he wanted to do so with Charles Janeway.

Medzhитov had been working on his doctorate by studying how molecules evolve to recognize each other; how, for example, a receptor and the signaling molecule that binds to it interact. As he read Janeway's theory about microbial patterns being picked up by human receptors, he was drawn to its logic. "Although I didn't know much about the subject," Medzhитov says, "I realized that the way he thinks, I think."

The problem was that Medzhитov's department in Moscow had no supplies and, thus, its students gained no lab experience. As a "theoretical" protein biochemist who knew no one with the prestige or resources to back him, Medzhитov almost gave up.

But he didn't. He photocopied the Janeway paper. This was no simple feat, as it cost half his monthly student stipend of \$2. Then Medzhитov began e-mailing Janeway, using the solitary account shared by 400 faculty, staff and students, each of whom was allotted only 300 words a day in order to control the costs of operating the account.

Janeway, meanwhile, had no idea of what to make of this unknown student who was writing to him. Recalls Bottomly, "Charlie told me, 'I've got this fabulously bright guy from Russia who wants to work in my lab.'" Not surprisingly, Bottomly was skeptical.

Medzhитov set to work. He won a fellowship given to scientists in developing countries by the United Nations Educational, Scientific and Cultural Organization. That would get him to the United States for three months in 1993 to work in the lab of Russell F. Doolittle, P.H.D., at the University of California, San Diego. Medzhитov scraped together the plane fare by borrowing from a cousin.

Money in hand, Medzhитov faced another hurdle before he could leave for California: getting a passport. As the Soviet Union was unraveling politically, Medzhитov was considered a citizen of nowhere, having been born in Uzbekistan, but not

residing there, and living in Russia, but not having been born there. In the end, the student wended his way through the bureaucracy. He reached California and began working in the burgeoning area of bioinformatics, in which scientists were beginning to write software to comb through and order databases of decoded DNA sequences.

Medzhитov continued to correspond with Janeway. In fact, the Moscow student spoke nonstop about Janeway's ideas to Doolittle, who in turn arranged a seminar at which Medzhитov could present his work. Attending that presentation, given in halting English, was Richard W. Dutton, P.H.D., then the president of the American Society of Immunology. When Dutton caught wind of Medzhитov's ambition of working with Janeway, Dutton immediately called his colleague in New Haven. He told him, "You have to hire Medzhитov."

And Janeway did. "Dick's phone call tipped the balance," he says.

Medzhитov arrived at Yale in January 1994 as Janeway's postdoc. He set out to show that the innate immune system could recognize molecules that did not belong in the human body—via alien patterns carried by the invaders. And once the system did its duty, Medzhитov had to show that it could transmit this information to the adaptive immune system. The first task was this: find at least one example of a pattern recognition receptor on some cell in the body that could be linked to innate immunity.

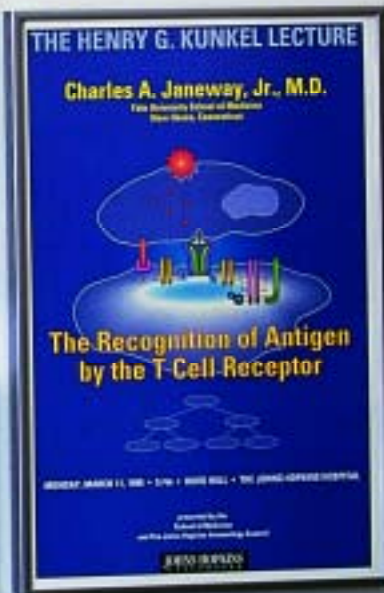
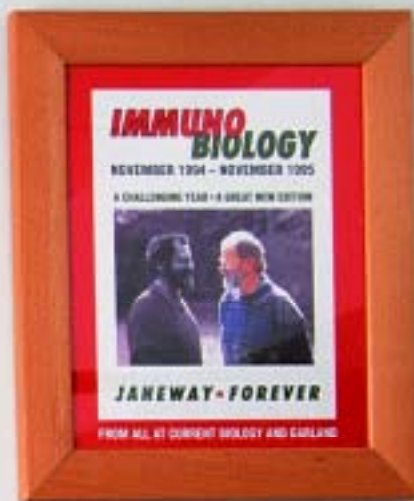
The beginning stages looked grim. Medzhитov says Janeway tried to instill confidence by telling him, "Lab work is a lot like cooking." Medzhитov answered sheepishly, "I've never cooked, either."

After several unsuccessful attempts to pinpoint the candidate receptor using conventional methods, Medzhитov turned to the experience he had gained in bioinformatics. He began with a template—a DNA sequence for a human gene that encodes the interleukin-1 (IL-1) receptor, a mammalian protein known to trigger inflammation. The receptor itself, however, is triggered by a cytokine, rather than a microbial pattern.

Perhaps humans bear another receptor like IL-1 that could spur the adaptive arm of immunity, the researchers reasoned. With the IL-1 gene sequence and others like it, Medzhитov began searching through warehouses of DNA for sequences for novel genes expressed by all kinds of organisms, from fruit flies to humans. In early 1996, he finally hit pay dirt.

Medzhитov found and decoded a new human gene. It resembled the gene for IL-1 and one other—a fruit fly gene





OPPOSITE Also displayed on Janeway's office wall are photographs of four generations of Janeway doctors. Top left, below the photo of the boat, is Janeway's great-grandfather, Edward Gamaliel Janeway—"beside a

body that could be living or dead as he was a professor of medicine and pathology at Bellevue," Janeway points out. "Below him is my grandfather, Theodore Caldwell Janeway, whom I never knew as he died in 1917 of pneumococcal

pneumonia. He described the famous 'Janeway lesions.'" Next is Janeway's father, who discovered gamma globulin deficiency, followed by Janeway and Bottomly three years ago at the wedding of their daughter Katie.

dubbed *toll* for the German word that means "amazing." Geneticist Kathryn Anderson, PH.D., at Memorial Sloan-Kettering Cancer Center, had shown in 1988 that insect *toll* orchestrates the assembly of flies' front and back sides during development. At the time of her discovery, however, no one could make a clear connection between fly development and human immunity.

Then in the spring of 1996 in the Cape Ann village of Annisquam, Mass., Medzhitov and Janeway hosted a meeting of scientists who wanted to delve into the connections between microbial defense in insects and human immunity. Fly guru Jules A. Hoffmann, PH.D., director of the Institute for Molecular and Cellular Biology at the Centre National de la Recherche Scientifique in Strasbourg, France, had written a Human Frontiers in Science grant and asked Janeway and others to join in. Janeway, in turn, saw the collaboration as an opportunity to advance the use of fly genetics to probe the molecules important in human immunity.

Says Hoffmann, in admiration, "Not many M.D.s would have been interested in flies." Especially when scientists had no hard evidence of any insect-mammal connections in this area of immunology.

At that meeting on Cape Ann, Hoffmann announced his surprising discovery: that flies with defects in their *toll* genes became hypersusceptible to fungal infection. He waved about a photograph of an infected fly covered with a fuzzy fur of fungus. The photo appeared on the cover of the journal *Cell* later that year.

Janeway and Medzhitov could barely contain their delight. Could their human *toll* perform the same antifungal tour de force? Immediately, Medzhitov set to work. In essence, he wanted to know if human *toll* functioned as a sensor—a molecular scout for microbes—as well as a signaler to the adaptive immune system. After a year of experimentation, the answer to both questions was a resounding yes.

"The discovery that *toll* was part of the recognition pathway gave the field a handle on the most front-line sensor within the circuit," says immunologist Michael A. Zasloff, M.D., PH.D., dean of research and translational science at Georgetown University School of Medicine.

The findings appeared in the July 24, 1997, issue of *Nature*.

THE FRENCH FLY CONNECTION

Two and a half years later, the idea of innate immunity in humans and its connections to defense in invertebrates had already taken hold. At least 150 scientists gathered at a

National Academy of Sciences colloquium in Irvine, Calif., entitled "Virulence and Defense in Host-Pathogen Interactions: Common Features between Plants and Animals." At the meeting, 12 researchers specifically discussed their work on *toll* in flies and "*toll*-like receptors"—as the mammalian versions are now known—and other aspects of innate immunity. Two dozen other scientists focused on patterns common to the insect and mammalian pathogens.

By March 2001, scientists had found 10 other human *toll*-like receptors, including *toll*-like receptor 2, which Shizuo Akira, M.D., and colleagues at Osaka University showed responds to a particular sequence found in bacterial DNA but not in mammalian DNA. To get an idea of how fast the field has grown since 1997, a literature search for the term "*toll*-like receptor" in February brought up 450 abstracts.

Other biochemicals that operate in the *toll* pathway have also come to light. Dozens of labs have focused solely on the tail end of the *toll* pathway—the production of the antimicrobial peptides that constitute the body's ancient first line of defense. For example, Hoffmann launched a pharmaceutical company in Strasbourg called EntoMed to exploit the antimicrobial peptides produced by flies, moths and other insects after *toll* pathway stimulation. Micrologix Biotech Inc. in Vancouver, B.C., for example, has reached the late phases of clinical trials for drugs to prevent catheter-related infections and is testing other compounds to treat acne and to prevent infections caused by a particularly recalcitrant bacterium known as methylene-resistant *Staphylococcus aureus*.

Georgetown's Zasloff has focused on boosting the body's ability to quickly spot and deal with a microbe. "We could create a class of immunostimulants," suggests Zasloff, whose laboratory is exploring compounds meant to do exactly that.

The evolutionary connections have also awed researchers, as they eventually found *toll*-like molecules in worms, mice, even plants. Plant geneticist Santosh Misra, PH.D., and colleagues at the University of Victoria in British Columbia have genetically engineered antimicrobial peptides into potatoes to get the crops to withstand fungal infection. Protective compounds produced by plants could conceivably work as new classes of antibiotics in people as well.

And there are even more fundamental questions being asked about *toll* and innate immunity. Quite simply, how are plants, flies and people connected in their defense against the microbes that infect them? And, as Janeway first proposed at the Keystone meeting, might the innate arm of immunity—

the more ancient system—actually be the means by which the body distinguishes itself from foreign invaders? If so, understanding its mechanisms might have crucial implications for the study of both infectious diseases and autoimmune disorders.

“This is the hottest area in immunology right now,” says Richard A. Flavell, PH.D., chair of the Section of Immunobiology.

Indeed, in the aftermath of their breakthrough, Janeway lobbied for Medzhitov’s recruitment for a faculty position at Yale. Medzhitov had seven other offers, including positions at Harvard and MIT, which he turned down. “I knew that at Yale I’d be given a lot of intellectual freedom to pursue riskier ideas,” he says.

Then, Janeway did something unusual: he handed over to Medzhitov the reins of their collaboration. Mentors often give away parts of projects to exiting postdocs. But to do so for “the biggest discovery in immunology in a decade is rare and typical of Charlie’s generosity,” Flavell says.

The decision had to do with Janeway’s personal circumstances as well as with Yale’s policy of discouraging direct competition between two faculty members working on the same project in the same department. In order to get Medzhitov in, Janeway would have to step aside. “It was an admirable move,” says Alfred L.M. Bothwell, PH.D., professor of immunobiology and an investigator in the interdepartmental Program in Vascular Biology and Transplantation.

The close-knit immunobiology faculty unanimously chose Medzhitov to join them as an assistant professor. They apparently bet on the right horse. Last year, Medzhitov was appointed a Howard Hughes Medical Institute (HHMI) assistant investigator, allowing him additional freedom to pursue less-conventional ideas. (Janeway, Flavell and four other members of the immunobiology faculty also have HHMI appointments.) Medzhitov has since identified at least seven more molecular players in the *toll* pathway and definitively characterized two of them, including an adapter protein he reported on in *Nature Immunology* last September.

When Medzhitov was first introduced to biochemistry, he was a college student in Tashkent as well as a field laborer required to pick cotton for two to three months each year (“one of the idiotic ramifications of the Soviet political system,” he says.). At 36, he is mapping new territory in an emerging discipline that has major implications for the treatment of disease. How did he get there?

“There is a hypothesis that if you have to struggle a bit early on, you’ll put more into it later,” says Bottomly.

Meanwhile, Janeway has added to his accomplishments. Two years ago, he was elected both to the National Academy of Sciences and to the American Academy of Microbiology.

“Charlie has had a succession of accomplishments,” says Carolyn W. Slayman, PH.D., the medical school’s deputy dean for scientific affairs. “But this [discovery of the essential role played by innate immunity] is the most colorful of them.”

A TEXTBOOK CASE

Despite his scientific success, Janeway has struggled in recent years. A researcher who spent his career studying the body’s defense system, he fell prey to its limitations. A year after Medzhitov arrived at Yale, Janeway began to complain of fatigue. A series of medical exams and tests over the next several months showed that Janeway had developed B-cell lymphoma, and that it had progressed from the bloodstream to his brain. He’s now in remission but a relapse in 1999 and several years of treatment have drained him.

He has reduced his lab personnel and steered back toward his initial interests. He is currently working on projects to develop vaccines against diabetes and autoimmune diseases such as multiple sclerosis. In December, he flew to London to work on the next edition of his immunology textbook. And this February, he traveled to another Keystone meeting to brainstorm with Hoffmann and other colleagues about ancient defense systems.

While cancer may have limited Janeway in some ways, people about the lab characterize him now as much more mild and reflective. Indeed, in talks and conversation, he refers often to his personal history, which is encapsulated on a wall of his cramped office.

There, in a display of photographs, hangs a column of personas, a legacy of medical minds. Near the top is a 19th-century photo of Janeway’s great-grandfather, New York City Health Commissioner Edward Gamaliel Janeway, M.D., posed in formal attire next to a person on a gurney. He is lecturing a crop of medical students. (Janeway notes that his great-grandfather was a pathologist, making it hard to say if the subject of the lecture was a patient or a cadaver.) Next is his son, professor of medicine Theodore Caldwell Janeway, M.D., who died in 1917 after contracting pneumonia from the soldiers he treated in an Army camp. Next there is pediatrician Charles A. Janeway, M.D., Janeway’s father and longtime chief of pediatrics at Boston Children’s Hospital, who in 1953 discovered, reported and successfully treated the first cases of gamma globulin deficiency. And there is Janeway himself, wearing a summer suit and boutonniere, standing next to Bottomly at the wedding of their daughter Katherine Anne Janeway in the summer of 1999.

In his presidential address to the American Association of Immunologists five years ago, Janeway referred to Robert Frost’s “The Road Not Taken,” comparing life’s choices to forks in the road. These decisions, sometimes taken on a whim, “have a profound impact on our lives,” he said. By handing the *toll* project to Medzhitov, he knew he was relinquishing a chance for greater fame, but his satisfaction in seeing his younger colleague thrive made awards seem unimportant. Choosing to mentor Medzhitov, says Janeway, has made all the difference: “He basically changed my whole outlook on immunology, on life.” **YM**

TRISHA GURA is a science writer in Cleveland, Ohio.

FRANK POOLE is a photographer in New Haven.



**Yale University School of Medicine,
Alumni Reunion Weekend
Thursday, Friday and Saturday
June 6, 7 and 8, 2002**

Thursday, June 6

Yale Surgical Society

A Tribute to the Contributions of the Section of Plastic and Reconstructive Surgery

Cocktail Reception

Surgical Grand Rounds

History of Plastic Surgery
Martin Robson, M.D., HS '71

Dinner

Union League Café

Friday, June 7

Tour of Historic New Haven

AYAM Executive Committee Meeting

Welcome to Reunion 2002
Francis R. Coughlin Jr., M.D. '52

Dean's Reception

Greetings and Remarks
David A. Kessler, M.D., Dean

New England Clambake

Saturday, June 8

THE GROWTH OF WOMEN IN MEDICINE: PROGRESS THAT BENEFITS US ALL

Moderator
Merle Waxman

How Women Were Admitted to the Yale School of Medicine in 1916
Susan J. Baserga, M.D. '88, PH.D. '88

Women's Health Research at Yale: Evolving Knowledge and Changing Practice
Carolyn M. Mazure, PH.D.

Women and Heart Disease: Translating Research into Practical Benefits
Teresa L. Caulin-Glaser, M.D.

AYAM Annual Business Meeting

Presentation of the AYAM Distinguished Alumni Service Awards
2002 Recipients
Daniel L. Arons, M.D. '67
Gilbert F. Hogan, M.D. '57

Sherry/Buffer Luncheon

Class Reunion Program

Guided Tours
CAB Building
Yale Center for British Art

CLASS DINNER LOCATIONS

- 1952 & prior**
The Graduate Club –
Friends of the 50th Dinner
- 1957**
Home of Dr. & Mrs. William Kissick
- 1962**
New Haven Lawn Club Lounge
- 1967**
Adriana's Restaurant
- 1972**
Graduate Club Library
- 1977**
Union League Café
- 1982**
Hot Tomato's Restaurant
- 1987**
Scoozzi's Restaurant
- 1992**
Zinc Restaurant
- 1997**
The Graduate Club –
Friends of the 50th Dinner

For ticket and additional information, contact: Sharon R. McManus, Director, Office of Alumni Affairs, Yale University School of Medicine, P.O. Box 7613, New Haven, CT 06519; (203) 785-4674, (203) 737-5153 Fax.

**Association of Yale Alumni In Public Health, Alumni Day 2002
New Haven Lawn Club**

Friday, June 7

PUBLIC HEALTH CHALLENGES OF THE 21ST CENTURY

Public Health Preparedness: Health Emergencies in Large Populations
Gilbert Burnham, M.D., PH.D., Johns Hopkins School of Public Health

Alumni Luncheon

Awards Ceremony

Distinguished Alumni Award 2002 Recipient
Sheila W. Wellington, M.P.H. '68, CEO, Catalyst Former Secretary of Yale University

Public Service Honor Roll Ceremony Presentation
Susan S. Addiss, M.P.H. '69, Chair, AYAPH Awards Committee

Public Health Preparedness: A View from the Field
Moderator
Paul Locke, DR.P.H. '80, J.D., General Counsel, Trust for America's Health

Panelists
Kelly Buller, M.D., M.P.H. '92, American Red Cross Disaster Program

Hilda Chaski, M.P.H. '87, Director of Epidemiology, St. Louis Health Department

Raul Cuadrado, M.P.H. '63, DR.P.H., Dean Emeritus and Professor, Nova Southeastern University

Michael Israel, M.P.H. '80, President & CEO, Duke Medical Center

Scot Phelps, M.P.H. '95, J.D., Manager, Emergency Services, Phelps Memorial Hospital Center

Marie Roberto, DR.P.H. '89, Chief, Health Policy, Planning and Evaluation, CT Department of Public Health

**Yale University School of Nursing, Alumnae/i Association
45th Annual Alumnae/i College Weekend**

Friday, June 7

THE HELIX OF HEALING RELATIONSHIPS

Seeing ...Hearing ... Feeling ... Creative Teaching Methods
Moderator
Linda Honan Pellico '89

The Year in Review
Catherine L. Gilliss, Dean

Linking Research to Mission
Moderator
Margaret Grey '76

Yale School of Nursing: Spring-board to Professional Excellence
Moderator
Paula Milone-Nuzzo

Social Hour and Banquet
The Quinpiack Club

Saturday, June 8

YUSNAA Annual Meeting

Silver Celebration of the Graduate Entry Program
Moderator
Dorothy Sexton

Lunch in Honor of Former Dean Donna Dier's Retirement

For information, contact Barbara Larkin, Yale University School of Nursing, 100 Church Street South, P.O. Box 9740, New Haven, CT 06536-0740; (203) 785-2389, barbara.larkin@yale.edu.

PSYCHOLOGIST TO LEAD CHILD STUDY CENTER

Alan Kazdin, an expert on the behavioral problems of children, is named center's fifth director.

Early in his career as a clinical psychologist, **Alan E. Kazdin, Ph.D.**, asked two fundamental questions about the work he was doing with emotionally troubled children: Does treatment work? And if so, why?

These questions might seem obvious, but Kazdin, the John M. Musser Professor of Psychology and professor in the Child Study Center, was surprised by how infrequently they were asked. "There are hundreds of interventions in practice but very few of them are examined in research. The key is making sure there is firm empirical evidence to guide patient care."

That desire to know what works, and why, has made him an expert on empirically based treatment and one of the most frequently cited authorities on aggressive and violent behavior in children. His reputation as a down-to-earth problem solver and a personable leader with a sense of humor helped him guide the Department of Psychology through a major period of transition from 1997 to 2000.

All of these qualities contributed to his appointment at the end of February as the fifth director of the Yale Child Study Center, one of the medical school's 22 academic departments and an international leader in child psychiatric treatment, research and professional training. The center was founded

in 1911 by child development pioneer Arnold Gesell, M.D., Ph.D.

"Of the 75 or so chair appointments I've made, this is one of the three or four best. Alan Kazdin is a distinguished scholar and [was] an extraordinarily successful chair of the Department of Psychology," Yale President Richard C. Levin said when he announced Kazdin's selection February 28 in the center's Harris Auditorium. In a letter to medical school faculty later that day, Dean David A. Kessler, M.D., cited Kazdin's accomplishments, including 10 years of MERIT funding from the National Institutes of Health, 500 journal publications and 35 books, then added: "What cannot come across in reading about Dr. Kazdin's background—but what I have come to learn and appreciate during countless hours of discussions with him over the last several weeks—is his deep commitment to child psychiatry and the Child Study Center. He has enormous respect for the center's faculty and its staff and is very eager to build on the pre-eminence of its programs."

A Cincinnati native raised in Los Angeles, Kazdin received his doctorate in clinical psychology from Northwestern University in 1970 before teaching at Penn State and, later, the University of Pittsburgh School of Medicine, where he directed both inpatient and outpatient services for children with psychiatric disorders. In 1989, Kazdin joined the Yale psychology department with a joint appointment in the Child Study Center. As the center's director, he succeeds Donald J. Cohen, M.D. '66, who died in October.

Kazdin, who assumed his duties on April 1, leads a faculty of about 90 members who are involved in an extremely wide range of activities and have special expertise in autism,

Asperger and Tourette syndromes, obsessive-compulsive disorder, developmental disorders and the problems of children exposed to violence. "The center today is a world-ranked institution," said Edward F. Zigler, Ph.D., a founder of the federal Head Start Program and a professor in both the Child Study Center and psychology department for the past 40 years. As for Kazdin, Zigler added: "He is without a doubt the finest child clinical psychologist in the United States today."

In an interview in March, Kazdin said he is awed by the center's greatness and, in close collaboration with the faculty, hopes to extend it.

"Yale has this tradition of taking a place that's really great and asking, 'How can we do this even better?'" he said. "The Child Study Center is Yale at its best. It has a stellar faculty and a tremendous reputation, and we are in the wonderful position of being able



MICHAEL MARSLAND

Alan Kazdin, former chair of the Department of Psychology, became director of the Yale Child Study Center on April 1.

**CAROLYN MAZURE, A LEADER
IN WOMEN'S HEALTH RESEARCH,
APPOINTED ASSOCIATE DEAN**

to build on that, thanks to commitments made by the president and dean." These include provisions for additional slots to hire new faculty, a review of the salaries of all existing faculty "to make sure the greatness we have here is secure" and additional resources to support the center's future growth. "Captain Kirk said space is the final frontier," Kazdin quipped. "That applies very much to a university, too."

As chair of the psychology department, Kazdin took charge at a moment when several senior faculty members were nearing retirement and others had moved to other universities. He guided the faculty in recruiting fifteen new members, including five in the senior ranks—more than half the current department, said Peter Salovey, PH.D., professor of psychology and of public health, who succeeded Kazdin as psychology chair. "Alan is an energetic recruiter and an inspired organizer of research," Salovey said. "I think he'll be terrific in this new role."

Kazdin will continue to direct the Yale Child Conduct Clinic, an outpatient treatment service for children and their families that he brought to Yale from Pittsburgh, but his focus will be on the Child Study Center.

"I'm eager to meet with the faculty and discuss what they perceive as strengths and weaknesses and to move on those issues with their help," Kazdin said before assuming his new duties. "We have to solve the problems of child psychiatry. That requires discipline and careful planning. It's something we'll do together, and my job will be to mobilize that plan."

Carolyn M. Mazure, PH.D., professor of psychiatry and director of Women's Health Research at Yale, has been named associate dean for faculty affairs at the School of Medicine. Her responsibilities include overseeing the appointment and promotion process, providing counsel to the dean and deputy dean for academic and scientific affairs regarding faculty issues and collaborating with other key members of the medical school administration to facilitate the academic life of the faculty. Mazure assumed her new role in February.

Mazure will also continue to direct Women's Health Research at Yale, the largest interdisciplinary women's health research program in the country. The program funds innovative studies in women's health and focuses on understanding sex-specific determinants of health and disease. Mazure has played a national role in support of research funding, testifying before the U.S. Congress in two consecutive years.

A member of the faculty since 1982, Mazure has focused her research on depressive disorders, and she remains an active clinician. She has served on special ad hoc and standing grant review committees for the National Institute of Mental Health. She is interested in predictors of illness onset and outcome in depression and, more recently, in addictive disorders. She is the principal investigator for the NIH-

funded Yale Interdisciplinary Women's Health Research Scholar Program on Women and Drug Abuse, and is the principal investigator for the Sex-Specific Factors core of the NIH-funded Transdisciplinary Tobacco Use Research Center, studying sex-specific factors in nicotine dependence and treatment.

Mazure was director of the Adult Inpatient Psychiatry Program for nine years, and more recently was chief of psychology for the Yale-New Haven Psychiatric Hospital. She is a fellow of the American Psychological Association and serves on two editorial boards.



JANE STITELMAN

Carolyn Mazure will oversee the appointment and promotion process and advise the administration on faculty matters.

**RENOWNED NEUROSURGEON,
SPECIALIST IN BRAIN TUMORS,
NAMED ENDOWED PROFESSOR**

Joseph M. Piepmeier, M.D., who specializes in brain tumors and spinal cord traumas, has been appointed the Nixdorff-German Professor of Neurosurgery. A member of the Yale faculty since 1982, Piepmeier serves as director of the Neuro-oncology Unit at the Comprehensive Cancer Center and is director of the School of Medicine's Neuro-oncology Laboratory. In both the clinic and the laboratory he focuses on neuro-oncology and is among the first neurosurgeons in Connecticut to use the gamma knife, an instrument that allows surgeons to operate on the brain without using a scalpel.

Piepmeier has served as a co-investigator on two research projects on spinal cord trauma, the National Acute Spinal Cord Injury Study II and the National Acute Spinal Cord Injury Study III. He was also the primary investigator on several grant-funded research projects on brain abnormalities. Piepmeier's honors include an Allied National Research Award and the Wakeman Award for Research in the Neurosciences. Piepmeier has been a visiting professor and lecturer at universities across the globe, including the Nippon Medical School in Tokyo, the Al Shorouk Hospital in Cairo, the Hospital Sainte-Anne in Paris, the University of Lund in Sweden and the University of Torino in Italy. The chair of the American Association of Neurological Surgeons from 1999 to 2001, he is currently secretary of the Neurosurgical Society of America and of the Connecticut Neurosurgical Society. He is editor-in-chief of the *Journal of Neuro-oncology*, and has served on the editorial boards of several other professional journals.



ROBERT LISAK

Joseph Piepmeier has been named the Nixdorff-German Professor of Neurosurgery.

NOTES

A *New York* magazine cover article titled "Surgery Without Scars ..." has included nine surgeons in the Yale Medical Group on a list of the top 100 minimally invasive surgeons in the tri-state area. The surgeons are **KEVIN R. ANDERSON, M.D.**, **JOHN A. ELEFTERIADES, M.D.** '76, HS '83, **AMY L. FRIEDMAN, M.D.**, **RICHARD GUSBERG, M.D.**, **JAMES C. ROSSER JR., M.D.**, **RONALD R. SALEM, M.D.**, **CLARENCE T. SASAKI, M.D.** '66, HS '73, **NEAL SEYMOUR, M.D.**, and **ROBERT UDELSMAN, M.D.**



SONJA V. BATTEN, PH.D., has been hired as the associate director of Women's Health Research at Yale. Batten has demonstrated talents in research, clinical work, supervisory responsibilities and educational outreach efforts. Her primary interest is the effect of traumatic events on women's psychological and physical health. Batten earned her PH.D. in clinical psychology from the University of Nevada, Reno, and interned at the Medical University of South Carolina. She is completing a two-year postdoctoral fellowship with the Women's Health Sciences Division of the National Center for Post-Traumatic Stress Disorder in Boston.



PAUL G. BARASH, M.D., professor of anesthesiology, delivered the Winter College Lecture to the College of Anesthetists at the Royal College of Surgeons in Ireland in December. His lecture was entitled *Myocardial Ischemia Monitoring: A Sequential Systems Approach*. This lectureship is one of two awarded annually by the Royal College and is delivered by a prominent individual who is nota fellow of the college. Barash also served as one of the judges for the Annual Registrar Research Award.



A symposium and reception to honor the contributions of **SIDNEY J. BLATT, PH.D.**, professor of psychiatry and psychology, were held on April 13 at the annual meeting of the American Psychological Association's Division 39 (Division on Psychoanalysis). Paul Wachtel, distinguished professor of psychology, and Diana Diamond, associate professor of psychology, both at the City University of New York, and former students of Blatt, made presentations at the symposium. The events were sponsored by institutions and organizations with which Blatt has been affiliated during his career, including the Yale Departments of Psychiatry and Psychology; the Austen Riggs Center in Stockbridge, Mass.; The Sigmund Freud Center for Psychoanalytic Research at the Hebrew University of Jerusalem; The Western New England Institute for

Psychoanalysis; The Institute for Psychoanalytic Training and Research; The Society for Personality Assessment; The Connecticut Society for Psychoanalytic Psychology and the Sections on Clinical Research and Clinical Practice of the APA's Division 39.



VALERIE MAHOLMES, PH.D., above, the Harris Assistant Professor of Child Psychiatry, and **JAMES P. COMER, M.D.**, HS '67, the Maurice Falk Professor of Child Psychiatry and founder of the 33-year-old School Development Program, spoke at the opening of The Discovery Room at Public School 28 in Paterson, N.J., in January. The Discovery Room is a Yale program that was first developed during Comer's "School Power" days. Maholmes revived the program and tailored it to meet the needs of children with behavioral problems. Students are provided with instruction and support and are taught how to interact appropriately in the classroom, with the ultimate goal of improving their academic achievement.



MARTIN E. GORDON, M.D. '46, clinical professor of medicine and chair of the Cushing/Whitney Medical Library Associates' board of trustees, was a finalist in the basic and clinical category of the Time Inc. International Health and Medical Media Competition in November, for his film *Microscopy, Tools of the Biomedical Sciences*. Created in honor of the Yale University Tercentennial Celebration, the film was supported by an unrestricted grant from the Carl Zeiss Foundation.



Yale School of Medicine Dean **DAVID A. KESSLER, M.D.**, was elected in January to chair the board of directors of The Elizabeth Glaser Pediatric AIDS Foundation. He will lead the foundation's efforts to improve the lives of children worldwide through pediatric research, training and advocacy. Kessler served as commissioner of the U.S. Food and Drug Administration from 1990 to 1997, where he spearheaded efforts to accelerate drug review, improve food labels and curb teenage tobacco use. In 2000 the Elizabeth Glaser Pediatric AIDS Foundation created the Glaser Pediatric Research Network, which consists of five academic medical centers that collaborate on finding better treatments for seriously ill children, training pediatric clinical investigators and serving as a united voice to advocate for policies that improve children's health worldwide.



WILLIAM V. TAMBORLANE JR., M.D., professor and section chief of pediatric endocrinology, is heading a national group that will be testing the most advanced blood sugar sensing technology for children with type 1 diabetes, research that may lead to the first artificial pancreas. The project, involving five centers around the country, is sponsored by the National Institute of Child Health and Human Development. In addition to Yale, the group includes

diabetes centers at the University of Colorado, Stanford University, the University of Iowa, and in Jacksonville, Fla. The first study the centers will undertake is validating the accuracy of the two available glucose sensors and how they work under various conditions, such as during exercise or after eating different meals.



ANTHONY N. VAN DEN POL, PH.D., professor of neurosurgery, was awarded a \$1.4 million grant from the National Institutes of Health to study a neurotransmitter whose loss in the brain is believed to be responsible for narcolepsy, an often-misunderstood disease marked by an uncontrollable desire to sleep. The grant will enable van den Pol and colleagues in his lab, including Xiaobing Gao, Ph.D., and Ying Li, Ph.D., cellular electrophysiologists, and Prabhat K. Ghosh, Ph.D., associate research scientist, to focus on the electrical behavior of the nerve cells in the hypothalamus that make hypocretin.

SEND FACULTY NEWS TO
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06519-0612, or via e-mail
to claire.bessinger@yale.edu.



ERIC KANE (7)

TOP As usual, pranks by other classes abounded at the Saturday night performance. This year a balloon mocked the show's title.

ABOVE Nancy Angoff, one of the show's many targets, wears a bemused smile as the Class of 2004 teases her, with affection.

ANOTHER SECOND-YEAR SHOW: UTTERLY FORGETTABLE, AND WELL WORTH REMEMBERING

Behind every great fortune, the saying goes, lies a great crime. The same could be said of the second-year show. Always committed with the best of intentions, the foul deed exists largely to drive the plot forward and send second-year students singing and dancing to a finale of forgiveness. In recent years the crimes have included the theft of the Cushing brain collection and the cloning of Robert H. Gifford, M.D., HS '67, the former deputy dean for education. The crime in *O Doctor, Where Art Thou?*, the revue presented by the Class of 2004 in February, was the kidnapping of Dean David A. Kessler, M.D. It fell to the second-years to find and rescue the dean since, as the script would have it, fourth-years were on the wards, first-years were busy with their studies and third-years just wouldn't show up.

The second-years raced through the medical school in search of Kessler, displaying a preoccupation with strange diseases, first-year students, sex, digital rectal exams, third-year students, anatomy professors, fourth-year students and bodily functions.

One of the show's leading targets this year was Nancy R. Angoff, M.P.H. '81, M.D. '90, HS '93, associate dean for student affairs. In a devastating impersonation, Michael Shapiro donned a salt-and-pepper wig plus Angoff's trademark calf-length skirt, boot and sweater combination, as he portrayed her announcing the dean's kidnapping to shocked students.

Angoff herself then appeared from the wings angrily demanding, "Who the hell are you?" By the end of the scene,

Angoff and Shapiro were singing a duet of "Bosom Buddies."

"You know I'll always be there for you if you ever have a problem," sang Angoff.

"Yeah, if I plan my problem three months in advance. Louise said you're booked until May," answered Shapiro.

No show would be complete without a dig at the dean and his past as a thorn in the side of the tobacco industry. With the dean missing, an impostor takes his place, but gives himself away by remembering people's names and, yes, smoking cigarettes. By show's end the kidnapper is revealed to be Peggy Bia, M.D., professor of medicine. Her motive? Kessler rejected her proposal for a symposium on—what else—sex.

At the end, the real Kessler confronts Bia, portrayed by Margo Simon, only to forgive her. After a tap dancing sequence featuring Jillian Catalanotti, Reena Rupani, Richard Chung, Michael Shapiro and Carlos Wesley, the entire Class of 2004 took the stage to sing the praises of Yale Med to the tune of "Footloose."

"It's Yale Med, Yale Med
Just as great as they said
Tests—pass/fail
Submit them over e-mail ...
Everything's great at Yale Med."

TOP Kavita Mariwalla played the host and Spencer Epps bared his chest as the cabaña boy in "Who Nabbed the Dean?," a game show spoof. **MIDDLE** Allyson Bloom in "Club Med," a dance sequence in the second act. **BOTTOM** Dean David Kessler appeared as himself in "The Payoff" as he returned from his "kidnapping."



TOP Cordelia Carter and Elena Gimenez in "Sexual History," which made fun of doctor-patient encounters. **BOTTOM** For the traditional finale, the entire class gathered on stage to sing "Everything is Great at Yale Med!!!!"





At “the game”

The latest installment of “The Game” brought almost 400 alumni, faculty, students and their guests to the Yale Bowl on November 17. A lunch of New England clam chowder, hot dogs, chicken breasts, steak burgers, veggie burgers and five-year kettle beans, served by Dean David Kessler, preceded the game. Despite high spirits and splendid weather, the game ended in a loss, as Harvard’s football team trounced Yale, 35-23. **TOP LEFT** Anya Szeglin Enriquez, scheduled to graduate next year, with her daughter, Acadia, and husband, Louie, a fourth-year medical student. **BOTTOM LEFT** Jorge Galvez, a first-year medical student, escorted Clara Saldarriaga, a medical student from Medellin, Colombia, who was at Yale for a cardiology rotation. **TOP RIGHT** John Muller, from the Class of 1991, brought his wife, Suzanne, and their three children, Carolyn, John and James, to the game. **BOTTOM RIGHT** John Forrest, director of student research, and Ombudswoman and Associate Dean Merle Waxman cheered the team.

STEFFEN GRETTELLA (4)

SPOTLIGHT FALLS ON ANTHRAX CASE

After the fifth fatal exposure last fall, alumni in Connecticut pieced together the clues behind death of woman, 94.

A case of inhalation anthrax discovered in a small Connecticut hospital in November gave Ramin Ahmadi, M.D., M.P.H. '97, the scare of his life—and he was 7,000 miles away.

Ahmadi, program director for internal medicine at the 160-bed Griffin Hospital in Derby, Conn., was spending a lonely evening in the small city of Maizuro, Japan, where he'd just arrived to teach a course on health and human rights at the local hospital. Ahmadi had settled down on the sofa with a book and an Asahi beer. He was half watching the news in Japanese when Patrick Charmel, M.P.H. '83, his boss from back home, appeared on the screen. "I wondered," said Ahmadi, "if I was having visual hallucinations."

Charmel, the president and CEO of Griffin Hospital, was on every channel. Searching for a program in English, Ahmadi switched to CNN and soon had an explanation: a 94-year-old woman from the rural town of Oxford, Conn., had been diagnosed with anthrax. She was a patient at the community hospital where Ahmadi worked.

Back in Derby, Charmel and Kenneth J. Dobuler, M.D. '76, HS '79, chair of medicine at Griffin, were caught in what Dobuler described as a media maelstrom. The calls from journalists began minutes after word got out on Tuesday, November 20, that a patient at Griffin had inhalation anthrax, and attention intensified when she died the next day. Television satellite trucks encircled the hospital.



AP/WIDE WORLD PHOTOS

A decontamination crew wearing hazmat suits stands outside Otilie Lundgren's Oxford, Conn., home after the house was declared a crime scene in late November.

When Otilie Lundgren had arrived at the hospital the Friday before, she seemed to have a mild illness and was admitted largely because she lived alone. Her case looked more complicated by the next morning, a Saturday, when four blood cultures were found to contain sporulating gram-positive bacteria. When Lydia Barakat, M.D., FW '00, heard about the lab results that morning, she drove to the hospital to have a look. Barakat, who had trained at Yale in infectious diseases the year before, recalls telling the laboratory technician: "This looks exactly like anthrax, but what are the odds?" She didn't think it was a likely diagnosis for an elderly woman living in a rural town in Connecticut.

She did take the possibility seriously enough to ask Lundgren if she'd opened any powdery mail; Lundgren remembered none. Barakat prescribed three

antibiotics, including Cipro. By Monday, with more test results in, Barakat felt pretty sure she was seeing anthrax. Lundgren was getting sicker. Still, the treatment had begun early. "I had hope," Barakat said.

When State Epidemiologist James L. Hadler, M.D., M.P.H. '82, heard about the case that Monday morning, he was incorrectly told that only one blood culture had come back positive for the bacillus. "I was a little bit skeptical," said Hadler, an assistant clinical professor of epidemiology and public health at Yale. He suspected the positive culture might have resulted from contamination on Lundgren's skin when the blood was drawn.

Since early October, when letters containing anthrax were sent to prominent politicians and journalists, the state health department lab had been working seven days a week on "powder

incidents.” “We were already in full anthrax mode without having had a single case of anthrax,” said Hadler. “Since early October, my job had been 100 percent anthrax.” Suspicious substances had included nondairy creamer and powdered sugar.

Despite his skepticism, Hadler arranged for immediate transportation of the organism to the state laboratory, which was able to do confirmatory tests not done in hospitals (a phage test and a direct fluorescence antibody test). By Tuesday morning it seemed clear that Lundgren had anthrax. Hadler called the state health commissioner, the FBI and the Centers for Disease Control and Prevention (CDC). In the next 24 hours the CDC sent a dozen advisors to Hartford, since no one knew if Lundgren would prove to be a lone victim or the first of many.

The CDC wanted to get final confirmation, based on a polymerase chain reaction test. When Hadler tried to send Lundgren’s blood on the next flight from Connecticut to Atlanta, the airline balked. Hadler says there’s no way to get anthrax from bacillus in blood, even if it spills, but the CDC had to send its own plane. Meanwhile, staff from the FBI, the state police and the state Department of Environmental Protection drove to Oxford and cordoned off Lundgren’s house.

Back at Griffin Hospital, Charmel knew he needed to talk to Griffin employees before the story became public. More than 300 of the 1,100 hospital staff members attended a meeting that afternoon. Charmel told them about the case, urged them not to tell anyone the patient’s name if they knew it and reassured them that anthrax could not be spread from one person to another.

At about the same time, word of the case reached the media: Gov. John G. Rowland had announced a 5 p.m. press conference on a Connecticut anthrax case, and “about two minutes after that went out on the [news] wire,” Charmel said, “the phone began to ring off the hook.” He had a plan for responding. “The conventional wisdom is to pick a single hospital spokesman,” said Charmel. “My gut told me that wasn’t right in this situation.” The press, he said, “wanted to talk to clinicians. The public needed to see and hear from credible experts, to be reassured that everything possible was being done for the patient and that they were getting accurate information.” The panel that answered reporters’ questions included Charmel, Dobuler, Barakat and Stephanie Wain, M.D., FW ’89, chair of pathology and laboratory medicine at Griffin. (Ironically, Dobuler is a rarity among American physicians in having seen anthrax outside a textbook. As a Yale medical student, he spent three months studying infectious disease in Iran, where cutaneous anthrax is common among shepherds. Seeing anthrax then was interesting, he said, “but clearly irrelevant to my future.”)

Charmel’s media panel held news conferences and answered reporters’ questions nonstop until 1 a.m. A *Washington Post* reporter even managed to get Dobuler’s pager number. On the whole, Dobuler said, “the press did a remarkably credible job given the frenzy.” Although the hospital refused to name the patient, it didn’t take long for reporters driving around Oxford to locate a house surrounded by yellow tape and monitored by people in white suits.

Lundgren died Wednesday morning—“a very sweet lady who was

beloved by her family ... murdered,” said Dobuler. She was the fifth American since early October to be killed by anthrax. Although investigators never found anthrax spores in her house, Hadler said investigators are now “pretty sure” that Lundgren was exposed to contaminated mail. Spores were later found on four mail-sorting machines in the Wallingford, Conn., distribution center, including the bin that contained mail for Lundgren’s route.

Hadler says the case seems to disprove animal studies suggesting that thousands of spores are needed to cause an infection. “In theory,” he said, “one spore, in the right place at the right time, can do it. She seems to have had a low-dose exposure.”

The day that Lundgren died, Ahmadi returned to teaching his course at the Japanese hospital to find himself an object of interest. Physicians, residents, interns—even the cleaning woman—had seen his supervisor on television and were asking about Griffin Hospital by name.

Traveling halfway around the world, said Ahmadi, “you think you are getting away from New Haven and Griffin and Yale and your usual surroundings. You think you are somewhere very far away. Then you are reminded that you’re part of a little global village. It’s kind of unsettling.”

A Boston reunion

Over cocktails and hors d'oeuvres, about 50 Boston-area alumni and guests gathered at a reception at the Café Louis on Berkeley Street on February 21. The alumni spanned nearly a half-century, from 1955 to 2001, and included house staff and public health alumni. Among those attending were **FROM TO P** Katherine Auerswald, Class of 1998, with her husband, Phil, and their daughters; **FLOYD ATKINS** (left), who completed his residency at Yale in 1967, and **DANIEL ARONS**, Class of 1967; **MICHELE BAKER**, Class of 1997, **JAMES MORGAN IV** and **ELISSA ARONS**, Class of 1970; **PADRAIC BURNS**, Class of 1955, with **Iko Burns** and Associate Dean **Jane Reynolds** (center); and **FAR RIGHT** **Elliott Marcus**, who completed his residency at Yale-New Haven Hospital in 1959, came with his wife, **Nuran Turksoy-Marcus**, also a physician.



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1940s

AARON T. BECK, M.D. '46, professor emeritus of psychiatry at the University of Pennsylvania, was named a Fellow of the American Psychological Association (APA) for 2002. APA fellows are selected for their contributions to the research, teaching or practice of psychology. The APA, headquartered in Washington, is the largest scientific and professional organization representing psychology in the United States.

RICHARD W. FINNER, M.D., HS '49, a psychiatrist from San Bernardino, Calif., writes to say that he has retired.

Since retiring from the practice of internal medicine eight and a half years ago, **DAVID E. MORTO**, M.D. '48, HS '55, has been busy writing books, playing tennis, bowling, motorboating, and traveling around America and Japan. Morton writes that he misses his former patients, colleagues and nurses, but not the stresses of HMOs, malpractice, Medicare and Medicaid.

1960s

HAROLD J. ALFERT, M.D., HS '65, retired in December from the faculty of the department of urology at The Johns Hopkins University School of Medicine. Alfert writes that he plans to do "gentleman farming" on a newly purchased farm in central Virginia.



JOHN D. BAXTER, M.D. '66, HS '68, professor of medicine and director of the Metabolic Research Unit at the University of California, San Francisco, has endowed

the John D. Baxter Lectureship in Endocrinology at the Yale Medical School. The Baxter Lectureship is given biannually to an individual who has made seminal contributions to the field of endocrinology.

LAURENCE A. BOXER, M.D., HS '68, professor and director of pediatric hematology/oncology at the University of Michigan, was named the Norman Kretschmer Professor in September at his alma mater, Stanford Medical School. Boxer was the Grover Powers Lecturer in Pediatrics at Yale in March 2000. His wife, **GRACE JORDISON BOXER**, M.D. '68, is in the private practice of medical hematology/oncology. Their son, David, is on the staff at Columbia Teachers College and is engaged to be married this year.



ALICE COBB IPSEN, M.P.H. '67, who is retired and has lived in Denmark for the last 29 years, writes to say that "I draw, paint and make lithographs on stones—a far cry from public health." During her career in public health, Ipsen was at the University of Pennsylvania and the University City Science Center in Philadelphia.



NEAL KOSS, M.D. '66, HS '74, of Palos Verdes, Calif., is still practicing plastic surgery part time, while pursuing his hobbies, which include computers, photography, tennis and travel. Koss also writes that he now has three grandchildren to add to his enjoyment.



ELI H. NEWBERGER, M.D. '66, HS '67, assistant professor of pediatrics at Harvard Medical School, child advocate and jazz musician, has been appointed to the Berklee College of Music board of trustees. Newberger plays piano but is best known as a jazz tuba player and has made over 40 recordings with the New Black Eagle Jazz Band and others.

CHARLES T. POST JR., M.D. '68, an ophthalmologist, writes to say that he and his wife, Bonnie, spent three months sailing around Central America last winter. "Too many pals getting heart attacks and cancer, so I took the winter off from ophthalmology, bought a Little Harbor 58 named *Flight*—and away we went. I kept a journal of my impressions, one of which describes our visit with former classmate **RODRIGO MARTINEZ**, M.D. '68, in Honduras. We are both pilots, hence the name of my boat."

1970s

ROBERT W. BUCKINGHAM, PH.D. '78, professor of public health at New Mexico State University, returned recently from a sabbatical in Thailand, where he was a distinguished visiting professor of public health at Mahidol University in Bangkok.



JAMES R. MERIKANGAS, M.D., HS '73, of Chevy Chase, Md., is director of the neuropsychiatry program at the Georgetown University School of Medicine in Washington. Merikangas, also a lecturer in psychiatry at Yale, has begun a collaboration with the Center for Public Integrity in Washington, D.C., regarding the criminal justice system and prosecutorial misconduct.



ROBERT M. PEARL, M.D. '72, a plastic and reconstructive surgeon, is executive director and CEO of The Permanente Medical Group Inc. (PMG), the largest medical group in the nation. Pearl, a member of the Federation Executive Committee of the PMG, is responsible for strategy development and implementation of the national Internet and e-health care efforts for Kaiser Permanente, and on a national level he oversees the health care provided to eight million citizens across the nation. Classmate **DAVID MOYER, M.D.** '72, chief of the allergy department at Kaiser Permanente, sent this news to us.

1980s



DAVID A. COTTRELL, D.M.D., HS '88, was named chair of the Department of Oral and Maxillofacial Surgery (OMS) at Boston University School of Dental Medi-

cine (BUSDM) in January. He is also the director of the OMS Residency Program and of OMS Resident Research at BUSDM.



ROBERT V. LEVINE, M.P.H. '80, president and CEO of Peninsula Hospital Center in Far Rockaway, N.Y., received the Award of Distinction from the Metropolitan Health Administrators' Association (MHAA) in collaboration with the American College of Healthcare Executives at the MHAA annual dinner held in June in Queens, N.Y.



DAVID R. MARKS, M.D. '89, a health reporter for WVIT Channel 30 in Connecticut for the past four years, is now a health reporter on *The Today Show* on NBC. In 2001, while at Channel 30, Marks won a statewide journalism award from the Connecticut Chapter of the Society of Professional Journalists. The award, the Best In-Depth Television Report of the Year, was for his story about the influence of pharmaceutical representatives on doctors' prescription writing.

1990s

BRIAN G. COLE, M.D., M.P.H. '95, is an internist with the Maui Medical Group in Hawaii, where he runs the Lahaina Clinic on the island of Maui. Cole says that he loves his job, which includes working closely with the board-certified neurosurgeon on the island. He plans to open his own practice this winter in the town of Kihei. Cole lives in Maui, has a second home in Paris and likes to travel.

ALBERTO PEREZ MORELL, M.D., FW '98, writes to say "that thanks to [his] visiting research fellowship in plastic surgery at Yale with John A. Persing, M.D., and colleagues, [he is] able to share the knowledge with [his] fellows and students working in reconstructive microsurgery at Padre Rachads Oncology Hospital in Caracas." While at Yale, Morell completed a research project, *Further Investigations on the Effect of Prolonged Clamping and Vascular Stasis on the Patency of Arterial and Venous Microanastomoses*, which was presented at the New England Society of Plastic and Reconstructive Surgery.



PAULA I. WATNICK, M.D. '91, PH.D., assistant professor at Tufts University School of Medicine and New England Medical Center in Boston, received the Interscience Conference on Antimicrobial Agents and Chemotherapy Young Investigator Award from the American Society for Microbiology in December in Chicago. Watnick was given the award, which is sponsored by Merck U.S. Human Health, for her research on the environmental survival of *Vibrio cholerae*, the infectious agent responsible for cholera. Her genetic analysis of *V. cholerae* has advanced the understanding of bacterial evolution and the emergence of new pathogens and has defined environmental signals and regulatory genes that control the way *V. cholerae* attaches to surfaces, a process known as biofilm formation.

SEND ALUMNI NEWS TO
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to claire.bessinger@yale.edu.



FROM TOP David Morton walks his daughter Aiko down the aisle last July at her wedding in Colorado Springs; Laurence and Grace Jordison Boxer; Rodrigo Martinez (left) and classmate Charles Post next to Martinez's Cessna 122 in Honduras; Brian Cole during a vacation to Santorini, Greece.

DAVID W. BARRY, M.D. '69, HS '72, a prominent AIDS researcher, died on January 28 of a heart attack while on a business trip. He was 58.

Barry graduated magna cum laude in French literature from Yale College in 1965 and received his medical degree from the School of Medicine. He served his internship and residency training at Yale from 1969 to 1972. In need of an expert on yellow fever, the Food and Drug Administration (FDA) recruited Barry, who had studied the disease for his thesis. A year later he became the deputy director of the agency's virology division.

In 1977 he joined Burroughs Wellcome and became head of clinical investigation, later serving as director of worldwide research. While at Burroughs Wellcome, one of his first tasks was to develop the herpes drug acyclovir. Barry also was a co-developer of AZT, the first drug developed to treat the AIDS virus. Working with the FDA, the Burroughs Wellcome team pushed the drug through clinical and review stages in 22 months, establishing a model for fast-track approval of treatments for life-threatening diseases. He was an advocate for the AIDS "cocktail" treatment, which uses more than one drug to fight the infection.

After 18 years, Barry left Burroughs Wellcome, when it merged with Glaxo Holdings plc., to help start Triangle Pharmaceuticals in Durham, N.C., where he served as CEO and chairman of the board. Barry saw Triangle as an opportunity to do the impossible in the field of drug development. Rather than focus on therapies for common ailments, he wanted to cure the incurable diseases.

FRED W. BUSE, M.D. '33, of Roslyn, N.Y., died on June 27, 2001, of congestive heart failure at the age of 93.

Buse, born in the Whitestone section of Queens in New York City, served during World War II in the Army's medical field service school and received the European Theater of Operation Ribbon, the American Theater Ribbon and a Victory Medal.

A general surgeon who later specialized in plastic and reconstructive surgery, Buse was known for his innovative treatment for patients with catastrophic burns. Buse had a private practice in Flushing, Queens, and in the Manhasset Medical Center (now part of the Long Island Jewish Medical Center) until he retired in 1979. He served on the staff at the New York Hospital Medical Center of Queens and the New York Flushing Hospital Medical Center.

An avid jogger, swimmer and sailor, Buse walked daily to his practice in Flushing. He was buried at sea in a military ceremony by the U.S. Coast Guard off Point Judith, R.I.

EDWARD L. EYERMAN JR., M.D. '57, a retired neurologist from St. Louis, Mo., died on December 15 of complications from cancer. He was 69.

Eyerman was among a group of neurologists and neurosurgeons who helped introduce the imaging techniques of computed tomography and magnetic resonance to the St. Louis area. After completing an internship and residency training at the University of Virginia, the NIH and Columbia, he returned to his hometown in 1964 as an assistant professor of neurology at the St. Louis University School of Medicine. He also established a private practice in St. Louis and later had offices in Belleville and south St. Louis County.

In the mid-1970s Eyerman co-founded the former Neuroscanning Associates in St. Louis. He also did extensive research on multiple sclerosis and published widely on neurological advances. During his career Eyerman served on the medical staff at Memorial and St. Elizabeth hospitals in Belleville and St. Mary's Health Center in Richmond Heights.

JAMES R. FITZGERALD, M.D. '57, an orthopaedic surgeon from Ozona, Fla., died on December 9. He was 70.

Born in Hartford, Fitzgerald graduated cum laude from the University of Connecticut in 1953 before studying medicine at Yale. He practiced orthopaedic surgery in the Hartford area for more than 25 years, and was a member of the American Academy of Orthopaedic Surgeons. Fitzgerald retired to Naples, Fla., in 1984 and moved to Ozona in 1995.

EDGAR L. GEIBEL, M.P.H. '49, of Stamford, Conn., died at the Highland Center in Brackenridge, Pa., on December 8 of complications from acute inflammatory bowel disease. He was 90.

Geibel, born in Butler, Pa., served as the health officer for the city of Butler from 1936 to 1943. He attended the Carnegie Institute of Technology and graduated from the University of Pittsburgh in 1941. He served as a captain in the Army Medical Corps from 1943 to 1947 on the hospital ship Chateau Thierry. He was awarded the World War II Victory Medal, the European-African-Middle Eastern Campaign Medal, the Army Commendation Ribbon, the American Campaign Medal and the Asiatic Pacific Campaign Medal.

After receiving his master's in public health, Geibel served for five years as the assistant director of Genesee Hospital in Rochester, N.Y. In 1954 he returned to Connecticut and began a 23-year tenure at Stamford Hospital as chief administrator. Under his leadership the hospital experienced significant change and growth. Geibel was a lecturer in epidemiology and public health at Yale from 1961 to 1978. His affiliation with the Connecticut Hospital Association (CHA) spanned more than four decades; he served on various committees from 1955 to 1979 and as president of the CHA from 1964 to 1965. After his retirement he was a special advisor to the CHA from 1977 to 1983.

JACOB D. GOLDSTEIN, M.D., a retired anesthesiologist, died on February 3 at the age of 89.

Goldstein was a clinical instructor in anesthesiology at Yale from 1969 to 1970, when he was named assistant clinical professor. Goldstein became associate clinical professor of anesthesiology in 1982.

JAMES Q. HARALAMBIE, M.D. '35, a retired pediatrician, died of cancer on January 6 at The Connecticut Hospice in Branford. He was 92.

Born in Philadelphia, Haralambie earned his A.B. degree in 1931 from Oberlin College and his M.D. from Yale. He interned at the Massachusetts General Hospital, where he was on the house staff in pediatrics from 1935 to 1936, and did his residency in pediatrics at Children's Memorial Hospital in Chicago from 1937 to 1939. Haralambie was an instructor in pediatrics and director of the Pediatric Outpatient Service at the New York Hospital, Cornell University Medical College, from 1939 to 1941.

Haralambie started a private practice in Larchmont, N.Y., in 1941, but in 1942 he joined the Army as a captain. In 1946 he left the service with the rank of major after commanding the 183rd Station Hospital in Alaska. He resumed his practice until his retirement in 1978.

Haralambie also taught pediatrics at New York Hospital, retiring as clinical professor of pediatrics emeritus and honorary attending physician. He served as president of the Westchester County Medical Society from 1965 to 1966.

DAME SHEILA SHERLOCK, M.D., FW '48, an authority on liver disease and a pioneer in the science of hepatology, died on December 30 at her London home. She was 83.

Born in England, Sherlock earned her medical degree from the University of Edinburgh, Scotland, in 1941, after medical schools in England refused to accept her because of her gender. She became chair of the Royal Free Hospital's Department of Medicine in 1959, where she helped setup and direct a clinical, research and training center for liver disease.

Sherlock was at Yale from 1947 to 1948 as a Rockefeller Foundation postdoctoral fellow working with physiologist C.N.H. Long, M.D., who was then dean of the medical school. In 1966, she helped create what is now a standard test for diagnosing primary biliary cirrhosis, and in 1971 she showed that treating autoimmune hepatitis with steroids was effective. Her reference book, *Diseases of the Liver and Biliary System*, now in its 11th edition, "put liver disease on the international map," according to James L. Boyer, M.D., director of the Yale Liver Center. Peter Scheuer, M.D., a colleague of Sherlock's who wrote an appreciation of her career in Britain's *Guardian* newspaper in January, said that when she was starting out "the specialty of hepatology did not exist; Sherlock was its main creator, and, in a glittering 60-year career, became one of the world's most famous names in clinical science."

RICHARD C. THOMPSON, M.D., HS '46, of San Mateo, Calif., died on October 8, 2000, at his home. He was 80.

Thompson, a California native, received his medical degree from Stanford. He served in the Navy during World War II as a physician in Guam, Saipan and Japan. Thompson completed his residency in anesthesiology at Yale. In 1960 he practiced on the hospital ship HOPE, and in 1968 he embarked on a missionary practice in Ghana, where he originated a new treatment for venomous snakebites.

Thompson designed a mechanical retractor that bears his name and is used around the world to alleviate problems of manual retraction at the operating table. He was on the staff of Mills-Peninsula Health Services in California for more than 30 years.

RUTH WHITTEMORE, M.D., HS '44, a retired pediatric cardiologist who provided pre- and postoperative care for the baby who received the first "blue-baby" operation, died on December 27. She was 84.

Whittemore, a graduate of The Johns Hopkins University School of Medicine, joined the Yale faculty in 1947 as an instructor of pediatrics. At the request of the Federal Children's Bureau in 1947, she established and served as director of the first rheumatic fever and cardiac clinic in New England, which was located in the pediatrics department at Yale.

With the introduction of penicillin, the incidence of rheumatic fever began to decline and Whittemore devoted more of her time to children with congenital cardiac abnormalities. Her major research contribution to this field was a detailed, long-term follow-up study of her former patients to ascertain the congenital anomalies in the next generation.

During her 45 years at Yale, Whittemore also served as instructor of pediatrics, clinical professor of pediatrics and director of pediatric cardiology. She created and directed a lipid clinic to evaluate the children of parents who had died from heart attacks or strokes.

SEND OBITUARY NOTICES TO
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Reinventing surgery *continued from page 23*

the operating room, not later. If it comes back malignant, then we've done a really good thing."

"Say 'E' for me," he tells the patient.

"Eeeee," says the man, from behind the drape over his face.

"That's so good," says Udelsman. "It makes me so happy to hear that!"

Udelsman pulls off his latex gloves and writes notes about the case. Leaving the operating room, he lowers his mask to reveal a trim graying beard, grabs his briefcase, and walks quickly down the hall, through the surgeons' lounge and into the cramped transcription room. He picks up the dictation phone and spits out the details of the case without checking his notes or seeming to pause for a breath. The dictation complete, he takes a yogurt out of his briefcase and phones his office. For a promotions committee meeting later that day, he wants to know, "Am I leading this committee this afternoon, or am I going for the ride?" He asks about plans for a department party at his home and reminds his administrative assistant about a problem with his computer. He finishes his yogurt, tosses the container in the trash and pricks his finger to check his glucose levels. He has type 1 diabetes, diagnosed less than two years before at age 43, and he wears a glucose pump. He chomps half a glucose tablet, snaps closed his briefcase and heads out to greet the next patient. After two more operations, he will attend committee meetings for admissions, promotions and fund-raising and meet with the dean of the School of Medicine. If he can find time before heading home at 8, he will work on his article for the *Annals of Surgery*, "656 Consecutive Explorations for Primary Hyperparathyroidism."

"My biggest problem is time management," he says.

But for now, he is heading back to where he wants to be: in the OR, teaching a resident and a medical student how to do what he does.

"It's not how many thyroids can I do in my lifetime. Isn't it far better if I teach another generation to do it well?" **YM**

CATHY SHUFRO is a contributing editor of *Yale Medicine*.

GALE ZUCKER is a photographer based in Branford, Conn.



FROM "FIFTEEN YEARS OF GROWTH: YALE MEDICINE 1952-1967" IN THE SPRING 1967 ISSUE: "Speaking at the Yale Alumni Meeting in St. Louis in January this year, Dean [Vernon] Lippard noted: 'When Whitney Griswold invited me to take on the deanship (in 1952), he pointed out a number of problems that had to be faced, and I soon discovered others. The physical plant had many deficiencies; the relationship with the Grace-New Haven Hospital, as it was then called, was cordial but needed definition; the clinical departments did not, in general, measure up to the preclinical; the Department of Public Health was seriously undernourished; and there was, as there still is, need for more financial support for operation. On the other hand, there were assets that money could not buy—association with a great university; a glorious tradition; a faculty that, although thin in spots, was loyal and devoted; and a brilliant group of students.'"



FROM "RESEARCH IN MOLECULAR BIOLOGY," WINTER 1970: "A new department of Molecular Biophysics and Biochemistry was established at Yale last year to promote the interaction between advanced research in the biological sciences and the development of clinical techniques in medicine. It brought together two disciplines that were previously in separate departments.

"The former Department of Biochemistry at the medical school was one of the oldest in the country, having been founded in 1875 as the Department of Physiological Chemistry. The former Department of Molecular Biophysics was part of the Yale Faculty of Arts and Sciences and grew out of the Department of Physics shortly after World War II. ...

"In the past decade, with the enormous proliferation of knowledge in the biological sciences, department lines have become more and more arbitrary. It has been especially difficult to draw any intellectually meaningful boundaries for molecular biology, which now pervades the entire field. Thus, the joining of Molecular Biophysics and Biochemistry in one department brings together investigators whose studies range from questions of theoretical physics and chemistry to problems of clinical medicine."

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