

# Yale Medicine

New leader  
at YMG

4

Historic medical  
texts online

10

YSM's unsung  
heroes

26

spring 2013

## Targeting cancer

While some Yale scientists partner with industry to develop new cancer drugs, others want to know whether stem cells are to blame for cancer.

12





# SPRING 2013

## CONTENTS

- 2 Letters
- 4 Chronicle
- 8 Books & Ideas
- 10 Capsule

### 12 **Killing Cancer's seeds**

A controversial theory focuses on so-called cancer stem cells within solid tumors. Some at Yale believe a revolution in cancer care may be in the offing.

*By Marc Wortman*

### 18 **Pharma and academia partner for better health**

Yale joins forces with the pharmaceutical company Gilead Sciences to search for targets for new and improved cancer therapies.

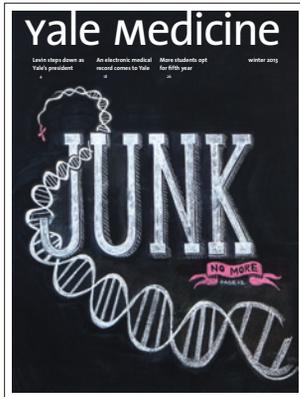
*By Kara Nyberg*

- 24 Faculty
- 26 Students
- 28 Alumni
- 32 In Memoriam
- 33 End Note

Illustrations by Sophie Casson

**On the Web**  
[yalemedicine.yale.edu](http://yalemedicine.yale.edu)

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



#### HOW TO REACH US

*Yale Medicine* welcomes news and commentary. Please send letters (350 words or fewer) and news items to *Yale Medicine*, 1 Church Street, Suite 300, New Haven, CT 06510, or via e-mail to [ymm@yale.edu](mailto:ymm@yale.edu), and include a telephone number. Submissions may be edited for length and content.

## Visit us on the Web

Our new website is up and running—and the feedback has been wonderful! Visit us at [yalemedicine.yale.edu](http://yalemedicine.yale.edu) and peruse the newest issue or issues going back to 1998.

### Meeting alumni on the residency trail

One of the highlights of my residency interview season was meeting alumni of our school. These encounters were among the most pleasant on the interview trail because the conversations would frequently turn to the Yale system. Having represented my colleagues on the school-wide Educational Policy Committee during medical school, I had the special privilege of helping carry out the committee's charge to interpret the philosophy of the Yale system and articulate its manifestation amid the challenges of modern medical education. With a certain pride and responsibility, I assured my alumni interviewers that indeed, there are still no class rankings or attendance lists; and yes, the thesis requirement still runs the graduating class a bit ragged around this time of year.

The unexpected reward from these interviews was discovering what happens after Yale. On the cusp of my own graduation I have wondered whether the Yale system and its pillars of self-motivated learning and innovation will still matter a few months from now. The answer, from the experiences of those who have come through the Sterling Hall of Medicine before me, is a remarkable 'yes.' One interviewer demonstrated the iPhone app he had designed to help patients track their lab results over time. Another described the fruitful collaborations she has made with faculty across her university to improve health outreach in the community. Another showed me pictures from her recent exhibition of paintings—a hobby she developed during an elective course at the Yale School of Art. What binds their stories together is not that Yale taught them how to program software, or find collaborators, or apply oil to canvas. These alumni suggested to me that the Yale system fostered an environment that encourages lifelong opportunities to augment their learning. They became physicians alongside the

exploration of complementary interests, not in spite of it.

As I prepare to retire my short white coat, I recognize now that the three words emblazoned across the left pocket—Yale Medical Student—represent much more than the position I have held for four years. I have been deeply inspired by the stories of these former students of medicine at Yale, and I am hopeful that my career as a physician will continue to be shaped by the Yale system, which has distinguished the school for over 80 years—and, as I have come to understand, finds new meaning in the lives of its graduates.

*Kevin Koo, M.D., '13  
New Haven, Conn.*

### Writing and medicine

The Internal Medicine Writers' Workshop was a big draw for me when I was interviewing for residency ["Writers' Workshop Celebrates 10 Years," *Yale Medicine Online*, Winter 2013]. I was an English major in college and I started to write stories about my experiences with patients during my third year of medical school. I began writing, and still do so, primarily as an outlet for the stresses of life in medicine. The first story I wrote was about an experience I had in med school taking care of a young woman who lost a baby during her second trimester. I write because the patients that we see every day—and their stories—are important. The Writers' Workshop has been the perfect outlet for me to share these stories. In the workshop, I have seen emotions and passions in my coworkers and friends that I had not witnessed while working side-by-side with them for 80 hours a week for the past few years. It's a safe environment where we can share thoughts and feelings without the pressured constraints of daily clinical life. Through my participation in the Writers' Workshop, I have been reminded of why I went into medicine—the interpersonal relationships, the ability to help heal others, sometimes simply by listening.

I am so thankful that we have the Writers' Workshop. It has helped to make me a more empathetic and well-rounded physician, and has made a major impact on me during these formative years in my training.

*Paul Fiorilli, M.D.  
Department of Medicine  
Yale-New Haven Hospital*

### The complexities of EMRS

I enjoyed reading "Yale's Epic Challenge" in the Winter 2013 *Yale Medicine*. As a former CMIO who trained in medical informatics and clinical computing at Yale, I know the challenges of EMR implementation are considerable, especially for an organization as large and complex as the Yale Health System. In fact, the term "EHR" is an anachronism; what Yale and others are now implementing are not simply electronic filing systems but enterprise-wide clinical resource and clinician control systems, with all the complexity that implies.

I do hope that Yale has learned well from the trials and tribulations of others' prior efforts. I still note many difficulties with commercial EHRs, resulting in unintended consequences up to and including patient injury and death.

Finally, I note that the statement [by one of the physicians quoted in the article] that "EMR use is mandated by federal authorities for everyone who's in the Medicare and Medicaid arena" is not accurate. While there are reimbursement penalties for non-adopters of HHS-"certified" EHRs in those programs, there are no federal or state requirements for their use.

Responsibility for the choice of EHR adoption and liability for patient safety problems that may result falls fully on the adopters. Health care leadership should remain ever mindful of this.

*Scot Silverstein, M.D., FW '94  
Philadelphia, Pa.*

## A new look for *Yale Medicine*

As it happens both of this issue's feature stories are about cancer. Marc Wortman reports on a controversial theory that holds that certain stem cells underlie cancer and that identifying these cells can lead to new possibilities for treatment. Kara Nyberg reports on a partnership between the School of Medicine and Gilead Sciences in which the pharmaceutical company underwrites research at Yale that could lead to new targets for drugs to fight cancer. Having two articles on a related topic in this issue owes more to serendipity than our editorial prescience, but starting with our autumn issue, the features in *Yale Medicine* will all be linked by a theme in science or medicine. This focus will allow us to explore in depth advances in science and medicine not just at Yale but around the world.

This thematic approach is part of a new vision for the magazine as we embark on a redesign to give the print edition of *Yale Medicine* a livelier and more modern look. We will expand our news and feature section and some sections that have traditionally appeared in our print issue—faculty, alumni, and student news—will appear online only. As part of our redesign we'll expand our online edition with regular postings in between print issues. Our print issue will continue to appear three times a year, in winter, spring, and autumn.

We hope that you will enjoy the new format of the magazine as we continue to bring you news of the School of Medicine community.

John Curtis  
Editor

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## SECOND OPINION BY SIDNEY HARRIS



"You've BEEN TRADED TO THE RED SOX FOR AN  
OUTFIELDER WITH A BROKEN ARM."

## yale medicine

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## As health reform looms, a new leader at YMG

Paul Taheri sees centralization, standardization, and primary care as keys to the practice’s success.

In March Paul Taheri, M.D., M.B.A., left Shelburne, Vt., a suburb of Burlington, for a new job in New Haven. Taheri, who had led the University of Vermont Medical Group since 2007, arrived to take over as CEO of Yale Medical Group (YMG). He moved from overseeing a

500-physician multispecialty group to leading one that has more than 1,000 physicians, mostly specialists.

“Yale is a bigger enterprise,” said Taheri, who will also serve as deputy dean at the School of Medicine. Yale’s location on an axis that includes such powerhouse medical centers as New York City and Boston places it, Taheri said, in the “hotbed of innovation and delivery.”

That said, Taheri’s move to New Haven comes at a time of imminent change in medicine both nationally

Paul Taheri began his new post as CEO of Yale Medical Group in March. He came to Yale from the University of Vermont, where he prepared the medical practice for the future of health care reform.



and locally. President Obama's health care reform takes effect next year, with anticipated cuts in reimbursement from Medicaid and Medicare as well as other changes in the financial model of medical practice. Many in medicine foresee a shortage of physicians at the same time that thousands of new patients are expected to enroll in Medicare. The shortage of primary care doctors is of particular concern, Taheri said. "The general trend in American health care is placing a greater emphasis on primary care," he said. "We have to figure out how to either integrate or build relationships with primary care providers. I suspect that is where the practice will grow."

The clinical practice at Yale has seen major expansion over the past decade—the size of the clinical faculty has grown; clinical revenues have nearly doubled; and clinical programs have expanded in breadth and depth—but leadership at the medical school and within YMG see a need for a more centralized and unified physician group practice.

Taheri agrees, and achieving that is among his immediate priorities. "Figuring out how we govern ourselves will be a very big issue," he said. "Ultimately things need to come to some pinnacle and have decisions made by the group."

He's also hoping to continue the move toward standardized customer service throughout the medical group's practices. "How does registration work? How are patients brought to the room? What person is doing what in the clinic?" he said. "Whether they go to New London or Bridgeport, it should be the same experience. There are huge benefits to standardization."

Taheri was credited with preparing the medical practice at UVM for the future of health care reform both financially and operationally. He established the Fletcher Allen Center for Health Care Management to provide business training for physicians,

nurses, and administrators; and he led the UVM Medical Group Revenue Department to achieve national ranking among its peers.

YMG, he said, is well positioned to weather coming storms, Taheri said. "You have world-class faculty," he said. "You have a great brand. You still have leverage with the payers. As long as we are data-driven, thoughtful, methodical, we can manage the changes and balance all the missions of the enterprise, and come out more able to bear risk."

Taheri succeeds David J. Leffell, M.D., director and later CEO of YMG, who led the transformation of YMG over the past 15 years while continuing to direct the Section of Dermatologic Surgery and Cutaneous Oncology. Leffell's leadership has advanced YMG's reputation for quality of care and service, and he spearheaded many initiatives, including the branding of the clinical practice under the name Yale Medical Group; establishing first-rate billing, collections, and compliance functions; and selecting Epic as the medical center's first integrated electronic health record. Michael Berman, M.D., who directed the initial restructuring of the practice, oversaw its operations as interim director and CEO during the past year.

—John Curtis

## et cetera ...

### HEALTH AND FAT'S EXCESS ENERGY

Yale scientists have found that excess energy is packaged into fundamentally different fat deposits, which are associated with many health problems linked to being overweight.

"The cell's inability to process all the excess energy—not the accumulation of fat itself—is what causes most health problems," said Tobias Walther, PH.D., associate professor of cell biology and senior author of the study published online February 13 in the journal *Developmental Cell*. Health problems start when molecules linked to fat synthesis overwhelm cells, rendering them unable to store energy as fat. That storage failure leads to inflammation, insulin resistance, fatty liver, and other problems associated with obesity.

Exploring ways to prevent failure of the cells' ability to accommodate excess energy may be a more effective way to tackle the health problems associated with obesity than simply trying to get rid of fat itself, Walther said. "Historically, concentrating on just burning fat has not worked too well," he said.

—John Curtis

### PREDICTOR FOR INPATIENT CARE

Though elderly people with heart failure often enter the hospital over and over, it's hard to estimate a specific individual's risk of landing there. One low-tech way may be to check gait speed.

Sarwat Chaudhry, M.D., associate professor of medicine, isolated health factors in elderly heart failure patients that were likely to precede hospital admission. Weak grip strength and slow gait, she found, were comparable to chronic kidney disease and diabetes for predicting admission. The results appeared in the *Journal of the American College of Cardiology* in January.

Her predictors make sense, says Chaudhry: Gait speed requires the smooth function of several organ systems, and is also the single best measure of frailty in the elderly. While it's important to keep track of chronic diseases, she added that measuring an elderly person's general functioning is also important: "Physical function turns out to be a simple and accessible marker of overall health."

—Jenny Blair

## When viewing their own possessions, hoarders' brains light up under fMRI

In the spring of 1947, two brothers named Homer and Langley Collyer were discovered dead in their Harlem brownstone. To reach them, police had to make their way through a barricade of 140 tons of treasure and garbage—including dress dummies, bales of newspapers, and the chassis of a Model T—that Langley had collected over decades.

Compulsive hoarding is a behavior both fascinating and tragic. Hoarders' penchant for accumulating innumerable but often worthless objects can disrupt careers, break up families, and even kill. And there are countless cases less famous than the Collyers'. In the reality television show *Hoarders*, people display blithe indifference to the mounds of belongings in their houses—yet grow panicky when faced with discarding them.

That peculiar combination of non-chalance and anxiety about possessions, which David Tolin, PH.D., adjunct associate professor of psychiatry, calls the “two basic head-scratchers” of hoarding disorder (HD), has now been captured on functional magnetic resonance imaging (fMRI) of the brain.

Tolin and his colleagues asked three groups of people—HD patients, obsessive-compulsive disorder (OCD) patients, and healthy controls—to bring in a pile of junk mail from home. Each piece was photographed, as were pieces of mail supplied by the lab. As the subjects lay in an MRI machine, they viewed photos of their own and the lab's mail, then decided whether each item should be kept or shredded.



BETTMANN/CORBIS

Compared with the other groups, HD patients experienced abnormally low brain activation in the insula (a structure within the cerebral cortex) and in the anterior cingulate cortex (ACC) when they assessed the experimenters' possessions. By contrast, those same brain regions lit up in a hyperactive pattern when the HD patients assessed their own possessions. (Perhaps unsurprisingly, the HD patients chose to shred fewer personal items than did members of the other groups.) The results were published in the August 2012 issue of the *Archives of General Psychiatry*.

“That biphasic abnormality maps on really well to some of the clinical puzzles that we have in hoarding,” said Tolin, who works with HD patients as director of the Anxiety Disorders Center at Hartford Hospital's Institute of Living, and who has appeared as a guest expert on *Hoarders*. “You can see that flip-flop occurring even clinically.”

While HD has long been considered a type of OCD, Tolin's results add to a growing body of evidence that it is a distinct disorder. “The more people we talked to who had hoarding problems,” Tolin said, “the more skeptical we became that this had anything to do with OCD.” In a previous study, he found that fewer than one in five hoarders meet the *Diagnostic and*

**The world's best-known hoarders were the eccentric and reclusive Collyer brothers, Langley and Homer. When they were found dead in their New York City brownstone in 1947, they were buried amid 140 tons of junk. Yale scientists have captured on fMRI some of the brain activity associated with hoarding.**

*Statistical Manual of Mental Disorders* (DSM) criteria for OCD.

In fact, HD may bear some relation to autism and anxiety disorders. The insula and ACC help a person decide whether an object is relevant to him or her; and HD patients' low level of activation in these regions while viewing experimenters' possessions is similar to the reaction of autistic patients to human faces. On the other hand, the hyperactive response echoes patterns seen in anxiety disorders. That, too, makes clinical sense: If every item seems relevant, then trying to decide which ones to throw away can be overwhelming.

HD will be included as a separate disorder in the upcoming fifth edition of the DSM, psychiatry's bible. In the meantime, Tolin cautions that abnormalities in brain MRIs don't mean that HD is untreatable. “Regardless of what's going on in the brain,” he said, with appropriate treatment “people can overcome hoarding. They can get better.”

—Jenny Blair

## Two key genetic mutations open new pathways to treating meningioma

Murat Günel, M.D., HS '98, can now look at the MRI of a patient with meningioma and tell with almost complete certainty which genetic mutation is causing the tumor, based solely on the tumor's location in the brain. Moreover, in time he may be able to cure the tumor without ever wielding a surgical blade.

Whereas most tumors contain a dizzying array of garbled DNA and broken chromosomes, making it difficult to target any single molecular abnormality for therapy, Günel's group found that meningiomas—which arise from the membranes covering the brain and are the most common form of primary brain tumor—feature only one or sometimes two key mutations in just five genes. What's more, these mutations are closely tied to the biology of the tumors, including their location and malignant potential, as reported in the March 1 issue of *Science*. These findings, said Günel, the Nixdorff-German Professor of Neurosurgery and professor of neurobiology and of genetics, can point the way to more straightforward treatment for meningiomas, which presently affect about 170,000 people in the United States.

Although 90 percent of these tumors are histologically benign, they sometimes require surgical treatment because they can invade such critical neurovascular structures as the optic canal. The 10 percent of meningiomas that are malignant also require surgical removal, as no medical therapies are currently available.

The culprits in about half of all meningiomas are mutations in the tumor suppressor gene neurofibromin 2, or *NF2*. Until now, however, the mutational causes of the other half of meningiomas remained a mystery.

To crack the case, Günel and his colleagues scoured meningioma exomes using whole-exome

sequencing technology developed at Yale. Their search turned up four new genetic culprits. Two of the mutated genes, *SMO* and *AKT1*, have been implicated in other cancers, including basal cell carcinoma and medulloblastoma. Another gene, *KLF4*, maintains embryonic stem cells and can prevent their differentiation. *TRAF7*, the fourth gene identified, occurs in about a quarter of all meningiomas but had not been previously linked to cancer.

The scientists found that these genetic defects do not run in the same circles. Rather, they are mutually exclusive of *NF2*, the suppressor gene, and sometimes even of one another. In about a third of the defects, the researchers found, *TRAF7* mutations worked in tandem with either *KLF4* or *AKT1* mutations.

Günel's group also discovered that these distinct mutational groups can predict where the meningioma will appear and how it will affect the brain. For example, tumors with *NF2* mutations border the brain's hemispheres and feature genomic instability that can lead to malignancy. In contrast, tumors with *SMO* mutations arise from the skull base near the midline where surgery is difficult, but they show a stable genetic profile that suggests they will remain benign. "One of the next steps is to perform clinical trials to see if we can cure these meningiomas with targeted therapies," said Günel.

These findings represent a breakthrough in treating meningiomas and also malignant brain cancers. Günel believes that malignant tumors are basically conglomerations of the different individual types of cells that form benign tumors. "If we have the drugs to attack all of those subpopulations, then curing a malignant tumor is not going to be different than curing a benign tumor. The problem is that we didn't have the tools until recently to understand the complex genomic nature of these cancers and how we would attack all of the cancer at the same time."

—Kara Nyberg

## et cetera ...

### WHY HEAVY DRINKERS CAN'T QUIT

The brains of heavy drinkers, Yale scientists reported in the *Journal of Clinical Investigation* in March, are more receptive to a chemical byproduct of alcohol consumption that may make it hard to quit.

Fourteen drinkers—half had had at least eight drinks a week, including four drinks per occasion once a week, and half had had fewer than two per week—were given acetate. The liver normally converts alcohol to acetate, which the brain uses for fuel and may come to prefer over blood sugar. That in turn may promote dependence, because people who stop heavy drinking lose not only the alcohol itself but also the acetate.

"There may be ways to support early sobriety with acetate or drugs that mimic some effects of acetate, and we need to investigate that with respect to effectiveness, safety, cost, and practicality," said senior author Graeme Mason, Ph.D., professor of diagnostic radiology and psychiatry.

—John Curtis

### MAKING AN OLD BRAIN YOUNG

Yale scientists have reversed a molecular switch that helps the brain make the transition from teenager to adult. They reported on March 6 in the journal *Neuron* making an adult mouse brain youthful, which promoted learning and healing.

Scientists have long known that adolescent brains are more malleable—youngsters learn languages more quickly and recover faster from brain injuries. The Yale team found that without this molecular switch—the Nogo Receptor 1 gene—juvenile levels of brain plasticity lasted into adulthood. When researchers blocked this gene in adult mice, they found that the mice recovered from injury as quickly as adolescents and mastered complex motor tasks more quickly than adults with the receptor gene.

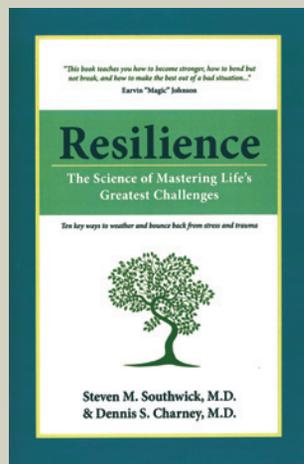
"It suggests we can turn back the clock in the adult brain and recover from trauma the way kids recover," said senior author Stephen Strittmatter, M.D., Ph.D., the Vincent Coates Professor of Neurology and professor of neurobiology.

—J.C.

## How to bounce back from trauma

Two psychiatrists explore why some people are better able to endure trauma than others.

Rear Admiral Robert Shumaker survived eight years in North Vietnamese prisons by helping to develop a secret communication lifeline among his fellow prisoners. While most people undergo some form of trauma during their lifetime—though not always as harrowing as Shumaker's—some bounce back more easily than others.

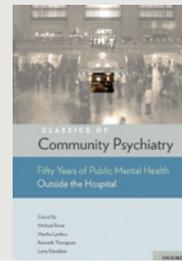


For 20 years, Steven M. Southwick, M.D., and Dennis S. Charney, M.D., HS '81, have been studying the biology and psychology of post-traumatic stress disorder and depression. In their book *Resilience: The Science of Mastering Life's Greatest Challenges*, Southwick, the Glenn H. Greenberg Professor of Psychiatry and professor in the Child Study Center; and Charney, a former member of the Yale

faculty who is now the Anne and Joel Ehrenkranz Dean of the Icahn School of Medicine at Mount Sinai in New York City, explore how some people are better able to cope with stress.

The authors interviewed Vietnam-era POWs, Special Forces instructors, and civilians who have led productive lives after severe psychological trauma. "... the resilient people we interviewed," they write, "tended to use the same or similar coping strategies when confronted with high levels of stress." The authors identify 10 resilience factors including optimism and strong social connections; delve into the scientific and genetic underpinnings of these factors; and offer practical advice on ways to foster resilience in everyday life. While acknowledging that human resilience is a complex and dynamic phenomenon, the authors maintain that people can improve their resiliency. "Ultimately, resilience is about understanding the difference between fate and freedom, and learning to take responsibility for one's own life."

—Jill Max



### Classics of Community Psychiatry: Fifty Years of Public Mental Health Outside the Hospital

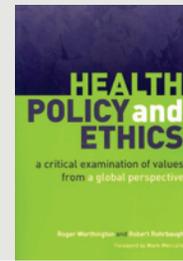
by Michael Rowe, PH.D., associate professor of psychiatry; Martha Lawless; Kenneth Thompson, M.D.; and Larry Davidson, PH.D., professor of psychiatry (Oxford University Press) This collection, which focuses on the American experience, contains 45 texts exploring the history of deinstitutionalization and the community mental health center movement; the community support model; and current conceptualizations of recovery from mental illness.

### Health Policies and Ethics: A Critical Examination of Values from a Global Perspective

by Roger Worthington, PH.D., M.A., assistant professor (adjunct) of medicine (general medicine); and Robert Rohrbaugh, M.D. '82, HS '86, FW '88, professor of psychiatry (Radcliffe Health) The authors compare and contrast ethical and policy issues from countries around the world, with a focus on the United States and countries in Africa and Asia. Worthington and Rohrbaugh address such issues as conflicts of interest; the balance between health care quality and cost; and the effects of geography and demographics on access to care.

### Practical Social Skills for Autism Spectrum Disorders: Designing Child-Specific Interventions

by Kathleen Koenig, M.S.N., APRN, associate research scientist in the Child Study Center (W.W. Norton



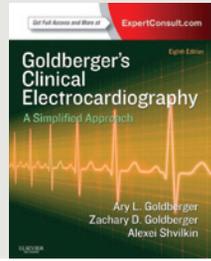
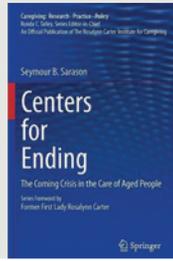
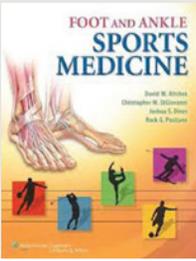
& Company) Koenig addresses ways to help children with autism spectrum disorders develop "social repertoires" that they can call upon in a range of day-to-day situations, from the classroom to the lunchroom to the family dinner table. The author uses case vignettes to illustrate the application of each intervention, suggests what to do when a child's response is inadequate, and offers a helpful guide to measuring the child's progress.

### Foot and Ankle Sports Medicine

Edited by David W. Altchek, M.D.; Christopher W. DiGiovanni, M.D.; Joshua S. Dines, M.D.; and Rock G. Positano, M.P.H. '89 (Wolters Kluwer/Lippincott Williams & Wilkins) This book covers pediatric sports injuries, sport-specific injury prevention, rehabilitation, and shoe selection, in addition to such adult sports-related injuries as tendon disorders, trauma, and injuries to the hindfoot, midfoot, forefoot, and lower leg. More than 40 specialists contributed to this guide, including physicians, physical therapists, and trainers for major sports teams.

### Principles and Practice of Geriatric Surgery, 2nd ed.

edited by Ronnie Ann Rosenthal, M.D., professor of surgery; Michael E. Zenilman, M.D.; and Mark R. Katlic, M.D. (Springer) The editors provide an overview of geriatric care in an evidence-based textbook that covers special issues which confront surgeons treating elderly patients, ranging from anesthesia complications to minimally invasive surgery. This updated edition presents new procedures, methods,



and information required to keep up with developments in the rapidly evolving field of geriatric surgery.

### **Centers for Ending: The Coming Crisis in the Care of Aged People**

by the late Seymour B. Sarason, PH.D., professor emeritus of psychology (Springer) The author used his firsthand experience as both practitioner and patient in senior facilities to reveal professional and moral failings. Sarason discusses such issues as insensitive medical personnel, poorly trained nurses and aides, indifferent administrators, and a prevailing culture that is content with treating “bodies” instead of complete human beings. He argues that such deficiencies engender feelings of loneliness, isolation, depression, and dependency among residents of these facilities; and he recommends the formation of a presidential commission to confront the crisis.

### **Goldberger's Clinical Electrocardiography: A Simplified Approach, 8th ed.**

by Ary L. Goldberger, M.D. '74; Zachary D. Goldberger, M.D. '04; and Alexei Shvilkin, M.D. (Saunders) The authors provide the fundamentals of ECG interpretation and analysis in this cardiology reference text, which offers guidance on understanding rhythm disorders and their clinical outcomes; broadens mastery of the material with online-only self-assessment ECGs and review questions; expands clinical skills

via online clinical highlights and review questions; and includes diagnosis and management tips as well as extended coverage of difficult-to-classify heart rhythms.

### **Seldin & Giebisch's The Kidney: Physiology and Pathophysiology, 5th ed.**

edited by Robert J. Alpern, M.D., dean and Ensign Professor of Medicine; Michael J. Caplan, M.D. '87, PH.D. '87, C.N.H. Long Professor of Cellular and Molecular Physiology; Orson W. Moe, M.D. (Academic Press) In this edition, previous chapters have been updated and new chapters have been added. The role of stem cells, the significance of cilia, and expansion of the section on pathophysiology are some of the updates incorporated in this text.

### **Meditations on the Good News: Reading the Bible for Today**

by Rev. Debra W. Haffner, M.P.H. '79 (Religious Institute Inc.) This book of 40 essays on Biblical verses is designed to introduce readers to positive messages in the Bible. The author highlights passages with inspirational and practical lessons to help lead a joyful life.

### **Madness & Glory: A Novel**

by Albert Rothenberg, M.D., HS '60 (Pegasus Publishers) This book follows Philippe Pinel, a French physician who pioneered the humane treatment of the mentally ill, and his patient in the Bicêtre asylum who learns of a plot against the leaders of the French Revolution—which puts both their lives in danger.

*The descriptions above are based on information from the publishers.*



RAY DOLAN

### **The neurobiology behind our choices**

When Ray Dolan, M.D., had to run an errand, he took a risk, did not feed the parking meter, and got a ticket for \$200. If he paid the ticket within 14 days, the fine print on the ticket informed him, he could cut the fine in half. Still he did nothing.

The parking ticket, said Dolan, the Mary Kinross Professor of Neuropsychiatry and director of the Wellcome Trust Centre for Neuroimaging at University College London (UCL), triggered a negative Pavlovian response associated with a hard-wired disposition not to act. Dolan's handling of the ticket was a case in point in his talk at the Yale/UCL Senior Scientist Lecture Series in March. The talk centered on his research into values, choice, decision making, and action.

Dolan described in neurobiological detail the interactions that occur in such regions of the brain as the orbital prefrontal cortex and the striatum when people are engaged in values-based decision making. “We have multiple systems controlling our behavior, and most of the time they are in alignment,” he said. “So it's striking when they come into opposition. This, I believe, accounts for lots of everyday behaviors in which people react suboptimally.”

—Jennifer Kaylin



HELENA HANSEN

### **Proposing new politics of medicine**

The United States, said Helena Hansen, M.D. '05, PH.D. '04, spends more on medicine than any developed country yet has poorer outcomes. Meanwhile, low-income countries like Cuba and India are improving health care.

“What's missing?” asked Hansen, an assistant professor of psychiatry and assistant professor of anthropology at New York University, speaking to members of the Yale Global Mental Health Program in March. “We have technology that practitioners in other countries can only dream about. But we focus on eradicating the patient's acute symptoms, not on the social or institutional factors that led to them.”

Calling for a “new politics of medicine,” Hansen said that American clinicians need to look beyond the patient and focus on where patients live as well as their level of education, diet, and income level. Clinicians also need to engage in interdisciplinary collaborations with such community partners as urban planners, educators, and criminal justice leaders.

“Doctors need to prescribe structural interventions, so that ailing systems become the patient, not only the individual,” Hansen said. “We need to push clinical professionals to think of themselves as agents for institutional change, social change, and policy change.”

—J.K.

PLATE 12.



Universal dermatitis (Morris).

## The world's medical heritage goes digital

The world's leading medical libraries make historic texts available online.

By Christopher Hoffman

It's 1909 and your child has diarrhea. The cure, according to that year's edition of the *Guide to the Clinical Examination and Treatment of Sick Children*, is opium.

"Opium is a valuable remedy in childhood," author John Thomson, M.D., writes. "It is chiefly of use in relieving pain and quieting the actions of the bowels."

Until recently, this window into early 20th-century pediatric medicine sat on a shelf deep in the stacks of the Cushing/Whitney Medical Library. Now the book is just a mouse click away through the online Medical Heritage Library, one of nearly 6,000 Cushing/Whitney rare books uploaded onto the site as of June 2012.

The Medical Heritage Library is part of an effort by Open Knowledge Commons, a digital curation collaborative—a network of librarians, universities, students, lawyers, and technologists—to create free digital libraries. The organization, founded in 2008, invited Cushing/Whitney and other leading medical libraries, including those at Harvard, Columbia, and the U.S. National Library of Medicine, to upload works into the site. The works will be available to historians, amateur scholars, laypeople, and anyone interested in the history of medicine. As of this spring, more than 40,000 works had been stored in

the library's virtual stacks, with more going online every day.

To avoid duplication, each library is assigned certain subjects. Cushing/Whitney's topics include surgery, pediatric medicine, gynecology, obstetrics, homeopathy, and phrenology, said Sarah McGlynn, M.L.S., the library's former preservation and collections management librarian. The eclectic collection includes textbooks, manuals, government pamphlets, self-help books, treatises on social issues, even novels and nonfiction—anything with a connection to medicine from the 19th and 20th centuries.

Yale's contributions include: *The Nightless City*, an 1899 "exposé" of Tokyo's then-red light district that could have doubled as a guidebook; *The Rules of Aseptic and Antiseptic Surgery*, by Arpad Gerster, M.D., a seminal work from 1888; and the 1877 *How to Teach According to Temperament in the School-Room and the Family*, which applies

phrenology—the belief that head bumps can be used as measures of personality and intelligence—to the hiring of teachers and instruction of children.

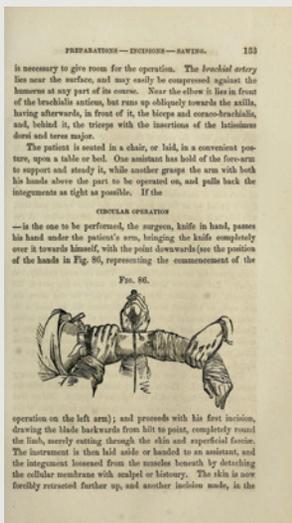
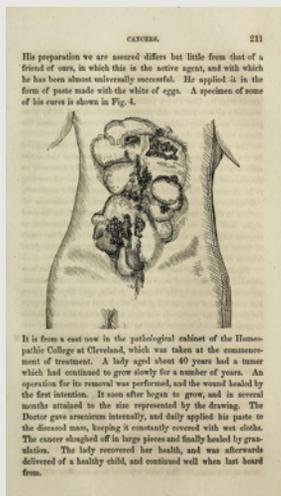
As the 19th century progressed, scientific medicine supplanted home remedies, quackery, and superstition. Melissa Grafe, PH.D., librarian for medical history, said that while the practices of yesteryear may repel, they were on the cutting edge at the time. "You look back and say, 'Oh, my God, that's crazy,'" Grafe said. "But, perhaps 100 years from now, people are going to look at us and say, 'Oh, my God, that's a little crazy.'"

Grafe's favorite Yale contributions are 19th-century "sexual hygiene" books offering women and girls advice on everything from improving the complexion to contraception. McGlynn's best finds include a novel called *The Lunatic at Large*, with a whimsically beautiful cover; and a self-help book titled *Talks with Homely Girls on Health and Beauty*.

Scholars are experimenting with data mining and other mass information extraction techniques to determine how best to use the trove, said John Gallagher, M.L.S., deputy director of public services for Cushing/Whitney.

Digitizing the books is a laborious process, he said. "The scanning is the easy part." A variety of library staff is involved in the project, reviewing, selecting, and cataloguing books as well as proofreading scanned texts. Volumes must be in good condition for the digitization machine, which automatically turns and photographs their pages. Because 19th-century works were often poorly made and are disintegrating due to the high acid content of their paper, they are given priority.

An exhibit on display at the Cushing/Whitney Medical Library focuses on the digitization process and displays discoveries from the work. To visit the Medical Heritage Library, go to [medicalheritage.org](http://medicalheritage.org).



**OPPOSITE** *Anomalies and curiosities of medicine: being an encyclopedic collection of rare and extraordinary cases, and of the most striking instances of abnormality in all branches of medicine and surgery, derived from an exhaustive research of medical literature from its origin to the present day*, abstracted, classified, annotated, and indexed, by George M. Gould, M.D., and Walter L. Pyle, M.D. Published in 1898 the book catalogued medical cases including this case of universal dermatitis.

**THIS PAGE** Left, a page from *The homeopathic practice of surgery, together with operative surgery*, by Benjamin Hill, M.D., and Jason Hunt, M.D., published in Cleveland, Ohio in 1855. This image illustrated the case of a woman with a tumor. Hill was a professor of obstetrics and diseases of females, and professor of surgery at Western Homeopathic College, which he founded in Cleveland in 1850. From the same book, third from left, a chapter offered instructions on amputations.

Second from left, early in the 20th century, Charles Lentz & Sons of Philadelphia published a price list for surgical instruments, hospital supplies, orthopedic apparatus, and trusses, among other items. Right, a page from *The rules of aseptic and antiseptic surgery*; a practical treatise for the use of students and the general practitioner, by Arpad G. Gerster, M.D., published in 1892.



# Killing Cancer's Seeds

A controversial theory focuses on identifying and treating so-called cancer stem cells within solid tumors. While doubters abound, some at Yale believe a revolution in cancer care may be in the offing.

By Marc Wortman

Illustrations by Sophie Casson

Hope crushed can be a terrible thing. Oncologist Alessandro D. Santin, M.D., sees that despair all too often. Santin, professor of obstetrics, gynecology, and reproductive sciences, typically treats ovarian cancer patients when their tumors have grown dangerously large and spread to other parts of their bodies. Most of these women undergo surgery first, then chemotherapy. After they have endured these complicated and painful treatments, though, often the most he can offer is a small measure of good news.

Nearly four out of five patients have no detectable disease left in their body; however, cancer will return in nearly 90 percent of the apparently “cured” women—the second time with a vengeance—and chemotherapy will no longer work. “There is very little we can do for them at that time,” Santin says.

Sitting in his School of Medicine office almost swallowed by the stacks of papers and journals that surround him, Santin speaks of the deceptively malevolent power of ovarian cancer cells to re-erupt after treatment. He has been studying the source of that power and thinks emerging insights reveal new possibilities for stopping it from killing women. “I’m targeting the cells that are resistant to treatment and therefore responsible for the cancer’s recurrence and the death of my patients,” he says. He has come to believe a very specific type of killer lies deep within tumors: cells that are not ordinary tumor cells.

“We are trying to identify a subset of cells that looks different, acts different, and reacts differently among cancer

cells. These are the cells you try to kill with anything,” but cannot, at least so far.

Santin’s research is among the most advanced efforts to translate the complicated biology of what some observers term “cancer stem cells” into novel treatments for one of the most aggressive and lethal forms of cancer. According to a controversial theory that is gaining wider acceptance among oncologists and cancer researchers, certain cells have a unique set of developmental differentiation and self-renewal powers—akin to stem cells that form tissues during embryonic development—needed to initiate tumors. According to this theory, tumors need these “cancer seeds” in order to spread through the body. Santin and a growing number of cancer biologists are also convinced that among the mass of tumor cells in an individual cancer, only a subset of tumor cells have the genetic endowment to resist treatment.

The idea that a separate type of tumor cell lies at the root of cancer completely reworks existing dogma about how cancers form, gain structure, and spread. The notion of a separate subset of cells within tumors, says Gil G. Mor, M.D., Ph.D., professor of obstetrics, gynecology, and reproductive sciences, who shares an office suite with Santin and also studies the role of ovarian cancer stem cells, marks “a big change in the concept we learned in biology as medical students. We were taught that tumors are a mass of identical cells.”

“This,” says Haifan Lin, Ph.D., professor of cell biology and of genetics, and director of the Yale Stem Cell Center, “is a paradigm-shifting idea.” He explains, “A small

number of cells are much more important within a tumor than others. These are seeding cells—cancer cells that are different from other cancer cells.” But Lin added, “cancer stem cells may not be responsible for all types of cancers.”

Thomas J. Lynch Jr., M.D. '86, the Richard Sackler and Jonathan Sackler Professor of Medicine (Medical Oncology); director of Yale Cancer Center; and a specialist in lung cancer, considers that notion controversial but says, “There is no doubt that a population of cells is responsible for propagating metastases. There is no doubt we have to target them to halt the process.” Lynch questions their designation as cancer stem cells, but he is convinced that “for therapy to be successful, you have to target that population.”

While oncologists almost universally acknowledge that only genetically aberrant hematopoietic stem cells can generate blood cancers, including most leukemias, there is no definitive way to distinguish cancer stem cells in solid-tumor cancers. Some say that's because the cells are not there. But Santin and Mor say that they have characterized traits of these cells, including unique surface proteins, in certain cancers that distinguish them from other cells within solid tumors. That characterization may provide targets for the development of new anticancer agents. Several efforts are now under way at Yale and elsewhere to find therapies that attack those so-called stem cells.

If the researchers succeed, a revolution in the way oncologists view—and more importantly—treat cancer may be in the offing.

### Cancer's seeds

Recent decades have brought enormous advances in knowledge of cancer's often baffling biology. But despite huge investments in treatment that have drawn on those insights, including the introduction more than 30 years ago of commonly used platinum-based chemotherapeutic agents, the odds and length of survival for most patients newly diagnosed with advanced solid-tumor cancers have barely increased. Eventually, in most cases of ovarian cancer—as well as lung, colorectal, breast, pancreatic, brain, and other solid organ-tissue cancers—the malignancy recurs after treatment, and that very often presages death.

Mainstream cancer biology points to tumor cells that escape even the most powerful targeted treatments as the culprits in cancer recurrence. Most oncologists believe that

cure rates would rise if it were possible to improve the newer agents' targeting accuracy or increase the potency of chemotherapy agents without putting the patient's life at risk. But the cancer stem cell theory puts treatment resistance and cancer recurrence in a very different light. It isn't that a few cells hide out only to proliferate anew; it's that certain cells have a genetic endowment that resists chemotherapy and enables them to regenerate tumors and spread the cancer.

“There are definitely cancer cell types that can initiate tumors and some that do not,” says Don Nguyen, Ph.D., assistant professor of pathology, who studies how lung cancer metastasizes, “and the cells that form tumors may be unique or more frequent depending on the cancer type.”

That opinion contrasts with traditional models of cancer biology. According to the most widely held view, malignant cells have mutations that make them genetically unstable. They accumulate further mutations and evolve into tumors that grow rapidly, encourage blood vessel formation, discourage immune responses, metastasize, and resist treatment.

Mor finds this model of malignancy “oversimplified.” The cancer stem cell model posits that rather than being made up of identical cells, the tumor is composed of genetically and functionally different cell types. Furthermore, within the tumor there is a hierarchy. “Only these mother cells can give origin to cancer cells and all the cells in the tumor, including the blood vessels to nourish the tumor,” Mor says. “We have isolated the cancer stem cells and we can recreate the complexity of the human tumors in the mouse. That only happens with the cancer stem cells.” He hopes to test therapeutic agents designed to treat recurrent forms of the disease in ovarian cancer patients. These advanced tumors appear, he says, “to be a different monster altogether” from the primary untreated cancer; and require “a completely different approach” to target resistant cancer stem cells as well as the other non-stem cells that make up a tumor.

Lin agrees. He expects that new drugs specifically engineered to seek out and kill cancer's seeds will stop at least some aggressive chemotherapy-resistant cancers. “The key is to find what is specific and different in cancer stem cells. That becomes their Achilles' heel,” he says.

But the most basic questions about the biology of cancer stem cells await answers because the existence of uniquely potent tumor-initiating cells with stem cell-like characteristics remains unproven.

### Where cancer comes from

The cancer stem cell theory arose out of a paradox observed in certain cancers in laboratory studies. Tumor cells—even large numbers of them—may fail to generate new tumors when transplanted into immunodeficient laboratory mice. At the same time, other tumor cells—sometimes just single cells—can generate new tumors physiologically identical to the parent cancer, and also spontaneously generate metastases.

In 1994 cancer biologists at the University of Toronto found that very specific human acute myeloid leukemia (AML) cells were needed to transmit the disease into immunocompromised mice. “In leukemia you can take out cancer stem cells and transplant them and create the cancer again,” says Lin. “Lots of leukemia cells cannot do that. Only leukemia stem cells can.” Evidence for the role of stem cells in other hematological malignancies followed. To cure AML patients, treatments require total destruction and replacement of the patients’ bone marrow to eliminate the cancer-causing stem cell component. Nine years after the Toronto discovery, however, the research focus began to shift from cancers of the blood to solid-tumor cancers. In 2003, University of Michigan researchers separated populations of what they said were rare stem cell-like cells from other cancer cells within specimens from human breast cancer tumors.

Since then scientists say they have characterized populations of cells resembling stem cells in many types of solid tumors through elevated levels of proteins typically found only on the surface of stem cell membranes. “There is a semi-consensus in certain cancers, probably not all of them, that stem cells exist,” says Joseph Schlessinger, Ph.D., chair and the William H. Prusoff Professor of Pharmacology.

The presence of such stem cells may explain a cancer’s ability to survive treatment. “A lot of drugs can kill regular cancer cells but not cancer stem cells,” says Lin. “They can evade every insult we throw at them.” Cancer stem cells, he believes, possess DNA repair mechanisms that allow them to resist chemotherapy. They also divide much more slowly than most cancer cells, making them less vulnerable to chemotherapeutic agents that attack fast-dividing cells. (Speed of division underlies the death of hair, nail, and certain blood cells during chemotherapy as well as the development of unbearably itchy skin and other chemotherapy-related side effects.) Moreover, studies indicate that when tumor cells die during treatment, they release

signaling proteins that may stimulate surviving stem cells to reproduce and differentiate into a new tumor. In effect, treatment may actually increase the proportion of the highly aggressive and resistant cancer stem cells within tumors, perhaps explaining why fast-growing deadly malignancies often follow therapy.

What matters then is not just how many tumor cells a cancer therapy eliminates, but also its capacity to kill the cancer at its source.

### Attacking cancer at the root

Lin studies genes that he calls the master regulators—they control other genes in the genome and decide whether a cell becomes a neuron or a heart, kidney, or skin cell. Genetic switches normally turn off stem cells once they have completed these tasks—except for small numbers involved in renewing and repairing blood, skin, bone, certain cells in the brain, and membranes in the lung and gastrointestinal tract. Lin believes that the stem cell genes may mutate through environmental insults like exposure to sun, tobacco smoke, and carcinogenic chemicals, or through genetic machinery gone awry; become overactive; and reawaken their self-renewing powers. This time, though, they lead to cancerous overgrowth. The parent cells that gave life transform into killers.

In the lab Lin’s team can manipulate genes in a normal stem cell to turn it into a cancer cell. In humans, he says, no one knows exactly how a stem cell becomes cancerous. Despite limited insights into how cancer stem cells develop, he contends that it is possible to develop drugs against them.

However, some cancer investigators question the notion of targeting cells that are so poorly understood. Scott Kern, M.D., associate professor of oncology and pathology at Johns Hopkins University School of Medicine, argues that alternate theories could explain the distinct class of treatment-resistant, tumorigenic cells under study. Says Kern, who studies cancer genetics, “We all know that the cancer stem cell theory explains at least some leukemias and teratocarcinomas [germ cell tumors, mainly cancers of the testes]. Nobody has debated that, to my knowledge. It is the extension of the idea to the common solid tumors ... that we find worthy of debate.” Existing theories, Kern argues, could explain the stem cell-like characteristics scientists claim to

see in certain cell populations within tumors. He thinks that methods being used to identify cancer stem cells in a tumor represent “fuzzy math” that weights statistical results of studies to conform to a stem cell theory. And what some call a distinct class of treatment-resistant tumor-initiating cells could in his view just as likely result from cancer-causing genetic and environmental factors and physiological processes that encourage tumor growth. “Instead of chasing stem cell-ness,” he says, “you’re chasing an unknown.”

Definitive ways to distinguish cancer stem cells from normal ones have yet to emerge. That has not stopped cancer researchers from trying to identify biological markers by studying the differences between tumors that respond to therapy and those that resist. Patients with those markers that suggest a large population of cancer stem cells may benefit from more aggressive treatment. “The key,” says lung cancer biologist Nguyen, “is to identify these patients and get treatment to them as quickly as possible.”

For some cancers, skin cancer among them, the role of stem cells is a bit different. Douglas E. Brash, PH.D., clinical professor and senior research scientist in therapeutic radiology, and professor of dermatology and of genetics, has found large clones of mutant progenitor cells, or skin stem cells, on the order of 30 per square centimeter in sun-exposed adult skin. These cells possess a mutation in the p53 tumor suppressor gene, which Brash showed came from sun exposure. When later exposed to beach-trip levels of ultraviolet radiation, the mutated stem cells produce more of themselves. In skin and other solid tissues, these progenitors are not professional stem cells: when they divide, they choose randomly between acting like a stem cell or acting like a differentiating cell. Brash theorizes that these mutated cells lead to a form of cancer known as squamous cell carcinoma. He is trying to create a mouse model in which the mutated skin stem cells can be observed while they are progressing to cancer. Shrinking a tumor 99 percent with a hammer may not be as effective as altering the stem cell’s choices with a screwdriver.

Santin does not claim certainty that a subpopulation of tumor-initiating cells exist in all or even most cancers, but he does believe that they exist in therapy-resistant ovarian cancer.

Much of Santin’s workday is spent either with patients or down the hall from his office in the laboratory where he

and his colleagues are studying ways to kill ovarian tumor specimens enriched in chemotherapy-resistant cancer cells. During the past few years his laboratory team has published findings that *Clostridium perfringens* enterotoxin (CPE), a type of bacterial poison found in the intestine and responsible for foodborne illness and diarrhea in humans, may attack and kill only cancer cells possessing a specific protein called claudin-4 on their surface. Santin showed that the same protein can also be found on the surface of chemotherapy-resistant tumor cells.

When exposed to the bacterial toxin, the previously resistant cells die within minutes. “It’s hard to believe how effective the toxin can be against these biologically aggressive tumor cells,” he declares. Santin is now working with W. Mark Saltzman, PH.D., the Goizueta Foundation Professor of Biomedical Engineering and professor of cellular and molecular physiology and of chemical engineering, and chair of the Department of Biomedical Engineering, to engineer a small section of that bacterial toxin into a nontoxic form suitable for use as a drug and as a diagnostic tool. The researchers are infusing a fragment of CPE linked to a fluorescent dye that lights up when it binds to a cancer cell. Santin hopes that within the next two or three years he can test the modified enterotoxin as a diagnostic method for chemotherapy-resistant ovarian cancer and then also be able to use it to treat patients with resistant ovarian cancer.

His departmental colleague Mor is looking for unique variants of the stem cell surface marker protein known as CD44 that may allow him to differentiate normal stem cells from the stem cells of ovarian cancer. Mor has already identified markers he believes may be present only in therapy-resistant ovarian cancer cells and has begun using the markers to look for compounds that might kill the cancer cells. “In recurrent disease,” he says, “you need to treat the cancer with a completely different approach. We have been successful in killing the fast-dividing cells. In the next 10 years, the challenge will be getting at the roots of cancer.” Even those who have raised doubts about the existence of cancer stem cells can agree with Mor about that.

Marc Wortman, PH.D., is a freelance writer in New Haven.



# Pharma and academia partner for better health

Yale joins forces with the pharmaceutical company Gilead Sciences to search for targets for new and improved cancer therapies.

By Kara Nyberg  
Illustrations by Sophie Casson

In 2008 Ruth Halaban, PH.D., began searching the DNA of melanomas in a quest for genetic clues to skin cancer. The obvious connection between sunlight, ultraviolet rays, and cancer, she said, had been determined through population studies. The genetic causal link remained to be discerned. Halaban hoped—naively, as it turned out—that with about 20 samples she could find a genetic anomaly that would provide that link.

But with the sequencing of each sample then costing \$2,500—and she also had to sequence a normal sample for comparison—the experiment grew costly. Funding from private foundations helped her launch the project, but Halaban, a senior research scientist in dermatology, soon realized she'd need far more than 20 samples. In the end, the cost of sequencing fell to about \$1,400 per sample, and Halaban sequenced almost 150 samples. Her findings led her to a gene called *RAC1*, which appears mutated in about 9 percent of melanoma tumors. She completed the research in 2012 thanks to a collaboration with Gilead Sciences, and her findings were published online in *Nature Genetics* in July of that year.

“We discovered that *RAC1* is a sunlight signature mutation,” said Halaban. “You can say that this is the culprit. This is directly related to sunlight.”

Halaban's findings are the fruit of a collaboration between Gilead and the School of Medicine that began in 2011. By studying the genetic and molecular mechanisms underlying different forms of cancer, Yale and Gilead scientists work together to pinpoint new molecular targets

implicated in cancer pathogenesis, and to develop agents designed to put a halt to the molecules' rogue activities.

Under an agreement with the School of Medicine, Gilead agreed to provide \$40 million over four years to support research to identify novel targets and new drugs for cancer therapy. The collaboration will continue, with evaluations after the fourth and seventh years, through 2021 with a total of up to \$100 million in funding over 10 years—the largest corporate commitment in Yale's history. As part of the agreement, Gilead has the option to license potential cancer therapies that result from the collaboration.

Although such collaborations are decades old, in recent years academia has sought new funding sources as the pharmaceutical industry seeks new research collaborators. The industry needs new drugs in its development pipeline, and researchers across the country worry about years of flat spending from the National Institutes of Health, sequestration—which mandates across-the-board federal spending cuts of 8 percent—and declines in funding of research from venture capital. Partnerships between universities and pharma also allow each party to leverage their respective strengths in research and drug development.

## Tapping into the best minds

The Yale-Gilead collaboration relies on some of Yale's top scientific minds, technology investments at the West Campus, and the resources of Yale Cancer Center, the Cancer Biology Institute, and Smilow Cancer Hospital. “Through this



collaboration,” says Howard Jaffe, M.D. ’82, president and chair of the board of the Gilead Foundation, and a member of the Yale-Gilead joint steering committee, “we’re tapping into some of the best minds on the planet who’ve done it before and are scientifically, technologically, and instinctively better than just about anybody else.”

Indeed, the joint steering committee brings some of Yale’s leading scientists and clinicians to the table to help select and nurture the Yale research projects that receive Gilead funding. Joseph Schlessinger, PH.D., chair and the William H. Prusoff Professor of Pharmacology, and director of the Cancer Biology Institute on the West Campus, chairs the six-member committee.

“When we find cancer targets that are new, we will work with Gilead on designing drugs, which they can then test in the clinic,” said Schlessinger, whose studies of molecules involved in cell signaling led to the development of many cancer drugs, including two developed by his biotech companies. “This is a tremendous opportunity for Yale and Gilead.”

The Yale half of the steering committee also includes Richard P. Lifton, M.D., PH.D., chair and Sterling Professor of Genetics, head of the Yale Center for Genome Analysis, and a Howard Hughes Medical Institute investigator; and Thomas J. Lynch Jr., M.D. ’86, the Richard Sackler and Jonathan Sackler Professor of Medicine (medical oncology), director of the Yale Cancer Center, and physician-in-chief of the Smilow Cancer Hospital at Yale-New Haven Hospital.

Three accomplished Gilead scientists round out the steering committee—Jaffe; William A. Lee, PH.D., senior vice president of research; and Linda Slanec Higgins, PH.D., vice president of biology.

### An old trend revived

The past two years have seen an increase in multimillion-dollar pharma-academia collaborations that focus on discovering drug targets. Notable partnerships include Pfizer and the University of California at San Diego; Sanofi-Aventis and Columbia University Medical Center; and Novartis and AstraZeneca and the University of Pennsylvania.

Since signing with Gilead in 2011, Yale has partnered with several other companies. December 2011 brought news of a collaboration with the Johnson & Johnson Corporate Office of Science and Technology to jointly fund activities at the Yale Molecular Discovery

Center on Yale’s West Campus. In May 2012, Yale announced a new partnership with GlaxoSmithKline to identify promising protein-destroying drug candidates in a variety of therapeutic areas. And in February, Yale and AbbVie announced a new collaboration. AbbVie will provide \$14.5 million over five years to support research into the molecular, cellular, and genetic underpinnings of autoimmune and inflammatory diseases. In return AbbVie has an option to negotiate a license for any invention made through the collaboration.

In 2002 Yale and Pfizer began a collaboration that led to the creation of Yale’s PET Center in 2007.

“The proximity of the clinical research unit Pfizer was building in New Haven made it ideal for Pfizer to partner with the Yale PET Center to achieve its goal of finding out whether the drugs they were developing were hitting the targets in clinical trials,” said Roopashree Narasimhaiah, deputy director of corporate and foundation relations in the medical school’s development office. Pfizer, the pharmaceutical company, contributed \$5 million to establish the center and provides \$2 million annually to support PET imaging studies of mutual research interest. In these studies Yale and Pfizer scientists have worked together to determine whether to pursue the development of certain compounds to drugs. “It was not a discovery partnership,” said Narasimhaiah. “The aim was not to discover, but to validate compounds that Pfizer was making.”

Such alliances between industry and universities may suggest a new trend; but as Jonathan Soderstrom, PH.D., managing director of the Yale University Office of Cooperative Research, explains, industrial sponsorship of academic research is not new. In fact, it is decades old. In 1982, Soderstrom said, Yale was already receiving almost \$4 million in industry-sponsored research. By 1994, that figure had swelled to almost \$18 million; the figures held steady between 2001 and 2009, with Yale averaging more than \$15 million per year in industrial funding.

Gilead, a company rooted in HIV and hepatitis research, also points to a long history of ties to academia. “We just celebrated the 25th anniversary of an interaction we’ve had with two universities in Europe that was basically the genesis of the HIV drugs we developed,” says Jaffe. “We’ve always been of the mantra that Gilead itself is only capable of a very minuscule fraction of the potential for innovation in the world, and that



we can expand dramatically on that by partnering with the right academic institutions.”

This recent spate of corporate agreements reflects a convergence of factors—advances in technology and a need to tap into academic research—that have opened the floodgates for academia-pharma partnerships. The prime force driving both academia and pharma to partner, however, is shrinking funding.

#### Creative solutions in tough times

Although the NIH budget doubled from 1999 to 2003, it has remained stagnant for nearly 10 years, topping out at \$30.6 billion for fiscal year 2012. Early this year the U.S. Congress passed a continuing resolution that maintained NIH spending at that level. As a result, ROI research grants from the NIH have failed to keep pace with biomedical research costs. Despite these years of flat funding overall, however, NIH grants to Yale have been increasing. In the fiscal year that ended in June 2011, Yale received almost \$340 million in NIH funding. While Yale in general has benefited, some labs at Yale have lost funding, causing worry among scientists.

The outlook for 2013 is one of uncertainty. When Republicans and Democrats in Washington failed to reach a budget agreement early this year, sequestration took effect, with an 8 percent reduction in federal spending. A White House report issued last September projected an 8 percent cut in funding for science.

The pharmaceutical industry is likewise going through a difficult time. The cost of drug discovery keeps rising, while many of the blockbuster drugs sustaining big pharma are about to go off patent, with few potential all-stars waiting in the wings. The floundering economy means less venture capital for startup biotech companies, which big pharma has recently relied on to identify drug targets and jumpstart the development of therapeutic agents. Pharma’s wellspring of research and development money is also beginning to slow to a trickle due to waning revenue growth, forcing the drug companies to look elsewhere for leads on drug candidates. Out of the search for potential fixes, academia and pharma have looked to each other’s complementary strengths, recognizing that together they have the potential for much greater research capacity.

Schlessinger cautioned, however, that the collaboration should not be seen as a replacement for the NIH. Much of the cancer-related research typically supported by NIH grants, he emphasized, “do not fit the goals of the Yale-Gilead collaboration. The collaboration’s goals are to identify genetic changes or other molecular alterations that take place in human cancers that can be used to develop novel targeted therapies, including small molecules, therapeutic monoclonal antibodies, or biologicals that selectively block cancer cell proliferation and/or stimulate programmed cancer cell death.”

Although the monetary perks of academia-pharma collaborations are obvious—academia gets money for



health-related research and pharma has the chance to identify a blockbuster drug that stands to turn a handsome profit—there are other benefits. The two sides need each other.

“The reason taxpayers in this country support \$30 billion in biomedical research every year is because of the expectation that it is going to lead to an ability to improve human health,” says Lifton. However, there is a catch-22. “We have almost no ability to make new drugs and pharmaceuticals in academia. We rely almost entirely on that happening in the private sector.” Toward that end, he says, there needs to be a translation from basic science to clinical development of a drug.

“I have long felt that there’s tremendous talent and depth of understanding of biology in academia, and tremendous talent and depth in chemistry in the pharmaceutical industry, and a very inefficient bridge between those two bodies of expertise that is necessary to translate basic discoveries into new therapies,” says Lifton. “Unless we have really effective pipelines for communication between academia and industry, we’re not going to achieve the realization of turning basic science discoveries into new treatments that are going to benefit the people who are funding the basic research—the taxpayers.”

To facilitate new research—rapidly—the Yale-Gilead steering committee has streamlined the funding process. “If someone has an idea, they can bring it to the steering committee and it can be funded two or three days later,” says Lynch. “Even in the best scenario, the NIH funds projects nine months

later from when you have your idea. So this really allows us to put resources to problems very quickly.”

Another beauty of the Gilead partnership and others like it is that they not only foster collaboration between academia and pharma, they also encourage collaboration among different medical disciplines on the Yale campus. Under standard operating procedures, an individual investigator receives an ROI grant to locate one small piece of the bigger cancer puzzle. For example, after a geneticist identifies a mutation underlying a particular cancer, advancing that information—and securing the funding to do so—sometimes gets a bit fuzzy.

“One of the real strengths for Yale has been the ability to build teams among clinical investigators who have access to patients and tissue samples; genomics investigators who know how to use those samples to discover genes that underlie specific forms of cancer; and biochemists and cell biologists who know how to go from specific genes and their mutations to assays to determine the consequences of the mutation that has been identified,” says Lifton. “It’s been really catalytic in terms of team-building across disciplines at Yale.”

Halaban concurs. Every Thursday morning, she attends a melanoma board meeting with surgeons, pathologists, medical oncologists, radiologists, and researchers, where the discussion may turn to her Gilead-funded melanoma sequencing project. “To hear clinicians talking about genes, asking me, ‘What did you find out about this gene or that gene?’ is amazing,” says Halaban. “These things were

not previously part of routine discussions. But now, the genetics of melanoma, currently mostly *BRAF* mutation status, changed it all.”

Yet another advantage is that the flow of cash promotes other non-Gilead-funded research. “They’ve infused resources that we may not otherwise be able to get, both to expand Yale’s genomic capability and to build other aspects of our infrastructure,” says Patricia Pedersen, PH.D., associate vice president for development and director of corporate and foundation relations, who played a key role in negotiating the collaboration. “Overall, the Gilead investment has increased our capacity, which was necessary to enable us to deliver results to them. In doing so, it has increased our ability to do more research, apply for more NIH grants, and get other funding.”

### Finding the right partner

Although academia-pharma collaborations create synergy through aligned interests and can be highly productive, negotiating the terms of the relationship can be difficult. Each stakeholder holds different core values. Academia prizes public pursuit of knowledge, research grant funding, and intellectual freedom. “We all have academic calendars that we live on, meaning that we want to get promoted, and for our careers to advance so that we get more grants. That’s why we have a never-ending desire to publish,” says Lynch.

Both sides are working to eliminate such potential sources of conflict as restrictions on publication, problems with licensing rights, and conflict over control of the intellectual property. “You have to pick your partner well,” says Lynch. “It’s like a marriage. It’s really important that you select a company that fits the university.”

“Indeed, Yale and Gilead have established strong links, productive collaboration, and common goals, and function as a harmonious couple,” Schlessinger said. Jaffe is an alumnus of the medical school; Gilead Sciences has previously funded faculty research projects; and the Gilead Foundation has supported a needle-exchange program and a mobile health care van in New Haven, so there is a history of camaraderie and collegiality. Adds Pedersen, “The company’s leadership is very academically minded.” For example, Gilead respects Yale’s mission to educate and disseminate information, placing few restrictions on the ability of Yale researchers to publish.

“I think that Yale can feel confident based on our long-standing relationship and Gilead’s track record of social responsibility. We have pioneered worldwide access to our HIV drugs, signing deals with 13 different generic manufacturers in India and having a no-profit cost,” says Jaffe. “We’re different. The major reason is that the people who created the value are still here. We’re all scientists or M.D.s. The core senior management of the company has been together over 20 years. We’ve been able to maintain a certain culture here, and I think that’s of benefit for the Yale group.”

Given the pressures on both pharma and academia, such alliances seem inevitable.

“I believe that there is great beauty in science, and that’s one of the compelling things about being a scientist,” said Lifton. “But in addition, there is the expectation that our research will ultimately contribute to improvement in human health. Today, that is almost always going to go through an industry partner. We need to recognize that that’s how our system works.”

Schlessinger agrees. “Many colleagues from other universities, as well as senior executives of major drug companies, emphasized to me the visionary aspects and the forward looking approach taken by the Yale-Gilead collaboration,” he said. “Moreover, as I believe that we are now in a golden age of drug discovery for cancer therapy and treatments for other diseases, we must come up with creative solutions to merge the best that academia and drug companies offer in order to develop new treatments that reduce the suffering caused by such devastating human diseases as cancer.”

Kara Nyberg, PH.D., is a freelance writer in Boulder, Colo.



Benjamin Polak

### New university provost named

**BENJAMIN POLAK, PH.D.**, chair of the Department of Economics, the William C. Brainard Professor of Economics, and professor of management, was appointed provost of the university in December. He replaces Peter Salovey, PH.D., who can now focus on preparing for his next assignment as president—the role that he assumes on June 30. Salovey replaces Richard C. Levin, who is retiring after 20 years as president of Yale.

Polak joined the Yale faculty in 1994 and has made important contributions to decision theory, game theory, and economic history. He received the William Clyde DeVane Medal for undergraduate teaching and scholarship in Yale College in 2005 and the Lex Hixon '63 Prize for Teaching Excellence in the Social Sciences in Yale College in 2006. In 1998 Polak won both the Graduate Teaching Prize and the Graduate Advising Prize in the Department of Economics; he was honored again with the Graduate Teaching Prize in 2005.

Polak was appointed the inaugural William C. Brainard Professor of Economics in 2008, and two years later was appointed chair of the Department of Economics. A member of the University Budget Committee, Polak has a strong grasp of the university's budgetary and financial conditions. He has also served on the executive committees of the MacMillan Center and the Institution for Social and Policy Studies and as a fellow of the Whitney Humanities Center and a visiting instructor at the Yale Law School.



Richard Flavell

### Researchers honored for immune system research

Two Yale School of Medicine researchers who study the immune system will share a 2013 Vilcek Prize for their long-standing and influential work on the innate immune system, the body's first line of defense against infection by bacteria and viruses. The prize went to **RICHARD A. FLAVELL, PH.D.**, chair and Sterling Professor of Immunobiology; and **RUSLAN M. MEDZHITOV, PH.D.**, the David A. Wallace Professor of Immunobiology.

Flavell, a native of England, and his Yale colleagues have discovered several important receptors responsible for innate immunity, and he has made major contributions to our understanding of how activation of the innate immune system triggers the adaptive system's more specialized immune response. Medzhitov, a native of Tashkent, Uzbekistan, immigrated to the United States in the early 1990s, having been inspired by the then-controversial theories of innate immunity championed by the late Yale immunobiologist Charles A. Janeway Jr., M.D. At the time, innate immunity was deemed unimportant and received scant scientific attention, but by 1997 Medzhitov, Janeway, and colleagues had identified a receptor of the human innate immune system that acts as a pathogen-detecting sentinel and activates adaptive immunity. In the wake of these findings, the study of innate immunity has seen explosive growth, and Medzhitov's work continues to have significant implications for autoimmune diseases, cancer, and other illnesses.



Ruslan Medzhitov

### Immunologist receives inaugural prize

**RUSLAN MEDZHITOV, PH.D.**, the David A. Wallace Professor of Immunobiology and a Howard Hughes Medical Institute investigator, has been awarded the inaugural Lurie Prize in the Biomedical Sciences from the Foundation for the National Institutes of Health. The award, which honors early-career researchers whose findings have advanced basic biomedical science, was given to Medzhitov for his groundbreaking discoveries about the workings of the innate immune system. A jury of scientists selected Medzhitov from a group of 154 nominees. The award, which carries an honorarium of \$100,000, will be presented to Medzhitov at a ceremony in Chicago on May 14.

Medzhitov came to Yale in 1994 as a postdoctoral fellow in the lab of Charles A. Janeway Jr., M.D. The two researchers made the breakthrough discovery that a human *toll*-like receptor, a component of the innate immune system, provides the adaptive immune system with the necessary information to create custom-made B and T cells that target specific bacterial or viral invaders through recognition of basic molecular patterns shared by microbial pathogens. Since then, *toll*-like receptors have become the subject of intense research activity in laboratories around the world.



Lynn Cooley



David McCormick

Three faculty members received the distinction of Fellow from the American Association for the Advancement of Science (AAAS) in February for their efforts toward advancing science applications that are deemed scientifically or socially distinguished. **Lynn Cooley, PH.D.**, the C.N.H. Long Professor of Genetics and professor of cell biology and of molecular, cellular, and developmental biology; Residential College Associate Fellow in the Faculty of Arts and Sciences; and director of the Combined Program in the Biological and Biomedical Sciences, was honored for her contributions to developmental cell biology, particularly for her analysis of oocyte growth during *Drosophila* oogenesis. **Pietro De Camilli, M.D.**, FW '79, the Eugene Higgins Professor of Cell Biology and professor of neurobiology, was honored for contributions to the cell biology of the synapse, and the discovery of the role of phosphoinositide metabolism in the control of endocytosis. **David A. McCormick, PH.D.**, the Dorys McConnell Duberg Professor of Neurobiology and vice director of the Yale Kavli Institute for Neuroscience, was honored for contributions to the understanding of the cellular mechanisms by which the central nervous system generates states of activity; how these states are related to behavior; and how they are determined by the actions of neuromodulatory transmitters.

Three Yale faculty members received awards for distinguished service from the Connecticut Chapter of the American College of Physicians (ACP) at its annual meeting in Southington, Conn., in November. ACP represents more than 2,300 physicians,



Cyrus Kapadia



Paul Barash

Richard  
Belitsky

Kimberly Davis



Anne Eichmann



Jordan Pober

Deborah  
ProctorMartin  
Schwartz

medical students, and residents practicing internal medicine and its subspecialties across the state.

The George F. Thornton Teaching Award, given annually to physicians in recognition of contributions to medical education and excellence in clinical teaching and motivational impact on students, residents, and colleagues, went to **Auguste H. Fortin VI, M.D., M.P.H.**, associate professor of medicine; and **Cyrus Kapadia, M.D.**, professor of internal medicine (digestive diseases). Fortin is director of the psychosocial curriculum for the Primary Care Internal Medicine Residency Program and director of communication skills education. He has a special interest in doctor-patient communication, the humanities in medicine, the psychosocial aspects of primary care, and professional burnout prevention.

As a gastroenterologist, Kapadia was instrumental in the development of techniques to identify precancerous changes in the colon. Kapadia directed the Internal Medicine Residency Program at Yale-New Haven Hospital from 1998 through 2011.

The 2012 Laureate Award was presented to **Stephen P. O'Mahony, M.D.**, assistant clinical professor of medicine, who launched one of the state's first hospitalist programs at Norwalk Hospital in 1999. He also began to use his expertise in computer engineering to integrate best practices and patient safety into clinical care through intelligent technology, decision support, and education.

**Paul Barash, M.D.**, professor of anesthesiology, received the Ralph M. Waters Award from the Midwest Anesthesia Conference at its annual meeting in Chicago in November. Barash was recognized for his contributions to the development of anesthesia in learning, practice, teaching, and research.

**Richard Belitsky, M.D.**, HS '82, FW '83, deputy dean for education, the Harold W. Jockers Associate Professor of Medical Education, and associate professor of psychiatry, was inducted into the University of Florida College of Medicine's Wall of Fame in October. The Wall of Fame award and recognition ceremony were introduced in 1991 to recognize outstanding alumni who have made contributions to medicine, government, education, and the community.

**Michael G. Caty, M.D.**, recently named the Robert Pritzker Professor of Pediatric Surgery, is a noted pediatric surgeon whose clinical interests include neonatal surgery, thoracic surgery, intestinal motility disorders, pediatric surgical oncology, pediatric laparoscopy, and minimally invasive thoracic surgery. He joined the Yale faculty in January 2012, when he was also named the chief of pediatric surgery at Yale-New Haven Children's Hospital.

**Kimberly A. Davis, M.D.**, is the president-elect of EAST (Eastern Association for the Surgery of Trauma), the largest trauma organization in the country. Davis will be installed as president in January 2014. Her term as president-elect began in January of this year.

**Anne Eichmann, PH.D.**, has been appointed Ensign Professor of Cardiology. She is noted for her research exploring the factors that determine the location of cell growth in blood vessels and lymphatic vessels, as well as understanding how the vascular and nervous systems influence each other's growth and function. Eichmann came to Yale in 2010 as a professor in the Yale Cardiovascular Research Center at the School of Medicine.

**T. Rob Goodman, M.D.**, vice chair of the Department of Diagnostic Radiology, was appointed the department's interim chair in January. Goodman will also fill the role of interim chief of diagnostic radiology at Yale-New Haven Hospital. His appointment follows the departure of James A. Brink, M.D., who will lead the department of radiology at the Massachusetts General Hospital. Goodman received his undergraduate degree from Dundee University in the United Kingdom and his medical degree from Cambridge University. He joined the School of Medicine faculty in 2003.

**Jordan Pober, M.D.** '77, PH.D. '77, FW '78, whose research focuses on the functions of vascular endothelial cells in inflammatory and immune responses and how inflammation and immunity affect vascular health and function, has been named the inaugural Bayer Professor of Translational Medicine. Bayer has established this professorship in recognition of the goals it

shares with the School of Medicine to improve the translation and delivery of fundamental scientific discoveries in human health. Pober serves as director of the Human and Translational Immunology Program and is vice chair of the Department of Immunology's Section of Human and Translational Immunology.

**Deborah Proctor, M.D.**, professor of medicine (digestive diseases) and medical director of the Inflammatory Bowel Disease Program, received the Angel Among Us Award from the Middletown (Conn.) Elks at a meeting in November. Proctor donates much of her time to helping patients pro bono. She started the Free Flex-Sig screening program, and she and her husband have made more than 10 trips to Honduras, where they have sponsored more than 40 children in an orphanage.

**Martin A. Schwartz, PH.D.**, recently named the Robert Berliner Professor of Cardiology, is a noted cardiovascular researcher whose studies of cell adhesion and behavior have led to new insights into atherosclerosis and heart disease. A professor of medicine (cardiology) and of cell biology, he is affiliated with the Vascular Biology and Therapeutics Program and is a member of the Yale Cardiovascular Research Center.

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JOHN CURTIS



## Seeing the unsung people “who care for us”

Medical students tell the stories of people who make their own lives better—a custodian, a bus driver, and a cook.

Anyone who’s taken the Yale Shuttle to the VA Connecticut Healthcare System in West Haven has likely crossed paths with Chris Ferguson, one of the drivers on that route. What passengers may not know is that Ferguson is a graduate of Hamden’s Paier College of Art who juggles his work schedule so he can indulge his passion for painting. Diners at Marigolds have probably encountered kitchen worker Lhamu Bhutia, without knowing that she’s a refugee from Tibet whose family once owned a restaurant in Nepal. Pearl Murphy, known to all as “Ms. Pearl,” is hard to miss. More than 6 feet tall, with an outsize

personality to match, she works nights as a custodian at the medical school—one of the two full-time jobs the single mother has held for 30 years.

Their stories, as told by three medical students, were the focus of an inaugural narrative project sponsored by the Program for the Humanities in Medicine with the aim of drawing attention to unsung heroes of the medical school. The students’ narratives were published in a book titled *The Art of Caring*, and the students read from their narratives at a lecture in March. Ferguson and Murphy, along with friends and family, were in the audience for the lecture.

“We never pay attention to those individuals who care for us in environments such as this,” said Thomas P. Duffy, M.D., professor of medicine (hematology) and director of the humanities program, at the lecture in the Cohen Auditorium. “It is those individuals who allow us to live the privileged lives that we live.”

Over the course of three months first-years Matt Meizlish and Lorenzo Sewanan, and second-year Christine Sunu interviewed Murphy, Bhutia, and Ferguson and used their subjects’ own words to describe their lives—from

**TOP** At a session in January, Alisa Anderson met with the students and described how the writing workshop would proceed. “One of the central focuses is that we interview people who often go unnoticed,” she said.

**MIDDLE** Under the guidance of Alisa Anderson (second from left) medical students Lorenzo Sewanan, Christine Sunu, and Matt Meizlish gathered the life stories of three medical school workers and published the oral histories in a book, *The Art of Caring*, in March. The students read from their stories at a Humanities in Medicine lecture in the Cohen Auditorium.

**BOTTOM** Matt Meizlish (back row, far right) told the story, in her own words, of Pearl Murphy, a custodian who’s worked at Yale for 30 years. At the humanities lecture in March, Murphy (seated, far right) was joined by her daughter Tennille Murphy, granddaughter Iyana Liburd, and (back row) George Keen, and Marquis McGraw.



TERRY DAGRADI (2)

Ferguson's passion not only for art, but for the religion that anchors him spiritually, to Murphy's amusement at her granddaughter's attempts to teach her how to text, to Bhutia's family's odyssey from Tibet to India to Nepal to the United States. Guiding the students through the process was Alita Anderson, M.D. '01, who impressed classmates and faculty in her student days with her portrayals of the workers and patients whose life stories she had gathered. At her first meeting with the students in January, Anderson described the process that would unfold, starting with deciding whom to interview.

"In this project one of the central focuses is that we interview people who often go unnoticed and are doing the work of caring for this community—people who are custodians, groundskeepers, security guards—and play a big role in creating the community that you live in every day," Anderson told the students. Over the next weeks Anderson, who lives in Atlanta, discussed the projects with the students during weekly conference calls.

The narrative project was the brainchild of Duffy; Nancy R. Angoff, M.P.H. '81, M.D. '90, HS '93, associate dean for student affairs; and Forrester A. Lee, M.D. '79, HS '83, associate dean for multicultural affairs. "It was decided that we would call on Alita Anderson to be an artist and writer in residence," Duffy recalled. "Out of that has come this remarkable manuscript."

—John Curtis

## From faltering English to leadership of a medical student group

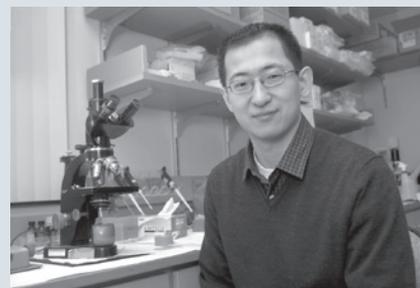
One Saturday when he was 10 years old, Hao Feng arrived in the United States from Shijiazhuang in northern China. Feng, who then knew fewer than a dozen words of English, started school on the following Monday. Today he speaks English with no trace of an accent, but the linguistic and cultural barriers of those early years have informed his approach to medicine.

Feng, now taking a fifth year for research at the School of Medicine, was recently elected chair of the Council of Student Members (CSM) of the American College of Physicians (ACP). His role as a leader of the internal medicine interest group during his second year of medical school led to an invitation to join the ACP Connecticut chapter's Governor's Council. The organization's support for medical students so impressed him that he applied for a position on the CSM, which represents the interests of approximately 28,000 students. As chair, Feng will become a voting member of the Board of Regents, the ACP's main policy-making body. He is the only medical student in the country to hold that privilege. "I will represent the opinions and interests of medical students across the nation," he said. Those interests, he said, include funding for graduate medical education, the huge debt burden faced by medical students, and changes in the health care system.

Feng explored law, biotechnology, teaching, and engineering as an undergraduate at the University of California, Berkeley, and graduated with a degree in molecular and cell biology. Medicine—the only profession in which he felt he could make an impact on both individuals and on society—became his first choice for a career.

Feng is well on his way to gaining experience in these areas. As a Doris Duke Clinical Research Fellow, he

Hao Feng, a medical student taking a fifth year for research in photopheresis, was recently elected chair of the Council of Student Members of the American College of Physicians, where he will advocate on behalf of medical students across the country.



JOHN CURTIS

is studying the mechanism behind photopheresis, an immunotherapy treatment that is effective for cutaneous T cell lymphoma, transplant rejection, autoimmune disorders, and graft-versus-host disease.

Feng also volunteers at HAVEN, a free clinic staffed by Yale students under the supervision of faculty. His early struggles with English, he said, "gave me a respect and understanding of how important it is to accept diversity and keep in mind that other people have different beliefs." Most patients at the clinic are Hispanic. When a patient told him that he felt "ice in his veins," Feng probed further. Although he and his colleagues were unable to make a definitive diagnosis, they asked the patient to return for another visit. "There are certain things patients offer because they feel it's important, and if we ignore that aspect we may be missing a component of what they're trying to tell us," he said.

Feng is still trying to decide on a specialty. In addition to being both a physician and a researcher, he would like to advocate for better health care and influence health care legislation. He believes he will be able to fit it all in. "If you're passionate about something, you'll make time for it," he said.

—Jill Max



ST. LOUIS BUSINESS JOURNAL/BRIAN CASSIDY

Jeffrey Lowell, a pediatric transplant surgeon, has advised the Department of Homeland Security on medical affairs, and laid the groundwork for regional responses to natural disasters in St. Louis.

## Medicine, community, and justice intersect

Jeffrey Lowell helps first responders, government officials, and health providers to prepare for disasters.

A few years after Jeffrey Lowell, M.D. '85, joined the faculty at Washington University School of Medicine in St. Louis in 1994, the liver and kidney transplant surgeon transitioned from spending his protected research time in a lab to spending it in support of the community.

"Initially, I was interested in the intersection of medicine, community, and justice. Physicians and law enforcement are both involved in high-stakes, fast-tempo work, and I thought that medicine could contribute something," Lowell said.

Completing coursework and training at the St. Louis Police Academy in 2001,

Lowell rose through the ranks of community and regional public service—receiving training in tactical medicine as a hostage negotiator and serving as the city's police surgeon, then serving as the mayor's regional medical critical incident director—until Tom Ridge, the first secretary of the Department of Homeland Security (DHS), invited Lowell to Washington to be his senior advisor for medical affairs.

When Ridge came to St. Louis in October 2003 on a national tour of town hall meetings regarding the fledgling DHS, he had already heard of Lowell's accomplishments in the mayor's office and the St. Louis region. Lowell had spearheaded projects that coordinated the city's hospitals and its first-response agencies—a need that St. Louis recognized during the 2001 anthrax attacks that followed 9/11. As in every major U.S. city, telephone lines at hospitals, post offices, and police, fire, and public health departments were jammed with calls about the dangers of unidentified white powders.

"We were chasing our tail around and didn't have any good program to deal with it, so Mayor [Francis] Slay asked if I would build a matrix organization that integrated the region's medical and health assets with all the other forms of local government, including first response," he said.

Lowell led the effort to devise and implement the St. Louis Hospital Mutual Aid Agreement, which binds the hospitals of the metropolitan area's eight counties across two states (Missouri and Illinois) to share staff, beds, equipment, and supplies in the event of a disaster—natural, industrial, terrorist, or other.

"It was a big deal. Hospitals are big business competitors. They would just as soon put a stake in each other's heart as help one another. But we got every hospital in the region to say that in the event of a disaster, they'll help one another," Lowell said.

The agreement laid the groundwork for the St. Louis Area Regional

Response System (STARRS), which Lowell led the effort to create. The network coordinates the fire departments, police departments, public health agencies, governments, and NGOs of the two-state metro area for disaster preparation and response. Ridge was seeking just this type of multiagency coordination and integration for his new department that would bring together all or part of 22 federal agencies when he invited Lowell to meet with him in St. Louis.

“When Congress built this department, they didn’t give him a top doctor, but almost everything that Secretary Ridge went to bed afraid of happening to America the next day had a medical or health implication,” Lowell said.

Shortly after the meeting, Ridge asked Lowell to work for him in Washington, D.C., as his senior advisor for medical affairs. In Washington, Lowell defined the role of a permanent medical advisor. Later, he shared these recommendations in a 2005 House Subcommittee hearing. Largely based on these recommendations, DHS launched the Office of Health Affairs and the holder of Lowell’s former position is now known as the DHS Chief Medical Officer and Assistant Secretary for Health Affairs.

Lowell’s recommendations also appeared in a report to Ridge that outlined a strategy to realign and strengthen the *Federal Medical Response*, which was released in January 2005 and later made national news. Eight months later, his assignment in Washington over, Lowell was back home in St. Louis, when Hurricane Katrina put his evaluation to the test, requiring the biggest National

Disaster Medical System (NDMS) deployment to date. The *Washington Post* quoted officials and NDMS team leaders who strongly supported Lowell’s assessment.

“I think a lot of my recommendations, if implemented, would have greatly improved our Katrina response,” Lowell said.

Back at work in St. Louis, Lowell continues to serve his city as the mayor’s senior medical advisor and director of the health department. As chief of pediatric transplant surgery at St. Louis Children’s Hospital, he has performed a liver transplant on a 10-day-old patient, one of the youngest known organ recipients. He also served on one of the first teams to perform a transplant in which a piece of an adult liver from a living donor was transplanted into an adult recipient.

A commander in the U.S. Navy (reserve), Lowell was deployed to Central and South America on a humanitarian mission and in support of Operation Enduring Freedom to the U.S. Army hospital in Landstuhl, Germany.

“It’s very rewarding, not only to be in health care and do something that people both need and otherwise wouldn’t be able to have, but to do it representing your country. Taking care of injured soldiers and marines has been my greatest honor. I am deeply grateful for having that privilege.”

—Sonya Collins

## Alum promotes chronic disease meds against inflammatory response

Statins. Metformin. Glitazones. Fibrates. Familiar drugs to clinicians who treat patients with cardiovascular diseases and diabetes. They tamp down inflammatory overreaction to the disease. Could they also work in acute illnesses, even infections? David Fedson, M.D. ’65, believes they could be useful against severe influenza, sepsis, trauma, and severe burn injury conditions that can also provoke a deadly inflammatory response. He believes this question is worth investigating and is waging a campaign to persuade researchers to do so.

Fedson, who is retired and lives in France near Geneva, Switzerland, where his wife works for the World Health Organization, is no stranger to public health. During medical school, he studied an experimental smallpox drug, but it turned out to be ineffective. In 1968, as a resident at Johns Hopkins, he participated in a research project in Kolkata (Calcutta) with investigators who were instrumental in developing oral rehydration therapy (ORT) to treat cholera. Later, he studied influenza vaccination at the NIH; and in 1976, while on the faculty of the University of Chicago, he organized the university’s swine flu vaccination program. Six years later he published a recommendation that is now national policy: routinely offering influenza and pneumococcal vaccination to patients being discharged from the hospital. After 13 years on the faculty of the University of Virginia, where he was head of the Division of General Medicine, he moved to France in 1995 to become director of medical affairs at Sanofi Pasteur MSD, a vaccine company. There he continued his work on the epidemiology and cost-effectiveness of influenza and pneumococcal vaccination.

In the early 2000s, when H5N1 avian influenza emerged as a global public health threat, Fedson recognized

David Fedson is campaigning to encourage physicians to use familiar drugs to treat acute illnesses, including infections. Fedson is retired and lives near Geneva, Switzerland.

that vaccination alone would not save many lives—it would be difficult to produce and distribute in a short period of time. Like many researchers, he also wondered why the 1918 influenza pandemic had spared children but killed young adults. Clinicians and epidemiologists, he said, have noticed similar mortality differences in patients with other infectious diseases, in trauma victims, and in those with acute lung injury due to malaria and sickle cell disease. Children fare better than adults because their immune systems tend not to launch a damaging and sometimes fatal inflammatory response. No one knows why, but Fedson believes it makes evolutionary sense. “Children may be programmed to devote their energy to growth, not immune defense. Once they reach an age where they can reproduce, energy metabolism is redirected to immune defense,” he said.

Fedson recalled a study in which adult mice reacted more severely to liver injury than juveniles. When researchers treated adult mice with the diabetes drug rosiglitazone, the adults had less severe inflammation and better survival. In effect, he said, the researchers “rolled back the host response of the young adult to that of a child.” Similar effects on acute inflammation have been seen in studies of statins for heart attack victims and in studies of other immunomodulatory drugs in animal models of sepsis and influenza. In each instance, these drugs act to restore homeostasis. Equally important, they are produced as inexpensive generics and are available in any country with a basic health care system.



But much work needs to be done to determine whether these inexpensive drugs could be used routinely to treat patients with severe acute illness, including avian influenza. Unfortunately, said Fedson, research on the muted host response to disease in children, as well as on strategies to mimic this response in adults, has been neglected—especially by influenza scientists and immunologists.

Fedson has lectured at conferences, published in medical journals and the lay press, and contacted dozens of prominent researchers, journalists, and policymakers. Responses to what he calls his “cry in the wilderness” have been few and mostly noncommittal. He blames narrow specialization and a driving desire among biomedical scientists to explain mechanisms of disease rather than seek practical ways to manage it.

It doesn’t help, he adds, that most experts are not M.D.s, but Ph.D.s, who have a better understanding of the virus than the host response it can produce.

ORT for cholera, Fedson pointed out, was introduced at a time when researchers were trying and failing to develop an effective cholera vaccine. ORT treated the

host response—the diarrhea and subsequent dehydration—without attacking the infectious organism. The strategy has saved tens of millions of lives worldwide. Might a physiologic treatment of the host response to pandemic influenza do the same?

“Let’s see if we can use what we’ve already got,” Fedson said. “We don’t know whether these agents will work, but we can’t afford not to do the research to find out.”

—Jenny Blair, M.D. '04

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### Familiar Faces

Do you have a colleague who is making a difference in medicine or has followed an unusual path since leaving Yale? We’d like to hear about alumni of the School of Medicine; Physician Associate Program; and the medical school’s doctoral, fellowship, and residency programs. Drop us a line at [ymm@yale.edu](mailto:ymm@yale.edu) or write to Faces, Yale Medicine, 1 Church Street, Suite 300, New Haven, CT 06510.



**Sherwin Nuland**



**Brian Kobilka**



**Steven Rasmussen**



**Vishal Agrawal**



**Rajesh Rao**

## 1950s

**Herbert Kaplan, M.D., HS '58**, received the Presidential Gold Medal from the American College of Rheumatology in November. The award recognizes outstanding achievements in rheumatology over an entire career.

**Harry C. Miller Jr., M.D. '54**, received the William P. Diduch Art and History Award from the American Urological Association (AUA) at its 2013 annual meeting in San Diego in May. Miller was an editor of the *Centennial History of the AUA*, published in 2003.

**Sherwin B. Nuland, M.D. '55**, HS '61, clinical professor of surgery emeritus, received the Jonathan E. Rhoads Gold Medal “for distinguished service to medicine” from the American Philosophical Society at its November 2011 meeting in Franklin Hall in Philadelphia.

## 1970s

**George J. Dohrmann, M.D., PH.D., HS '78**, received the 2012 Career Achievement Award from the Chicago Neurological Society. Dohrmann was honored for expertise, knowledge, dedication, and recognition in neurosurgery and neurological research. Dohrmann is a member of the neurosurgery faculty at the University of Chicago Medical Center.

**Richard Kayne, M.D. '76**, received the Volunteerism and Community Service Award in November from the Connecticut Chapter of the American College of Physicians (ACP). Kayne's son, a survivor of osteosarcoma, attended Paul Newman's Hole in the Wall Gang Camp in Ashford, Conn., in 1995.

The next year Kayne volunteered as a counselor for the camp, and he became a member of its board of directors in 2002.

**Barbara R. Pober, M.D. '78, M.P.H.**, has joined the founding faculty of the Frank H. Netter M.D. School of Medicine at Quinnipiac University in Hamden, Conn. Pober will teach genetics at the medical school, which will open this fall. Pober, professor of pediatrics at Harvard Medical School, is recognized as an international expert on Williams syndrome, a genetic disorder marked by cardiovascular disease, developmental delays, and learning disabilities.

**Eddie Reed, M.D. '76**, was named clinical director of the Intramural Research Program at the National Institute on Minority Health and Health Disparities (NIMHD) of the National Institutes of Health in January. Reed will oversee outpatient, inpatient, epidemiological, clinical, and laboratory-based investigations, and will build a multi- and interdisciplinary research program geared to translating basic research into clinical trials and interventions.

## 1980s

**Brian K. Kobilka, M.D. '81**, professor of molecular and cellular physiology and of medicine at Stanford University School of Medicine, won the 2012 Nobel Prize in Chemistry in October. He shares the prize with Robert J. Lefkowitz, M.D., of Duke University Medical Center, for their work on sensors lodged in the cell membrane known as G-protein-coupled receptors (GPCRs). Their work has contributed to improved understanding of the ways cells sense and respond to

their environment—almost half of all medications achieve their effects through GPCRS.

Lefkowitz began using radioactively labeled hormones to identify their receptors at Duke in 1968, and soon discovered the  $\beta$ -adrenergic receptor, which binds adrenaline on the cell surface and sets off a biochemical cascade inside the cell. Kobilka joined Lefkowitz's lab as a postdoctoral fellow in the 1980s.

In 2011, Kobilka's team captured an image of the  $\beta$ -adrenergic receptor at the moment that it is activated and sends a signal into its cell. In announcing the prize, the Nobel committee declared, “This image is a molecular masterpiece—the result of decades of research.”

**Steven Rasmussen, M.D., HS '83**, known for his research in developing circuit-based neuromodulatory treatments for psychiatric disorders, has been named chair of the Department of Psychiatry and Human Behavior at the Warren Alpert Medical School of Brown University.

## 1990s

**Brian Adams, M.D. '95, M.P.H.**, has been named interim chair of dermatology at the University of Cincinnati College of Medicine, where he completed his internship and residency. Adams joined the faculty of the Department of Dermatology in 1999 and serves as residency program director and director of medical student education.

**Keith von Eigen, M.D. '90, M.P.H., PH.D.**, received a Laureate Award from the Connecticut Chapter of the American College of Physicians (ACP) in November. The award

is one of the chapter's highest honors for distinguished service to patients and the profession.

## 2000s

**Vishal Agrawal, M.D. '02, FW '96**, has been named president of the Harris Corporation's Healthcare Solutions business. Agrawal has more than 15 years' experience developing strategies for and advising government and commercial health care organizations in North America. At the School of Medicine he was a Howard Hughes Medical Institute research fellow and in the Department of Molecular Biophysics and Biochemistry.

**Rockman Ferrigno, M.D. '01, HS '04**, has been named the interim chair of the emergency department of Connecticut's Bridgeport Hospital, where he has worked for seven years.

**Rajesh C. Rao, M.D. '07**, a vitreoretinal surgery fellow in the Department of Ophthalmology and Visual Sciences at Washington University School of Medicine in St. Louis, submitted one of 10 entries selected by the National Eye Institute, part of the National Institutes of Health, for its Audacious Goals challenge. Rao's proposal involves restoring vision in patients whose retinas have deteriorated from diseases like age-related macular degeneration.

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**Margaret J. Albrink, M.D.** '46, HS '47, FW '51, M.P.H. '51, died on December 23 in Morgantown, W. Va. She was 92. Albrink was one of the rare women of her generation to pursue a career in academic medicine and was the first researcher to establish the significance of serum triglycerides in coronary artery disease. Albrink joined the Yale faculty and served as instructor in medicine from 1952 to 1958. She became assistant professor of medicine in 1958. She and her husband, Wilhelm S. Albrink, M.D., joined the faculty of the West Virginia University School of Medicine in 1961.

**Robert S. Briggs, M.D.** '61, HS '65, died of complications of Parkinson disease in Litchfield, Conn., on November 25. He was 80. After residency and a fellowship in hematology at Yale, Briggs moved to Litchfield in 1965, where he joined an internal medicine practice.

**Peter R. Cunningham, M.D.** '49, HS '50, a retired pediatrician, died on October 11 in Johnson, Vt. He was 86. After graduation, Cunningham worked at the Navy hospital in Newport, R.I., before completing his residency in pediatrics. He had pediatrics practices in Guilford and Westville, Conn., for over 30 years before retiring to Vermont in 1986.

**Herbert S. Harned Jr., M.D.** '45, a retired pediatric cardiologist, died on January 7 at University of North Carolina Hospitals in Chapel Hill. He was 91. During his career Harned saw the development of diagnostic and interventional cardiology as it involved children; the near-demise of rheumatic fever; the development of surgery for complex cardiac conditions; and the creation of intensive care units for newborns and children.

**Louis J. Kaplan, M.A.**, associate dean for government and community affairs during a turbulent era in the history of the School of Medicine, died on January 8 in Springfield, Va. He was 96. Kaplan's work helped

to establish the Connecticut Mental Health Center (CMHC) and the Yale Comprehensive Cancer Center.

Kaplan was hired as director of field services for the Connecticut Mental Health Association in 1956, where he worked with community members, government agencies, and other institutions. Kaplan also conducted a series of fundraising events with celebrities—including Vivian Vance, Lucille Ball's best friend in the *I Love Lucy* series, and baseball great Jackie Robinson—to raise public awareness of mental health issues.

Kaplan became the executive director of the association in 1966 and was recruited to the planning team for the new CMHC. The following year he became assistant to Dean Frederick Redlich, M.D. Not long after, the city of New Haven was engulfed in racial riots similar to those that swept other cities at the time. Kaplan worked with community representatives and government officials to quell the violence and initiate new programs to address many of the local issues that had sparked the unrest.

**Leo D. Kellerman, M.D.** '42, of Douglaston, N.Y., died of natural causes at the home of his daughter in Avon, Conn., on November 18. He was 95. The child of Russian immigrants, Kellerman practiced ophthalmology in Queens, N.Y., and volunteered his medical services in Kenya and the West Indies.

**Arthur E. Laidlaw, M.D.** '39, a retired pediatrician, died on November 19 in Cooperstown, N.Y. He was 97. Laidlaw served in the Army Medical Corps during World War II, returning to practice medicine in New Hampshire and upstate New York until his retirement in 1975.

**Jack Love, M.D.** '58, PH.D., died on November 19 in Santa Barbara, Calif. He was 82. After his second year of medical school, Love received a Rhodes Scholarship and studied experimental

pathology at Oxford, where his thesis advisor was the Nobel laureate Sir Howard Florey, PH.D. Love served as a thoracic surgeon in the U.S. Army Medical Corps and later was a member of the surgery faculty at Johns Hopkins School of Medicine and the UCLA School of Medicine.

**Ellen P. MacKenzie, M.D.** '44, died on December 14 in Gretna, La. She was 92. MacKenzie opened her private practice in pediatrics in Gretna in 1949 and received psychiatric training at Louisiana State University School of Medicine and the Charity Hospital of New Orleans.

**John H. Meyers, M.D.** '50, a retired dermatologist, died in Glen Cove, N.Y., on October 6. Meyers was a captain in the U.S. Army Medical Corps and chief of dermatology at Fort Belvoir, Va.; he later served as an adjunct professor of dermatology at New York Polyclinic Medical School and Hospital before becoming chief of dermatology at the Glen Cove Hospital.

**Richard A. Moore, M.D.** '61, a retired pediatrician, died on November 26 in Cleveland, Ohio. He was 77. Moore was chief medical resident at Rainbow Babies and Children's Hospital in Cleveland before moving to Elyria, Ohio, where he practiced for over 40 years.

**Edmund L. Piper, M.D.** '49, died on October 30 in Exeter, N.H. He was 87. Piper practiced dermatology in the Portsmouth area for most of his career.

**Giles Stevens Porter, M.D.** '43, a retired general practice physician, died on November 23 in Eugene, Ore. He was 95. Porter served as a medical officer in the U.S. Navy in the Pacific Theater during World War II. After the war, he moved to Eugene to open a general surgical practice. Porter also worked as a trauma specialist in the emergency department of Sacred Heart Hospital in Eugene.

**Frank H. Ruddle, PH.D.**, professor emeritus of biology, died on March 10 at Yale-New Haven Hospital. He was 83. Ruddle received his doctorate in zoology from the University of California, Berkeley, in 1960, and completed postdoctoral work at Glasgow University. In 1961 he joined the Zoology Department (later Biology, and then Molecular, Cellular, and Developmental Biology) and had a joint appointment in the Department of Human Genetics until his retirement in 2007. Ruddle served as chair of the Biology Department several times and held endowed chairs as the Ross G. Harrison Professor and the Sterling Professor of Biology. He was noted for his seminal studies on human gene mapping, his development of the transgenic mouse, and his work on homeobox genes, important regulators of development. His achievements were recognized by his election to the National Academy of Sciences, the Institute of Medicine, and the American Academy of Arts and Sciences. He was the recipient of many awards, including the Dickson Prize in Medicine, the William Allan Award of the American Society of Human Genetics, and the 2000 Connecticut Innovations Special Achievement Award. Ruddle served on numerous NIH review boards, was president of the American Society for Cell Biology, and was editor of such scientific journals as the *Journal of Experimental Zoology* and *Genomics*.

**Arlene Sweedler, M.D.** '58, died on December 17 in Urbana, Ill. She was 80. After a residency at Bellevue Hospital in New York City, Sweedler spent several years working in Japan. Along with her husband, Daniel, whom she met at the School of Medicine, she started a medical practice in Livermore, Calif.

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SEND OBITUARY NOTICES TO  
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## A climb for health and history

“What do the Blumenfeld lab, 27 flights of stairs, and the pictures below have in common?” So read an invitation from Hal Blumenfeld, M.D., PH.D., to his lab. “We have a lab outing every year,” said Blumenfeld, professor of neurology, neurobiology, and neurosurgery, and director of the Yale Clinical Neuroscience Imaging Center. “This year I thought I would combine historical tours and stair climbing. I walk the stairs regularly. It’s a good way to be fit and healthy.”

The pictures in the invitation were of locations on the outing—dubbed CFANHY, Climb for Fitness And Neuroscience History at Yale—in which a dozen members of Blumenfeld’s lab joined him on March 20. Their stair-climbing tour took in the Cushing Center, the top of the Sterling Hall of Medicine, the Clinic Building, Smilow Cancer Hospital, and the helicopter landing pad at Yale-New Haven Hospital. At each high point Blumenfeld arranged for discussions of history that covered neurosurgeon Harvey Cushing, New Haven’s hospitals, and the era of Dean Milton Winternitz, M.D. The tour ended with lunch at BAR.