

# yale medicine

## resilience

Recovering from injury  
to body or mind

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Autumn 2014  
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**Article brings back memories**

I was happy to see the article in your Spring issue regarding Seymour Lipsky on page 22 [Building a Better Mousetrap (and Mouse), *Yale Medicine*, Spring 2014]. The picture, however, should have been dated 1958 and the caption should have stated that the research being done at that time and through the early 1960s was the development of gas chromatography.

I was a colleague of Dr. Lipsky during those years and co-authored about 20 research papers with Dr. Lipsky and such others as James Lovelock in the development of this new technique. I also used the technique in collaboration with Dr. Lou Gluck in his search to identify the surfactant material in the lungs of newborns.

So thank you for reviving some old memories for me.

Robert A. Landowne, Ph.D. '58  
Westport, Conn.

*Thanks to Dr. Landowne for clarifying and adding to the record of this historic achievement. The photograph is indeed from 1958*

*and shows instrumentation for gas chromatography, an advance that contributed to the development of a related method, high-performance liquid chromatography, in the 1960s.*

**Thanks for your latest issue**

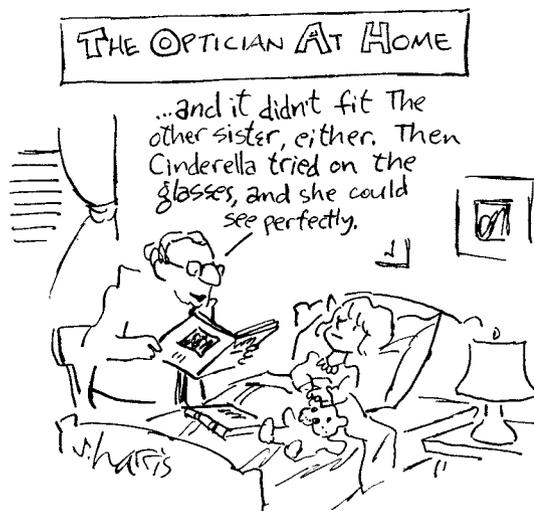
I wanted to congratulate you on the latest issue of *Yale Medicine* [Spring 2014]! I literally read it cover to cover. The articles are diversely fascinating, deftly

combining science and human interest, and the colorful design is beautiful and inviting. Thanks to the magazine, although I have left New Haven, I feel as though I'm still in touch with what's going on at Yale, both in the lab and in the clinic. Thanks so much for your work on this ingenious issue!

Michaela Panter, Ph.D. '12  
New York, N.Y.

**SECOND OPINION**

BY SIDNEY HARRIS



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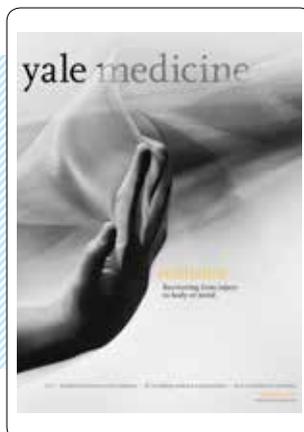
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## “A medical school operates in an always-changing environment”

WHAT DOES IT MEAN TO BE RESILIENT? While exploring this topic for this issue of *Yale Medicine*, we asked students and faculty (see excerpts on pp 30–31), including Dean Robert J. Alpern, M.D. He shared his thoughts from the vantage points of an administrator managing a billion-dollar-plus budget, a faculty member interested in the work of colleagues, and a basic researcher who ran his own labs in California, Texas, and at Yale.

**What is resilience?** The ability to survive is based on homeostatic mechanisms that maintain our bodies in a constant state, in spite of a variable environment. So the temperature outside goes up and down, but our bodies remain at about 98.6 degrees, as long as we’re healthy. That’s homeostasis.

When we talk about resilience, we refer to the ability of the homeostatic mechanisms to function within environmental extremes. This plays a role in health from so many perspectives: psychological resilience after trauma, the body’s ability to heal after an injury or severe infections, the resilience of communities and populations, just to name a few.

**As a nephrologist, can you discuss how the kidney figures into this topic?** If you ingest a low-sodium diet, the kidney retains sodium. If you eat a high-sodium diet, the kidney excretes sodium. The kidney is all about homeostasis and resilience.

**What about deans? Do they have a homeostasis mechanism?**

A colleague once said to me that the reason there are more nephrologists serving as deans than from other specialties is because nephrologists understand that what goes in has to equal what comes out. So we’re very good at balancing budgets and addressing extreme homeostatic challenges to the institution.

**What kinds of challenges?** A medical school operates in an always-changing environment, and we have to maintain our excellence in the midst of this—changes in health care law, the competitive environment, NIH regulations, NIH budgets. And sometimes they’re extreme: sequestration for example. You need to be resilient.





## Play-Doh and 3-D apps bring neuroscience into psychiatry training



Research has found that adults retain only 5 percent of what they hear in lectures. So at a training conference, presenters taught neuroscience by having their audience build brains from Play-Doh.

“HELLO, MY NAME IS JOSH GORDON from Columbia University, and I’m going to show you how to build your brain out of Play-Doh,” said Gordon, M.D., Ph.D. Two hundred psychiatry residency program directors from across the country watched Gordon on a video on their laptops, tablets, and other personal devices at the 2014 BRAIN Conference—the one-day, neuroscience-focused pre-meeting to the American Association of Directors of Psychiatric Residency Training conference in March in Tucson, Ariz. Gordon made the instructional video after the conference workshops were beta-tested ahead of time in New York. “Josh is something of a Play-Doh savant,” said David A. Ross, Ph.D. ’04, M.D. ’05, assistant professor of psychiatry, who helped plan the event. While many beta testers struggled to assemble the building blocks of the brain, Gordon was sculpting NMDA receptors, critical cellular structures for learning and memory. “It was stunning,” said Ross. At the conference, the residency program directors molded their own Play-Doh brains, following along as Gordon explained that the wad of yellow Play-Doh on their screens was the brain stem—a conduit through the spinal cord between the brain and the rest of the body. Layer by layer, from the multicolored blobs of nontoxic modeling material, a 3-D model of the brain emerged.

Neuroscience can be overwhelming, said Ross, one of three psychiatry educators spearheading the National Neuroscience Curriculum Initiative (NNCI), which aims to provide universities with the tools to teach neuroscience effectively. The NNCI provides a framework for neuroscience education, relying on expert neuroscientists and educators to generate content. The Play-Doh brain, the first module of the initiative, is a kinesthetic learning exercise that serves as an introduction to the complex organ. “We’re going to start with something simple and fun,” said Ross. “Let’s play.”

The NNCI was created in response to the rising demand for better neuroscience education in psychiatry. Historically, a deep divide has existed between neuroscience’s biological approach to the mind and the more traditional—and humanistic—psychiatric perspective. In the past, neurobiological findings have not readily translated into patient care, but technological advances over the last two decades have the potential to revolutionize both our understanding of psychiatric illness and the development of new treatments. Advances in neuroimaging allow physicians to see healthy and abnormal brains in action, and advances in genetics have allowed researchers to identify rare genetic variants that contribute to such neuropsychiatric disorders as Tourette syndrome.

Surveys conducted at Stanford and Georgetown found that psychiatry residents overwhelmingly agreed that they needed better training to translate those advances into clinical practice. Still, only a handful of universities, Yale among them, have comprehensive neuroscience education programs.

One of the barriers to incorporating neuroscience into psychiatric training is the difficulty in teaching the subject effectively. Graduate medical education traditionally follows a lecture-intense format—a limited approach, according to Ross. “The literature on adult learning is that less than 5 percent of what’s presented in a lecture setting is retained, and even that, I think, is wonderfully generous,” he said. “There would be a tragic irony if we, as the psychiatrists and neuroscientists who are studying how adults learn, failed to take that into account in the way we’re teaching our trainees.”

Melissa P. Arbuckle, M.D., Ph.D., associate professor of clinical psychiatry and the associate director of resident education at the Columbia University College of Physicians and Surgeons, and chair of the 2014 BRAIN conference, teamed up with Ross and Michael J. Travis, M.D., associate professor of psychiatry at the University of Pittsburgh and director of Residency Training at Western Psychiatric Institute and Clinic at the University of Pittsburgh,

to develop the BRAIN conference program—“Neuroscience: Why, What, and How to Teach It”—around novel ideas for ways to teach neuroscience. They dropped the traditional keynote lectures, opting for a workshop-driven day filled with new experiential learning approaches to neuroscience that other program directors could test at the conference and then incorporate into their own programs.

It worked. In the weeks immediately following the conference, the NNCI organizers began receiving positive feedback from programs around the country that had already implemented the Play-Doh exercise. Other modules developed for the BRAIN meeting included an integrative case conference, which explores a case from biological, psychological, and social perspectives; a translational neuroscience module, in which participants look at cutting-edge clinical neuroscience research and discuss how those advances could reshape psychiatry; and a module called Talking Pathways to Patients, in which participants role-play physician-patient interactions using a laminated card with images from the 3-D brain app to explain to a patient the neural systems underlying a disorder.

“Building on this success, we wanted to formalize a structure for continuing this work on a broader scale,” said Ross. He and colleagues built a website



## THE REAL PEGGY BIA

Will the real Peggy Bia please stand up? Four students who played Bia in second-year shows reprised their roles at a reception in June, as faculty, alumni, and students offered hilarious and affectionate remembrances.

Photo gallery, as well as other online-only content, can be found on our home page at [yalemedicine.yale.edu](http://yalemedicine.yale.edu).

to house the modules and their content, where programs across the country or the globe could access the materials and implement them into their own neuroscience programs. “They’re thinking past their own institutions,” said Joyce Y. Chung, M.D., the program director of the National Institute of Mental Health (NIMH) clinical research training program, who saw the potential of the initiative at the BRAIN conference and advised the group on their NIMH grant application. “When I saw what they had done *without* funding, I could only imagine what they could do *with* funding,” said Chung. In June of this year the group received a supplementary education grant of about \$450,000.

The team created teaching guides for each module so that anyone without a background in neuroscience can feel comfortable teaching it.

Programs at Yale, Columbia, and Pittsburgh, which provide the framework for the NNCI, are at the leading edge of trends in psychiatry training. “At present, these advances in neuroscience education are a matter of passion for those involved,” wrote Mayada Akil, M.D., professor of psychiatry and vice chair for education at Georgetown, and her co-authors in an April 2014 commentary in *Academic Psychiatry*. “We hope that in five to 10 years they will become a matter of course.”

—Kate Wheeling



## Passing of the torch in clinical skills education

A Greek inscription carved into the stone face above the entrance to the Sterling Hall of Medicine translates: “Those having torches will pass them on to one another.”

“It’s something Plato said,” said Margaret J. Bia, M.D., FW ’78, known for her tenacious personality, her Brooklyn accent, and her contributions to the clinical skills education of more than three decades of School of Medicine graduates. According to Bia, the clinical skills program, with approximately 140 faculty members who educate the next generation of physicians, exemplifies the value extolled by Plato. This year she’s passing on the torch.

Bia is retiring from medical education, though she’ll continue as a senior transplant nephrologist at Yale-New Haven Hospital. Jaideep S. Talwalkar, M.D., HS ’04, assistant professor of medicine and of pediatrics, will take over just as the medical school prepares to implement a redesign of the curriculum. Talwalkar will direct the clinical skills program at large, ultimately determining how it will fit into the new curriculum that emphasizes early clinical experience, an integration of the basic sciences and clinical medicine, and a restructuring of the clerkships. “With the curriculum redesign, we’re going to have to remake what the clinical skills program looks like,” said Talwalkar.

Barry J. Wu, M.D., clinical professor of medicine, will run the clinical tutor program.

Bia has been the face of the clinical skills program at Yale for the last 15 years. When she took over in 1998, the program was heavy on didactics and light on practice, but under her leadership that all changed. “Dr. Bia has really changed the landscape entirely,” said Nancy R. Angoff, M.P.H. ’81, M.D. ’90, HS ’93, associate dean for student affairs.

Historically, the first two years of medical education at Yale had focused on the basic sciences, and until the 1980s, clinical skills education began at the end of the second year. Students’ only clinical training before then was a physical diagnosis course. In the 1990s, faculty added sessions on interviewing and patient communication, and started the tutor program. Today, clinical skills education begins before students even arrive at Yale, with the psychosocial communication curriculum run by Paul D. Kirwin, M.D., associate professor of psychiatry. Essays that students write during that curriculum influence the content of the clinical skills program, which is overseen by Barbara Hildebrand, the program manager.

Bia arrived at Yale in the mid-1970s as a transplant specialist. Teaching had always come naturally to her, but she never imagined that she would have a seminal role in the formal education of medical students. Her

love of medicine and doctoring led Bia to grow the clinical skills program into what it is today—a program that includes 44 skills sessions and 44 clinical tutorials in the first two years, 10 additional sessions for advanced skills training in the third and fourth years, a tutorial program, and sessions on LGBTQ issues, hospice, observation skills, and more.

“The skills program is very much where [students] learn the art of medicine,” Bia said. Much of that learning takes place in the tutorial program, in which a seasoned physician partners with four incoming students. Bia expanded and standardized the weekly tutor-student meetings that take place throughout the first and second years, ensuring that students and tutors get the most out of each session by outlining the goals and objectives.

According to Wu, the mentoring relationship between students and tutors sets Yale’s program apart. “The longitudinal relationship is something that’s really celebrated here,” he said.

“I always wanted Yale to be as known and famous for medical education as it is for science and research,” said Bia. She assembled a dream team of clinical educators that created the program as it is today. “It is not my program—it is the team’s program,” said Bia.

Auguste H. Fortin VI, M.D., M.P.H., associate professor of medicine, was teaching patient-centered interviewing skills to

primary care internal medicine residents when Bia invited him to do the same for medical students. Patient-centered interviewing allows physicians to obtain biological, psychological, and social information and to create a more holistic description of a patient. According to Fortin, it can increase diagnostic accuracy as well as professional satisfaction among physicians, and decrease the risk of burnout and malpractice suits. “I think there’s a rich tradition of humanistic care at Yale, and it was part of the informal curriculum,” said Fortin.

“[Dr. Bia] brought it front and center into the formal curriculum.”

To further improve physician-patient communication skills, Bia brought on Matthew S. Ellman, M.D., associate professor of medicine. Ellman, director of Medical Student Palliative and End-of-Life Care Education, teaches the students how to communicate with patients at the end of life. “This isn’t considered one of the traditional medical skills, like taking a medical history or performing a physical exam, but she recognized that this is a skill that all medical students at Yale should get before they graduate, because no matter what specialty they go into, they’re going to, from time to time, be faced with patients that they can’t cure,” said Ellman.

“There’s something that’s just Dr. Bia that you can’t replace. You can’t really describe how much she cares about the program, but you can tell how much she cares about it,” said Samuel Sondalle,



a third-year M.D./Ph.D. student. “The success of the program is reflective of that.”

Talwalkar hopes to build upon that success in the program in the future by beginning clinical learning even earlier, getting residents more involved in medical student teaching, and having students work within interprofessional care teams. “I don’t look to be replacing [Dr. Bia] in any way,” said Talwalkar. “I look to be building on what she’s already put in place.”

—Kate Wheeling

Margaret Bia has been a leader in medical education, particularly in the teaching of clinical skills, since she arrived at Yale more than 30 years ago. “The skills program is where students learn the art of medicine,” she said.



ONLINE EXCLUSIVES

Educating the educators on Med Ed Day

How two Iranian doctors landed in jail for treating HIV/AIDS

Big data rule on Student Research Day

Full stories and event photo galleries, as well as other online-only content, can be found on our home page at [yalemedicine.yale.edu](http://yalemedicine.yale.edu).



**Satiety hormone may have role in treating diabetes**

With a name that derives from the Greek word for “thin,” the leptin hormone regulates the amount of fat stored in the body by controlling the feeling of hunger. It was discovered in 1994, with high hopes that it would provide a groundbreaking treatment for a growing national epidemic of obesity. After an extensive clinical trial, those hopes were dashed.

Since that first study, the “satiety hormone,” as leptin is known, has proved useful in other ways. A team led by Gerald I. Shulman, M.D., Ph.D., the George Cowgill Professor of Medicine (Endocrinology), professor of cellular and molecular physiology, and a Howard Hughes Medical Institute investigator, found that leptin could treat lipodystrophy, a condition common in HIV patients. The disease redistributes body fat in atypical ways, removing it from such areas as the arms, legs, and face and depositing it in the abdomen or the back of the neck. Leptin gained FDA approval for treatment of lipodystrophy in April of this year.

Now, on the 20th anniversary of the discovery of leptin, Shulman and colleagues have found another potential use for the hormone. In a study published in June in the advance online publication of *Nature Medicine*, the team reported that treatment with leptin reverses hyperglycemia, or high blood



sugar, in rats with poorly controlled type 1 and type 2 diabetes.

Like obesity, diabetes is one of the most common chronic conditions in the United States, affecting nearly 30 million Americans. Despite currently available treatments, many patients still struggle to control the high blood sugar levels that characterize the disease and result in complications, including heart disease and blindness. According to Shulman, previous studies had shown that leptin lowered plasma glucagon, a hormone that raises sugar levels in the bloodstream, producing the opposite effect of insulin. Using methods including noninvasive nuclear magnetic resonance (NMR) spectroscopy, a technique pioneered by Shulman in the study of diabetes, his team studied why this was happening. “We came to a very different conclusion,” Shulman said.

The team showed that instead of having its effect mostly through plasma glucagon, leptin

reduced blood sugar in the rats by inhibiting a major neuroendocrine pathway, the hypothalamic-pituitary-adrenal axis. This interaction of three glands controls the body’s reaction to stress and regulates other body processes including digestion, energy storage, and metabolism. Further, the team found that leptin did in fact reduce plasma glucagon, but much later in the course of the treatment than through the newly discovered pathway.

Shulman, who is also co-director of the Yale Diabetes Research Center, noted that though typical cases of diabetes can be successfully treated with insulin, “some cases are still difficult to control, and it may be in that subset that leptin therapy might be useful.”

Leptin treatment for lipodystrophy made a very successful leap from rodent to human, said Shulman, who hopes the same is true in the case of diabetes treatment. “Clearly, leptin has been shown to be efficacious in patients with severe lipodystrophy and has made a great improvement in quality of life,” he said, “and now the question is whether it might be beneficial in patients with poorly controlled type 1 and type 2 diabetes.” Shulman and his team are currently working to develop a clinical trial of leptin in human diabetes patients.

Though these are “still early days,” Shulman said, “we are very excited about the data.”

—Jeanna Canapari

# round up

a collection of recent scientific findings



## MY COUNTRY, MY MICROBES

The microbes on your hands could reveal where you live, according to work by Yale researchers published in May in *Microbiology*. Analysis of bacteria on the hands of women in Tanzania and the United States showed that U.S. participants had more distinct species, while women in Tanzania had 11 times more bacteria per square centimeter of skin. The findings reinforce the role of the environment in the development of the microbiome. "How and where we interact with the environment affects our skin microbiota—which, for hands, can vary dramatically between groups," said Jordan Peccia, Ph.D., professor of environmental engineering and the project's principal investigator.



## WALKING KEEPS SENIORS MOBILE

Walking as little as 20 minutes a day can keep older adults moving independently, according to Yale researchers. The Lifestyle Interventions and Independence for Elders Study evaluated 1,635 sedentary men and women aged 70 to 89 who were at risk for mobility disability. The clinical trial, published this May in *JAMA: The Journal of the American Medical Association*, found that participants in

a moderate-intensity physical activity program saw an 18 percent reduction in the risk of disability compared to participants in a health education program. "Maintaining independence for older adults is both a public health and a clinical priority, and modifying lifestyle is an important approach to maintaining independence," said Thomas M. Gill, M.D., Humana Professor of Medicine and study co-author.



## READING MINDS WITH fMRI

Researchers at the School of Medicine can reconstruct images of human faces based on fMRI readings of what's embedded in our brains. Alan S. Cowen, a Yale undergrad at the time, postdoctoral fellow Brice Kuhl, Ph.D., and their advisor Marvin M. Chun, Ph.D., professor of psychology, created a library of subjects' responses to hundreds of pictures of faces. When subjects saw new faces, the researchers reconstructed what the subjects were viewing by comparing the scans to a mathematical model based on that library of responses. Cowen believes that as the accuracy of these reconstructions increases, they could be applied to research on how autistic children respond to faces. The research was published in *Neuroimage* in March.

## FROM THE OTTOMAN EMPIRE, A GENETIC MUTATION PERSISTS

At the height of the Ottoman Empire—16 generations ago—a single individual passed on a genetic mutation that still afflicts Turkish children with a rare neurodegenerative disorder. In the April 24 issue of *Cell*, researchers identified a mutation in a gene involved in tRNA metabolism as the cause of the disorder that results in intellectual disability, seizures, delayed motor development, and atrophy in several regions of the brain. "By dissecting the genetic basis of these neurodevelopmental disorders, we are gaining fundamental insight into basic physiological mechanisms important for human brain development and function," said Murat Günel, M.D., HS '98, Nixdorff-German Professor of Neurosurgery and study co-author. "We learn a lot about normal biology by studying what happens when things go wrong."





# resilience

Recovering from injury  
to body or mind.

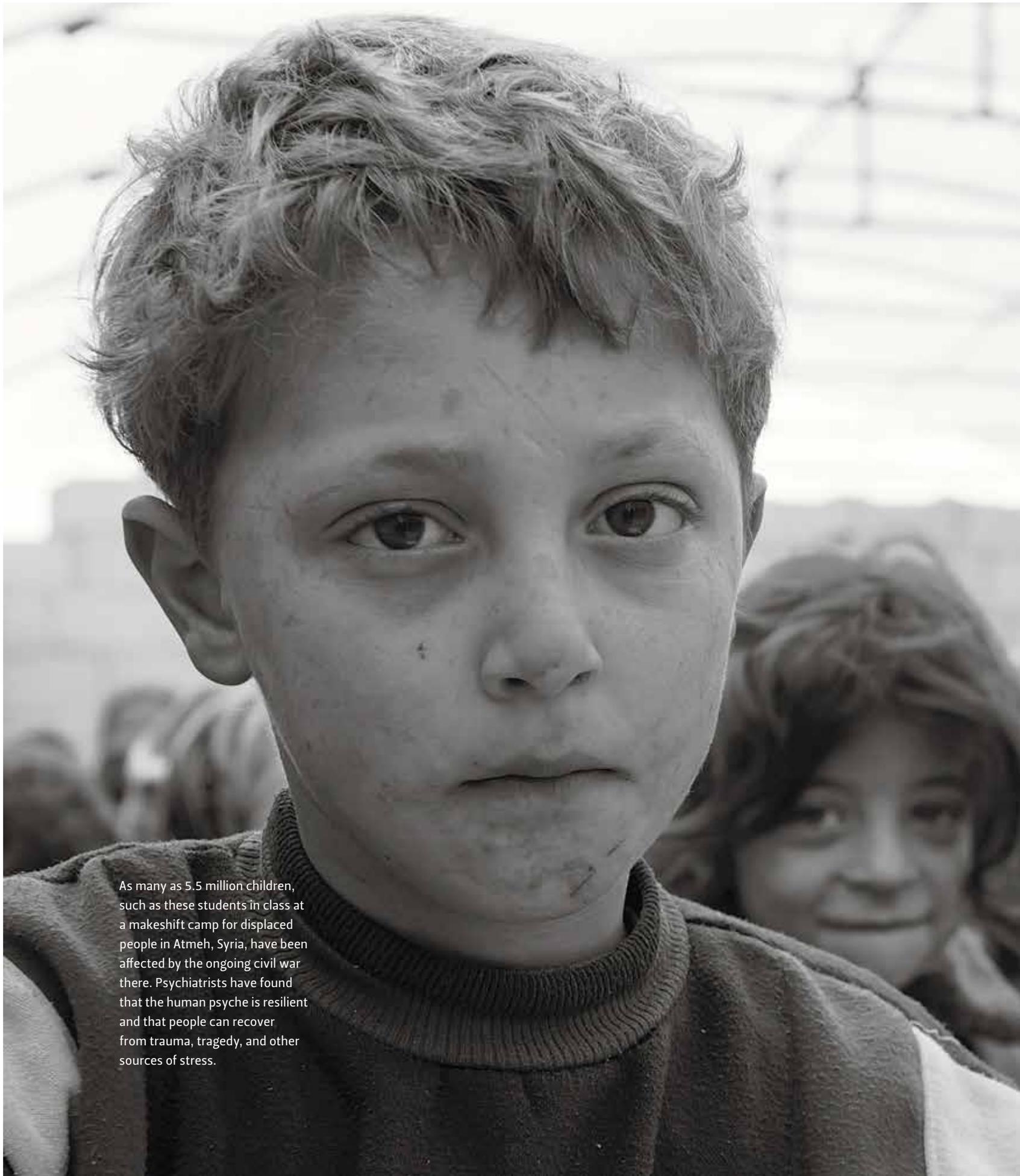
AFTER A DAY OF SAILING, SWIMMING, AND JOGGING at his vacation home on Campobello Island in 1921, 39-year-old Franklin Delano Roosevelt went to bed early and suffered chills throughout the night. By the end of the next day, his legs were paralyzed from polio, and he never walked unaided again. Yet 11 years later he won the first of four presidential elections, and went on to become the longest-serving president of the United States. He reshaped American politics, brought the nation through the Great Depression, implemented the New Deal, and led the Allies to victory in World War II.

How many of us could persevere in the face of a crippling disease, let alone lead a troubled nation and world? Some of us can't even sleep at night for stressing about our daily lives. Others, however, easily recover from natural disasters, terrorist attacks, and combat. "It's about the stories people tell," says psychiatrist Charles A. Morgan III, M.D., FW '01, "And some people do more storytelling in their heads than others."

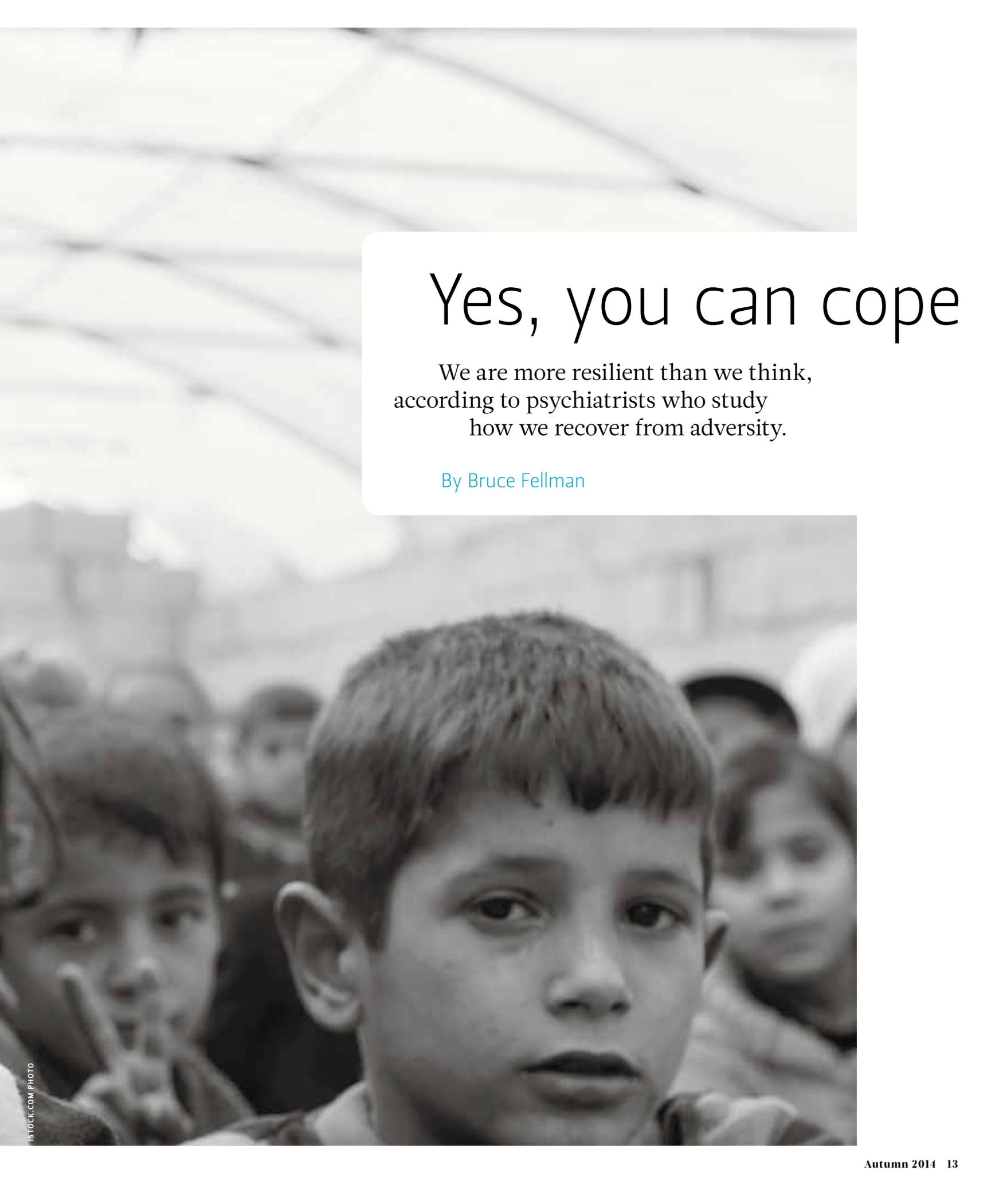
As we set out to explore the theme of resilience for this issue of *Yale Medicine*, we learned that it comes in all different forms. We look at a woman's recovery from a stroke and a dancer who overcame a career-ending injury and now cares for other dancers. Microbiologists describe how microbes survive not as individuals, but as populations. Child psychiatrists help children who have confronted violence. And faculty and students describe moments in their lives that led them to dig deep into their own stores of resilience.



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As many as 5.5 million children, such as these students in class at a makeshift camp for displaced people in Atmeh, Syria, have been affected by the ongoing civil war there. Psychiatrists have found that the human psyche is resilient and that people can recover from trauma, tragedy, and other sources of stress.



# Yes, you can cope

We are more resilient than we think,  
according to psychiatrists who study  
how we recover from adversity.

By [Bruce Fellman](#)

# Life is often something less than the proverbial bed of roses

—but when Steven M. Southwick, M.D., the Glenn H. Greenberg Professor of Psychiatry, PTSD, and Resilience, worked with people who'd been through wars and famines, earthquakes and hurricanes, violent crime and terrorism, or something more mundane like losing money or going through a divorce, he discovered that most people are far stronger than they had ever imagined.



watch [The Exam Room: Resilience  
and the Optimistic Outlook](#)  
(with [Steven M. Southwick, M.D.](#))  
at [youtube.com/YaleMedicine](https://youtube.com/YaleMedicine)

“Almost everyone experiences a significant traumatic event—a serious accident; the loss of a loved one, job, or home; assault or rape; a natural disaster; or something worse—yet most of us make it through and sometimes even grow stronger,” said Southwick, one of a number of researchers at Yale and elsewhere who are looking at resilience, the human characteristic that helps us make our way through life.

Resilience is an easy concept to understand but a hard one to nail down with scientific precision. It has proven hard to study, and little is known about it. There are only hints of biochemical markers, so in their absence, the American Psychological Association defines resilience as “adapting well in the face of adversity, trauma, tragedy, threats, and even significant sources of stress—such as family and relationship problems, serious health problems, or workplace and financial stresses.” In a sense, it’s similar to how an engineer would define resilience in a material: substances that bounce back to their original shapes when stressed. But in humans, there’s often an additional wrinkle. Think of a green twig that bends in a gale but doesn’t break. After the wind dies down, the twig not only survives but also continues to grow.

Southwick and colleague Dennis S. Charney, M.D., HS ’81, a former Yale professor who is now dean of Icahn School of Medicine at Mount Sinai Hospital in New York, recently pooled their insights in a book titled *Resilience: The Science of Mastering Life’s Greatest Challenges*. It’s a look at some of the most resilient folks on the planet, from POWs to survivors of 9/11, which examines the latest research—a good deal of it being done at Yale—about what goes on in their brains. The book also explores key characteristics—which can be learned through good coaching and steady practice—that help people roll with the punches.

“In interviewing these extremely resilient people, we kept noticing the same factors coming up again and again,” said Southwick—everything from realistic optimism, the ability to face one’s fears, and a strong moral compass, social support network, and spiritual sense, to mental and physical fitness, the availability of resilient role models, psychological flexibility, and skill in finding purpose and meaning.

Underlying these hallmarks is the right kind of neurophysiology, the components of which a number of Yale researchers, Southwick among them, are uncovering.

Charles A. Morgan III, M.D., FW ’01, associate clinical professor of psychiatry, for example, studies members of the military’s elite special operations force. “Many people try out for special ops, but most don’t get

in,” said Morgan. “That selection process is a funnel.”

After some 20 years of working with special ops soldiers, Morgan notes that one factor has become abundantly clear. “These people are different biologically, psychologically, and physiologically from the average person in the general military and civilian populations,” said Morgan. “They’re experts in resilience. They have a tough, tough job that exposes them to constant stress and almost unimaginable trauma, and yet they’re so well suited by temperament and training to the work that the risk of untoward psychological side effects is significantly reduced.”

The rate of post-traumatic stress disorder (PTSD) among soldiers in general is, not surprisingly, higher—between 12 and 15 percent, according to Morgan—than the 8 percent found in the civilian population, but in special ops, it’s remarkably low: between 1 and 2 percent. “This is a paradox, but we’re beginning to understand what’s going on,” he explained.

The brain is constantly under stress, but most of the time and in most people, it’s also perfectly capable of handling the situation, after which it damps down the stress circuitry. One tool is a calm-restoring brain chemical, neuropeptide Y (NPY), which is released alongside the brain’s alarm molecule, norepinephrine. “We’ve found that special ops soldiers have the capacity to release greater amounts of NPY than is typical, and this can blunt the negative impact of norepinephrine and other stress hormones,” said Morgan. “We’ve also shown that these people have higher levels of another stress-protecting neurochemical called DHEA, and we suspect there are other important molecular differences as well.”

There is certainly a genetic component at work here. One of the most compelling studies to examine the gene/environment interaction is research by Joel Gelernter, M.D., a Foundations Fund Professor of Psychiatry and professor of genetics and of neurobiology. Four years ago, in the journal *Depression and Anxiety*, Gelernter and his colleagues reported on more than 600 adults who’d been in the paths of the unusually severe group of hurricanes that pummeled Florida in 2004. They found a twofold increase in a condition known as generalized anxiety disorder (GAD), and among the GAD sufferers, there was an almost fourfold increase in the occurrence of a gene variant linked to lowered production of NPY.

“We all arrive on the scene different,” said Morgan. “There’s genetic variability, so when life comes your way, there’s a differential impact.”

A growing body of research shows, however, that nonstop, uncontrollable stress is universally problematic. “Higher exposure to adverse life events is related

to a reduction in brain volume in the regions important to executive functions, such as reasoning, memory, emotional regulation, and perception,” said Rajita Sinha, Ph.D. ’92, a Foundations Fund Professor of Psychiatry as well as director of the Yale Stress Center, which studies the neurophysiology of stress and ways to deal with it. “Not having any stress in your life is not a good thing,” said Sinha, echoing a well-known quote by stress research pioneer Hans Selye that “the absence of stress is death.”

Fortunately, human evolution has endowed us with the ability to adapt to the many stressors we face. There’s increasing evidence from animal studies, noted Sinha, that recovery is possible, with rats and mice regrowing stress-damaged connections and regaining lost deficits in such key areas as working memory. “During a very stressful period we might be unable to remember the plots of movies and find ourselves more easily distracted,” she said. “But we have developed a wide variety of coping mechanisms in the brain that enable us to avoid damage, learn from stress, and not only keep going but also to grow.”

While there’s no single recipe for resiliency, Sinha explained, there are universal elements that enable people to weather the storms and recover afterward. “Social support, keeping your basic needs well regulated, drinking plenty of water, eating right, getting enough sleep, staying away from alcohol and other drugs, and regular exercise—these are critical,” she said, adding that overcoming stress can be difficult. “People need help, and often they lose a lot or hurt badly before transformation can occur.”

There are also medications—antidepressants and anti-anxiety drugs among them—that can help in recovery, and there are a variety of therapies aimed at enabling people who’ve been through trauma to get better. “It takes real guts to confront this,” said Southwick. He has used a technique called logotherapy—it’s modeled after psychiatrist and Holocaust survivor Viktor Frankl’s “healing through meaning” insights—with chronic PTSD sufferers at the VA Connecticut Healthcare System in West Haven. “We work to find a way for each vet to participate in some kind of meaningful community service, say, for the homebound to serve meals to elderly shut-ins, or vets who are distressed about kids to work with traumatized youngsters in schools. This is important because altruism is strongly associated with resilience and can generate meaning from adversity, which can be a source of tremendous strength.”

Nietzsche declared that “he who has a ‘why’ to live for can endure almost any ‘how,’” and many trauma sufferers find ways of turning their ordeals into meaningful action plans. Despite his almost lifelong imprisonment, Nelson Mandela found a way to forge an end to apartheid in South Africa. Jerry White, a Brown University undergraduate who lost his leg to a land mine in Israel, helped spearhead a Nobel Peace Prize-winning organization aimed at banning land mines. Parents of children murdered in the Sandy Hook school work to support efforts aimed at curbing gun violence, and people affected by trauma find that trying to help others cope with something similar can give meaning to their lives—and both ease pain and turn it into personal and societal progress.

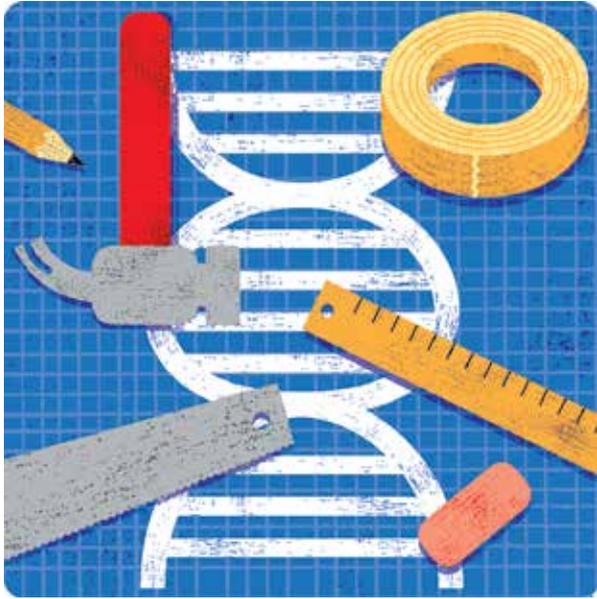
Southwick has a coping strategy that combines a number of resilience techniques. He is always looking for ways to get stronger and be more resilient, which often means “trying to learn from the many role models we have had the privilege to interview. ... I’ve learned to meditate and I really like to exercise, so Dennis Charney and I decided to challenge ourselves by entering a 90-mile three-day kayak race in upstate New York.”

After less than an hour of paddling, Southwick was in agony. He hadn’t trained enough, and his neck and shoulders were hurting. “I thought I’d made a huge mistake and that I’d have to drop out, but then I remembered that I’d entered this event as an experiment in a meditation technique known as mindfulness—a way to ignore all those internal discussions you didn’t actually choose to have and focus intensely and nonjudgmentally on the moment.”

The technique, which can help restore a sense of control and tamp down overactive fear circuits, has recently been introduced as an alternative or complementary treatment for PTSD, and while Southwick felt more than a little discomfort throughout the grueling race, reorienting his thinking helped ease his muscular pain. In short order, he began to enjoy the kayak trip through exquisite Adirondack scenery.

Southwick and Charney didn’t win the race. But by practicing what they’d long been preaching, they managed to finish, resilient to the core. “It was very liberating,” said Southwick. Six weeks later, once the inflammation in his shoulders had subsided, he was again able to pick up a kayak paddle. ***/yale medicine***

*Bruce Fellman is a freelance writer in North Stonington, Conn.*



## The epigenetics of child abuse

CHILDREN WHO SUFFER abuse, neglect, or trauma often develop depression and other psychiatric illnesses. As adults, they have a greater incidence of medical illnesses, including cancer, cardiovascular disease, and diabetes. But then again, many such children escape those dire consequences. What explains who succumbs and who rebounds?

Part of the answer may lie in genetics, and the genetic predispositions of children who show resilience and those who don't. But part of it may also lie in epigenetics, or how experiences influence gene activity. Epigenetic changes don't alter the DNA in a gene, but rather how a gene is expressed. A common epigenetic change involves the addition of methyl to the chromatin structure around a gene, which typically suppresses the gene. Different life experiences can increase or decrease methylation

through mechanisms researchers are still trying to understand.

"It's exciting to realize that genetic effects are not fixed and how dynamic the interactions are between genes and the environment," said Joan Kaufman, Ph.D., associate professor of psychiatry. In a recent collaboration with Joel

Gelernter, M.D., a Foundation Fund Professor of Psychiatry, and professor of genetics, and of neurobiology, she compared epigenetic changes in 96 children with a history of early adversity and 96 children without such a history. The researchers focused on differences in the methylation marks in the genomes of these children.

"Based on animal studies elsewhere looking at the effect of maternal neglect, we expected to see epigenetic changes affecting genes involved in the brain's stress response," she said. "We were surprised to see them across the entire genome, not only in genes implicated in mental health and psychiatric disorders, but also in cardiovascular disease, diabetes, obesity, and cancer—all health problems long associated with early adversity."

Epigenetic changes are long term, and these changes may be passed down to children and grandchildren. But the effects of adverse childhood experiences don't have to be permanent, Kaufman said. The concept of a "critical period" in which a brain pathway becomes fixed has given way to a "sensitive period" when the brain is more susceptible to environmental influences but retains some plasticity. In animals, environmental enrichment has reversed deleterious brain effects mediated by epigenetic changes caused by early deprivation.

"However, to show such reversal in humans," Gelernter said, "we would have to study the same individual over time to see if the epigenetic markers revert in people who have less pathological outcomes."

"There's reason to be optimistic that we could intervene and ameliorate the consequences of early childhood adversity," Kaufman said.

—Cathryn Delude



## How children rebound from their worst nightmares

“IMAGINE THAT YOU ARE 10 YEARS OLD, or 15, and you awake to the sound of your parents in a heated argument. Then imagine that the sounds turn to screaming as you enter the room where your mother is being beaten and your father is threatening to kill her. ... Is your heart rate up? Are you actively trying to push away the images?” asks Steven Marans, M.S.W., Ph.D., professor of psychiatry and director of the Childhood Violent Trauma Clinic at the Yale Child Study Center.

Every year, Marans says, millions of children in the United States are exposed to community and domestic violence, natural and human-made disasters, and medical emergencies. “A traumatic event is the realization of your worst nightmare,” says Marans. “The worst has happened, and happened in a way that leaves one dysregulated and powerless.” Without help, too many children will be unable to fully wake up from the nightmare. Unable to recover, these children may suffer the scars of trauma over a lifetime.

Children with untreated trauma can grow up to become adults with a disturbing medley of mental and physical illnesses. But Marans and his colleagues at the Childhood Violent Trauma Clinic, Carrie Epstein, M.S.W., and Steve Berkowitz, M.D. (now at the University of Pennsylvania), have developed a brief early-intervention model. The Child and Family Traumatic Stress Intervention (CFTSI) is now helping children who have seen, heard, and felt too much.

As humans, we share a distinct set of fears: loss of life, limb, lucidity, and love. Children are particularly vulnerable to traumatic events. They depend on adults to see them through stressful events until they develop the cognitive and psychological maturity to handle such situations on their own. One of the most powerful predictors of outcome after trauma, says Marans, is the degree of external social support. Linda C. Mayes, M.D., FW '85, the Arnold Gesell Professor of Child Psychiatry, Pediatrics, and Psychology in the Child Study Center, agrees that in order to be resilient, children need “to be protected and buffered from

overwhelming stress—to have adults who care.”

Unfortunately, children may not have the skills to communicate their traumatic reactions, and their caregivers may not recognize the symptoms. Moreover, many of the children at the greatest risk of exposure to such traumatic events as domestic violence are often the least likely to receive support. One of the many ways the CFTSI aids in recovery is by bolstering communication and support between children and their parents or caregivers. The intervention teaches children how to talk about their mental and physical reactions to trauma and teaches caregivers to recognize when those reactions become symptoms of traumatic stress.

The CFTSI grew out of more than two decades of collaboration between the Child Study Center at Yale and the New Haven Department of Police Service. The collaboration between police officers and mental health professionals has brought many at-risk children from urban and economically disadvantaged families who have been exposed to violence to the attention of clinical service providers. It fills the gap between existing acute responses deployed at the time of the traumatic event, and longer-term treatments designed to address trauma symptoms and disorders that are already

established. In as few as five sessions, the CFTSI can ease current suffering and symptomatology in children and prevent traumatic stress disorders from taking hold by returning a sense of control to both children and their caregivers.

Instead of leaving children alone with their traumatic terror and helplessness, a CFTSI-trained clinician coordinates with police, social services, and medical providers. They ensure safety while addressing post-traumatic reactions that so often follow overwhelming events. Over five to eight sessions, children and parents or caregivers are helped to identify and verbalize symptoms in ways that increase communication with and support from caregivers. They also learn such techniques as focused breathing, re-establishing routines, and recognizing what triggers post-traumatic reactions, with the aim of regaining control of their minds and bodies. As symptoms decrease, a sense of safety and competence can return, while the traumatic threat to developmental progress is diminished.

Children who received CFTSI services were 65 percent less likely to develop PTSD three months after a potentially traumatic event than children who received a standard intervention. And after the CFTSI sessions, caregivers seem to be more in tune with the trauma symptoms as they present in children. “CFTSI reduces the discrepancy between reports of symptoms by both parents or caregivers and children,” said Marans.

In addition, the CFTSI serves as an assessment tool, helping clinicians identify children in need of further psychotherapeutic treatment. While many children who

receive CFTSI services experience significant reduction or resolution of post-traumatic symptoms, there are those children who will require longer-term trauma-focused or other mental health treatment provided by the Trauma Clinic and other clinical services of the Child Study Center. This work, Marans said, is supported by the Substance Abuse and Mental Health Services Administration, and is being disseminated to mental health clinicians and agencies around the country.

By capitalizing on a growing understanding of the factors that contribute to a healthy and happy human experience, the intervention decreases the likelihood that trauma will be damaging to a child’s future. It restores to children and their caregivers the sense of control that they often lose after traumatic events. Trauma doesn’t have to lead to lifelong afflictions, according to Marans, “It’s not a fait accompli.”

—Kate Wheeling



watch *Among the Traumatized in Ukraine, “an Immense Need”* at [youtube.com/YaleMedicine](https://www.youtube.com/YaleMedicine)



With the help of her daughter, Sarah, and husband, Chris, Helen Bolan recovered from a stroke caused by a rare condition that results in constriction of arteries in the brain.

# Why our bodies, and brains, bounce back

As soon as something breaks, tears,  
or malfunctions within us, the instructions  
in our cells begin to supervise repairs.

How this regeneration happens  
and how it might be exploited  
are the subjects of intense investigation.

By Kate Wheeling

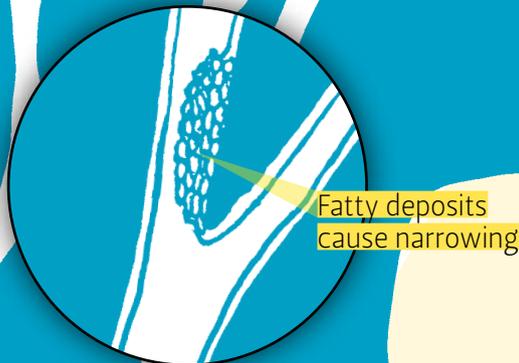
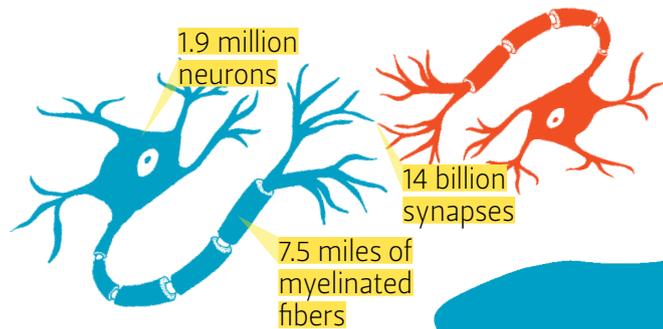
## On January 22, 2013, Helen Bolan sat down to dinner

with her husband, Chris, and their 10-year-old daughter, Sarah, at their home in Trumbull, Conn. Helen was about to comment on the ocean of hot sauce that Chris was pouring onto his stew, but the words wouldn't come out. As she struggled to speak, it became clear that something was seriously wrong. Chris dialed 911, and an ambulance rushed Helen to the hospital.

*/continued on page 24*

## EVERY MINUTE

a typical stroke goes untreated,  
a person loses ...



## 90 PERCENT

of strokes are ischemic,  
caused by a narrowing  
or blockage of  
the blood vessels  
in the brain

## 10 PERCENT

of strokes are  
hemorrhagic, caused by  
bleeding in the brain

The average stroke lasts

## 10 HOURS

Every hour without  
treatment, the brain  
ages effectively by

## 3.6 YEARS

Stroke patients can't  
compensate for the loss  
of brain cells by making new  
neurons, but they often  
recover some function  
by making new neural  
connections, or synapses.

## A “decoy” for reversing

**the effects of stroke** A protein in nerve cells—the neurite outgrowth inhibitor, or Nogo—inhibits the formation of new synapses. A newly discovered molecule that blocks the receptor and helps synapses to form may help stroke patients recover. This “Nogo receptor decoy” is in early-stage drug development.



While frightening, the episode was only a warning—an event known as a transient ischemic attack, or TIA. Often called mini-strokes, TIAs are temporary blockages of the arteries that feed the brain, causing stroke-like symptoms that last no more than 24 hours. Exactly two weeks later, almost down to the minute, Helen had another TIA. Sarah called an ambulance, and Helen watched her reflection in the mirror as paralysis overtook her right side. Helen’s doctors didn’t see anything on her initial brain scans to explain the attacks, but Helen had a history of migraines, and the intense headaches are known to present with TIA-like symptoms. After her second TIA, she started taking a migraine medication, and Chris and Helen hoped that her neurological woes were behind them. Helen went a full four months without another TIA. Then, on June 14, she had a stroke.

### “OUTSTANDING PROGRAMMING”

The body is a battlefield. It deals with insults and injuries every day, from the sting of a paper cut to the massive damage that can occur during a stroke. Immune cells fight off infection, torn muscles recover, and broken bones mend. Even an organ as fragile as the brain can recover. Speech and motor function may return even after large swaths of brain cells perish during a stroke. “Almost all the people who have strokes recover some function between one week and six months,” said Stephen M. Strittmatter, M.D., Ph.D., the Vincent Coates Professor of Neurology, professor of neurobiology, and co-director of Yale’s Program in Cellular Neuroscience, Neurodegeneration and Repair.

The human body and brain are designed to bounce back from injury. “Part of that robustness comes from the fact that the cells in our bodies have outstanding programming, and they can repair and reconstitute tissue and organ function even after an insult,” said Laura E. Niklason, M.D., Ph.D., professor of anesthesiology and of biomedical engineering. To a large extent, the body heals on its own, but those natural healing mechanisms can falter or fail. Researchers at Yale are looking for ways to bolster the body’s ability to bounce back by studying the human body where it is most vulnerable—and where it is most resilient (see sidebar).

“Different tissues and organs have different degrees of resilience,” said Ruslan M. Medzhitov, Ph.D., the

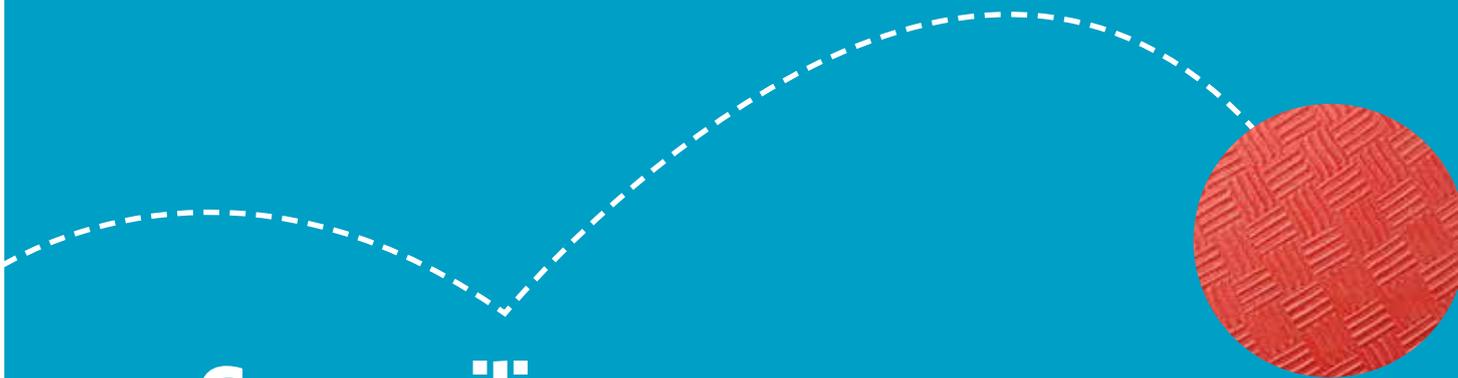
David W. Wallace Professor of Immunobiology and a Howard Hughes Medical Institute investigator at Yale. “What makes us really sick, and what can kill an organism, animal, or human, is when the most vulnerable aspect of our physiology—the organs or tissues or processes that have least resilience—are affected enough to push them over the edge.”

The brain is especially sensitive, and so the body has developed a host of defenses to protect it from insults. A hard skull shields it from mechanical blows, and internal mechanisms maintain the supply of glucose and oxygen to the brain even at the expense of other tissues. “These mechanisms ultimately increase the resilience of the entire organism because they protect the weakest links in the system,” said Medzhitov.

None of those mechanisms can protect the brain from a stroke, but neurologist David M. Greer, M.D., Ph.D., hopes that a new application of an old technique can help to buffer the brain from stroke-induced injury.

Greer, the Dr. Harry M. Zimmerman and Dr. Nicholas and Viola Spinelli Professor of Neurology and professor of neurosurgery, is Yale’s principal investigator of a nationwide Phase II/III clinical trial to study the effects of induced hypothermia in limiting brain damage during the acute phase of stroke. Induced hypothermia—lowering a patient’s body temperature to 91 degrees Fahrenheit—has been used for years in the operating room and, more recently, following cardiac arrest. The precise mechanism is unclear, but therapeutic hypothermia appears to allow the body—and the brain—to get by with less oxygen. Greer and his co-investigators believe cooling could prevent stroke-related damage in a number of ways: hypothermia slows the metabolic rate of cells, stabilizes cell membranes, halts the release of harmful neurochemicals and enzymes, and reduces inflammation. The investigators plan to test the technique in combination with tissue plasminogen activator (tPA), a naturally occurring protein administered during a stroke to dissolve blood clots in blocked vessels.

If the stroke team can prevent too much damage from occurring, the brain will take over its own healing. But often stroke victims don’t arrive at the hospital in time to receive such acute treatments as this one, according to Greer. Helen Bolan didn’t.



# Can resilience be engineered?

Of the many factors that influence the body's ability to heal, age is perhaps the most critical. "The younger you are, the more resilience you have," said Joseph A. Madri, M.D., Ph.D., professor of pathology and director of education. As researchers have noted for more than three decades, the womb is a good place to heal. "If you look at cases of in utero surgery you'd be hard pressed to find surgical scars," said Madri, who directs the undergraduate course "Biological Reaction to Injury."

In all likelihood, some combination of the growth factors, immune components, and stem cells in the uterus, plus the relative lack of biomechanical stress, allows not only the repair of fetal tissue but also its complete replacement. As a graduate student, Anjelica Gonzalez, Ph.D., an assistant professor of biomedical engineering, was intrigued by fetal regeneration and wondered how one might harness the regenerative capacity of fetal cells to promote healing.

Like her colleague Laura Niklason, M.D., Ph.D., professor of anesthesiology and of biomedical engineering, Gonzalez is looking closely at the elements involved in healing to find new ways to manipulate them in our favor. Her lab is investigating the chemical messengers that are active during fetal development for ideas that might lead to better treatment of severe burns in children. Niklason is pursuing a similar line of inquiry, with the aim of building better replacement blood vessels.

Gonzalez has focused much of her work on neutrophils, the immune system's first responders to a burn injury. These white cells follow a trail of chemical signals through blood and tissue to arrive at the sites of inflammation. Once there, they ingest dead and dying cells within the damaged tissue, along with anything else—such as microbes looking for a way into the body—that may hinder healing. But if neutrophils remain at wound sites for too long, they can interfere with healing.

The amnion, the membrane that surrounds the fetus, contains natural proteins that recruit neutrophils and other leukocytes to the site of a wound and then block that recruitment once the white cells' job is done. Gonzalez is trying to identify those amniotic signals that initiate and then terminate the inflammatory response and replicate them in an artificial scaffold—a structure that mimics

the extracellular matrix and supports the three-dimensional growth of tissue. Gonzalez's scaffolds would allow for inflammation but prevent it from becoming chronic, so that the regenerative programming in human cells can take over: cells divide, new tissue is born, and the wound heals. That inherent programming is also what allows Niklason to grow blood vessels in the lab.

Blood vessels are inherently resilient. They expand and contract with each heartbeat, roughly 100,000 times a day. Ironically, however, the same mechanisms meant to protect blood vessels from stress and damage can also lead to their failure.

When patients have high blood pressure, the blood vessel wall resists that force by growing thicker. But as the inside of the vessel narrows, the pressure and the risk of either rupture or blockage increase. Surgeons can bypass the damage to an artery with a vessel graft—a section of transplanted or prosthetic blood vessel that redirects blood flow around the damaged stretch of artery. Because veins are plentiful, they are a common source of grafts, but they aren't built to withstand the same pressures as arteries. Synthetic grafts made of such plastics as Teflon are stronger, but they also fail over time.

Niklason is growing arteries from the body's own smooth muscle cells instead. The cells are the seeds from which tissue will grow, but they need more than a Petri dish to grow into fully formed and functional vessels. Niklason harvests smooth muscle cells from donated tissue, seeds the cells on a biodegradable scaffold, and exposes them to mechanical and chemical cues that induce tissue growth. These are not the exact instructions that the cells would have received from a naturally occurring extracellular matrix, but they're close enough. "The biological system for regeneration is robust enough that we don't have to get it exactly perfect," said Niklason.

As the muscle cells proliferate, the degradable polymer mesh that guided their growth disappears and is replaced by connective tissue—an extracellular matrix laid down by the cells themselves. Before the grafts are implanted, the cells, which contain the majority of the immunogenic cues, are removed, leaving behind a tube that will serve as a new artery.

Ideally, the graft will be repopulated by the host cells, which will produce their own mesh of protein-rich extracellular matrix. Over time the tissue will remodel until the graft that was implanted isn't really there any longer: it has been completely replaced by host tissue. "That," said Niklason, "is regeneration in the truest sense."

—Kate Wheeling

### AFTER AN INSULT, THE BRAIN REARRANGES

Bolan didn't know she'd had a stroke until four days following the event, during a regularly scheduled appointment with her doctors at Bridgeport Hospital. To Helen, the stroke was unlike her TIAs: she was groggy but fully mobile, and her trouble with words came on gradually rather than all at once. Her husband was out of town. There was no one to notice anything amiss. By the time she saw Greer, a lot of damage had been done. Her speech was significantly impaired—she knew what she wanted to say but words escaped her—and her right side was weak and sore.

In August 2013, Greer diagnosed Helen with Moyamoya syndrome—an uncommon disease that causes the constriction of arteries in the brain. Looking at her brain scans, Chris and Helen could see the tissue that had been lost, and they saw the dark line of her carotid artery collapse as it curved into the left side of her brain. “It was quite startling,” said Chris. “[Her] brain was starving.”

To preserve her undamaged brain tissue, surgeons rerouted an artery to supply more blood and oxygen to her left hemisphere. After the surgery and months of rehab, Helen slowly recovered the functions she'd lost. But she's not quite her old self. “I'm not as talkative as I used to be,” she said.

“There is a significant amount of recovery that happens naturally,” said Strittmatter. The brain doesn't regenerate; it rearranges. One region of the brain can take on functions like speech and movement that were previously the province of regions now damaged by stroke or trauma. “So the function is moving,” said Strittmatter.

How this reconfiguration happens is something of a mystery, according to Strittmatter, though animal studies indicate that it's likely to be some combination of changes in the wiring and biochemistry of synapses, the conjunctions between nerve cells. While it is unlikely that the brain can make new nerve cells to replace those lost during a stroke, it can make new connections. Scientists can see this process unfold in mice. Using two-photon excitation microscopy to look inside the brains of living animals, they can watch single nerve fibers and their synapses change over time. After a stroke, new pathways and bridges around the damage can emerge from surviving axons. “Those new connections may make up for a dead neuron that was lost in a stroke or trauma,” said

Strittmatter. But only up to a point; the more damage that is done, the fewer brain cells we have in reserve.

### DISSOLVING THE NEURAL GLUE

“The ability to make new connections and rearrange connectivity drops as the brain develops,” said Strittmatter. As we enter adulthood, the brain starts making molecules that inhibit rearrangements, locking synapses into place like neural glue. Strittmatter's lab is looking for ways to dissolve that glue selectively. Over two decades of research, his group has identified neurite outgrowth inhibitor, or Nogo, a molecule that inhibits the sprouting of new synapses, and has characterized the receptor protein by which Nogo transmits its instructions. They have also found molecules that block that transmission by trapping Nogo and preventing access to the receptor. Testing in rats has identified compounds that enhance recovery from stroke without side effects. Strittmatter co-founded Axerion Therapeutics to develop medications based on these findings, though he says it will be 18 to 24 months before any drug candidates are ready for clinical trials. Such drugs would hold promise for patients like Helen, who don't reach the hospital in time to receive the clot-busting agents that must be given no more than three to four hours after symptoms appear. By blocking Nogo's inhibitory effects, the drugs could allow patients to make more neural connections and experience faster and more complete recovery not just from stroke but from any traumatic neural injury.

Even without drugs to enhance the plasticity of her brain, Helen regained nearly all of the function she had lost. The first sign that she had recovered came almost eight months after the stroke. “After the surgery, Helen got bored,” said Chris. Once her rehab assignments weren't challenging enough to keep her engaged, she knew it was time to go back to work, and in April she returned to her job as an accountant. She still has trouble finding the right word sometimes, and her right side feels sore on occasion. “I know it could have been a lot worse,” said Helen. “I was very lucky in a lot of ways.” */yale medicine*

*Kate Wheeling was Yale Medicine's 2014 writing intern.*



## Building strong societies, one dad at a time

Much of the emphasis on resilience research and therapy centers on the individual—but according to Catherine Panter-Brick, D.Phil., professor of anthropology, health, and global affairs, societies can be better structured to “foster, rather than hinder,” the natural resilience of their citizens. Panter-Brick’s work in Afghanistan, Africa, the Middle East, the United Kingdom, and the United States offers insights into ways of “providing resources to people who are resourceful—helping them overcome dire circumstances and, when things get better, enhancing life opportunities rather than putting up barriers.”

One of the foundations of more-resilient societies is that they have in place the proper legal and economic structures that can expedite recovery well in advance of disasters. Achieving such macro-level transformations requires strong leadership, said Panter-Brick, who also works in the Child Study Center—but there is plenty that can be done without a Gandhi or a Mandela. She has been working on a program aimed at helping young fathers do a better job of rearing kids—which ultimately results in more-resilient dads and children. “We focus on men who’ve been involved in crime, and we’ve found that when they have fathered a baby, there’s a tipping point,” said Panter-Brick. “If we provide resources then—such as job training, housing assistance, and social support—we can change a young man’s trajectory and, in the process, use his resilience to bring about a better future for everyone.”

If engaged at the proper time with the right resources, other strong leverage points can help people do what most researchers feel is natural: bounce back, and in the best cases, grow. “I have a lot of faith in ordinary people and families,” said Panter-Brick.

—Bruce Fellman

An injury ended Mamie Air's career as a dancer. Now she uses what she learned from her own injury to care for other dancers.



## Dancing through pain

WHILE A STUDENT at the School of Medicine, Mamie Air, M.D. '09, was juggling her courseload with the demands of performing ballet, jazz, and modern dance with Yale Dancers when she developed severe pain in her hip. Sitting on an exam room table at Yale-New Haven Hospital, she didn't yet know that she would face surgery and the end of her dance career. Her urgent care doctor's conclusion hit her, as it would any dancer, like a death sentence: "Well, obviously you've got to stop dancing."

Since she began dancing at the age of 5, Air had performed through nasty blisters, overused joints, and agonizing tendinitis. Serious dancers will not be surprised by this catalogue of miseries. "Dance is a culture of resilience," said Cordelia Carter, M.D. '04, a sports medicine specialist at Yale Orthopaedics & Rehabilitation Services who has cared for dancers in the Boston Ballet. "Dancers are some of the physically strongest people I've ever worked with. There's a lot demanded of them physically—and repeatedly—and I think that's where the mental toughness comes from. There's a culture of pushing through pain."

Air, a double board-certified and fellowship-trained physiatrist in sports and interventional spine medicine in California, now cares for dancers. Her patients, she believes, have an inherent resilience

fostered in highly demanding environments. "From a very young age, there is an unusual emphasis on physical accomplishment of extremely difficult technique, both quantitatively and qualitatively, mental focus, self-control, and an aesthetic which defies normal human anatomy and physiology," Air said. "They function in a sport which demands diametrically opposed physical traits. They must be strong, yet flexible; muscular, yet skeletal; durable, yet delicate; and powerful, but gravity defying."

Research has shown that up to 97 percent of dancers experience injuries in a given year, Air said. It is not uncommon for dancers to put

off seeing a doctor for as much as 12 months, if they receive treatment at all. Air's research, which has received national and international recognition, has also shown that fewer than 20 percent of dancers' injuries may be evaluated by a physician. "Many dancers will—at least initially—dance through the pain, self-treat, or seek help from a colleague."

All this capacity for endurance would seem to add up to a classic picture of resilience. But what happens when a dancer can't dance anymore? Air, whose Yale medical thesis explored the psychological aspects of dance-related injury, says dancers face tremendous psychological distress when injured. "Pretty much all dancers know that ultimately they will retire from their dance careers. But you never actually think it's going to happen to you. When it does, particularly if it is a forced or unexpected retirement due to injury, you go through a grieving process, if not identity crisis," Air said.

While some dancers may lose their way in this process, others, like Air, look for a silver lining. She won a Fulbright scholarship to learn more about caring for injured dancers at the Medical Centre for Dancers and Musicians in the Netherlands. During her residency, she co-founded the Seattle Dance Medicine free clinic, which offers free medical care to injured dancers. While no longer dancing at the performance level, Air continues to call upon the qualities she developed as a dancer. "My injury made me a better doctor. And for that, I am grateful."

—Kathy Katella



watch An Accident, a Broken Neck, Then Medical School at [youtube.com/YaleMedicine](https://www.youtube.com/YaleMedicine)

# on resilience



**Laura Niklason**  
BIOMEDICAL ENGINEER //

“They say that laboratory work is composed of good days and bad months. And I think that having a conviction that you can think your way out of problems and engineer your way to solutions is a big part of resilience in this field. ... It took us 18 years to get from the start of the [engineered blood] vessel project to the first implant in man, and that’s actually making pretty good time.

“I was trying to finish up some key studies, some key proof-of-principle studies in pigs. This was like 15 years ago. I had nearly a year of culturing and experimental failures for reasons that it took me a very long time to figure out, and I can remember almost quitting then.”



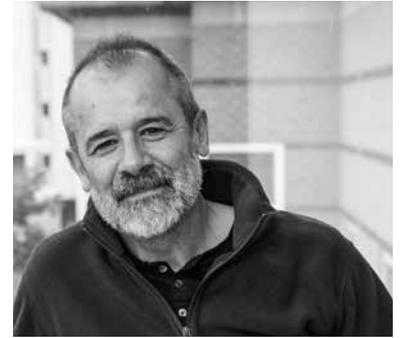
**Pranay Sinha**  
FIRST-YEAR RESIDENT //

“When I’ve made mistakes, I’ve had to sit down and remind myself that this happens to everybody, and crying about it right now or letting it affect the rest of my day isn’t going to make things any better. So the only way I can deal with this is to keep moving and pay more attention to what I’m doing. And this is part of the greatness of medicine. It forces you to become this stronger person who takes his work very seriously but doesn’t take himself that seriously.”



**Steve Southwick**  
PSYCHIATRIST //

“There is no one accepted definition of resilience, but I think most of us would think of it as a bending, but not breaking, and bouncing back in response to adversity—sometimes even growing. I think that another way to think about it is how adaptable we are and how flexible we are during difficult times, how we adjust.”



**Jorge Galán**  
MICROBIOLOGIST //

“If you don’t have stamina and resilience as a graduate student, you’re not going to graduate, because most experiments do not work. That’s a dirty little secret. Yes, you can learn through the do-not-work part, but the reality is that it’s not that you do a couple of experiments, figure 1, a couple of experiments, figure 2. ... Most of the time, things don’t work, so science is all about resilience. If you don’t have that in you, you just couldn’t be a good scientist.”



**Anjelica Gonzalez**  
BIOMEDICAL ENGINEER //

“There was a person whom I admired scientifically who told me that I had a poor work ethic and should get out of the field. ... Every step of the way I’ve worked very hard, and to tell me that that’s the reason I would fail was demoralizing. I didn’t go to class for two days. ... then I thought that if I don’t go, then I’m proving to him that I won’t work. I think that was the hardest time, for me to get up and go to school and go to lab.

“Three weeks ago a colleague was at Baylor University for a seminar and this guy was saying how I’m doing great work. ... and it was him!”



**Chris Zirker**  
MEDICAL STUDENT //

“I’m a C6 tetraplegic. I broke my neck snowboarding when I was 20 years old. I had to relearn how to walk. I had to relearn how to eat. ... I’m able to walk. I’m able to touch type. My hands are relatively functional but I don’t think I’ll do anything like surgery or things where I need fine motor skills and dexterity. I think I’m going to be a lot more focused on more intellectual fields where you talk to patients and interact with them more that way.”



**Peter Jokl**  
SPORTS PHYSICIAN //

“I went to Yale, was on the track team. I was pretty good; I certainly wasn’t the best. You get injuries and you try to maintain a positive outlook, and during an injury you try to find ways that you can maintain your athletic competence while healing. If someone injures an arm or a leg, I’ll tell them they’ve got three other extremities and their heart and lungs work so you can do other things.”



**Ruslan Medzhitov**  
IMMUNOBIOLOGIST //

“Because I was growing up in communist Russia, there were all sorts of perturbations on the way to attempting to perform studies and science. I was in graduate school during the economic crisis when the country was breaking apart, when the economy was destroyed, transitioning from a communist economy to a market economy when resources were nonexistent for science. During that period it was almost impossible to perform any kind of science. Even literature was not available to read.

“You have to be resilient in that environment in order to maintain interest in science and not go into business or something else.”



**Rick Lifton**  
GENETICIST //

“Resilience is perseverance in the face of adversity. ... When I was starting my career, my first NIH application received a score that is no longer obtainable because of the way we triage grants now. On a scale of 1 to 5, my application got a score of 5, which meant that if there were an infinite amount of money and nobody else was applying, my grant should not be considered for funding.”

## How two physicians deal with their own illnesses

PAUL KALANITHI, M.D. '07, was nearing the final year of his neurosurgery residency at Stanford when his weight started to drop, his back hurt, and he felt tired all the time. As the symptoms worsened, he suspected cancer. A CT scan revealed masses lacing his lungs and deforming his spine. In May 2013, Kalanithi, a 36-year-old who didn't smoke, was diagnosed with stage IV non-small-cell EGFR-positive lung cancer. His first response was to prepare to die and to encourage his wife to remarry. But he quickly realized that coping meant making a commitment to living his life and values instead of resigning himself to dying. He began treatment with erlotinib and returned to work. Then Kalanithi and his wife, Lucy Goddard Kalanithi, M.D. '07, chose to have a baby. "Having children was something we planned to do, and there was no reason not to continue living and achieving the things we wanted to achieve with whatever time I have left," he explained. Elizabeth Acadia ("Cady") Kalanithi was born on July 4.

Kalanithi and Christopher H. Lee, M.D., HS '09, FW '10, an associate research scientist in the Department of Emergency Medicine at Yale, both faced severe illnesses that radically affected their lives as well as their families. Both recognized that normal would no longer be what it had

been, and both found ways to cope, with the help of friends and family.

Having seen families fall apart when faced with illness, Kalanithi made family a priority. "The illness doesn't just happen to the person," he explained. "It happens to the whole family. It's very important to be aware of how everyone is doing emotionally and how they are impacted by my illness." As a result, he and Lucy have grown closer.

Over the past year, as Kalanithi battled a chronic cough, fatigue, excruciating back pain, and the effects of chemotherapy, friends and family have helped, doing everything from providing meals to running errands. But relinquishing self-reliance wasn't easy. "We knew if we were going to do some of these life-affirming things, like having a baby, we would need lots and lots of help," he said. "It's a funny side of resilience to recognize that you are dependent on other people." Accepting support became easier when Kalanithi saw how meaningful it was for friends and family to offer their help.

For Kalanithi, resilience includes finding purpose. When his essay "How Long Have I Got Left?" was published in *The New York Times*, the public response and the purpose he derived from writing surprised him. In the essay, he shared his feelings about the devastating diagnosis, his quest for certainty in statistics, and how the words of Samuel Beckett, "I can't go on. I'll go on," helped him move forward. Then, a relapse this spring required chemotherapy and two hospitalizations. "Relapsing means again finding a way to get back involved in the world," he said.

Lee was also just 36 years old when, in November 2010, a spontaneous arterial dissection led to a stroke that paralyzed him from head to toe on his left side. It also affected his speech and ability to multitask.

In the four years since the stroke, Lee, who is working on a Ph.D. in investigative medicine, has progressed from a wheelchair to a cane to walking independently, and his speech is now completely normal. Focusing on work has helped him rebound cognitively and emotionally. He recently passed the written and oral qualifiers for his Ph.D. program. “It is huge. It’s reaffirming to know that I can do this and it feels good. It makes me feel like a whole person again,” Lee said. “Appreciating each new accomplishment gives me perspective when life feels difficult.”

For Lee, resilience at its core means perseverance in the face of the severity of his paralysis and the cognitive hit from the stroke. “I am constantly reminded of things I used to take for granted. Who thinks twice about walking across the kitchen to get a drink?” said Lee, an avid athlete prior to the stroke. “Are you going to persevere? Are you going to live and reclaim your life from adversity?”

Lee walks with a limp and has some gait and stability issues. He doesn’t have full use of his left hand, and it is uncertain how much he’ll recover. A former snowboard instructor, he said that his family’s prodding sent him back to the slopes with adaptive equipment last winter. It was a great experience, but he admits feeling conflicted about trying old activities in new ways. “It’s really an ego thing—you can’t let your ego get in the way of doing things,” he said. “I’m learning to accept that life won’t be just like it was before. And I’ve realized that I need to take advantage of things that I’m resistant to embracing.”

But Lee also feels that acknowledging loss is integral to coping



and recovery. “Being able to grieve and mourn what has been lost is human,” he shared. “It is important to accept that bad things happen that are entirely out of your control. The only control you have is how you respond.”

Practicing medicine ensures regular encounters with disease, disability, and death. But when the physician becomes the patient, confronting illness can take on

new meaning. Lee and Kalanithi both stressed the importance of a strong support system, finding purpose, and participating in life. Kalanithi completed his residency in June 2014 and is trying to regain stamina so that he can enjoy being a father, continue writing, and perhaps perform neurosurgery again. Lee is re-engaging in sports and is researching therapeutic hypothermia for cardiac arrest survivors. He hopes to return to clinical practice. “Resilience is like the third act of a movie,” Lee said. “There’s always some obstacle to overcome.”

—Katherine L. Kraines



“We are no match for these creatures,” says microbiologist Jorge Galán of such bacteria as *Salmonella*, which have proven their resilience over time. Microbial pathogens, he says, have evolved unique ways to interact with their hosts, and terms of this interaction often reflect the co-evolutionary balance that the host and pathogen must reach in order to survive.



# A bug's journey

How evolution and selection help microbes adapt to changing circumstances

By Ashley P. Taylor

## So you think you have food poisoning.

You go to the doctor. The source? *Salmonella*. Do you go home with an antibiotic? Hopefully not, said Jorge Galán, Ph.D., D.V.M., chair and the Lucille P. Markey Professor of Microbial Pathogenesis and professor of cell biology. The frequency of antibiotic resistance tends to be high, Galán said, so there is a chance that such a drug may not work. More importantly, an antibiotic will wipe out your intestinal flora—the gut bacteria that otherwise would compete with the pathogenic intruders, leaving the resistant bugs to thrive unimpeded. A good doctor will not prescribe antimicrobials in this case, Galán says, because that could turn a few days' discomfort from a self-limiting infection into a lethal outcome.

It's for that same reason that if you do end up needing antibiotics, doctors urge you to finish the course even after you feel better in order to kill every last bug. Not doing so could leave you—and the world—with resistant infections.

From the human perspective, the emergence of antimicrobial resistance is a public health nightmare. For microbes, however, the ability to flourish in the face of a drug challenge is a success story and one of resilience: the ability to bounce back from challenges.

We tend to think of human resilience as the way in which individuals recover from such setbacks as the loss of a job or a loved one. Microbial resilience, in contrast, operates at the population level. When faced with an environmental change or selective pressure, individual microbes that are genetically unprepared simply die—but those that remain, such as the resistant *Salmonella enterica* Galán speaks of, are suited to their circumstances and can flourish, benefiting the microbial population. Through natural selection, bugs can evolve to withstand almost anything.

### “MASTERS OF EVOLUTION”

Galán likes to engage his students in a thought experiment. If you wanted to perpetuate your genes forever, he asks, and could choose between having a brain the size of Connecticut or being able to reproduce every 20 minutes, which would you pick? “To me, it's a pretty easy choice,” Galán said. “The replication every 20 minutes combined with genetic plasticity to change the genetic content will ‘outsmart’ the brain the size of Connecticut. We are no match for these creatures.”

Bacteria exhibit impressive genetic diversity, but such RNA viruses as hepatitis C, poliovirus, influenza, and HIV are diverse to a gargantuan degree. Brett D. Lindenbach, Ph.D., associate professor in the department of microbial pathogenesis, calls RNA viruses “masters of evolution.” Their populations are so varied that no matter what situations they face, some will have the genetic makeup to survive.

At work behind this microbial resilience are the concepts of genetic diversity and followed by natural selection. We often think of mutations as mistakes and sources of human disease, but they are simply genetic changes, and sometimes they are beneficial. Mutations are in fact critical to microbial survival, assuring that in any population at least one bug will survive any situation. Bacteria and viruses share high genetic diversity, but they achieve it in different ways.

First, some background. Bacteria have DNA genomes, the genetic blueprints that they pass on

to their offspring; viruses may have either RNA or DNA genomes. Lindenbach studies RNA viruses. The enzymes that make copies of the genetic material, either RNA or DNA, during microbial replication are called polymerases.

### HOW MISTAKES MAKE BUGS STRONGER

To generate diversity, RNA viruses like those Lindenbach studies depend largely on replication mistakes. The RNA polymerase of the hepatitis C virus, for example, makes so many mistakes that every new virus particle produced contains on average one mutation. “That's an incredibly high error rate,” Lindenbach said. In comparison, the error rates for bacterial DNA polymerases are 1,000 times smaller.

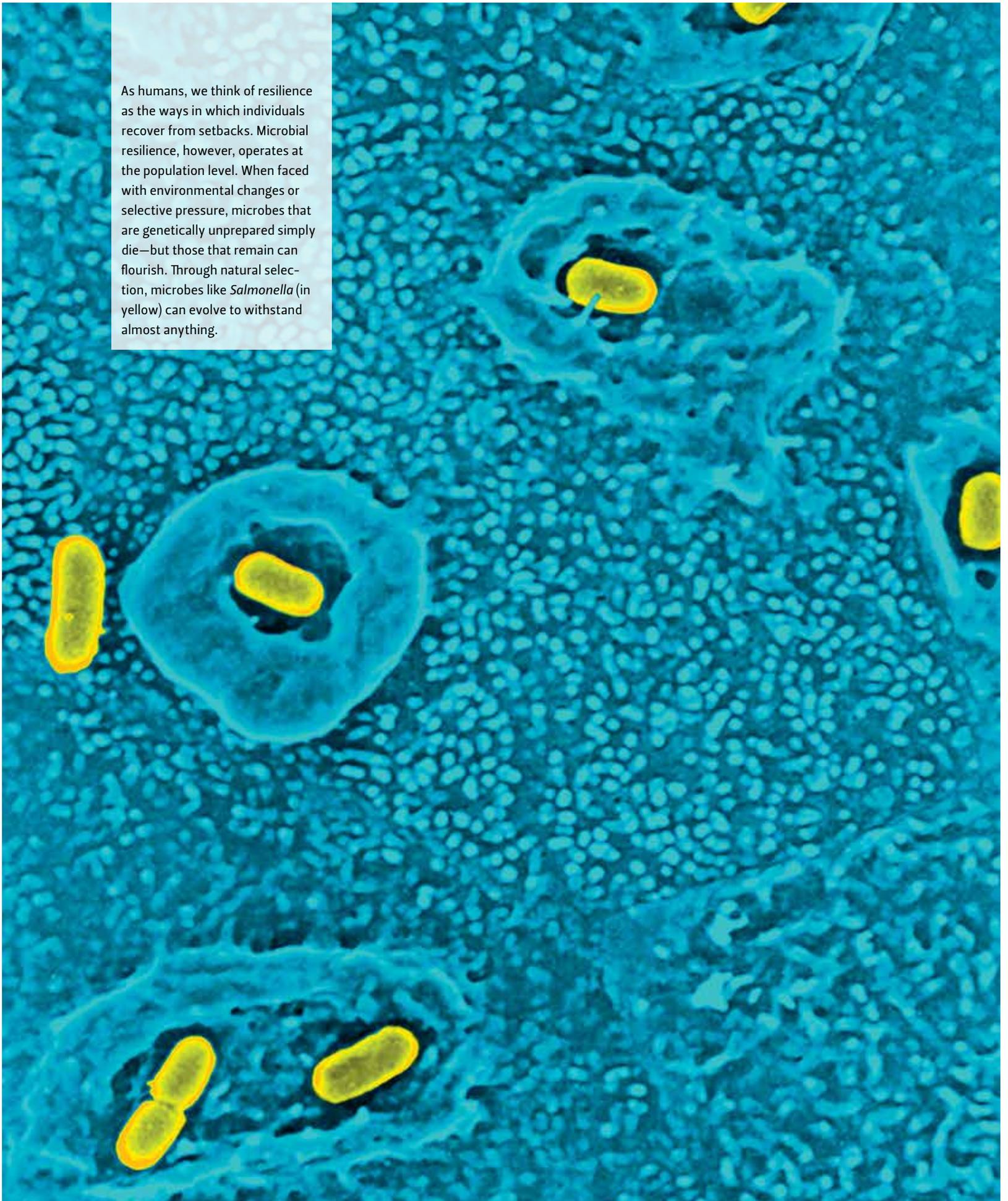
Because of this high error rate, the evolution of RNA viruses diverges from the traditional “survival of the fittest” model, which predicts that for any gene, the version that confers the greatest selective advantage will become dominant. But that's not how it works for RNA viruses. Because their polymerases are so prone to error, rather than having a single “correct” sequence, RNA viruses exist in what microbiologists call “swarms” or “clouds,” hovering around theoretical master sequences but constantly deviating from them, the way individual bees in a swarm shift in space relative to the general path of their group.

“RNA viruses really are masters of evolution,” Lindenbach said, “because [in] fairly short generation times they give rise to large populations of divergent daughter genomes, and then evolution can just take over.”

Not only do RNA viruses tolerate their faulty polymerases; they actually depend on their “mistakes.” Lindenbach noted that the Kirkegaard laboratory at Stanford compared the survival of different poliovirus clones whose polymerases had different error rates. The researchers found that mistakes were valuable to the viruses. “The idea is that the virus needs a certain amount of variability in order to adapt to the environments that it's encountering in an animal,” Lindenbach explained.

Beyond mutation, bacteria have additional ways to achieve genetic diversity that viruses lack. Different strains of bacteria can exchange genetic material with each other in what's called horizontal gene transfer—horizontal because it occurs within a generation rather than during reproduction. There are three ways in which horizontal gene transfer can happen: transformation, in which a bacterium takes up a closed loop of DNA called a plasmid from the environment;

As humans, we think of resilience as the ways in which individuals recover from setbacks. Microbial resilience, however, operates at the population level. When faced with environmental changes or selective pressure, microbes that are genetically unprepared simply die—but those that remain can flourish. Through natural selection, microbes like *Salmonella* (in yellow) can evolve to withstand almost anything.



transduction, in which a bacteria-infecting virus, a bacteriophage, moves DNA from one bacterium to another; and conjugation, in which two bacteria connect physically and DNA passes from one to the other. Bacteria use all three methods to achieve genetic diversity, Galán said, making mutation relatively less important to bacteria in comparison to RNA viruses.

Then there is the issue of replicating every 20 minutes—or rapidly, anyway. The more frequently microbes replicate, the more opportunities they have to experiment with genetic possibilities and the faster they can adapt. It's hard to compare the replication rates of viruses and bacteria, Lindenbach said; they replicate very quickly within a cell, but outside their hosts they can spend periods of time not replicating at all. In the scheme of things, viruses also have short life cycles.

Though genetic diversity is useful overall, individual mutations are usually harmful. For example, a study of one RNA virus, vesicular stomatitis virus, found that 60 percent of mutations were deleterious. There is, therefore, a limit to the frequency of mistakes that RNA viruses can tolerate. If viruses accumulate so many mistakes that they destroy their essential genes, Lindenbach said, they will go extinct in what's termed an error catastrophe.

### FINDING UNKNOWN STRENGTHS

It's a common theme in movies. Our heroes live quiet and unremarkable lives until disaster strikes. Suddenly, the characters find strength that they didn't know they had. In an analogous way, the importance of genetic diversity becomes clear when environmental conditions change and the pressure of natural selection is applied. The most familiar kind of selection, and the one that gets public health attention, is that of an antimicrobial drug.

Resistant strains of tuberculosis, a disease that is topped only by HIV in the number of people it kills annually worldwide, emerged as soon as doctors began treating TB with antibiotics in the 1940s. Since then, drug resistance has spread in frequency and geographic scope—450,000 cases of multidrug-resistant TB were reported around the world in 2012. Drug-resistant strains of malaria, gonorrhea, and *Staphylococcus aureus* (better known as MRSA) also threaten global public health. Take it from the World Health Organization (WHO): Antibiotic resistance is “a problem so serious that it threatens the achievements of modern medicine,” states a 2014 report on antimicrobial resistance. “A postantibiotic era—in

which common infections and minor injuries can kill—far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century.”

Of course, not only bacteria but also RNA viruses like hepatitis C become resistant to drugs. For example, nucleoside analogs are one class of drugs that have been developed against hepatitis C; they work by interfering with the viral RNA polymerase. Mutations in the polymerase that prevent the drugs from binding can confer resistance to the drugs, Lindenbach said.

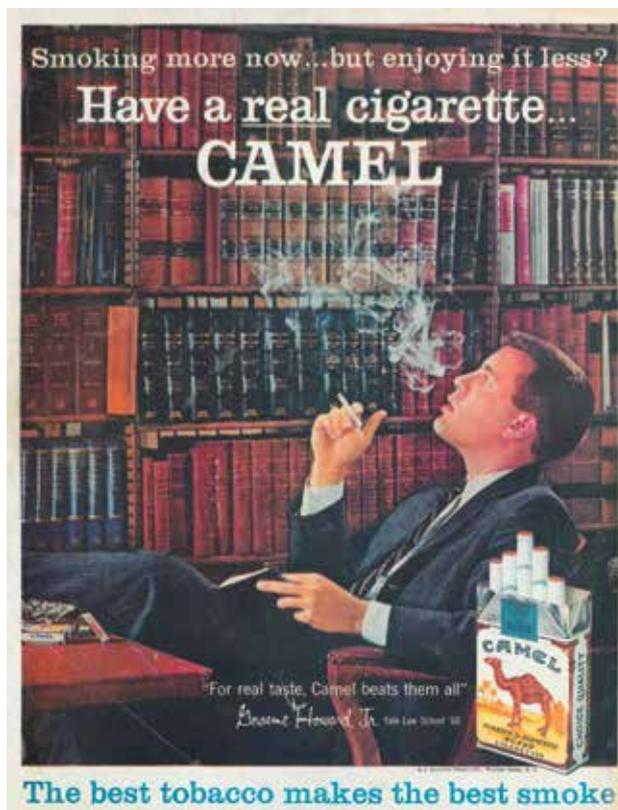
There is a silver lining, however, because in this case, the mutations that confer drug resistance come at a cost to viral fitness. “Those mutations also attenuate the normal function of the polymerase, even in the absence of the compound,” Lindenbach said, “so that those viruses that have that mutation are resistant to the polymerase, but they're very weak viruses.”

### HOPE FOR FUTURE ANTIMICROBIALS

Galán believes that, in the future, antimicrobial drugs will be designed not to test microbial resilience. “In terms of dealing with pathogens,” he said, “a strategy that is beginning to gain some traction, and that some of us have been preaching for a long time, is instead of developing drugs to kill the bug, the notion is to develop drugs that will hamper its ability to cause disease and then let our defense mechanisms deal with it.” By chance, some bugs may well resist the drugs, but others will be susceptible. The key is that with this new kind of drug, the resistant microbes will not be the only ones left alive, and they will therefore not come to dominate the way they would under the selective pressure of a microbe-lethal agent.

Designing drugs that tweak microbial machinery to prevent disease will require a specific understanding of the way in which that machinery works. This is exactly what Lindenbach and Galán spend their days doing. “As we know more and more how pathogens engage the host, cause disease, enter cells, attach to cells,” Galán said, “then we can develop highly specific drugs that will target those abilities.” */yale medicine*

*Ashley P. Taylor is a freelance writer in Brooklyn, N.Y.*



## The fight to control smoking

How anti-smoking efforts pushed back against the tobacco industry

By Kate Wheeling

A photograph of Harvey W. Cushing, M.D., lies flat in one of the glass cases that ring the rotunda in the Cushing/Whitney Medical Library. In the picture, the pioneering neurosurgeon leans against a stone barrier along the Axenstrasse roadway in Switzerland, his face pensive as he peers at unseen landscapes, a cigarette balanced easily in his left hand. Next to the photo sits an advertisement: “More doctors smoke Camels than any other cigarette.”

The photo and ad are part of a library exhibit highlighting the dueling campaigns of the tobacco industry and the anti-smoking movement. “Selling Smoke: Tobacco Advertising and Anti-smoking Campaigns” ran from May 15 through Sept. 12.

The tobacco industry is notorious for shamelessly persuasive advertising, using

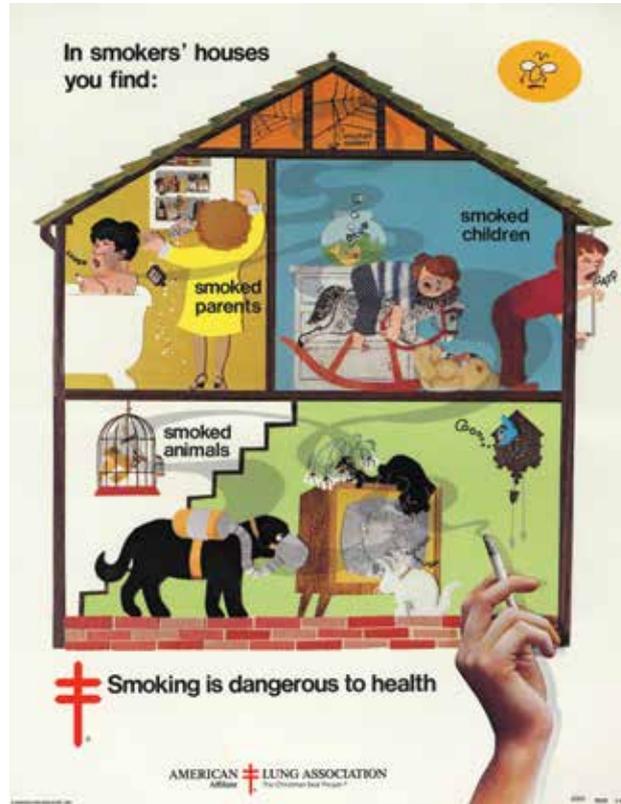
everything from sex to Santa to sell its products. They hired celebrity spokespeople (“Smoke [Philip Morris] for pleasure today,” says Lucille Ball, of *I Love Lucy*, in an ad. “No cigarette hangover tomorrow,” adds her husband and co-star Desi Arnaz); advertised promotions and giveaways (“1,000 gifts you can get for free with B&W Raleigh Coupons ...”); and even touted supposed health benefits (“Smoking Camels has been found to have a marked beneficial effect on digestive action. ... Camels set you right!”). The industry aimed to integrate smoking into everyday life and largely succeeded. Appliance companies gave away lighters with refrigerators; restaurants and businesses advertised on

matchbooks; and tobacco ads regularly appeared on primetime television. Americans spent much of the 20th century cloaked in clouds of cigarette smoke.

By 1964, the year of the first U.S. Surgeon General’s Report on Smoking and Health, 70 million Americans were smokers. Nearly half of all adults smoked, fueling an \$8 billion industry. Smoking’s negative health effects were well known, but tobacco sales remained unregulated even as the famed Marlboro men began to die of smoking-related diseases like chronic obstructive pulmonary disease.



“The funny thing is the Food and Drug Administration didn’t step in to try to extensively regulate tobacco until 1996,” said Melissa Grafe, Ph.D., the John R. Bumstead Librarian for Medical History and a curator of the exhibit. “But the Federal Communications Commission and the Federal Trade Commission engaged early in the fight against the tobacco industry, especially concerning false advertising.” The FTC brought lawsuits against cigarette companies as early as the 1930s for misleading advertisements. The American Cancer Society and the American Lung Association took up the fight against Big Tobacco, but what really launched the anti-smoking movement was secondhand smoke.



All told, cigarettes caused 100 million deaths in the 20th century, and many of the dead were nonsmokers. “I remember getting on a plane and asking for a nonsmoking seat,” recalled Jocelyn Malkin, M.D. ’52, who identified smoking as a risk factor for cancer in her medical school thesis. “I was in a nonsmoking seat, but the seat next to me was a smoking seat. That’s what was going on and it wasn’t so long ago.” Smoking wasn’t banned on domestic flights in the United States until 1998.

Lawsuits against the tobacco industry by innocent victims of tobacco—such as

flight attendants stuck for hours in airliner cabins with smoking passengers—were critical to the success of the anti-smoking movement. (Other innocent victims included children and unborn babies.) “The estimate is that 8 million lives have been saved because of anti-smoking efforts,” said Grafe.

Today only 18 percent of adults are smokers, and 26 states and the District of Columbia have banned smoking indoors. Alas, history may already be repeating itself. The use of traditional cigarettes may be declining, but e-cigarettes—battery-operated devices that deliver nicotine, flavor, and other chemicals—are growing in popularity. And e-cigarettes are not yet regulated by the FDA.

#### FROM FAR LEFT TO RIGHT

A 1959 ad exhorted readers to “Play it smart” and “Get the honest taste of a LUCKY STRIKE.”

“For real taste, Camel beats them all.” This ad featured a 1960 graduate of the Yale Law School, Graeme Howard Jr.

Lucille Ball and Desi Arnaz, stars of the wildly popular 1950s TV show *I Love Lucy*, extolled the pleasures of Philip Morris cigarettes.

By the 1970s, the American Cancer Society was pushing back against cigarette advertising, as with this 1977 ad that warned of the dangers of smoking to unborn children.

The American Lung Association, in an ad from 1982, told smokers that their children and pets were at risk from second-hand smoke.

#### BELOW

Place cards from Lucky Strike did double duty as bridge favors, with a place to tally scores on the back. Users could insert cigarettes in the holes to act as legs for the Swiss man and Scottish woman. A match in the man’s hand could serve as a stick or a sword.





## Straddling medicine and journalism, a former resident keeps an eye on the science press

IVAN ORANSKY, M.D., HS '99, ISN'T SHY ABOUT RUFFLING FEATHERS, and he wants the medical community to share his concerns about the ways in which medical and scientific news reaches scientists and the public. Oransky is the co-creator of the science publishing watchdog site Retraction Watch, and in 2013 he became the global editorial director for MedPage Today, an online news service for physicians. After 15 years as a full-time medical journalist, Oransky uses his role at MedPage Today to communicate his passion about the importance of skepticism in both reporting and medicine.

Oransky developed an interest in the orchestrated dissemination of medical and scientific news while a reporter and executive editor of the *Harvard Crimson*. Embargoes, he came to believe, restrict critique and force science journalists into a herd mentality of following journal publication schedules. He's also concerned about the Ingelfinger Rule, which not only bars scientists from publishing the same original findings in more than one outlet but also scares some of them out of talking to the press. Though the rule is well intentioned, Oransky feels it constricts the free flow of scientific information.

“Thinking about how journals and the media control the flow of information is important to everyone, including taxpayers, patients being treated, and the people doing the research and treatment,” he mused. “Any practicing doctors should understand how the sausage is made, why they read only certain studies in certain journals or in the news, and how their release is timed.”

Oransky's move from medicine to journalism came a year after he graduated from medical school at New York University in 1998. He came to Yale for a psychiatry internship, drawn by a tradition that bridged psychoanalytic practice and modern psychopharmacology. Splitting his internship between Yale-New Haven Hospital and the VA

Connecticut Healthcare System in West Haven, Oransky also found time to write. He contributed op-eds to *USA Today* and had a regular column in the Jewish newspaper *The Forward* (as “The Doctor”) where, for example, he wrote about the use of foreskin tissue in research. But it was his monthly column about life as an intern in *American Medical News* (which ceased publication last year) that really got people's attention—and not in an entirely good way.

“Residents and interns worked a lot of hours, and I wrote honestly about what it was like to be an intern,” said Oransky. “One



Ivan Oransky //

“Knowledge is gained by challenging what we think is true and looking at the evidence. ”

Ivan Oransky switched from psychiatry to a career as a gadfly, sharing his concerns about transparency in the dissemination of medical and scientific news. “Any practicing doctor should understand how the sausage is made,” he says.



ONLINE EXCLUSIVES

Downs Fellowship brings student to a home she never knew

Two students garner Soros Fellowships for New Americans

Transition: from basic to clinical science

Reunion 2014

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of the deans wasn't crazy about that." Oransky was chastised in a letter that circulated to senior medical school faculty. Oransky has no regrets. "It reminded me that my core identity is as a journalist, constantly challenging things," he said.

After his internship, Oransky chose journalism over the practice of medicine. "It wasn't the easiest for my parents to get used to, but once they saw that I was really happy and accomplishing things and adding value to the world, they got it," he recalled. He was hired as founding editor in chief of *Praxis Post*, a webzine that was dubbed "*Vanity Fair* for doctors." Following that, he was deputy editor of *The Scientist* and managing editor of *Scientific American*.

In 2010 Oransky started two blogs to keep tabs on the science communication ecosystem: Retraction Watch, which analyzes research corrections and retractions and which he runs with *Anesthesiology News* editor Adam Marcus; and Embargo Watch, a site that monitors premature news breaks and the effects embargoes have on news coverage. After four years as executive editor of Reuters Health, Oransky joined MedPage Today in July 2013.

Another goal of Oransky's is to create a health care provider blog network at MedPage Today. "This is clearly the next step in the great and rapid evolution of the site," he said. "We want to give doctors, nurses, and

physician assistants a voice and a platform to have conversations and share expertise and insights." Oransky will be tapping established bloggers, but said he is happy to hear from alumni of the School of Medicine in the health care community who would be interested in having their blogs join the MedPage network.

Blogs are powerful and lower the publishing barrier, said Oransky, and they are a great way for patients and doctors to talk to one another. While the line between traditional journalism and blogging is blurring, a common thread that he carries through his day job and his blogging is skepticism. "Knowledge is gained by challenging what we think is true and looking at the evidence," said Oransky. Medical education, like journalism, he said, could always use more critical thinking and challenges to convention.

—Amanda Alvarez



### A Renaissance man looks back on 50 years in medicine

Some people might call Alfonso Esguerra, M.D. '64, HS '66, FW '69, a modern-day Renaissance man. Aside from co-founding a renowned medical center in Bogotá, Colombia, he has participated in civic service, commissioned architectural projects, formed philanthropic and social enrichment organizations, written two books

on Latin American paternalism, and established a flower farm that exports over a million stems each year. Esguerra says these endeavors are borne from a "why not?" attitude and what he calls "responsible self-learning"—a value ingrained in him by the Yale system.

Although he has enjoyed a successful career, Esguerra did not always think that medicine was his destiny. An early fascination with the visual arts often competed with the lure of his family's tradition—both grandfathers, his father, and two of his three uncles were physicians. But it took only a few premed classes at the Universidad de Los Andes in Bogotá to ignite his passion for the biological sciences.

After completing his medical education at Yale, followed by an internship at the Hospital of the University of Pennsylvania, a radiology residency at Yale-New Haven Hospital, and subspecialized training as the Yale William Wirt Winchester Fellow in Thoracic Radiology, Esguerra returned to Colombia in 1969 at age 30. He practiced radiology in Bogotá, where he was soon recognized for his professionalism and leadership.

But Esguerra had a broader vision—to establish a comprehensive nonprofit medical center in Bogotá. Of course, he said, this venture would never have become a reality were it not for the unwavering support of his wife, Gloria, who also donated the land where the

hospital stands. Their first recruit for the project was José Félix Patiño, M.D. '52, HS '58, a former Colombian minister of health. "It took me two years to convince him of the idea and instill in him the enthusiasm Gloria and I felt for the project," Esguerra said.

The Esguerras and Patiño were among the six founding members of Fundación Santa Fe de Bogotá (FSFB) in November 1972. It would take seven years to obtain financing from Colombia's banking community. Another Yale alumnus, architect George Nelson, B.F. Arch. '31, designed what Esguerra envisioned to be "a hospital so humane it would not look like a hospital." Nelson dubbed the project "The Colombian Garden of Health."

In 1979, Esguerra was named the general director of FSFB, charged with "getting the job done." It was no small task. He began by forming an executive team, and hiring hospital planners and equipment consultants. He supervised the hospital's construction, and participated in selecting the members of a top-notch medical staff. FSFB opened its doors on January 31, 1983. Two years later Esguerra considered "the job done" and resigned his post.

A 7.5-acre plot of land in a tree-lined neighborhood at the foot of the Andes Mountains became a major medical center under Esguerra's leadership. Today it consists of a tertiary care hospital, an outpatient



specialty clinic, an emergency clinic, and an oncology institute serving 150,000 patients a year. It operates within Colombia's national health system, which insures more than 90 percent of the population. Esguerra is most proud of the degree of institutionalization FSFB has achieved. "It should be the organizational characteristic of all major Latin American enterprises," he adds.

After extensive self-retraining, Esguerra returned to radiology in 2002 following a 20-year hiatus. As chief of the chest section in the FSFB diagnostic imaging department, he founded the Center for Interactive Digital Education in Radiology (CIDER) and its companion website ([fsfbcider.org](http://fsfbcider.org)), of which he remains editor in chief.

As Esguerra readies to retire after 50 years in medicine, he says he "remains committed to becoming a better person. What has mattered most is making a difference as one shares and contributes to community interests." Esguerra looks forward to spending quality time with Gloria; their two daughters, Beatriz and Maria, their sons-in-law, and their four grandchildren. He also plans to document the history of FSFB, paint, tend to his garden, cook. "... and someday soon, visit New Haven to enjoy once more the bells of the Yale carillon, as they play Cole Porter songs."

—Amanda Crowe

After a successful career as a physician in his native Colombia, Alfonso Esguerra pursued a broader vision—to establish a comprehensive medical center in Bogotá. Under his leadership a plot of land in the Andean foothills has become a major center.

# **Colleen Kelly Alexander flatlined twice after being hit by a 30-ton truck. Now, she's running marathons.**

COLLEEN KELLY ALEXANDER KNOWS WHAT IT MEANS TO BOUNCE BACK. An experienced triathlete, she was cycling home from work one day in October 2011 when a 30-ton truck ran through a stop sign and over her on Boston Post Road in Madison, Conn. Her injuries were overwhelming: her lower body was ripped apart, her pelvis was crushed, and she flatlined twice after nearly bleeding to death.



watch a short film about  
Colleen Kelly Alexander at  
[yalemedicine.yale.edu](http://yalemedicine.yale.edu)

In the three years since, Alexander has undergone 22 surgeries at Yale-New Haven Hospital and has another handful ahead of her. That she survived at all is impressive, but even more remarkable is her approach to life in the wake of the accident. A long-time activist for community service and human rights, she now advocates for road safety and

raises money for organizations that have played a role in her recovery. Since the injury she has participated in more than 30 races, including eight triathlons and two Ironman events. A buildup of scar tissue limits her mobility, and she can only run slowly—she had to walk during 90 percent of her last Ironman—but she is proud to cross the finish line at all and is redefining what it means to be an athlete.

Alexander, 39, credits a large part of her recovery to her medical team at Yale and the support of her husband, but it is clear that her exceptional resiliency and spirit have spurred her achievements. She spoke with *Yale Medicine* this summer about how she has managed to thrive despite unremitting pain and the limitations caused by her injuries.

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*Yale Medicine*, 1 Church Street, Suite 300, New Haven, CT 06510 or email [yymm@yale.edu](mailto:yymm@yale.edu)

**The trauma you suffered would be life crippling in a different person. Why do you think this hasn't been the case with you?** None of these injuries have made me lie on the couch because there's no room for that in my life. Too many people worked too hard; too many people gave their blood, gave their time, gave their energy, gave their prayers. For me, giving up was never an option.

**How important was your previous athletic training to your physical and psychological recovery?** Being an athlete prior to being run over has been a blessing and a curse. For a very long time I wasn't able to leave the bed. The athlete in me was always screaming to get back out there to run and to bike and do all these things that I love. Suddenly, all of that was taken away. My dad said to me that when athletes are injured it's a bigger curse than if you're not an athlete, because all you know is that

active lifestyle, and suddenly it's taken away from you and it's such a huge loss. But what it did provide me with was a strong, beating heart. So being an athlete has allowed me to sit here today and be shining, which is really nice.

**Since the accident, you've dedicated yourself to physical activity and social activism. What made you choose this route?** I was an athlete and activist before, so I'm not going to let the poor choice of someone that blew a stop sign ruin my life. Certainly, I'll never be the athlete that I could have been, or the mother, or the wife, but I am who I am now, and I'm so grateful for this life and I'm grateful for this opportunity. If anything, it fuels me even more because I want to be able to get out there and move and be active and show people that anything is possible.

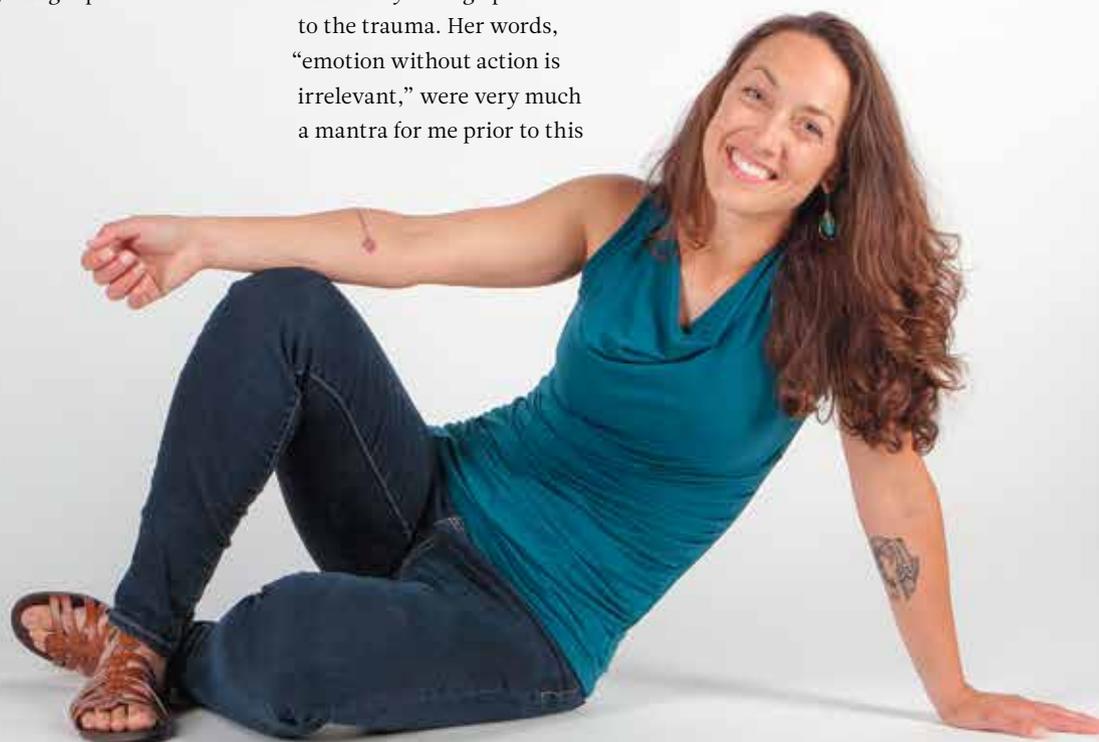
**How chronic is your pain? How do you compete and function while in pain?** I am in pain, but I'm not going to let it completely define me. I've had pain way past a 10. I typically hover around a six. Sometimes I spike up, sometimes I go down to a two or three. I made a decision early on that I wasn't going to take heavy drugs more than I needed to because I knew there was a chance of addiction, and I didn't want that to be an option. If I wasn't in weekly psychotherapy, I would have a much tougher time handling my pain.

**You've had the opportunity to meet some famous and wise people, such as Jody Williams, who won the Nobel Peace Prize in 1997 for her efforts to ban land mines. Did they shape your philosophy?** Jody Williams was my kick in the pants. I met her years ago prior to the trauma. Her words, "emotion without action is irrelevant," were very much a mantra for me prior to this

trauma. After the almost seven weeks at Yale-New Haven Hospital and close to three months at Gaylord Hospital, I finally developed depression and anger and frustration, and I remembered those words. And I thought, if I'm this angry and in this much pain, I can harness this and do something with it. That began a change in my outlook.

**You've said that during triathlons you need to pull over and cry at least once. Why and what makes you keep going?** I've got this hidden battle inside. As my heartbeat picks up and my breathing picks up, it brings me back to the accident. So that fear that I have starts to take over—and it does take over—when I pull over to the side of the road, that's when I offer up gratitude that I'm on this earth.

We covered Colleen's start on the road to recovery about a year after the accident. Visit [yalemedicine.yale.edu/longroad](http://yalemedicine.yale.edu/longroad) to read that story.



# How cats and dogs became our best friends

A Yale-trained geneticist looks at how humans turned wild animals into beloved pets

By Cathy Shufro

By the time they graduated from the School of Medicine, David Grimm, Ph.D. '04, and his fiancée, Amy S. Duffield, M.D. '05, Ph.D. '05, had wanted a cat for years. After landing in Baltimore—Grimm as a deputy news editor of *Science*, Duffield as a pathology resident at Johns Hopkins—they felt ready to adopt two kittens. Not long after, one of the kittens spent

three days in a veterinary ICU. The bill came to nearly \$3,000.

Why, Grimm wondered, had he and his fiancée gone into debt to save the kitten? He decided to explore what he describes as “the evolution of dogs and cats from wild animals to quasi-citizens.” Americans, he soon discovered, spend a lot on their cats and dogs—\$55 billion in 2013—and more households have dogs or cats than have children.

His research took him to laboratories, animal shelters, an animal law conference, and a prison. The result is *Citizen Canine: Our Evolving Relationship with Cats and Dogs*, a broad examination of the history of how humans interact with dogs and cats and how the pets have affected art, religion, law enforcement, public policy, and even the course of epidemics.

Grimm, who studied genetics at Yale, begins by investigating how dogs evolved. The household pet we know as *Canis lupus familiaris* shares 99.9 percent

of its DNA with the gray wolf, *Canis lupus*. One explanation for the evolution is “pup abduction”—our ancestors may have kidnapped wolf pups and raised them to be gentler than wild wolves. But Grimm doubts that the abductors would have imagined that wolves could be made gentle: people found them terrifying. (Consider *Little Red Riding Hood*, a tale told by two other Grimms.) Furthermore, early humans had yet to domesticate any animal. As one scientist tells Grimm, “They weren’t thinking, ‘You know, in a century or two, we’ll create this really handy animal, the dog.’”

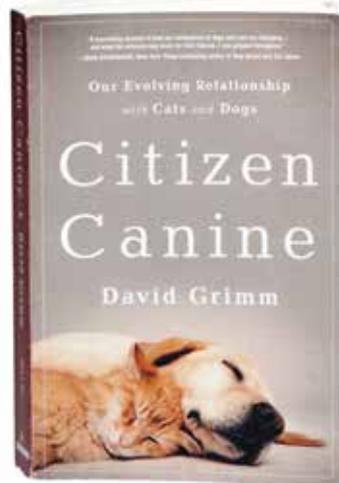
A more likely scenario, Grimm believes, is that wolves evolved somewhere between 15,000 and 30,000 years ago as they followed early humans, scavenging for bones and food scraps. Humans in turn found canines useful for carrying loads and warning of intruders. Cats proved similarly valuable with the advent of agriculture about 12,000 years ago—they killed mice that ate stored grain.

A 20th-century experiment showed how quickly human-animal interactions can lead to genetic changes: the Russian geneticist Dmitri Belyaev began in 1959 to

breed caged silver foxes selectively, allowing only the friendliest to reproduce. In just nine years, the foxes’ ears became floppy, their tails curled, and they had lower levels of the stress hormone cortisol. Instead of biting people, they licked their hands. Grimm also notes reversals in the fortunes of dogs and cats—whereas ancient Egyptians venerated felines, in 1233 Pope Gregory linked cats to Satan. Millions of cats were massacred, a boon to the rats that helped spread the plague.

The social standing of cats and dogs has improved markedly since then. Support for medical experimentation on animals is waning. Laws protect animals from harsh treatment, and among Grimm’s field trips was a stint shadowing the anti-cruelty team of the Los Angeles Police Department as they investigated the beheading of two dogs. Americans view their dogs and cats as family members: during Hurricane Katrina in 2005, people risked death rather than leave their pets behind.

Grimm’s account brings us to an era in which canines and felines increasingly look almost like citizens. As Grimm demonstrates, the story of our bond with cats and dogs is still unfolding.



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## Laid-back 'spokesdog' on TV

KYLA HORN (in photo), a neuroscience student, makes a point of visiting Finn the Therapy Dog in the medical library on Fridays.

"He helps me take a breather from everyday stress and just live in the moment for a while," says Horn.

Horn is not alone in appreciating a few minutes with the gentle 3-year-old mix. Horn's visit in early September came a few days before Finn appeared on *The Today Show* on Sept. 9 in a segment about the Canine Cognition Center at Yale. The segment showed Finn and two other dogs taking tests to determine whether they trust their owners and can distinguish between "good" and "bad" puppets.

Finn's owner, Krista Knudson, M.S.N., a nurse practitioner in a doctoral program at the School of Nursing, enrolled Finn in the center's research project a few months ago. "His temperament lent itself to being the one that got showcased," Knudson said.

—John Curtis

