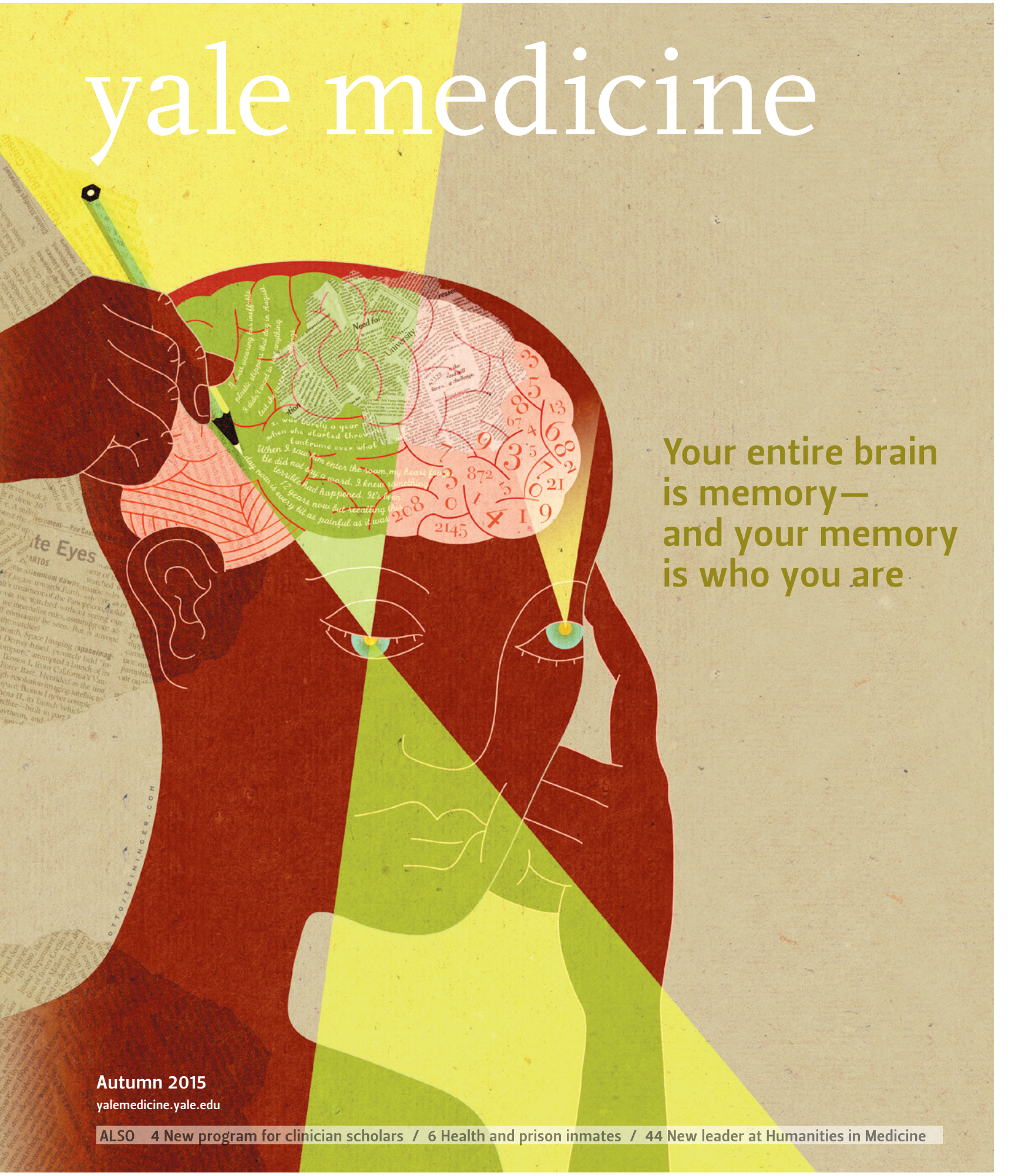
yale medicine



Your entire brain is memory— and your memory is who you are

Autumn 2015
yalemedicine.yale.edu


granny is getting more forgetful every day. The other day I asked her if she had watered the plants and she couldn't remember. She couldn't remember when aunt Emma stopped by, either. Today she asked I for his name. Leary. I will have to have her checked. This can't go on. The house is simply to big for her to keep living there by herself
during that time it was not uncommon to smoke during morning meetings.
The department head used to bring back Gauloises from when he visited his in-laws in the Pyrenées. His fingers as well as his salt and pepper moustache were yellow from those stenchers. As were his teeth. I think I was trying to impress Mme Dupont, who would occasionally drop in on those meetings. The whole unit knew he had a crush on her.
I would have to air my clothes for a whole week after those two-hour meetings. It took a while for Michael to stop interrogating me when I came home reeking of these yellowish
when he had is
frightful.
He got doored by a parked car on 23rd street.
He went flying over that door and landed face first in the street, face all smashed up.
Thank goodness for that helmet. When he got up he couldn't lift his right arm. If this thing had happend to 80's of all Germans in the early thirties, Hitler would have never risen to power, he quipped (because they couldn't have lifted their
Which Side Are They On?
Natural Born Gunslin
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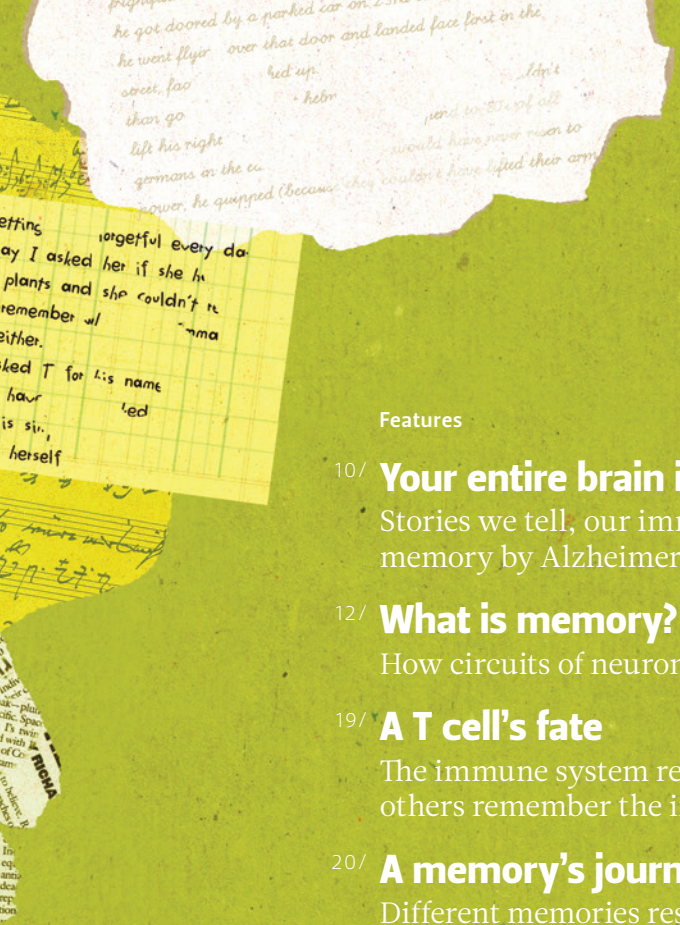


Features

OTTO STEININGER ILLUSTRATION

autumn 2015 departments

letters

Beeson evokes memories of Yale

With all due respect to the "Iron 'Terns" and their considerable accomplishments ["Six Degrees of Paul Beeson," *Yale Medicine*, Spring 2015], Paul Beeson, M.D., attracted and inspired many outstanding classes of house officers during his 13-year tenure as chairman (pardon the old designation) of the Department of Medicine at Yale. He was aided in this task by an outstanding faculty: Gerald Klatskin, M.D., in liver diseases, Philip Bondy, M.D., in endocrinology, Stuart Finch, M.D., in hematology, Howard Spiro, M.D., in gastroenterology, Allan Goodyear, M.D., in cardiology, and Elisha Atkins, M.D., his partner in the study of fever, just to name a few. I was privileged to meet Dr. Beeson when I was but an intern in surgery at Yale in the 1953-54 academic year. I had recently returned from a brief convalescence in Florida following a nine-week hospitalization for what was known then as serum hepatitis contracted from a needle stick. Dr. Beeson was facing an abdominal operation and, thinking ahead, wondered whether convalescing in Florida was a good idea, and he asked me! I didn't think he knew I even existed, let alone that I had been ill. Our very pleasant professional and even personal relationship continued through my residency in surgery and my years on the faculty before I moved to Stanford in March 1965 at the invitation of Bob Chase. Dr. Beeson was planning a sabbatical year at Stanford to begin in July 1965, and I was doing a little house and school searching for him and his family. In May of that year, I received a letter from Dr. Beeson saying that he would not be coming to Stanford because he had accepted the offer to become Nuffield Chair of Medicine at Oxford—as understandable a reason as one could imagine for such a change in plans.

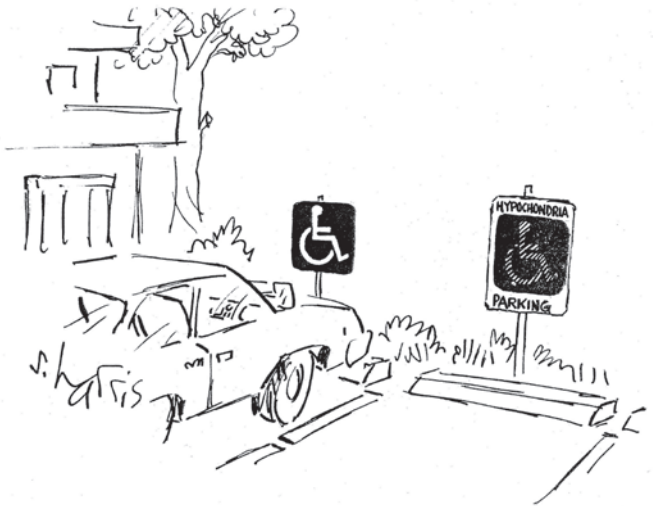
Paul Beeson was a towering figure in medicine, at once highly accomplished, quietly stimulating, approachable, and modest. Maybe someone has constructed a family tree of his trainees similar to the "Iron 'Terns." If not, someone should. That might even be a suitable project for a Yale School of Medicine thesis or a talk at a meeting of the Yale Historical Society.

James B. D. Mark, M.D., HS '54
Professor of Cardiothoracic Surgery, Emeritus
Stanford University School of Medicine

Having fond memories of Paul Beeson, M.D., upon receiving the recent *Yale Medicine*, I open immediately to the double-page photograph of the Iron 'Terns. Imagine my surprise and delight in seeing myself 50 years younger in the group. I'm the funny-looking guy with glasses standing in the front row, second from the right—between John Burke (#14) and Harold Federman (#15). I was an assistant resident, having graduated from Yale School of Medicine in 1963, and having been an intern in 1963-64. For the record, while not as academically distinguished as many of my fellow interns, I subsequently was in the private practice of internal medicine for 30 years in a small Vermont city, served as president of the medical staff at the Rutland Regional Medical Center, and was a clinical instructor in medicine at the University of Vermont.

David F. Cross, M.D. '63, HS '64
Glade Hill, Va.

SECOND OPINION
BY SIDNEY HARRIS



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Please limit letters to 350 words and include a telephone number. Submissions may be edited for length.

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Abbreviations used in *Yale Medicine* include HS to denote the final year of residency for house staff, FW for the final year of a fellowship, and YNHH for Yale-New Haven Hospital.

Yale SCHOOL OF MEDICINE

Memory has a role in almost every biological process

IT HAS BEEN SAID that our memories make us who we are. We turn our memories into stories with meaning and wisdom, and share them in the hope that others can learn from them. Our memories take different forms—some fleeting and others hardwired into our brains, available for quick recall. Our immune system remembers foreign invaders in order to stop them before they do damage, and our cells remember whether their DNA has suffered damage and undergone repairs. *Yale Medicine* spoke with Dean Robert J. Alpern, M.D., about the importance of memory in medicine, science, and beyond.

Why is the study of memory so important? The study of memory is important because of its role in almost every biological process. We think of the brain as the location of memory, but almost every cellular and molecular process in the body uses memory to increase its efficiency. However, understanding memory in the brain is uniquely important because this form of memory defines who we are. We now live in an age where we survive cancer and heart disease, but later many become impaired by diseases such as Alzheimer's.

How will Yale's new Alzheimer's Disease Research Unit advance the study of disease and, hopefully, lead to better diagnosis and treatment? When we performed strategic planning 10 years ago, one of the highest research priorities identified was neurodegenerative diseases, and in response the Center for Cellular Neuroscience, Neurodegeneration and Repair (CNNR) was formed. The success of CNNR contributed to our ability to become an Alzheimer's unit. We still don't completely understand what causes amyloid protein or tau to accumulate in the brain, but we hope to use the Alzheimer's Disease Research Unit to advance our understanding and develop new therapies to address this disease.

What aspect of memory do you find most interesting? The ability of the brain to create its own memory. People have memories that actually never happened or may not have happened exactly as remembered. If you tell a story enough times, it starts to become a true memory, triggering all of the biological mechanisms associated with long-term memory. This fascinates me.

What should readers remember from this issue of *Yale Medicine*? They should remember the beauty of biology. While simple memory occurs in the simplest of organisms, the complex memory performed by our brains required a long time to evolve and defines the human species and other high-level species. To preserve these memories is one of the goals of medical research.

FRANK RAMSPOTT ILLUSTRATION

Team-based science is focus of new clinician scholars program

Cary Gross has led the transition to a new clinician scholars program, which for the first time teams residents with students from the School of Nursing.

WHEN THE ROBERT WOOD JOHNSON FOUNDATION (RWJF) ended its longstanding Clinical Scholars program last year, it was a loss not only for the Yale community but for the city of New Haven as well. Since the program's inception more than 40 years ago, scholars have worked on projects designed to address health inequities and improve health care throughout the city. The more than 160 Yale scholars who have graduated from the program since 1974 have had a strong impact on New Haven through community-based research that assessed a range of topics, including the availability of healthy foods in a New Haven neighborhood without a supermarket, HIV/AIDS status, gun violence, immigrant and refugee health, and access to health care for the homeless.

"I've never been part of a training program that is blessed with so much loyalty, appreciation, and dedication among the alumni, the faculty, and the institutional and community partners," said Cary P. Gross, M.D., professor of medicine and co-director of the RWJF program at Yale. "That is why we simply had to find a way to continue training the next generation of scholars who will lead our efforts to improve the health care system and enhance the health of individual patients, our communities, and the nation."

Though RWJF decided last year to stop funding the clinical scholars program, the four host sites—the University of California, Los Angeles; the University of Michigan; the University of Pennsylvania;

and Yale—took up the mantle to begin a new independent fellowship in a spirit similar to that of the original program.

"Forging ahead was an unspoken mandate," said Gross, as the four sites decided that the work of the program is not yet complete. "When we discussed the challenge with leadership at Yale, the question was never whether to continue training scholars; it was how to do it. Dean [Robert J.] Alpern has been incredibly supportive." The new National Clinician Scholars Program (NCSP) will share many features with the original program, but the consortium made key changes in order to adapt to a new element of the changing health care landscape—an increased emphasis on team-based approaches to research as well as clinical care. As a result, the NCSP will train doctoral-level nurse-scientists side by side with physicians.

In clinical practice, such team-based approaches as patient-centered medical homes are increasingly common, and they bring together physicians, nurses, physician associates, and others to collaborate with patients in making decisions about care. "Team-based care is a common and effective part of our health care system," said Gross, who is leading the planning of the NCSP at Yale. The decision to include nurse-scholars in the NCSP builds upon the interdisciplinary framework of the RWJF program, which trained physicians from various specialties together, including internists, surgeons, pediatricians, and others.

"No profession can do it all themselves, and we each have important roles to play in the delivery of health care across the health continuum," said Margaret Grey, Dr.P.H., M.S.W. '76, dean of the Yale School of Nursing. "The more we educate people in silos—whether for clinical practice, or clinical research, or health services research—the less likely it is that they will work collaboratively when they get out in the real world." In addition, she noted, postdoctoral training slots for nurses are limited, and the NCSP will provide a much-needed avenue for nurses who seek to combine clinical work with research.

The new two-year program will select approximately five physician- and nurse-scholars per year to complete coursework together at Yale, sharing mentors from across the professions. NCSP scholars will lead their own policy-relevant research projects, guided by faculty and community partners. They will also learn the value of collaboration as they participate as team members in their peers' projects.

Scholars will be encouraged to translate their research discoveries into real-world change by working with community partners, health care providers, or government agencies to ensure that they are asking questions that are important to stakeholders and that the results of their studies will have an impact. Scholars will build upon collaborations that have grown with the existing clinical scholars program, which has included such partners as the VA Connecticut Healthcare System, Yale-New Haven Hospital, Columbus House, Integrated Refugee & Immigrant Services, Project Access of New Haven, and New Haven Family Alliance, among others. "One of the hallmark features of the scholars program has been the link between scholarship and action," said Gross. "We place a great emphasis on teaching scholars not just how to do research but also how to instill change, working either from within the health care system or from outside the system."

While the NCSP is aimed at early-career, post-training physician- and nurse-scientists, the trend toward interprofessional education, or IPE, increasingly appears at all levels of medical education. The Liaison Committee on Medical Education, an accreditation body, has established a new standard that requires medical schools to include collaborative education as part of their core curricula. At Yale, when the School of Medicine redesigned its curriculum, Eve R. Colson, M.D., professor of pediatrics, joined with colleagues from the School of Nursing and the Physician Associate Program to add an

HAROLD SHAPIRO PHOTO

ONLINE EXCLUSIVES

Alumnus Vivek Murthy, M.D. '03, M.B.A. '03, returns to Yale as the U.S. Surgeon General.

Lessons from the Ebola crisis at this year's Global Health Day.

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IPE component to the course she leads, the Longitudinal Clinical Experience. That program places medical students in community-based clinical settings from their first days of medical school. Now, first-year nursing and physician associate students are also included, said Colson.

Having the NCSP at Yale will contribute to IPE's goal of collaboration, Colson said, by providing students with role models for how to work together across professions. "How many hours does a basketball team practice together before they play a game?" said Colson. "Whereas in medicine, all of us who take care of patients, we don't really practice together. We just play the game."

Gross said the four-member consortium is eager to get started on the NCSP, which will accept up to 25 scholars across all sites for the program's first cohort in 2016, with the hope that new institutions will subsequently join the founding sites. "It was really exciting to see how the leadership at the four university sites really banded together," Gross said, "and realized that the whole would be greater than the sum of our parts if we continued to work together. This really shows that the benefits of working in teams applies to large universities, just as it applies to individual clinicians and researchers."

—Jeanna Canapari

Health and the justice system

As an intern on an emergency department rotation at the University of California, San Francisco, in 2003, Emily Wang, M.D., was shocked to learn that many of her patients had recently left prison, some within the past few days. Equally shocking, she realized, was that for many of these patients, prison offered them their first access to health care.

The U.S. Supreme Court has ruled that health care for inmates is required by the Eighth Amendment to the U.S. Constitution. Upon an inmate's release, however, the mandate disappears and significant barriers to care arise. Most newly released inmates have no primary care providers and no insurance, and do not know how to navigate the health care system. For the 85 percent of inmates who received regular care in prison for such chronic conditions as diabetes and hypertension, one of their first stops upon release is the emergency department.

"To me," said Wang, an associate professor of medicine, "that was an incredibly inefficient way to run a health care system. It was frustrating. It was inhumane."

In 2005, during her last year of residency, she began the Transitions Clinic Network (TCN) to help recently released inmates adjust to life outside prison by providing access to health care. What began as one clinic in San Francisco has

grown into 15 clinics in seven states and Puerto Rico, with plans to expand. TCN has two clinics in New Haven, at the Yale Primary Care Center and the Cornell Scott-Hill Health Center.

This is how it works: TCN community health workers, all of them former inmates, meet former prisoners on their release. They help patients get insurance, see a primary care physician, and connect with services to help with housing and employment.

Kathleen F. Maurer, M.D., MPH '85, director of Health and Addiction Services and medical director of the Connecticut Department of Correction, views the peer advocate aspect of TCN as crucial. "These patients relate to their peers in a way they couldn't relate to a physician," she said. In Connecticut, inmate patients are released with a four-week supply of medication and get help connecting to Medicaid, often their only source of insurance. Maurer said that the Department of Correction relies on TCN to help them stay connected to health care.

The criminal justice system has an enormous scope: 63 million Americans have criminal records, and 13 million move in and out of correctional facilities each year. It's clear from medical literature, Wang said, that poor health can prevent former inmates from getting a job, and employment is one of the most important factors in helping them stay out of prison. Data from TCN show that former inmates who saw a primary care physician within a month of release had fewer emergency department visits and hospitalizations than those who did not. "It seems like a place where the smallest sorts of adjustments can make the biggest gains," Wang said.

With funding from the Yale Center for Clinical Investigation and the Patient-Centered Outcomes Research Institute, Wang and her colleagues are developing a Web-based platform that will disseminate to TCN clinics, patients, and community stakeholders the data she has collected through nationwide studies of TCN patients. TCN has also formed a partnership with Yale Law School to help TCN patients in New Haven address legal needs related to housing, employment, and other social issues related to the health of former inmates. "There won't be a singular solution," Wang said, to addressing the criminal justice system's impact on health equity, "but a collective one."

—Jeanna Canapari

»

Safer hospital transitions

Every year Yale-New Haven Hospital (YNHH) admits more than 50,000 patients. Once in the hospital, patients may move, for example, from the emergency department to intensive care or from medicine to Smilow Cancer Hospital. Each of these transfers carries a degree of risk. Health care providers and hospital administrators have long studied the "handoff," when a new doctor takes over patient care during a shift change or a move from one service to another and crucial information can fall through the cracks. But now a team of doctors and providers is taking a broader look at those transitions to anticipate problems and find ways to mitigate them.

Over much of the past year, Alana Rosenberg, M.P.H., has spent many hours in the hospital standing in hallways, at nurses' stations and, in the emergency department, watching residents, attending physicians, nurses, business associates, and patients. With an anthropologist's eye, Rosenberg, a research associate in internal medicine, is part of a team that observed those moments when a patient enters the hospital, moves from one part of the hospital to another, or leaves the hospital for home, hospice, or a care facility. Then the team interviewed the people involved—doctors, nurses, staff, and patients. Part of the impetus for the study comes from the Institute of Medicine's 1999 report, *To Err Is Human: Building a Safer Health System*. The report, which estimated that between 44,000 and 98,000 people die each year because of preventable medical errors, convinced clinicians and investigators that new studies of patient safety were needed.

MATT DALEY ILLUSTRATION

ONLINE EXCLUSIVES

Welcome to the Class of 2019! A new class dons the white coat.

A clinic founded by Yale med students expands its reach in the wake of Nepal's devastating earthquake.

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"Patients are moving through the health system at a very fast pace, and the technology that we have is increasingly complex and sophisticated," said Sarwat Chaudhry, M.D., FW '05, associate professor of medicine. "The diagnostic evaluations that we're doing and the data that we as clinicians are juggling are mind-boggling compared to 20 or 30 years ago. You really need multiple checks and systems in place to make sure that things are happening the way they're supposed to."

While past efforts have followed the traditional route of devising an intervention, testing it, and analyzing the results, the Center for Healthcare Innovation, Redesign and Learning (CHIRAL) is taking a new approach. Funded by a grant from the U.S. Department of Health & Human Services' Agency for Healthcare Research and Quality (AHRQ), CHIRAL starts with an in-depth problem analysis of patient safety in three areas, and then works with clinicians and experts from such industries as aviation and engineering to devise solutions.

"We have a lot to learn from other industries that are ahead of medicine, where you just count on the individual remembering to do the right thing," said Chaudhry, principal investigator for the part of the project that involves transfers within YNHH. The other projects, headed by Marc Auerbach, M.D., assistant professor of pediatrics, and Grace Y. Jenq, M.D., FW '04, associate professor of medicine (geriatrics), will look at patients entering the Yale-New Haven Children's Hospital emergency department, and patients moving out of YNHH into skilled nursing facilities. "Clinical deterioration can happen during transport because you're not monitored like you were on a floor," said Beth Hodshon, J.D., M.P.H., R.N., project director for CHIRAL.

As part of a months-long study, Alana Rosenberg interviewed health care workers and patients to find out what works and what doesn't work during transition points in hospital stays.

CHIRAL, a joint venture between the School of Medicine and YNHH, was among the first centers funded by the AHRQ initiative. "We're one of the largest health systems in the country," Chaudhry noted. "We have the medical school and a world-class hospital and health system, but bringing together expertise from both sides and both perspectives was an important opportunity."

Following a year of ethnographic observations for each of the three projects, CHIRAL looked at such specific issues as communication, handoffs, and data flow. Team members observed and interviewed everyone involved in transitions—health care providers, ancillary staff, business associates, and patients—while the data team studied information collected in Epic, the electronic medical record. In August, the team met with national and local experts to study interventions that might be effective. Unlike traditional studies that end after an intervention is tested and the results are reported, the interventions devised by CHIRAL will be continuously designed, implemented, and tested in a process that will end only when a solution is shown to be effective.

"Protocols can be put in place, but it's everyone's reaction [to how things are done] that really matters in the end," Rosenberg said.

—Jill Max

round up

a collection of recent scientific findings

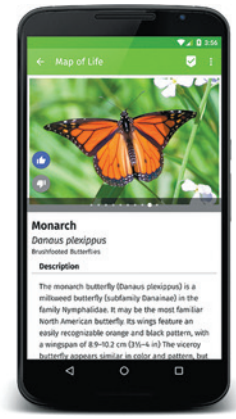
THE BUZZ ABOUT HIV

Men with detectable HIV infections need less alcohol to feel "buzzed" compared to uninfected men, according to recent work by researchers from Yale and the Veterans Health Administration. Survey responses from over 2,600 men in the Veterans Aging Cohort Study, 607 with detectable HIV infections and 871 with suppressed HIV, showed that men with detectable infections need a quarter of a drink less than their counterparts to feel the effects of alcohol. "All else equal, people who have HIV infection have a lower tolerance for alcohol than similar people without HIV infection," said Amy C. Justice, M.D. '88, M.Sc., Ph.D., professor of medicine and public health and senior author on the study. The study was published in April in the journal *AIDS and Behavior*.

UNLIKELY VIRAL ALLIES

Lassa virus, which can cause deadly hemorrhagic fever similar to Ebola, and was first described at Yale in 1969, kills approximately 5,000 people a year, according to the Centers for Disease Control and Prevention—but now it's helping in the fight against brain cancer. VSV, a virus related to rabies, previously showed promise getting past the blood-brain barrier and targeting cancer cells, but it could also cause a potentially lethal brain infection. Yale and Harvard researchers used viruses in which VSV proteins were replaced with portions of the Lassa virus, creating a safe "chimeric" virus that successfully destroyed brain tumors in mice without causing disease, according to a study published in the April issue of *Journal of Virology*. "We are very excited about these new chimeric viruses that contain genes from multiple viruses. They work well in targeting cancer in animals, and we hope that they will also work effectively if tested in humans," said Tony van den Pol, Ph.D. '77, professor of neurosurgery and the study's senior author.

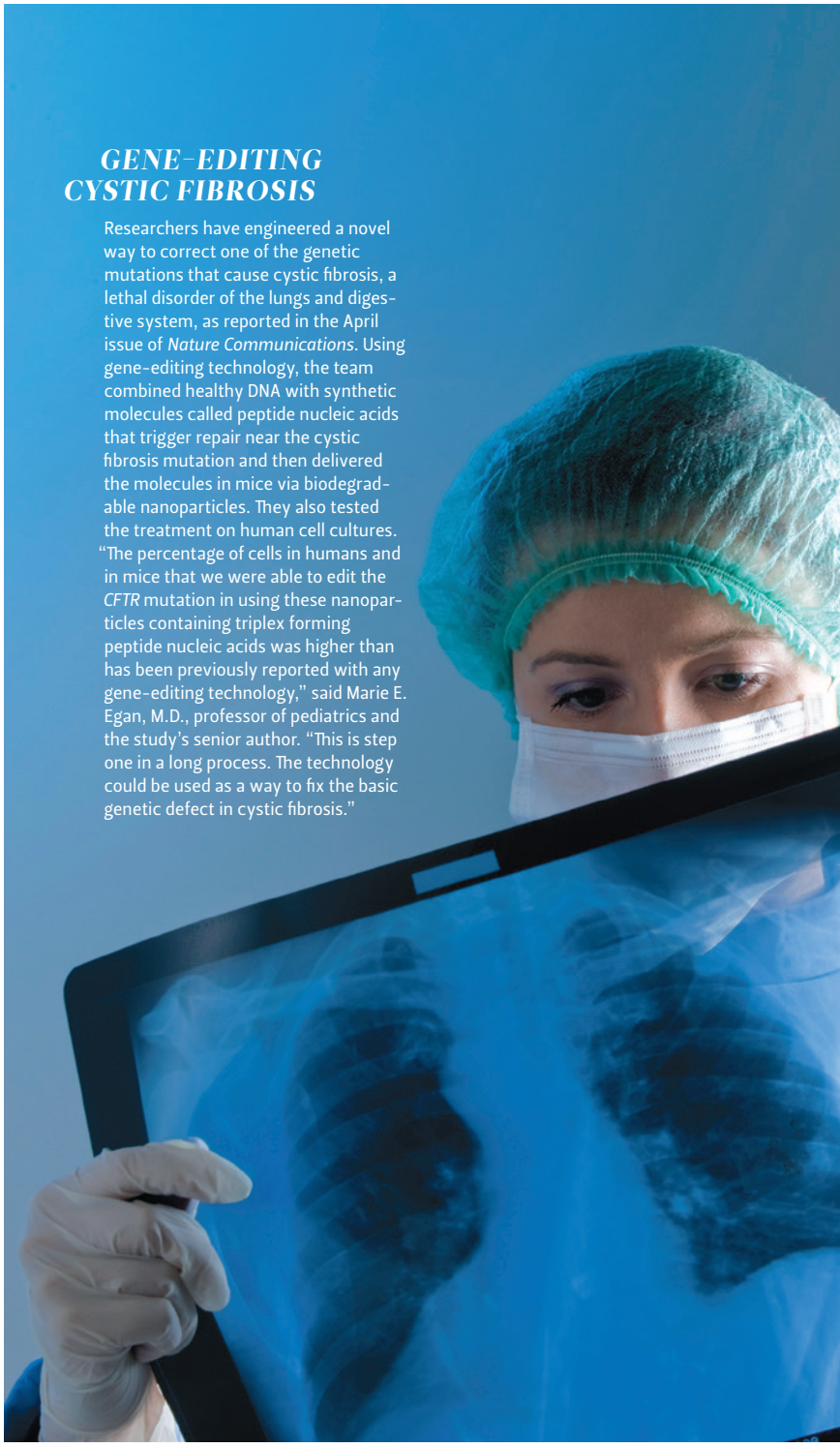
POCKET-SIZED DIVERSITY



It might be time to toss those clunky paper field guides. Researchers from Yale and the University of Florida just unveiled a new smartphone app called Map of Life to track plant and animal species around the world. The app is based on a global scientific database that launched in 2012 to catalog biodiversity. Users can not only see an informative list and photographs of all the species in their area, but also contribute their personal observations. "This vast information, personalized for where we are, can change the way we identify and learn about the things we see when traveling, hiking in the woods, or stepping in our own backyard," said Walter Jetz, M.Sc., D.Phil., associate professor of ecology and evolutionary biology, and the visionary behind Map of Life. To download the app, visit http://mol.org/mobile.

GENE-EDITING CYSTIC FIBROSIS

Researchers have engineered a novel way to correct one of the genetic mutations that cause cystic fibrosis, a lethal disorder of the lungs and digestive system, as reported in the April issue of *Nature Communications*. Using gene-editing technology, the team combined healthy DNA with synthetic molecules called peptide nucleic acids that trigger repair near the cystic fibrosis mutation and then delivered the molecules in mice via biodegradable nanoparticles. They also tested the treatment on human cell cultures. "The percentage of cells in humans and in mice that we were able to edit the *CFTR* mutation in using these nanoparticles containing triplex forming peptide nucleic acids was higher than has been previously reported with any gene-editing technology," said Marie E. Egan, M.D., professor of pediatrics and the study's senior author. "This is step one in a long process. The technology could be used as a way to fix the basic genetic defect in cystic fibrosis."



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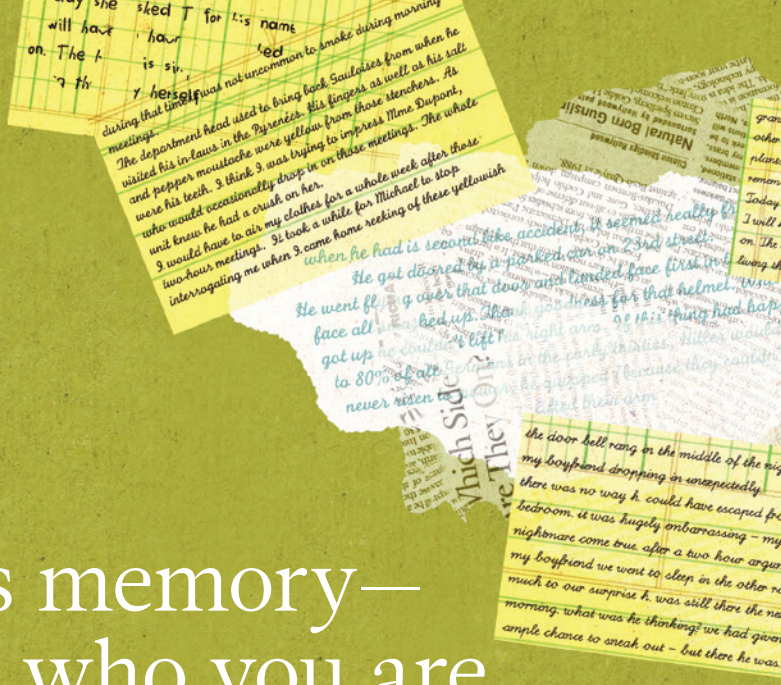


Your entire brain is memory—and your memory is who you are

MEMORY FASCINATES US. We've created a genre of literature we call memoir. We take our memories and toy with them until they form a coherent narrative, one that makes sense of our lives and allows us to live with things we might like to forget. We're embarrassed when we have a "Rick Perry" moment and can't retrieve from our brain something that should be on the tip of our tongue. We recall vividly a night from 10 years back but can't remember what we discussed at last week's staff meeting. And we know that our memories are not set in stone, and that we can be induced to "remember" events that never happened.

Neuroscience tells us that memories are patterns of synaptic connections among the billions of neurons in our brain. Where our memories are stored depends on what kind of memories they are. Is this phone number destined to be a short-term memory, staying in our brain just long enough to dial? Is this memory procedural, involving motor skills like tying a shoelace or strumming a guitar? Is it traumatic or emotional, requiring the services of the amygdala to process? Is it a semantic memory, the kind of fact that keeps us up at night while we cram for a test? The brain has a spot for each of them, but we still don't know where all of our memories reside.

This issue of *Yale Medicine* is devoted to these notions of memory and different ways to understand them. We asked doctors who write for their perspectives on how and why we turn our memories into stories. Doctors tell us why Alzheimer disease, which erodes our memories, is one of the most feared disorders in the country.

As Oscar Wilde put it, "Memory is the diary we all carry about with us."

OTTO STEININGER ILLUSTRATION

What is memory?

How circuits of neurons become the narratives of our lives.

By Karen Zusi Meriel Jane Waissman Illustrations

“Close your eyes and think of a lollipop,”

instructs Marvin Chun, Ph.D., professor of psychology and neurobiology. “Now, if I test you a week later by showing you a picture of a lollipop and asking, ‘Did you ever see this?,’ you’re probably going to say yes even though you just imagined it.”

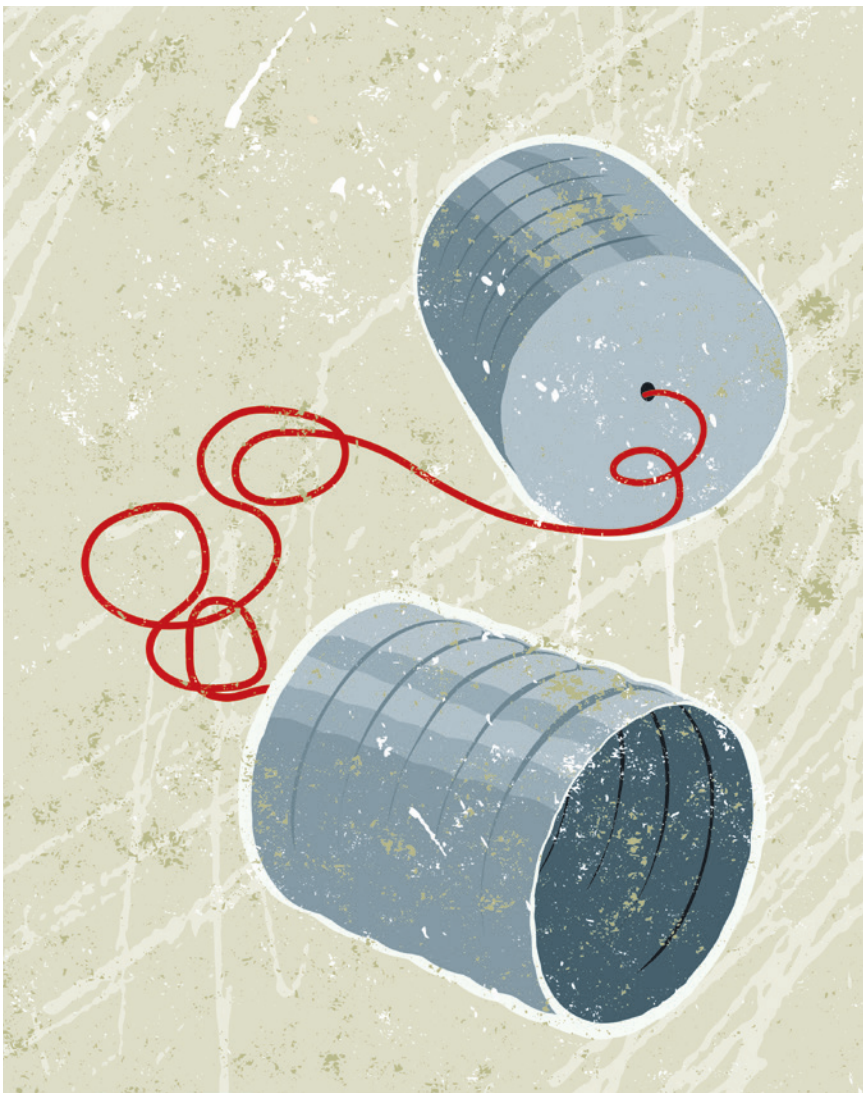
Memory is a story. The entirety of our lives, real and imagined, is grounded in memories of learning, thinking, and doing, making our memories inextricably linked to our identities. Every time you recall something, a series of neurons lights up your brain, covering it like a patterned spider web of energy. Remembering the details of where you were, whom you were with, and what an event looked or sounded like causes your brain to activate and occasionally modify this pattern. Like a children's game of "Telephone," details can get altered or lost in translation; the brain doesn't operate like a perfect videotape. But its changeability ensures that we can create and store memories in vast numbers of adaptive neural connections, constantly adding threads to the tapestries of our persons.

WHERE MEMORIES START

There's a lot that scientists still don't know about how we form and store memories, but the beginnings of one are easy to trace. All memories start with perception. Through thinking, touching, hearing, seeing, tasting, and smelling, we process our surroundings and things that affect us. "Today I walked into the door and bumped my elbow," offers Jessica Cardin, Ph.D., assistant professor of neurobiology, as an example. "You have to have a context for that memory. You have to see that you're in your office." In the brain, the cortex receives all of this information from various systems and funnels it into the hippocampus, which creates associations throughout the neural network. But from there, everything depends on what type of memory is being formed.

Muscle memory—learning how to play the piano or ride a bike—uses a different part of the brain than remembering how you celebrated your birthday last year. Spilling coffee on yourself during a meeting is recalled differently from how to use a knife and fork, which is different from remembering the dates you studied for a history test the night before. Some memories are constantly reinforced by our environments and therefore made stronger—it's easier to forget where you placed your keys last night than it is to forget the route from your home to the office.

Mistakes, however, often occur in the perceptual phase. "People are terrible observers most of the time," says Cardin, who studies the interplay between neurons in both healthy and diseased brains. Eyewitness testimony is notoriously fallible due to missing or imagined details. Psychologists have also conducted experiments in which a subject takes a sheet of paper from someone behind a desk, who then bends down to retrieve something. A different person behind the desk stands up—and the subject rarely notices. The experiment isn't meant to embarrass people, or to point out how little they remember about the people they just met, but rather as an example of how they prioritize where they direct their attention. In these cases, were the clients later asked to recall what the person behind the desk



looked like, odds are they would offer only general details: gender, or perhaps race.

For items or events to which we do pay attention, we build chemical connections to consolidate a memory. Compared to the number of neurons in the average brain, a single person will have a seemingly unlimited number of experiences. "You can't assign one memory per neuron," says Cardin. Even with 100 billion neurons, there simply aren't enough. Instead, rather than selecting one cell to hold all memories of a family member, we create a pattern involving only a portion of the available neurons, combining them in different numbers and sequences.

A DISCRETE "THING" IN THE BRAIN

Researchers once envisioned memory as a discrete "thing" in the brain, but now they search for these patterns of replay that indicate information being recalled. Your brain can ignite the pattern for recall in multiple ways, along any part. According to Cardin, smell is one of the best ways to activate a memory. The nerves that react to and process smells in the air connect directly to the limbic system—which includes the hippocampus. We can also ignite patterns of recall by envisioning specific details or places. If someone asked you to remember something about your childhood, you might start with an image of your elementary school building or your first pet and build from there.

When we reactivate such a neural recall pattern, it becomes malleable. It's unlikely that anyone would believe they actually saw a lollipop since reading Chun's instructions, but that might change a week later if subjects were unaware of the test's purpose. Memory is like a wax seal, Chun says: First, you heat up the wax to press an imprint into it, which then solidifies. But the act of retrieval warms up the wax again. "That malleability—the fact that it becomes reprogrammable—that physical fact is what allows memories to become stronger or weaker," says Chun. "There's no such thing as reading out exactly what was encoded. It all involves opening the files, making the wax warm again, because we're just dealing with proteins in the brain."

False memories can be created by something as simple as a leading question. "You can do it experimentally by having people witness an event," says Cardin. A subject might observe a brown-haired person bumping into someone, with an experimenter afterwards asking the witness what time the blond person bumped into the other. A week or two later, when asked to describe the event, the witness is more likely to say that a blond-haired person bumped into someone. The immediate follow-up by the experimenter is crucial; when recalling the event later, the witness's brain activates the pattern of neurons and therefore heats up the wax again, allowing the memory to be modified by the suggestive question.

Change occurs to some types of memory more easily than others. Memory of our personal timeline, referred to as "episodic memory" or memory with a date and time stamp, is most susceptible to alteration or decay. The memory of what you gave a friend for a birthday or who attended the party is less resilient than the memory of what purpose a chair serves. Similarly, forgetting that the sky is usually blue or that a zebra is striped would be unlikely without some type of brain damage. These learned memories, ingrained factual information outside our personal experiences, are categorized as "semantic memory." Psychologists still debate whether the brain handles the information in one system or two and how much reinforcement the brain needs before a fact becomes part of semantic memory, but no one argues that a distinction exists.

TRAUMA AS A RESEARCH TOOL

Traumatic brain damage and neural disease provide critical information about what memory is and how it works. Some of the brain's memory systems are particularly robust. While episodic memory is often the first to go, skill memory—the eponymous "muscle memory"—is one of the most resilient. Even amnesiacs don't forget how to walk. Those who have difficulty forming new personal memories can still learn new motor skills, including complex tasks like writing backwards on a mirror. The brain stores skill memory in a different region from plain information.

When humans do forget things, the process may occur in a few different ways. The act of trying to remember is akin to searching for something on a computer hard drive or in a messy room. If the computer files are organized, or the room has been recently

cleaned, the search is easier—but with time and entropy, finding things becomes difficult. "Memory is the exact same thing," says Chun. "Sometimes, it's hard to find because of all the other stuff." Whether memory patterns, if formed through proper attention, can ever be truly "deleted" from our brains is still an open question in psychology. However, they decay and can be overwritten by more important information.

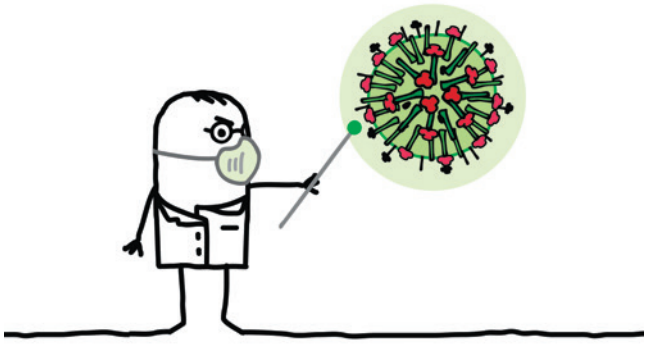
This notion of forgetting or lost memories has long been a source of fascination for pop culture. Movies across all genres deal with the topic: *The Notebook* for Alzheimer disease; *Memento* or *50 First Dates* for anterograde amnesia, in which the main characters cannot form new memories; *The Bourne Identity* and *Eternal Sunshine of the Spotless Mind* for a more science-fiction take on lost memories. "We don't really understand forgetting that well," says Chun, but he points out that an abnormal rate of memory loss is one of the most debilitating situations in which patients can find themselves: "It robs you of who you are and how people relate to you."

Clinically, forgetting as a process receives significant research attention. Even though memory patterns are spread throughout the brain, conditions like Alzheimer disease hit memory the hardest of all the brain functions. "What we can do to stave off and understand that disease is probably our most pressing challenge," says Chun. "The more you can understand memory and the more you can map it onto the brain, and the more you can understand when it goes bad and when you can preserve it—what all memory researchers do is helpful for that effort."

But our brains have also created forgetting as an adaptive function, and researchers are harnessing it to treat other disorders. With chemicals that block neurotransmitters, scientists are researching memory alteration as a potential therapy for post-traumatic stress disorder, drug addiction, delusions, and phobias. By activating a memory and then using an agent that weakens connections in the brain, researchers may be able to remove the emotional attachment or craving that accompanies the memory pattern and stop it from being reinforced.

Memory as a higher brain function defines who we are. We rely on our memories for experience, wisdom, relationships, flexibility, and any ability to learn. Even in Greek mythology, the Muses—goddesses of inspiration and knowledge in the arts and sciences—were daughters of Mnemosyne, the goddess of memory. But when our identities are predicated on a temporal continuity, what does it mean when it turns out we're not exact documentaries but some flavor of creative, narrative film? Our brains simply do the best they can—the rest is up to us. */yale medicine*

Karen Zusi was Yale Medicine*'s writing intern in 2015.*



A T cell's fate

Healthy humans are born with billions of infection-fighting machines called T cells. We need so many because a T cell exists for virtually every type of virus, bacterium, or parasite. T cells respond to foreign intruders by replicating like mad to generate an army of these defenders, including killer T cells. As the infection clears, millions of those T cells die off. Only 5 to 10 percent remain in the blood, poised to attack like a boxer anticipating a familiar foe's first punch. These are memory T cells.

"Your immune system gets imprinted physically with cells that are generated during the first infection," said Susan Kaech, Ph.D., associate professor of immunobiology and a Howard Hughes Medical Institute early career scientist. This is why vaccines are so crucial, she said. The immune system remembers the infectious agent so it can ward off infections immediately, rather than letting nature run its slower (and sometimes fatal) course.

But how do T cells become memory T cells? Scientists had long assumed that the process was random and largely governed by external forces. Research over the past decade, however, suggests that certain T cells may be more intrinsically fit to become a long-lived memory T cell. During a viral infection, some T cells express a receptor designed to detect a cytokine called interleukin-7, and those cells live to fight future infections. Most other T cells do not express that receptor, and they don't survive.

Yet research also suggests that environmental forces might be at work. The more inflammation T cells are exposed to, for example, the greater their chances of differentiating into killer T cells that can help clear the present infection. This exposure, however, also makes them more likely to die after an infection. In contrast, T cells only mildly exposed to inflammation or to anti-inflammatory signals are more likely to develop into memory T cells.

How such diversity of T cell fates arises remains a puzzle. Are T cells born as either memory or terminal T cells? "I think that would be kind of scary. It would be like predetermining the fate of a person while they were still in the womb," Kaech said, noting that infection is unpredictable, never giving advance warning of which pathogen might strike, when or where it comes from, and how much you'll be exposed to. In the face of such random events, the immune system must remain pliable. "You don't know what someone will become before they are born; and similarly, you wouldn't want your immune system deciding if a T cell was going to live or die before it has even seen the pathogen it recognizes."

—Kathleen Raven

NLSHOP ILLUSTRATION

A memory's journey

On their journey through the brain, our memories pass through the hippocampus, a temporary transit hub. Where they go next depends on whether your brain is recording the capitals of the 50 states, your reaction to the latest Seth Rogen movie, or the shock of witnessing a traffic accident.

For every memory, the brain creates a new circuit of neurons, or alters or strengthens an existing circuit. And each memory has a context—it's encoded in the brain based on meaning and association. Long-term memories fall into two types, declarative and nondeclarative. Under declarative memories—which are encoded by the hippocampus, entorhinal cortex, and perirhinal cortex, but consolidated and stored in other parts of the brain—come episodic memories. Episodic memories are our personal experiences, including the emotional charge of those experiences: the day I started med school … the time I spilled coffee on my suit just before a job interview … the first time I laid eyes on the love of my life. These personal memories end up in the medial temporal lobe and neocortex. Anything emotional or traumatic involves the amygdala. Semantic memories are the things outside of our personal experience that we learn, say, from textbooks. What's the capital of Estonia? When was the Battle of Waterloo? Can you recite pi to 10 digits? These types of memory reside in the lateral and anterior temporal cortex and the prefrontal cortex.

Nondeclarative memory lets us remember how to ride a bicycle, strum a guitar, or hammer a nail. These procedural memories are encoded and stored by the cerebellum, putamen, caudate nucleus, and motor cortex.

Short-term memory, or working memory, has been likened to a scratch pad where we jot down a phone number. Unless we make an effort to retain that number, it will disappear. The central executive part of the prefrontal cortex handles these types of memories. Ever wonder why we break up phone numbers and credit card numbers? That's "chunking," breaking a long number into chunks, which allows us to increase our short-term memory capacity.

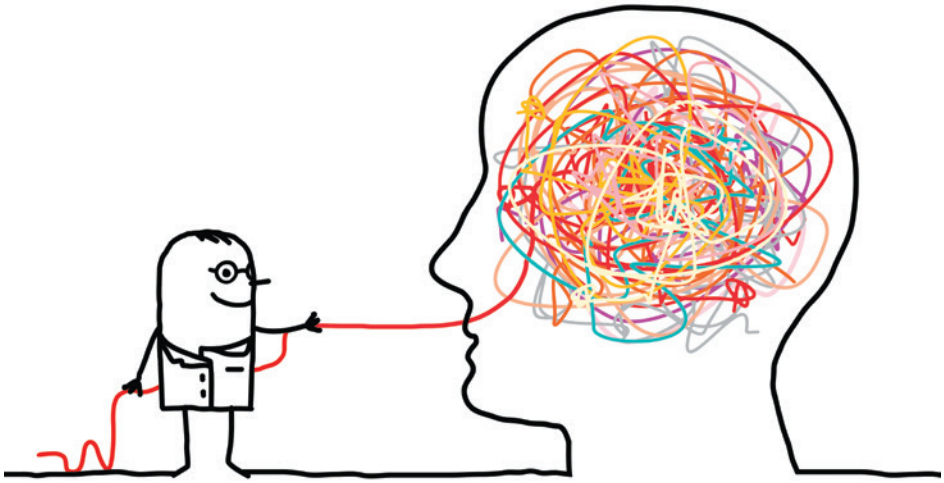
There are things we just remember, and the things we work at remembering, like studying for a test in microbiology or American history. What year did Lincoln deliver the Gettysburg address? What's the difference between DNA and RNA? These learned facts and figures outside of our personal experience become part of our semantic memory, but not everything in our semantic memory comes from textbooks. These memories can be the facts common to our culture, like the name of our state capital or the current president, and include other facts we acquire over a lifetime. Trying to cram all these things into our brain the night before a test is probably the worst thing we can do. Research has shown that we need to sleep in order to consolidate our memories.

"Mechanical memories," which we now call procedural memories, were first observed in 1804. This is knowing how to do things. These are the skills we acquire and never forget, like riding a bicycle. If you play an instrument it seems like the muscles in your fingers remember, too, and know exactly where to strike that key or form that chord. Without even thinking, we know, in a given song, which note comes next. Procedural memory allows the muscles in a quarterback's or pitcher's arm to throw the ball with accuracy, and without even thinking about it. Likewise, hammering a nail is one of those skills that stays with you. Your muscles just know.

Why do we write to-do lists? Even our working memory has its limits. We use it to hold on to something for as long as we need it and no longer—usually just a few seconds. What's the number of that takeout Chinese place? What's that email address? In the 1950s, it was posited that our capacity to hold on to information is limited to a handful of "chunks." That's why we break up long series of digits like our phone numbers or social security numbers. And, as we age, working memory is among the functions most likely to decline.

There are things in our lives, like slipping on the sidewalk and breaking an arm, that remain as episodic memories—the stories of our lives. Somehow we organize these memories into coherent narratives with a beginning, middle, and end. Along with the broken arm, we'll remember where we were coming from, where we were going, whether we were distracted by our cell phone, the ice on the sidewalk, the moment of slipping, the realization that we were going to fall and that it was going to hurt. But episodic memories can also be pleasant—a Labor Day barbecue at the beach with friends, the conversation, the sound of the surf, and the food. Through these memories we travel back in time, from last weekend to 30 years ago.

OTTO STEININGER ILLUSTRATIONS



What's in a doctor's brain, and what's online

In the typical adult human, there are 206 bones, at least 700 named muscles, 78 organs, 12 pairs of cranial nerves and 32 pairs of spinal nerves, and a formidable array of named veins and arteries, all of which, during medical training, a budding doctor will be asked to commit to memory. That, of course, is only the beginning. There are an untold number of procedures to memorize, as well as a host of diseases—currently more than 30,000—to cram into the cerebral cortex, and when the training process is complete, assuming it is ever really done, physicians are expected throughout their careers to dig into their brains' hard drives and retrieve relevant information quickly, effortlessly, and flawlessly.

But in the modern technological era, when tablets and smartphones are as much a part of a doctor's regalia as a white coat and a stethoscope—Yale students receive iPads when they enter medical school—does it still make sense to engage in all that memory work? Neurobiologist Michael Schwartz, Ph.D., associate dean for curriculum, said that's a question worth exploring. With the explosion of knowledge and the ease with which it can be accessed by technology, he said, we need to be more thoughtful about which facts need to be in the memory for immediate application. "Memorization takes up far too much cognitive bandwidth when we should be focusing more on the application of knowledge. Technology now gives us the opportunity to access all that information instantaneously, and this is changing the way we train doctors and practice medicine."

Internist Auguste H. Fortin VI, M.D., M.P.H., believes that it's mostly a change for the better. "Most of medical education has revolved around filling up the empty vessel with facts, but with scientific knowledge growing explosively, no one can possibly keep it all in mind," said Fortin, who teaches communication skills and always has his iPhone handy in the exam room.

While there had been fears that computers of any variety would be seen by patients as intrusive, those worries haven't played out. "I'll tell patients when I'm looking something up that I'm almost positive about the condition, but I just want to double-check and make sure my recollection is correct," Fortin explained. "And I show them what I'm doing so they know I'm not texting or checking my shopping list. The iDevice has become a partner, a way to ensure quality control and improve patient care."

The fact that Fortin is less reliant on memory is a big plus since he freely admits that his memory is less than photographic. "I remember sometimes having to invent a pretense to leave an examination room so I could go back into the office to look something up in a book," he explained. "There was a bit of shame in this—I didn't want a patient to know that I didn't have it all in my head."

That shame is gone, but while Fortin may not have the entirety of *Harrison's Principles of Internal Medicine*

at his cognitive fingertips, he has all of his specialty's typical procedures, to say nothing of an impressive array of facts, at his disposal. This doesn't include the proper dose of every medication imaginable—these are readily available online—but Fortin and his fellow internists know by heart the proper flow of a patient encounter and the skills needed to draw out a patient to effect a differential diagnosis. "You memorize the more common situations, like if you see someone with chest pains who has these particular qualities, you might be looking at diagnosis A, B, C, or D," he said. "You vaguely recall that there could also be E or F, but you'd have to look up the specifics."

The emphasis on methodology rather than memorization is where medical training is heading. "We're actively trying to determine the base level of knowledge a physician absolutely requires to do the job, especially in an emergency when you simply don't have time to look things up," said Schwartz. "Figuring this out is one of the primary challenges of modern medical education."

But if the jury is still out on precisely what a doctor needs to memorize, the proper habits of mind are clear in the iAge—or any age. "One of our central tasks as teachers is to instill in students the value of looking things up and, of course, teaching them where to obtain the highest and most reputable quality information out there. This is where medical research librarians are worth their weight in gold," said Fortin. "You have to be confident in what you know, as well as confident that you can find out what you don't know or can't quite remember. But above all else, you can't forget that the patient—not the iPhone, tablet, or any other iTool—is your focus. These devices are just another way to make sure that you have things right."

— Bruce Fellman

NLSHOP ILLUSTRATION

Our memories, our stories

The things we remember become tales with morals and meanings.

By Jenny Blair Sophie Casson Illustrations

As chief resident on the arduous Osler service at Johns Hopkins in the 1960s,

Thomas P. Duffy, M.D., was asked to verify the suicide of a young nursing student.

Alone, he entered her room and found the student upright in bed, dressed in lace, stained with vomit, dead from an overdose of sedatives. A supervisor soon joined him and asked Duffy to fill out death forms and search the room for anything embarrassing. He found a risqué snapshot of a happy young man wearing only combat boots.

Minutes later, Duffy hurried to grand rounds. Determined to maintain equanimity, he chose not to discuss or even think further about the young woman's death or his role in sanitizing it.

Years later, as a professor of medicine at Yale, Duffy sat down to write an article for the journal *The Pharos* about his Hopkins years. As he thought back, the memory of this incident returned full force. For the first time, he mentally revisited the young woman's deathbed, and he included her story in the article. His failure to acknowledge the young woman's death had been callous, he wrote, while his need to put it out of his mind illustrated a system that was unaware of the emotional disruption that encounters with tragedy could trigger in young doctors. The program's pyramid system winnowed half of each residency class annually while demanding what Duffy wrote was an "almost superhuman effort" and a "conspiracy of silence" about traumatic experiences. For the house staff, he wrote, this training amounted to "self-torture."

Duffy believes it is important to share such experiences. "If one does not address moments like that, at some point in the future one pays the toll," he said. "It comes back to haunt you."

Denial and machismo hardly make for healthy souls. Yet studies of interventions for post-traumatic stress disorder (PTSD) show that recounting a traumatic incident right away can sometimes mean worse stress symptoms later, too. Stories that bring healing and insight can take time to assemble from the raw material of the memory. Decades, even.

Narrative underlies most, if not all, of our attempts to make sense of the world. Yet the links between memory and stories are many and complex. Memory is less like a set of index cards and more like a set of systems that direct decisions, many unconscious, about how to reconstruct and interpret events in the past. From such decisions, stories arise. How these processes take place, how they heal or harm, how faithfully they affect reality, are by no means straightforward questions.

To create compelling stories aimed at other readers, fiction writers draw upon their own experiences. But too much reliance on memory can paradoxically weaken prose, according to novelist Bret Anthony Johnston, who urges his writing students to buck the advice "Write what you know." By all means, he writes in a 2011 essay for *The Atlantic*, set stories in a familiar setting and festoon them with details from memories. But then route the plot away from memory. Let characters do things you've never done. Fiction's narrative and emotional integrity can and should trump the literal truth of what happened.

"Stories aren't about actions. Stories are, unto themselves, actions," Johnston writes.

Medical professionals who want to write accounts of their patients are faced with a practical and ethical concern: how to conceal patients' identities and protect their privacy. Anna B. Reisman, M.D., associate professor of medicine and co-director of a writing workshop for residents, recommends that residents (and any health care professional writing about patients) either remove enough detail to hide patients' identities or ask their permission, which is also fraught with ethical issues. Ideally, one does both; another option is to go beyond simple de-identification. Write a story, she advised in *The Atlantic* in February, free from dependence on the facts of what happened. To Reisman, fictionalizing a medical history not only is the more clearly ethical option, but it can also yield truths independent of literal accuracy. "Sometimes, the truth can emerge more clearly—and more kindly—through the prism of fiction," she writes.

The mind seems to think so, too, as memory routinely obliges the present by rewriting the past. Eyewitness testimony is so malleable, its underlying memories so subject to suggestion and prone to distortion, that it can wrongly convict a defendant. The 1980s recovered-memory movement sent many innocents to prison after their accusers came to believe that they had been abused as children, often encouraged by well-meaning therapists to tell stories of rape or Satan worship. Researchers now understand that false memories can be implanted by storytelling.

Anna Reisman // Read more on page 44

"You read a great novel and you really empathize with the characters, you get into their heads, you see things from their perspective. What better training to be a good doctor than to be able to imagine what a patient is going through!"

In everyday life, too, simply recalling and retelling memories can alter them. The act of retrieving and reconsolidating a memory seems to render it susceptible to change, as if we could reread only while highlighting and crossing out. This effect is so strong that researchers are looking to tweak it for better PTSD treatments.

"In order to incorporate [memories] into the story, what was vague has to become concretized. So no question, we polish them," Duffy said. "[Knowing] how it all played out, now the memories are refracted through a different prism."

Stories can heal, a truth well-known to Annita P. Sawyer, Ph.D. '81, assistant clinical professor of psychiatry and a practicing psychotherapist. In 1960, as an adolescent traumatized by family abuse, Sawyer was misdiagnosed with schizophrenia, hospitalized, and subjected to shock treatments that erased much of her memory. She built a successful life, keeping the hospitalization a secret. But in 2001, she decided to read her own medical records from that long-ago time.

Disturbing memories rushed back, shaking her deeply. Clinical experience told her that she must have had PTSD back then, not schizophrenia. Compelled to rethink her own identity, she realized she had a story to tell.

During the decade that followed, as Sawyer read, remembered, and wrote, an ingrained feeling of disconnection from daily life gradually disappeared. So did her lifelong shyness. Her life story retold lost its frightening energy, and she felt whole. She published *Smoking Cigarettes, Eating Glass: A Psychologist's Memoir* last spring.

Whether in therapy or in memoir, Sawyer says, constructing a true story allows another person to hold your experience, helping transform "inchoate, churning" memories into something orderly and coherent. (Her patients' lives are so much like novels, she says, that she has no trouble remembering all the characters from their stories.)

Even if this story doesn't perfectly correspond to reality, even if it's filled with the kind of ugliness her book's title suggests, a story based on truth can restore a fragmented sense of self.

"People don't have to have prettiness," Sawyer said. "People don't need a story to be pretty; they need it to make sense." /***yale medicine***

Jenny Blair, M.D. '04, is a frequent contributor to Yale Medicine.

Can ginkgo tea preserve our memories?

Fish oil, ginkgo tea, dark chocolate, and periwinkle extract have all been touted as brain enhancers, along with countless infomercial pills. But do any of them preserve memory as we age? Says one Yale neurologist—well, forget about it.

"Dietary supplements have pretty much failed," says Jaime Grutzendler, M.D., associate professor of neurology and neurobiology and director of the Center for Experimental Neuroimaging. "Vitamin B12, vitamin E, vitamin C—all the studies that have been done so far have not shown any long-term benefits."

For Grutzendler, Alzheimer disease and other brain conditions are the ultimate challenge. His lab studies different pathologies in the brain using real-time cellular imaging; like early astronomers gathering information by watching the night sky, he enters research with no agenda. He just wants to find out how things work. "We don't have a preconceived notion of what the system should do or how it should deteriorate," he says. With these methods, Grutzendler's work has shed light on theories about how we fall into cognitive decline.

The causes of cognitive decline are nearly as varied as the supplements sold to prevent it. In his office, where Pollock-like images of fluorescent brain cells decorate the walls, Grutzendler points to a series of images on his computer screen. They depict structures in the brain associated with dementia, primarily the plaques famously found in Alzheimer patients and the lesser-known but no less common neurofibrillary tangles. These tangles are built-up proteins inside neurons, as opposed to plaques, which form outside the cells and can cover large portions of the brain. They both interfere with cellular signaling.

Aging itself is associated with plaques and tangles, which lead to some degree of cognitive slowing and potential memory loss. But they don't always appear in the same places or at the same times. "Aging is complicated," says Grutzendler. "Aging is not one disease. It's the disease of almost everything, like an old car—basically, everything starts to fall apart in some way." Neurologists look at different types of damage in the brain that may lead to the same symptoms, just as a dead battery or a faulty ignition switch both mean a car won't start.

So, are all humans doomed to some form of cognitive decline if we live long enough? Grutzendler speculates yes—but not all hope is lost. Supplements haven't worked conclusively in preventing or slowing dementia, but vascular health—making sure your circulatory system gets blood to body parts that need it—is important at any stage of life. And factors affecting vascular health aren't so difficult to pin down.

Uncontrolled diabetes, obesity, hypertension, and smoking are all associated with damage to small blood vessels in the brain. When these vessels are affected, less blood makes it to the neurons, weakening their connections. Scientists haven't yet demonstrated a bulletproof connection to cognitive decline, but Grutzendler concludes that these are serious risk factors.

Sleep is another factor believed to affect cognitive health, though those links have not been fully demonstrated. The best science, however, still tells us that sleep, exercise, good nutrition, and control of such risk factors as smoking and high blood pressure are some of the keys to a healthy lifestyle—and a healthy brain.

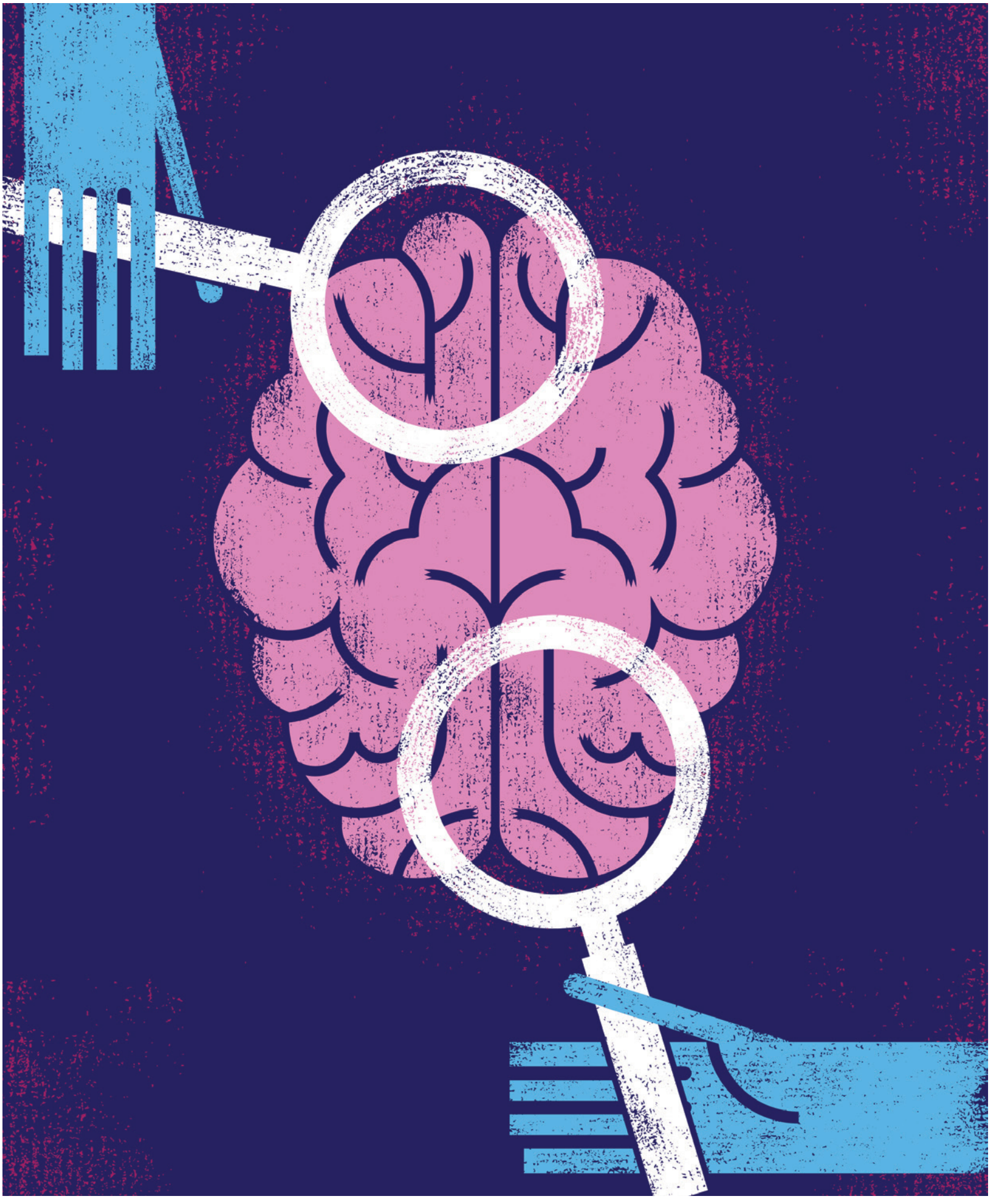
—Karen Zusi

NLSHOP ILLUSTRATION

The first things to go

Misplaced keys and forgotten appointments are among the episodic memories that are lost to Alzheimer disease. Yale clinicians and scientists are looking for new ways to predict the disease and find a cure.

By Ashley P. Taylor Matthew Daley Illustrations



It was at his maternal grandparents' 50th wedding anniversary

that Chris H. van Dyck, M.D., first noticed something different about his grandfather. The retired Presbyterian minister, then 83, was at the head of the table making a speech to old friends. "He looked like Granddad there, doing his thing. And he was reasonably coherent," van Dyck, then about 20 years old, recalls. Until he'd finished the speech. "I went over to him and said, 'Hello, Granddad,' and he looked at me and said, 'Who are you?' "

That was the summer of 1975, and van Dyck's grandfather was in the beginning stages of Alzheimer disease, an illness that would later claim both of his maternal grandparents, and which van Dyck, a geriatric psychiatrist, would study as the director of Yale's Alzheimer's Disease Research Unit.

Alzheimer disease is characterized by a gradual loss of what, arguably, makes people who they are: their memories. It starts with innocent forgetfulness. "Usually the first thing to go is episodic memory," says Arash Salardini, M.D., co-director of Yale's Memory Disorders Clinic, referring to memories with specific contexts in space and time. "Based on that, you can see what sort of memories usually go first. People misplace things. They forget appointments." People first lose the ability to form new memories, while long-term memories—the sort van Dyck's grandfather was probably recounting at the anniversary—are more resilient. As the disease progresses, people start to lose executive functions: the ability to make and carry out plans. They lose interest in hobbies; they can no longer use the phone, drive a car, or balance a checkbook. Eventually, they can no longer attend to their own basic needs and become dependent on others. In the United States, Alzheimer disease ranks high on the list of diseases people most fear.

After van Dyck's grandfather became ill, van Dyck says, his mother bought her parents a house near her home in northern Vermont so that she could take care of them. As the grandfather's dementia progressed, van Dyck's mother ended up hiring nearly 24-hour live-in care. Almost immediately after his grandfather died, van Dyck says, his grandmother began to show signs of memory loss, too; she died of Alzheimer disease a few years later. Then his mother's second husband, van Dyck's stepfather, got the disease, and his mother cared for him until his death. "She was immersed in Alzheimer disease," van Dyck says. His mother, now 89, shows no signs of dementia.

Though he believes his choice to focus on Alzheimer disease was in part intellectual, van Dyck feels that his family history also nudged him in that direction. "Seeing my mother do heroic work caring for these people was impressive, and showed what that was like for families and the need for treatments."

A DISEASE THAT DEFIES DIAGNOSIS

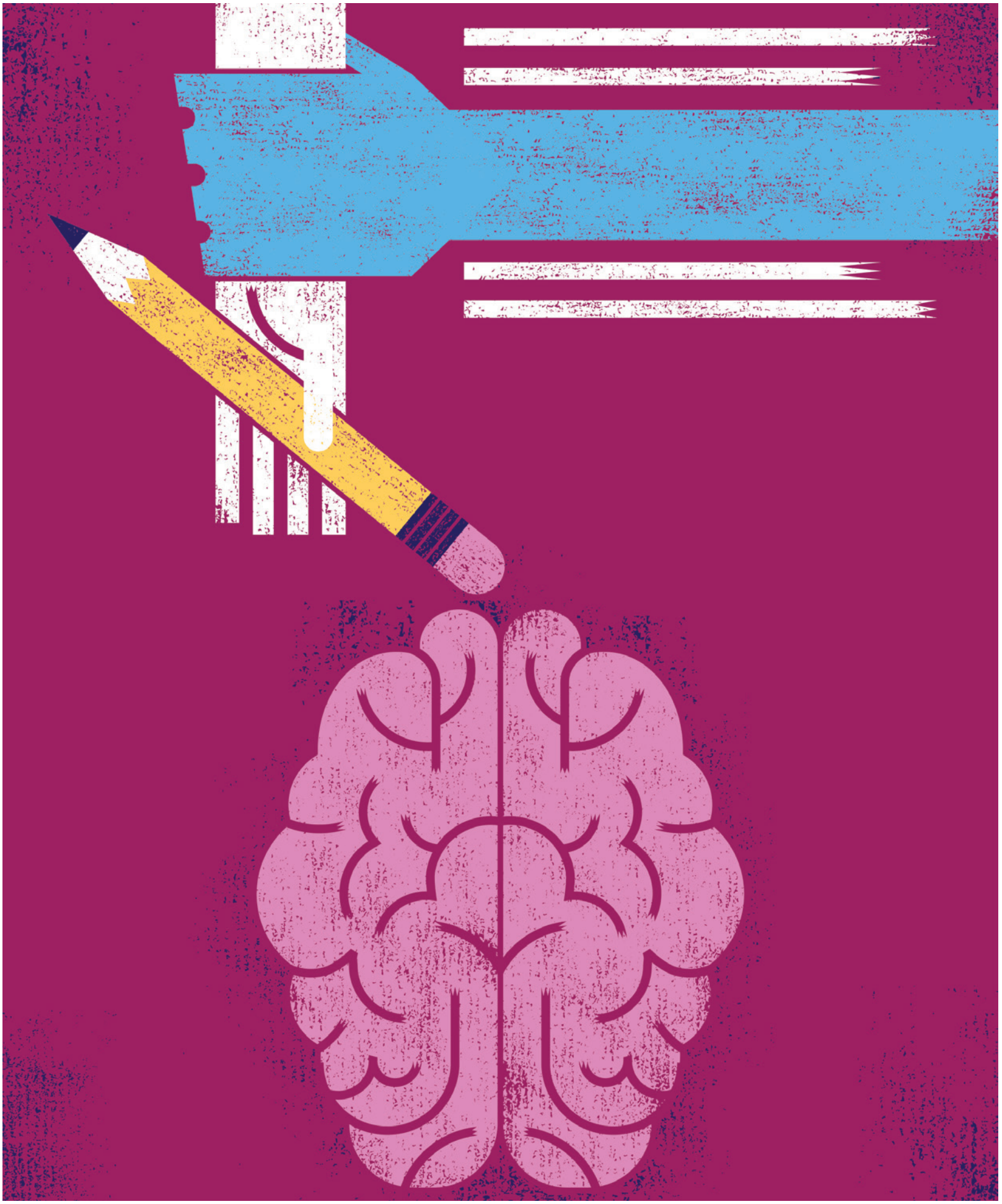
In the past, Alzheimer disease could be definitively diagnosed only upon autopsy. Doctors observed two kinds of brain pathologies: large plaques of a protein called beta amyloid crowding the spaces outside neurons, and inside them, what are called neurofibrillary tangles of another protein, tau. An accurate clinical diagnosis relied on the results of memory and neurological tests and ruling out other potential causes of dementia.

Van Dyck began utilizing neuroimaging to study the aging brain. He and Yale colleagues (including Richard E. Carson, Ph.D., director of the Yale PET Center) were among the first to adapt Single-Photon Emission Computed Tomography (SPECT) and positron emission tomography (PET) to visualize molecules in the brain. In conjunction with the Alzheimer's Disease Neuroimaging Initiative (ADNI) of the National Institutes of Health, van Dyck and the Alzheimer's Disease Research Unit have helped to evaluate PET imaging methods to visualize pathological changes in the brain linked to Alzheimer disease.

In the past 10 years, the ADNI consortium, along with other research teams, has demonstrated that PET imaging could be used to visualize beta amyloid in the brains of patients with Alzheimer disease and that markers of beta amyloid could even be seen in people at high risk for the disease before the onset of symptoms. Based on this work, amyloid PET scans are now approved for use in the diagnosis of Alzheimer disease.

For Salardini, PET scanning is an important diagnostic tool, particularly when trying to distinguish Alzheimer disease from other types of dementia. These brain scans have also brought new understanding of the disease itself. Alzheimer disease's hallmark amyloid plaques, researchers have found, accumulate decades before symptoms arise. Using PET scans, doctors are getting better at diagnosing Alzheimer disease and at determining who is at risk for developing it, paving the way toward early interventions.

"You don't want to treat the disease once the manifestations occur and you already have memory loss," says David Hafler, M.D., M.Sc., chair of neurology and neurologist-in-chief at Yale-New Haven Hospital. Instead, you want to use multiple tests to determine who's at risk and "get patients on treatment before they



develop the disease. That's my vision for what we want to do at Yale."

The glitch, however, is that there is no treatment for Alzheimer disease. Yale researchers are trying to change that. One clinical trial is testing a drug that interferes with a chain of molecular events—triggered by beta amyloid—that causes the brain's neuronal connections to break down. Another is testing whether keeping beta amyloid from building up could prevent Alzheimer disease.

HALLMARKS OF ALZHEIMER DISEASE

On a molecular level, Alzheimer disease is characterized by the build-up of beta amyloid. Although neuroscientists still aren't sure what it does, the beta amyloid peptide is part of the healthy brain, where it "gets made and rapidly cleared," explains Stephen M. Strittmatter, M.D., Ph.D., Vincent Coates Professor of Neurology, professor of neurobiology, and director of the Yale Memory Disorders Clinic. In patients with Alzheimer disease, however, beta amyloid takes abnormal forms. Fibers clump together outside neurons to form the disease's iconic plaques. But it's a third type of beta amyloid, in which several copies of the protein come together to form what are called oligomers, that researchers suspect is a culprit in Alzheimer disease. Unlike plaques, which are stuck in place, the oligomers can float around in the brain, interacting with—and possibly destroying—neurons.

According to research from the Strittmatter lab, these beta amyloid oligomers damage synapses—the connections between neurons—creating gaps in the brain's communication system. Beta amyloid doesn't damage neurons directly—it starts a domino chain of molecular events that shrivels synapses. In mice with Alzheimer disease-like symptoms, the Strittmatter lab found that using a drug to block one of the proteins in this chain, called Fyn kinase, halted the damage and allowed both synapses and memory to bounce back. To see whether these results carry over to humans, van Dyck is testing the drug (saracatinib) in a nationwide clinical trial for people with mild symptoms.

Another clinical trial is testing whether an antibody that binds to beta amyloid and removes it from the body could prevent Alzheimer disease from developing in the first place. When tested on Alzheimer disease

SIDEBAR PHOTO, HAROLD SHAPIRO

Yale designated research center by NIH

In a vote of confidence, the federal government has designated Yale as an Alzheimer's Disease Research Center (ADRC)—the medical school will receive funding from the National Institutes of Health to compile and analyze data on Alzheimer disease patients. The designation comes with a five-year grant of more than $1.5 million per year that will support many facets of Alzheimer disease research, including basic research, collection of clinical data, community outreach, and education. The Alzheimer's Disease Research Unit, the Yale Memory Disorders Clinic, and the Dorothy Adler Geriatric Assessment Center already provide excellent care to Alzheimer disease patients. The grant will allow these groups to synthesize their information and resources, thereby fostering greater knowledge and advancing potential treatments, says Stephen M. Strittmatter, M.D., Ph.D. (in photo, at left), the Vincent Coates Professor of Neurology, professor of neurobiology, and director of the Yale Memory Disorders Clinic, and principal investigator of the ADRC grant from the NIH. He and Chris van Dyck, M.D. (in photo, at right), director of the Alzheimer's Disease Research Unit, co-direct the Yale ADRC; Arash Salardini, M.D. (in photo, center), co-director of the Memory Disorders Clinic, is its assistant clinical director. "The ADRC is composed primarily of people at Yale who were previously carrying out separate tasks. Through the new center they now work as a team in the sense of meeting together, sharing ideas and reagents, and coordinating studies across the translational research scale," Strittmatter says.

As the search for a treatment continues, the number of Alzheimer disease cases—an estimated 5.3 million Americans in 2015, according to the Alzheimer's Association—continues to grow as the population ages.

Arash Salardini //

> "Almost everybody who has amyloid deposition beyond a certain amount will get Alzheimer disease, and almost nobody without amyloid deposition has Alzheimer disease."

patients, the overall finding was that the antibody (solanezumab) did not work. In a subset of patients with mild dementia, however, the drug slowed disease progression by about a third, van Dyck says.

This finding prompted researchers to ask, as van Dyck puts it, "What if you go milder than mild, all the way to preclinical, presymptomatic? Maybe it's a question of intervening before too much brain damage is done." The study is testing that hypothesis in patients 65 or older who are cognitively normal but who have abnormally high levels of beta amyloid, as measured by PET scans. In the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Study, which is still enrolling participants, half the patients receive monthly intravenous infusions of the drug and half receive a placebo. The study is "blind"—neither researchers nor participants know who receives the drug. At the end of the three-year study, a second PET scan for beta amyloid will show whether the drug prevented the protein from accumulating, and "unblinding" the results will reveal whether the treatment prevented memory loss.

Whether or not removing beta amyloid from the brain proves effective in preventing Alzheimer disease, it is emerging as a key predictor of risk for the disease and crucially, one that shows up long in advance of disease symptoms. "Almost everybody who has amyloid deposition beyond a certain amount will get Alzheimer disease, and almost nobody without amyloid deposition has Alzheimer disease," says Salardini, adding that such a build-up can begin 20 years before symptoms emerge. One day, van Dyck predicts, screening for Alzheimer disease using amyloid PET scans may be as routine as getting a colonoscopy. "That is the kind of paradigm we're talking about," he says. "We don't even want to wait until people have lost a bunch of gray matter; we'd like to be able to intervene at an earlier stage." But an earlier, more accurate diagnosis will be most valuable only when there's a treatment. Without a treatment, there's no way to act on an earlier diagnosis.

"If we had an intervention that could save people, [PET scanning] would just so obviously pay for itself," van Dyck says, noting that insurance doesn't usually cover the scans. "The cost of a PET scan would be trivial when you compare it to, besides the individual costs, just the sheer economic costs to society."

Strittmatter is optimistic that research will lead to possible treatments, and he believes that the partnership between the new Alzheimer's Disease Research Unit and the NIH will advance that research.

"I think that research that is going on is opening new doors. We have to find out which one will make a difference for people." /*yale medicine*

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

Stem cells also remember

The New England Patriots would never call a timeout mid-game to proclaim their status as the weaker team. Animal stem cells, however, confess their lesser rank to others all the time. In a display of altruism, they send signals to neighboring cells about their levels of stress, oxygen, or nutrition. Whatever their status, they serve a common goal—the fitter the cell, the more competitive it is in the race to produce healthy progeny.

Ruslan M. Medzhitov, Ph.D., the David W. Wallace Professor of Immunobiology, and his lab members are studying how stem cells become winners or losers in this game of reproduction. Stem cells, they have found, appear keen to communicate a very technical aspect of their performance: their past. A stem cell's DNA bunched inside chromosomes may look as good as new, but this doesn't stop the cell from remembering and divulging its history. If surrounded by healthy cells, the cell with a previously repaired genome will graciously back out of the race.

When Medzhitov injected mice with stem cells that had been exposed to low-level radiation, histone proteins rushed in to "bookmark" damaged regions of DNA. DNA repair genes mended the broken letters and several days later turned themselves off. The histone proteins disappeared and the stem cell's genome appeared perfectly normal. But a patch job is just that—a patch job. It doesn't guarantee against errors that might occur during the repair. This is why previously damaged stem cells declare themselves in the first place: they want to pass on only healthy cells to their offspring. (Cancer cells, which don't play fair, never blow their cover by disclosing past damage.)

Medzhitov and his team believe that these memories of damage and repair are stored in the form of slight mutations in the telomeres, regions of repetitive DNA at the ends of chromosomes. "It's important to understand the selection processes that go on in stem cells," Medzhitov said. A better understanding of how everything works could affect bone marrow transplant patients, he said. This fragile patient population needs lots of healthy stem cells so that their blood-making, or hematopoietic, system has a long life and is not rife with mutations that could later lead to such health problems as cancer.

—Kathleen Raven

NLSHOP ILLUSTRATION

The history of human monstrosity

An exhibit at the Harvey Cushing/John Hay Whitney Medical Library explores the "marvel and wonder" of human abnormalities.

By Karen Zusi

In 1834, a Mexican woman named Julia Pastrana was born with protruding lips and thick black hair covering her face. Her appearance was caused by two rare conditions: hypertrichosis, a genetic mutation causing her hair growth; and gingival hyperplasia, an abnormal thickening of her gums. Both went undiagnosed in her time.

Lacking a medical explanation, Pastrana became a sideshow oddity, billed as the "missing link" between humans and apes. She married one of her managers and had a child with him in 1860, but the baby was stillborn and Pastrana died shortly thereafter. Her story doesn't end there—her husband had the two bodies stuffed, and they remained on display for over a century. In 1976 they were stored in Norway, and in 2013 they were finally repatriated for burial in Mexico. "She's a particularly sad case," said Courtney Thompson, M.A. '12, M.Phil. '13, Ph.D. '15. "There's supposed to be a level of historical distance, but it's hard not to respond to her on an emotional level."

Two handbills of Pastrana's show appeared this year in the Cushing/Whitney Medical Library's "Teratology: The Science and History of Human Monstrosity" exhibit, curated by Thompson, a historian of science and medicine; and Melissa Grafe, Ph.D., the John R. Bumstead Librarian for Medical History.

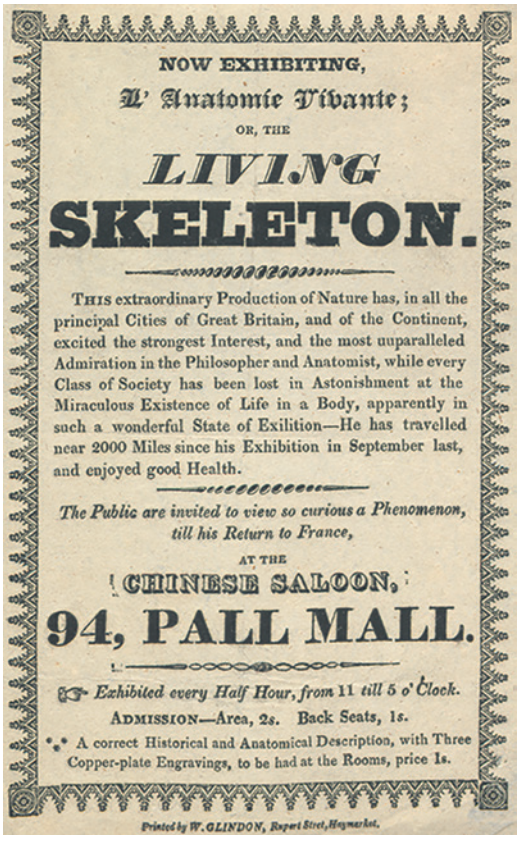
Teratology, from the Greek *teras* meaning "monster" or "marvel," is the study of human abnormalities. The exhibit focused on the changing medical understanding of these differences through history. "People think of freak shows when they think about extreme bodily abnormalities," said Thompson, "but what I wanted to show is that there is a scientific way of looking at these bodies that often undergirds the popular culture."

Thompson and Grafe began the exhibit with a pamphlet from 1495 about a pair of conjoined twins. With the invention of the printing press in the mid-1400s, collectors and early scientists began publishing catalogues of the natural world, including unusual humans. "Some of these were monsters, people with hairy faces or scaly skin, giants, dwarfs, or conjoined twins," Thompson said.

Starting in the 18th century, the scientific focus shifted toward explaining and classifying these physical differences. "The marvel and wonder became stripped from the scientific enterprise," said Thompson. "They were emotions associated with the vulgar masses." Included in the exhibit was an 1891 medical text, *Human Monstrosities*. Part of a four-volume set with a classification scheme for various human deformities, it included a large number of stillborn fetuses that were either photographed as skeletons or dissected specimens.

In the 19th century, the "freak show" also appeared. The exhibit included sideshow broadside posters for Pastrana, the "Irish Giant," the "Living Skeleton," and a pair of tickets to such sideshows. The autopsy report for Chang and Eng Bunker, the original "Siamese twins," was also on display.

The exhibit concluded in the 20th century, as the medical focus turned from morphological classification to the underlying causes of abnormalities, both genetic and environmental. A photograph of a young German girl without arms accompanied a *LIFE* magazine photograph of Frances O. Kelsey, M.D., Ph.D., the Food and Drug Administration scientist who led efforts to ban thalidomide, a drug taken for morning sickness that caused birth defects. Also displayed was a scientific journal titled *Teratology*. The cover depicted a pregnant woman with a red cross over her stomach and the words "Don't Get Pregnant," implying that environmental factors cause too many complications during fetal development—at least in the authors' minds. The "Teratology" exhibit highlighted medicine's ever-narrower lens, zooming in from the outward perception of "monsters" to the microscopic causes of their differences.



TOP LEFT An anonymous British printmaker of the 19th century made this lithograph of two conjoined twins, Chang and Eng Bunker, who lived from 1811 to 1874 and were known as "The Siamese Twins." At the time the lithograph was produced, they were 18.

TOP RIGHT A 19th-century poster touted both the "curious history" of both Julia Pastrana, who suffered from two undiagnosed conditions that gave her extreme hair growth and thick gums, and the "double-bodied boy," a boy with a parasitic twin, a rare type of conjoined twin.

BOTTOM LEFT A London handbill from 1825 advertised a showing of Claude Ambroise Seurat, "The Living Skeleton." Seurat was born in Champagne, France, and as he grew, his soft tissue, including flesh, turned to bone.

IMAGES COURTESY OF CUSHING/WHITNEY MEDICAL LIBRARY

Tinker, sailor, Golgi, sly

JAMES D. JAMIESON, M.D., PH.D., has spent a career dividing his time among so many responsibilities—running a lab, directing a program, mentoring students, among others—that it's difficult to know how he found time for lunches with students in Marigolds or harbor tours on his sailboat. But Jamieson was always available to students in Yale's M.D./Ph.D. program, which he directed for 32 years. "The thing I learned from Jim was the care and concern and gentleness with which he treated students," said Michael Caplan, Ph.D. '87, M.D. '87, chair and the C. N. H. Long Professor of Cellular and Molecular Physiology, and professor of cell biology. Being a mentor, Caplan learned from Jamieson, is a large part of being a scientist.

When Jamieson, professor of cell biology, arrived at Yale in 1973, his task was to launch a cell biology department. (He would later spend eight years as its chair.) The following year he became director of Yale's Medical Scientist Training Program, funded by a grant from the National Institutes of Health and known as the M.D./Ph.D. program. The physician-turned-cell-biologist continued research he'd begun at The Rockefeller University under the guidance of Nobel laureate George Palade, M.D. He studied the mechanisms of secretion of proteins by the pancreatic acinar cell and other cell types. He closed his lab in 2001 to devote his attention to the M.D./Ph.D. program, known more colloquially as "mud/fud."

During his tenure some 300 students graduated from the program; and with the recent expansion of the program from 12 to 20 students per year, M.D./Ph.D. students make up 20 percent of each medical school class. "This makes Yale's program one of the largest nationally, reflecting Yale's preeminence in the basic and clinical sciences," Jamieson said. In addition, he said, electives that he started, such as one in translational medicine in pediatrics, "energize and feed positively into the med school curriculum."

Susan J. Baserga, M.D. '88, Ph.D. '88, noted that Jamieson can think critically about research design with the same ease with which he runs admission committee meetings. Sam B. Sondalle, a fourth-year M.D./Ph.D. student in her lab, came to Yale in part because of Jamieson, said Baserga, professor of molecular biophysics and biochemistry, of genetics, and of therapeutic radiology. When he met Jamieson in December 2010, Sondalle said he was struck by Jamieson's friendliness and his generosity in offering advice. When Jamieson learned about Sondalle's interest in a rare genetic disease, he introduced him to Baserga as a potential research advisor. Given Baserga's extensive experience in

After more than 30 years, James Jamieson has retired as director of the M.D./Ph.D. program. Students and mentees remember his friendliness and generosity.

TERRY DAGRADI PHOTO

ONLINE EXCLUSIVES

Global warming affects New Haven's poor and elderly.

A medical school curriculum should integrate science and care, allow for individual exploration, and develop lifelong learners, said a speaker at Medical Education 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.

genetics, the match was a perfect fit, Sondalle said.

Caplan described Jamieson as down-to-earth and outgoing. "He had an extremely paternal—in the best sense of the word—connection to the program and students," Caplan said, adding that Jamieson had a "nitty-gritty, nuts-and-bolts understanding of how to do experiments." Jamieson's lasting imprint on the program, Caplan said, is his devotion to students.

Barbara Kazmierczak, M.D., Ph.D., associate professor of medicine, infectious diseases, and microbial pathogenesis, who became the program's director last year, said she witnessed that devotion at a Christmas party at Jamieson's house. Jamieson and his wife, Cynthia, stayed up late trading movie recommendations with a handful of students. "It was one of the moments when I realized they were embedded in the Yale community and really loved New Haven, and thought of students as family," she said. "He has the curiosity that the best scientists have. And it extends to curiosity about people, motivations, and relationships." Regarding his accomplishments, Kazmierczak highlighted a crucial decision that Jamieson made. Rather than wait until after they finish their Ph.D. training to begin the required 12 months of clinical clerkships, Jamieson decreed that M.D./Ph.D. students complete half their clerkships before beginning their graduate study. "With very few exceptions, students value this protected period of time when they see how the book learning translates into taking care of patients," Kazmierczak said. "For some of them, the clerkship period informs the thesis they will do."

Jamieson said he enjoys helping the M.D./Ph.D. students blow off steam by offering rides in his sailboat or helping out with student video parodies for the annual Second-Year Show—for example a spoof on the Disney movie *Frozen*—produced by the Class of 2017. Jamieson makes a sly cameo appearance in the show. Framed on the wall in his office is a photo of Jamieson with another class of students from earlier days. "For our fearless leader," reads a sign next to the photo.

—*Kathleen Raven*

A doctor's love affair with medicine and literature

For Anna Reisman, M.D., it was a summer novel that pointed her to a career in medicine.

As a rising Yale senior and English major with no thought of becoming a doctor, she read Thomas Mann's classic 1924 novel *The Magic Mountain*, a tale of tuberculosis patients at a Swiss sanatorium. Surprised by her own fascination with the disease, she went on to read physician-writers Oliver Sacks, M.D., Richard Selzer, M.D., HS '61, and Lewis Thomas, M.D. Soon she was a medical student at New York University.

Now an associate professor of internal medicine, Reisman (pronounced "Reeseman") has maintained a connection to literature that affects how she teaches and practices medicine. In essays for such publications as *The Atlantic*, *Slate*, and *The New York Times*, she has pointed out the problem with overly dapper doctors, defended nurse practitioners who want to practice primary care without physician oversight, and described her own reluctance to set foot in a hospice for the first time. (Its homey coziness surprised her.) She has even explored the troubling ethics of writing about patients.

With Lisa Sanders, M.D. '97, HS '00, associate professor of medicine and author of the Diagnosis column in *The New York Times Magazine*, she co-directs the Yale Internal Medicine Residency Writers' Workshop. The workshop guides residents as they turn patient care experiences into thoughtful narratives. Reisman also directs the standardized patient program through the Teaching and Learning Center and plays flute with a klezmer group, the Nu Haven Kapelye, and the Yale Medical Symphony Orchestra.

In March, Reisman became the new director of the Yale Program for Humanities in Medicine, inheriting the post from Thomas P. Duffy, M.D. Duffy had led the program since 1999 upon the retirement of founding director Howard Spiro,

M.D., an English major, published writer, and tireless advocate for intertwining the humanities and medicine. What began as a lecture series has under Duffy's tenure added a Yale Medical Symphony Orchestra and figure drawing classes at the School of Art. The idea is to provide what Duffy calls "an opportunity to frolic in all of those realms, to keep alive that spirit" of passion for the humanities during medical training. Reisman intends to weave humanities right into the medical curriculum, exposing students to film, literature, and visual arts that give the science a human context. She also plans to create a social media presence for the 32-year-old program.

Lectures, poetry readings, dancing, drawing, creative writing, open mics—all pleasant, perhaps. But does reading a work of literature (or pondering a painting) really make students better doctors?

"Of course it does!" Reisman said. "You read a great novel and you really empathize with the characters, you get into their heads, you see things from their perspective. What better training to be a good doctor than to be able to imagine what a patient is going through!"

On the lookout for lecturers and collaborators across the university, Reisman is combing places like the School of Drama, the Whitney Humanities Center, and the Yale Center for British Art. "There's so much stuff going on!" she said.

A novel about tuberculosis patients sparked Anna Reisman's interest in medicine. She now leads the Yale Program for the Humanities in Medicine.

Reisman has the right disposition for her work, said Geoffrey Liu, M.D. '15, who developed a reflective writing workshop for third-year medical students and worked with Reisman to train students to succeed him. Reisman, he said, combines an easygoing manner with "bluntness and a kind of candor that I've really come to appreciate."

Born at Yale-New Haven Hospital and raised in Hamden, Reisman earned her English degree at Yale. She graduated from medical school in 1993, then did her residency in primary care internal medicine at NYU Medical Center/Bellevue Hospital, staying an extra year as chief resident. Then, she and medical school classmate Cary Gross, M.D., professor of medicine, moved to Baltimore; they married in 1998 and returned to Connecticut a year later.

Since then, Reisman has worked in primary care for the VA Connecticut Healthcare System in West Haven (including a four-year interlude of house calls). The move brought them closer to Reisman's sister Lisa, who had just been diagnosed with a glioblastoma. (Lisa Reisman's memoir of surviving that tumor, *5 Months 10 Years 2 Hours*, was published this spring; she recently delivered a lecture as part of the humanities program.)

People sometimes profess surprise when an English major chooses a career in medicine. But to Reisman, the connection between the two fields is obvious. "More than anything else, medicine is about the human condition—people, their lives and experiences," she said, "and that's what the humanities are about."

—Jenny Blair

TERRY DAGRADI PHOTO

How Roy Herbst became a media go-to guy on immunotherapy

watch a short film about Roy Herbst at youtube.com/YaleMedicine

WHEN THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY met in Chicago this spring, one of the hottest topics was the promise of immunotherapy against cancer. And one of the point men for the media was Roy S. Herbst, M.S. '84, Ph.D., M.D., chief of medical oncology at Smilow Cancer Hospital, associate director for translational research, and Ensign Professor of Medicine, who appeared on CNN, Fox News, and in newspapers from as far away as South Africa and the United Kingdom. He has spent more than 20 years both in the lab, studying the underlying science of cancer, and in the clinic, bringing novel treatments to patients. He shares his colleagues' excitement about immunotherapy, which harnesses the body's immune system to fight tumors.

Even as a student at New Rochelle High School in New York, Herbst was interested in science. "I knew that I wanted to help people, and I always thought of medicine as a career."

He came to Yale as an undergraduate, leaving in 1984 with both bachelor's and master's degrees *summa cum laude*. He earned a Ph.D. from The Rockefeller University in 1990 and an M.D. from Cornell in 1991. He completed his residency at Brigham and Women's Hospital (BWH) in Boston and fellowships in oncology and hematology at Dana-Farber Cancer Hospital and BWH, and he received a master's degree in clinical investigation from the Harvard-MIT clinical investigator training program. He then went on to the M.D. Anderson Cancer Center, where he led the lung cancer section for almost 10 years.

Five years ago he returned to the School of Medicine, where he had come as a Yale freshman to study biophysics and biochemistry. "I studied molecular biology and gave my master's thesis defense in the conference room where we now have our developmental therapeutics seminar once a month," he said. "The blackboard looks exactly the same."

Why did you choose to devote your career to oncology?

At Cornell and Rockefeller, I was interested in science and medicine, and cancer seemed like an area where you could bring science to bear on difficult problems. In my second year of med school, my mother developed breast cancer. I remember taking her slides to the pathology group to confirm her diagnosis and exploring treatment options with my professors and mentor. This seemed like a natural area for me because of the pathology, the science, and the new therapies that were evolving. You could bring together the science and the caring for people all in one career.

Do you see yourself as a clinician or a scientist?

I see myself as someone who is looking to the lab for new ideas and new drugs, while serving on the front line of the clinical translation. I want to develop drugs that are safer and more effective for cancer patients by understanding why they work or why they don't work. Every Tuesday I see patients at the Smilow hospital in the lung clinic, which I lead, and seek to implement the most novel protocol-driven care. I also maintain a small lab where we're doing some basic translational studies, but we mostly collaborate with some of the top labs at Yale and elsewhere.

What is your role at Yale?

My primary goal is to make sure that medical oncology offers state-of-the-art care while building a grant-funded research program. As the chief of medical oncology I lead an ever-expanding group of medical oncologists with a robust clinical service. As the associate cancer center director for translational research, my team and I are working to enhance and build a grants infrastructure to do more to bring scientists into the study of cancer. We want to get more people working together on the common problem of how to better treat someone with an incurable cancer. There is so much expertise at Yale in basic science and clinical care, but the real trick is to get everyone working together to combat human disease. My real goal is not just the lung program. I need to see every program in the cancer center succeed in the same way.

Why has immunotherapy emerged as such a breakthrough? What better than the specificity, memory, and adaptability of one's own immune system to attack a cancer? It really is the identification of the immune checkpoint PDL1 and the establishment of PD1/PDL1 inhibitors that have changed the field. You have these tumors, and you would hope that the immune system's T cells would recognize the tumor as foreign. But the tumor makes a protein, PDL1, which camouflages the tumor, making it invisible. The new therapies are trying to knock down that PDL1. A lot of this work, by the way, comes from the studies of Lieping Chen here at Yale. Patients with lung cancer who previously would succumb to their disease within a year are now alive at two, three years or more. We are seeing tumors shrink more than 20 percent of the time in lung cancer, 25 percent of the time in melanoma, and 15 percent of the time in renal cancer. These agents are benefiting people, but it's not a home run. Only 20 to 25 percent of patients benefit. We clearly have to do better, and current work is aimed at identifying biomarkers of response and resistance so we can develop even more effective combinations.

What are the next steps?

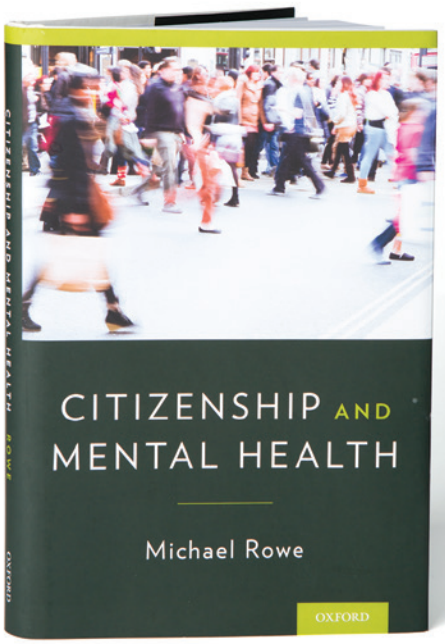
One of our big initiatives at Yale is to collect tumor samples from patients who have responded to immunotherapy and from those who have not. We are performing immunopathology, sequencing tumors to understand what it is about those that respond versus those that don't respond. The tumor can, unfortunately, learn how to become resistant. The immune system has memory; and hopefully, as the tumor adapts, the immune system also adapts. In some cases this does not occur and hence we are developing even more new combinations among targeted therapies, vaccines, and other immunotherapies.

How did you become one of the public faces of ASCO?

Our medical oncology section, led by Mario Sznol, Harriet Kluger, and Scott Gettinger, did some of the earliest immunotherapy studies for cancer. I led one of the earliest Phase 1 trials in immunotherapy, which was published in *Nature* last year. Since my work has been focusing on both the clinic and the science. I'm able to talk not just about the clinical results, but also about the science behind the results. And what good is your work if you can't make people realize what you're doing to help patients, to obtain grants, to encourage philanthropy and encourage other researchers to work with you?

To nominate a subject for Q&A, contact
Yale Medicine, 1 Church Street, Suite 300, New Haven, CT 06510 or email ymm@yale.edu

TERRY DAGRADI PHOTO



A sense of community for people with mental illnesses

By Cathy Shufro

Citizenship and Mental Health began when a man who'd once been homeless said that he wanted to give up his apartment and return to the streets of New Haven.

Jim, said sociologist Michael Rowe, Ph.D. '96, was a veteran who heard voices. He had initially resisted the overtures of a peer outreach worker who gradually won his trust, convinced him to get treatment for his illness, and helped him find an apartment. "Jim was the quintessential success story of outreach," said Rowe, an associate professor of psychiatry and co-director of the Yale Program for Recovery and Community Health.

And then, one day, "his outreach worker came into our team meeting and said 'Jim wants to live out on the street again,' " said Rowe. Team members were incredulous: why would Jim want to return to the pavement under the Water Street overpass? The outreach worker explained, "Because there he knew people. He felt that he belonged." Rowe recalled: "That was a heartbreaking moment that revealed to me the limitations of what we were doing."

That day in the mid-1990s led Rowe to launch what would become the Citizens Collaborative. Its aim was to integrate people with mental illness into communities beyond those created by the mental health system. "Even the most innovative mental health programs, in which work was more than work, went beyond the clock, and even smashed the damned clock, could not make people neighbors, community members, and citizens," Rowe wrote. He envisioned people with mental illness walking down streets to greetings from neighbors and invitations to join in a neighborhood clean-up or take part in discussions about upcoming elections.

Rowe and colleagues created and studied citizenship programs in New Haven, funded by the National Institute of Mental Health, the Connecticut Department of Mental Health and Addiction Services, and the Melville Charitable Trust. They registered people to vote; helped clients connect with people who shared their interests, such as fellow cycling enthusiasts or stock traders; and encouraged clients to help others, for example, by serving on an advisory board.

Citizenship, as the team came to define it, comprises rights like freedom from stigma, responsibilities like knowing how to manage money, roles as parents or employees, resources like housing and religious communities, and relationships with others.

A randomized controlled study of 114 people who received mental health services showed that those who participated in a citizenship program were more satisfied with their lives and less apt to misuse alcohol and drugs.

This need to foster citizenship, said Rowe, is rooted in the deinstitutionalization of the 1960s and "came out of the success of mental health outreach work—reaching its limit and hitting the wall." To thrive, people with mental illness need more than just services, said Rowe. They need to "come in from the margins."

A guide for setting up citizenship programs will be posted at medicine.yale.edu/psychiatry/prch/.

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The most cooperative of patients

THIRD-YEAR STUDENTS beginning their clinical clerkships took to the new Yale Center for Medical Simulation on June 15 to practice clinical skills best learned on a manikin instead of a live patient. At the expanded center, which opened in January, they used bag-valve masks for manual ventilation and inserted catheters and nasogastric tubes into the practice manikins. "Our patients today are cooperative for you," joked Leigh V. Evans, M.D., director of health care simulation. In addition to learning technical procedures, clerkship students have the opportunity to lead medical teams in simulated case studies based on real patients. "It's active learning, it's feedback, and they get to practice," said Evans.

—Karen Zusi