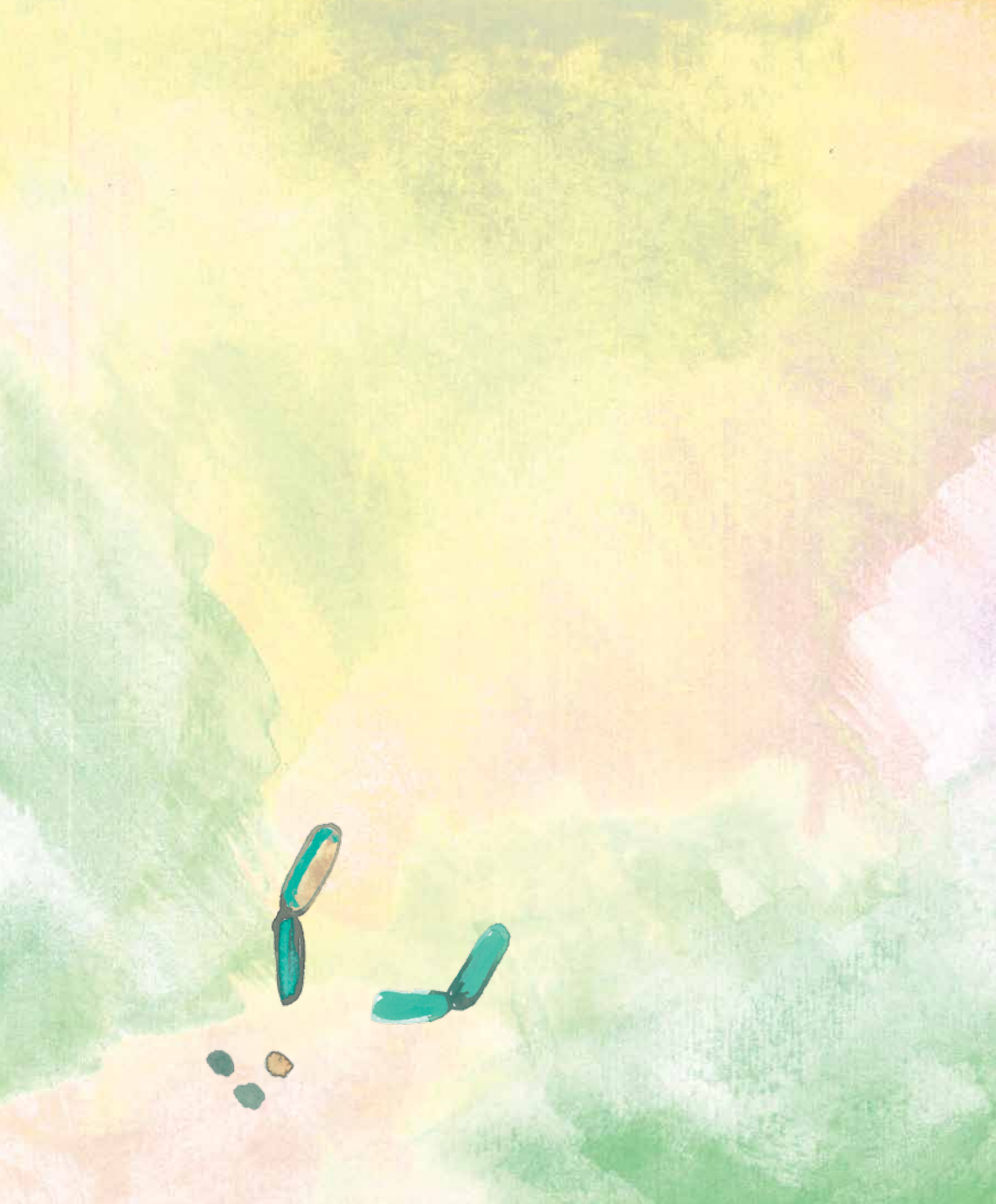
yale medicine magazine

GO WITH YOUR GUT

The microbiome: helping keep bodies healthy

Autumn 2018



Features

COVER AND THIS SPREAD: MAYA SZATAI ILLUSTRATION

autumn 2018 departments

letters

The Importance of Allies

Regarding the article on Drs. Ment and Duncan: in service of focusing the issue on women, you downplayed the role of Dr. Duncan, senior—Dr. Ment's husband, and a preeminent physician. As part of a two-academic-career Yale household (my husband is a Yale PhD), I suspect this inadvertently takes Dr. Ment's career out of its essential context. For them both to succeed, surely a tremendous amount of behind-the-scenes sharing of roles and renegotiating of responsibilities had to occur.

Yale has a remarkable number of couples in medicine who have excelled at this (so many that when I was a medical resident we had a whole trivia category on married Yale physician couples with different last names). They served as role models for younger physicians who aspired to balance career, marriage, and children with their equally talented and dedicated partners.

Dena Rifkin, MD '01
LaJolla, Calif.

Remembering Sofia Simmonds, PhD (and others)

I was very surprised that there was no mention of Sofia Simmonds in your recent issue of *Yale Medicine Magazine: A Century of Women at Yale School of Medicine*. I was a graduate student from 1952 to 1957 in the Microbiology Department across Cedar Street from the Biochemistry Department. The Biochemistry Department was unusual for the number of women graduate students there, among them Maxine Singer, PhD. Sofia Simmonds, PhD, was the wife of Joseph Fruton, PhD, the biochemistry department's chair. In retrospect, the large number of female graduate students was probably due to the influence of Professor Simmonds.

Maurice Margulies, PhD '57
Rockville, Md.

I am surprised that your issue on a century of women at Yale Medical School did not mention Professor Sofia Simmonds of what was then Yale's Biochemistry Department, and which is now a component of the Department of Molecular Biophysics and Biochemistry (MB&B). Not only did she co-author (with Joseph Fruton, her husband) the first comprehensive biochemistry textbook, which they updated in a second edition, but she also received the Garvan Medal from the American Chemical Society for contributions to chemistry by a female scientist. Even more importantly, she served as a role model and source of inspiration for female students desiring to enter the field of biochemistry.

Gerald J. Putterman, PhD '65
Hamden, Conn.

Editor's note: 52 pages might seem like a lot, but even that wasn't sufficient to highlight all the remarkable accomplishments of women graduating from Yale School of Medicine or on the faculty. Simmonds is represented on the "100 Years of Women in Medicine Website," and can be found here: medicine.yale.edu/centuryofwomen.

SECOND OPINION
BY SIDNEY HARRIS

Send letters and news items to
Yale Medicine Magazine, 1 Church Street, Suite 300, New Haven, CT 06510 or email ymm@yale.edu.
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 Magazine* 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.

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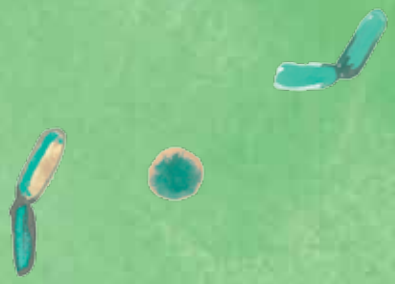


The bottom-up revolution driving microbiome research at Yale

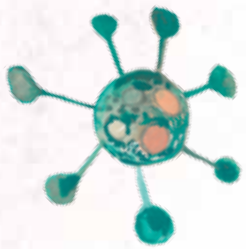
FUELED BY TECHNOLOGICAL BREAKTHROUGHS and a wealth of information gleaned from private research and government-funded programs, lines of inquiry into human and non-human microbiomes have proliferated in recent years. Robert J. Alpern, MD, dean and Ensign Professor of Medicine, describes the field's blossoming significance, and how YSM has fostered research in New Haven.

How have attitudes toward the microbiome evolved during your professional career? While in the past, there were interesting observations about the potential importance of the microbiome, today, the microbiome is one of the more exciting frontiers of medicine. While it hasn't fully defined itself in terms of its importance to homeostasis, or how useful it will be in preventing and treating disease, there's accumulating evidence that it will be very important to both. "Health" as we think of it may actually be the result of an interplay between our individual genome and the composition of our microbiome and the effects of both on our homeostatic processes, so it's a vital area of research.

What has the School of Medicine done to prepare for increased activity with the microbiome? First, we've recruited outstanding scientists. Second, we've built facilities to support those scientists. We've staked out a leadership position in this field and ensured that we have a framework to capitalize on what appears to be a likely upcoming boom of investigators (and investigations) into the microbiome. From the standpoint of the school, we want to establish core facilities that allow any researcher, no matter their area of interest, the ability to work with the microbiome.

Was that by design? Yes and no. A number of departments decided to recruit in this area. We agreed to build facilities to support their efforts. I think this is a typical bottom-up success story where departments decided the scientific priorities, the areas they think Yale needed to investigate, and YSM supported those priorities. Then, once the right people were here, and the facilities came online, other people who weren't necessarily working in the area chose to expand their research.

How has this affected the field of nephrology? The kidney is significantly affected by immunologic diseases, a class of disease that has seen significant correlative overlap with microbiome research. One disease that affects the kidney, IgA nephropathy, involves an antibody that occurs in mucosal interfaces. I wouldn't be surprised if it turns out that IgA nephropathy was influenced by the microbiome. It's exciting to be a doctor or researcher at Yale today, with all these longstanding mysteries being resolved—and new questions posed for future scientists!



Yale and the VA: Joined at the hip

ON THE FIRST DAY OF HER RESIDENCY ROTATION AT THE VA hospital in West Haven, Susan Kashaf, MD, MPH, treated Kevin Barbour, a Vietnam War veteran. Barbour was exasperated by lingering pain from earlier knee surgery—and he let her know about it.

It was a rough start for a young doctor. "He scared the heck out of me," recalls Kashaf.

Today, 20 years later, Kashaf is an attending physician at the VA and an associate professor of medicine at Yale School of Medicine—and Barbour is still one of her patients. She has a thank-you card that he sent her after she helped him quit smoking. "It's a nice reminder of what we do," says Kashaf.

Barbour says he rarely sends thank-you notes, but, he felt compelled to reach out to Kashaf. "She has been my primary care doctor for 20 years. It's nice to know that somebody is watching over me," he says.

The warm feelings shared by Kashaf and Barbour are emblematic of the deep and multifaceted relationship between Yale School of Medicine and the VA Connecticut Healthcare System in West Haven that goes back more than 60 years. People involved say the tie is critically important to the delivery of high-quality medical care to veterans in Connecticut—and to vets with complex cases from across New England.

The majority of physicians who work at the VA in West

Many doctors at Yale, including Susan Kashaf, right, and hospital resident Mary Barden, treat veterans at the VA Connecticut Healthcare System's West Haven facility. Kashaf has been providing service at the VA since her residency 20 years ago, and has developed lasting relationships with her patients.

Haven have faculty appointments at Yale. "Our patients get the latest advances in care applied to their problems. They get the depth and expertise of a medical staff associated with Yale, and they can get consultations with the top experts at Yale and Yale New Haven Hospital," says Michael Ebert, MD, the chief of staff at VA Connecticut. At Yale, he is a professor of psychiatry and associate dean for veterans' affairs.

Yale School of Medicine leaders say the association provides Yale medical students, residents, and fellows with valuable hands-on training. Plus, the VA's a fertile environment for conducting medical research. "Yale's longstanding relationship with the VA is a win-win. It's been mutually beneficial for the medical students, residents, and fellows who train there; the faculty who conduct research there; and the veterans who receive exceptional care," says Robert J. Alpern, MD, dean of Yale School of Medicine and Ensign Professor of Medicine (Nephrology).

These days, the Veterans Health Administration is under attack from critics who want to replace it with private health care. However, leaders at VA Connecticut and Yale say the VA system provides outstanding lifelong care in most cases to a patient population whose medical issues tend to be complex and whose physical ailments are often compounded by mental health problems. "The VA is a unique national system that offers a seamless web of services from primary care to specialized services to hospital to geriatric and nursing care. When done correctly, it's a national model for providing health care," says John Booss, MD, professor emeritus at Yale School of Medicine, formerly the national program director for the VA's neurology service.

When Theodis Fenn Sr. returned from Vietnam as a combat infantryman in 1967, he suffered from malaria, hepatitis, anxiety, and burns on his feet from a base camp accident—and had been exposed to Agent Orange, the toxic defoliant. His initial encounters with the VA were disappointing. "They never addressed my problems," he says.

But eventually Fenn obtained Daniel Federman, MD, a professor of medicine at Yale, as his primary care physician, and things turned around. Fenn has received treatment for PTSD, lung and prostate cancer, diabetes, high blood pressure, and chronic abdominal pain. "Dr. Federman is my lifesaver. Without him, I'd be dead," says Fenn.

Leaders at Yale and the VA say veterans like Fenn who have complex health problems benefit from the expertise in diagnosis and treatment that medical school faculty can offer. For instance, Yale and the VA Connecticut Healthcare System helped define and establish PTSD as a diagnosis back in 1980, and today researchers at the VA are developing innovative treatments for it.

In return for their dedication to better health care for veterans, Yale faculty physicians and students who practice at the VA get tremendous satisfaction from treating veterans, who are typically grateful and willing to volunteer for studies that might help their comrades. A number of Yale faculty members treat patients at the VA without compensation.

Some veterans become like family to the med students and residents. Uyen To, MD, assistant professor of medicine and a Yale transplant hepatology fellow who did her residency at Yale as well, says she became particularly close to one elderly man—even telling him about her wedding plans. At one point he was near death. He grabbed her hand and vowed, "I'm not going to die before you get married." He pulled through.

For Yale's medical students, residents and fellows, the West Haven hospital provides an excellent place to learn and practice in a hands-on environment. In a typical year, more than 200 medical students complete clinical rotations there in a wide range of medical specialties, working closely with attending physicians who also provide classroom training. At any given time, 15 percent of the more than 1,100 residents and fellows are on rotations at the VA—during which time the VA covers their salaries.

"The patients want to help them learn. They have incredibly interesting medical histories and social histories around

ROBERT LISAK PHOTO

ONLINE EXCLUSIVE

A safer way to live with guns: residents and doctors at Yale learned first-responder techniques this fall, in order to spread knowledge to parents and children who might be exposed to shootings. If legislation limiting access to firearms is not forthcoming, everyone needs to know first aid.

For more on the classes, visit ymm.yale.edu/safe

their military time, so it's a rich learning experience," says Seonaid Hay, MD, assistant professor of medicine and associate program director of the Yale Traditional Internal Medicine Residency Program at the VA.

Yale faculty members teaching at the West Haven VA have introduced a number of innovations there. One is the Center of Excellence in Primary Care Education, in which faculty members teach residents how to provide primary care through interprofessional teams. At the VA Connecticut clinics, residents work with teams that include nurses, medical assistants, psychologists, pharmacists, and others to provide care for patients tailored to individual needs. The program started in a few clinics and now includes most of the clinics at the West Haven facility.

The VA provides tremendous research opportunities for students, junior faculty members, and senior faculty alike. The VA is a fertile environment for research partly because of its size and scope. Researchers can study large groups of patients at VA medical centers around the country. Because the VA was a pioneer in electronic medical records in the 1970s, much of its historic data is easily accessible.

"Another attraction is the patients. They're willing to participate in research because they want to help their buddies. There's an altruistic drive," says Fred Wright, MD, the director of research at VA Connecticut and a professor of medicine (nephrology) and of cellular and molecular physiology at Yale.

The VA Connecticut Healthcare System has 25 labs in West Haven, with more than 500 active research projects funded to the tune of $45 million in grants and run by 80 principal investigators—all from Yale. Those labs are currently conducting more than 50 clinical trials.

The program includes several high-performing organizations. The Center for Neuroscience and Regeneration Research, headed by Stephen Waxman, MD, PhD, Bridget M. Flaherty Professor of Neurology, discovers ways to restore function in the nervous system after injuries and strokes. The VA-Yale Clinical Neurosciences PTSD Research Program, headed by John Krystal, MD, Robert L. McNeil, Jr. Professor of Translational Research and professor of psychiatry, and of neuroscience, seeks biological approaches to the treatment of trauma-related disorders. And the NIH-DoD-VA Pain Management Collaboratory Coordinating Center, run by Robert Kerns, PhD, professor of psychology, of neurology, and of psychiatry; Cynthia Brandt, MD, MPH, professor of emergency medicine and of anesthesiology; and Peter Peduzzi, PhD, professor of biostatistics, helps guide clinical trials of nondrug approaches to pain management.

Yale faculty members who serve at the VA are dedicated to making life better for today's veterans by providing the best care available, and to improving care for generations to come via research and teaching. Every faculty member interviewed for this story said they chose the VA because it's so gratifying to help veterans.

Veterans interviewed returned the warm feelings. Vietnam vet Bill Broumas shunned the VA after he returned from the war. He received private insurance through his employer. But a few years ago he decided to give the VA another chance—partly because of the Yale connection. Now he's a fan. "Every single person I meet there—they're totally interested in me," he says. "They all treat me like a human being."

—*Steve Hamm*

Ten years of music from Yale Medical Symphony Orchestra

The Yale Medical Symphony Orchestra (YMSO) kicked off its 10th year with a concert in Harkness Auditorium that was filled to the rafters. "We love looking out and seeing a packed auditorium," said symphony conductor Robert Smith to the crowd, which used every seat and included people lining the walls of the auditorium. "Eight years ago, we had only about a third of the auditorium filled."

Now a group of more than 50 musicians from the School of Medicine and Yale community perform composers like Tchaikovsky and Brahms to a

full house. Lynn Tanoue, MD, professor of medicine (pulmonary), the group's founder, started the orchestra after speaking with a school friend who, like Tanoue, is a musician. "We wouldn't be here without Dr. Tanoue," said Smith, as she was presented with flowers after the anniversary performance.

Tanoue soon discovered that medical school orchestras are rare, but she found a supporter in Thomas Duffy, MD, professor emeritus of medicine, then the director of the School of Medicine's Medical Humanities and the Arts Council. Duffy agreed to provide initial funding, and Tanoue reached out to the medical school community, seeking musicians who might be interested in playing together.

Tanoue said 200 people responded, and she scheduled an open rehearsal where everyone would sight-read music together. Tanoue asked Adrian Slywotzky, director of instrumental music at the Hopkins School in New Haven at the time, to conduct the group.

"That first night, all these people start showing up. It was unbelievable," Tanoue said. "Adrian shows up with his arms full of music. [On the top] is Beethoven's Fifth. I said, 'Adrian, you don't understand. We're doctors.' He said, 'No, no, it's okay.'"

That night, Tanoue sat in the Harkness balcony to listen to the newly assembled group play a piece by Rossini. They rose to Slywotzky's challenge, she said. "Wow," she remembers thinking.

YMSO recruits musicians from the School of Medicine and the broader medical community in New Haven. They're held to a high standard.

ROBERT LISAK PHOTO

"We could totally do this." And the group was off and running: 50 people from across the School of Medicine made the commitment to rehearse and eventually perform as an orchestra.

The symphony began regular weekly rehearsals in February 2008, and at its first concert, performed Beethoven's Symphony No. 1. Two years later, Robert Smith, who had taken over Slywotzky's position at the Hopkins School, joined the orchestra as conductor. Since those early days, the symphony has steadily moved on to more challenging works. At the May concert, the orchestra debuted its first Tchaikovsky symphony, No. 5, a piece, said Smith, that goes beyond the capacity of most similar orchestras. "They work so hard every week, even though they have pagers and are constantly attending their patients," said Smith.

YMSO plays two concerts a year: one in spring and another in winter. There are often special concerts at Halloween. Costumes, jack-o-lanterns, and a glow-in-the-dark conductor's baton accompany an underscore set to creepy Halloween poetry readings. The 2013 Halloween concert was a breakthrough moment for the group. "It opened everyone's eyes that we were a real orchestra," said Smith. "We've been packing the auditorium ever since." To celebrate their 10th anniversary, Smith said, another Halloween concert is planned for October 27, with the winter concert on December 7.

The participating musicians come from all parts of Yale School of Medicine. In addition to faculty members and physicians, the players include volunteers, students, and staff from many departments across the school as well as from Yale New Haven Hospital and the schools of Nursing and Public Health.

ONLINE EXCLUSIVE

Calamity struck in August, when over 40 New Haven residents were poisoned on the Green by a synthetic cannabinoid. Doctors from Yale helped organize the response, while first-responders treated victims on the scene.

For more on the poisoning, visit ymm.yale.edu/poison

"Music is the great equalizer. Your stand partner could be a famous scientist, or they could be a lab technician or a student," said Tanoue. "The hierarchy that is so strong at the university and certainly in medicine totally disappears, so that nobody is more important than anybody else. No one is running that team except the conductor. And many of these people in their everyday lives are in charge of whatever they're doing."

"Medicine is all about relationships and listening—with patients, with nurses, doctors, hospital staff, office staff, family members of patients," said Anna Reisman, MD, associate professor of medicine, director of the Program for Humanities in Medicine, and a symphony flutist. "You get nowhere if you're not good at listening, which also means you have to be able to adapt your response depending on what's said and how it's said. The same thing happens in an orchestra."

To Smith, it's no coincidence that people who spend their days steeped in science are also talented musicians. Much of the group performed through high school and college, he said. Some were music majors as undergraduates or principal chairs in their high school orchestras. "The idea of grasping for perfection, that kind of drive and work ethic serves both populations. It's part of a person's character to do these things at a high level and work hard at it. And in both, they are using their hands. It's a technical application."

Aishwarya Singh, a 2014 graduate of Yale College and current second-year medical student, nearly went to Julliard to pursue the violin but chose Yale College instead. She shares the first stand with Brian Rash, PhD, the orchestra's concertmaster and an associate research scientist in neuroscience. "Music is one of those things when you are always learning, and medicine is like that too," said Singh. "It's not finite. That's why I think, for a lot of people, both appeal to them. For a busy clinician it's nice to have something that's an escape."

Players connect at weekly rehearsals, in between concentrating on whatever piece they are working on. Graduate students meet professors who might share their clinical interests; chamber music groups formed of orchestra members perform beyond the symphony. Smith said that there is little attrition from year to year, so the musicians have come to know each other well and form a tight-knit community. "We come in and we have this joyful, hardworking time together," Tanoue said.

Going into its 11th year, the symphony is looking ahead to the future, and is seeking new ways to become sustainable, so that it can keep growing. As admission to its concerts is free, the symphony's funding comes from grants and donations from its members. Money for the various incidentals required by a symphony, including equipment, music, and support for the conductor wasn't always easy to come by, but that changed recently. Thanks to an effort in spring of 2018 led by longtime music and YMSO fans Robert J. Alpern, MD, dean and Ensign Professor of Medicine and his wife, Patricia Preisig, PhD, professor of medicine (nephrology), a $100,000 endowment was created to pay the YMSO's conductor a stipend.

Retaining a professional musical visionary is a key component of the symphony's long-term success, and guarantees that Yale's medical community will continue to meet and connect outside professional settings. Alpern and Preisig's efforts to institutionalize the conductor's position will be a significant piece of their legacy.

"The conductors, we couldn't function without them," Tanoue said. "And both Adrian Slywotzky and Robert Smith have been amazing."

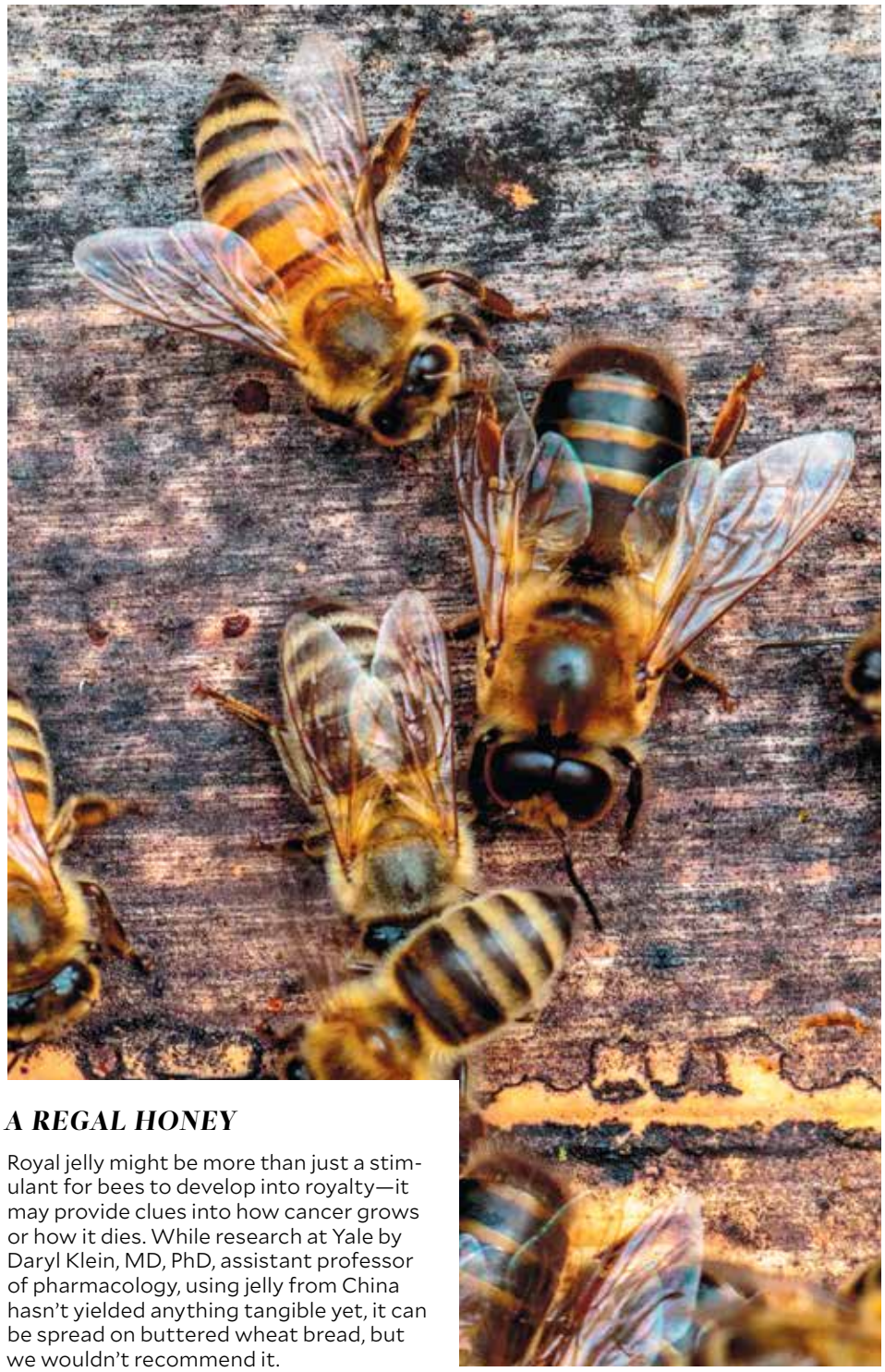
Funds also mean YMSO can take on different projects like lecture series tied to performances and concerts; the ability to bring music to patients' bedsides; and children's concerts. "The orchestra dreams big," said Tanoue. "Why not?"

Smith said the group is ready to take on those big dreams. Musically, "I feel like we are where we need to be with the orchestra," Smith said. They are ready to perform bigger, more iconic pieces for bigger audiences. "Now the fun begins."

—Jeanna Lucci-Canapari

round up

a collection of recent scientific findings

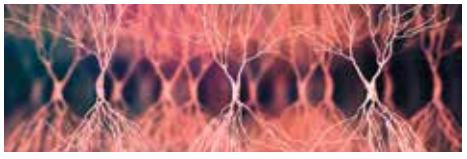


A REGAL HONEY

Royal jelly might be more than just a stimulant for bees to develop into royalty—it may provide clues into how cancer grows or how it dies. While research at Yale by Daryl Klein, MD, PhD, assistant professor of pharmacology, using jelly from China hasn't yielded anything tangible yet, it can be spread on buttered wheat bread, but we wouldn't recommend it.

ANOTHER DOWNSIDE TO DEPRESSION

If you think the depression of a spouse or loved one is making life sadder, you may be right. A recent study published in the *American Journal of Geriatric Psychiatry*, conducted by Yale researchers and their colleagues in Pittsburgh and Ann Arbor suggested a correlation between the two.



MEMORY IN MODULES

Yale researchers have uncovered fascinating clues into the nature of human memory based on its mechanisms. Modules of cells can be triggered and recombined in the hippocampus, according to George Dragoi, MD, PhD, assistant professor of psychiatry and of neuroscience and senior author of the study published in *Neuron* in August.

ALL THE BEST ONES AREN'T TAKEN

Molly Crockett, PhD, assistant professor of psychology, conducted a study with some counterintuitive conclusions about what we say versus what we prefer. Most people prefer to date or marry individuals who prioritize the good of their family and friends over strangers, which isn't exactly altruistic. We want to feel good more than we want to be good.

GO WITH YOUR GUT

The microbiome: helping keep bodies healthy

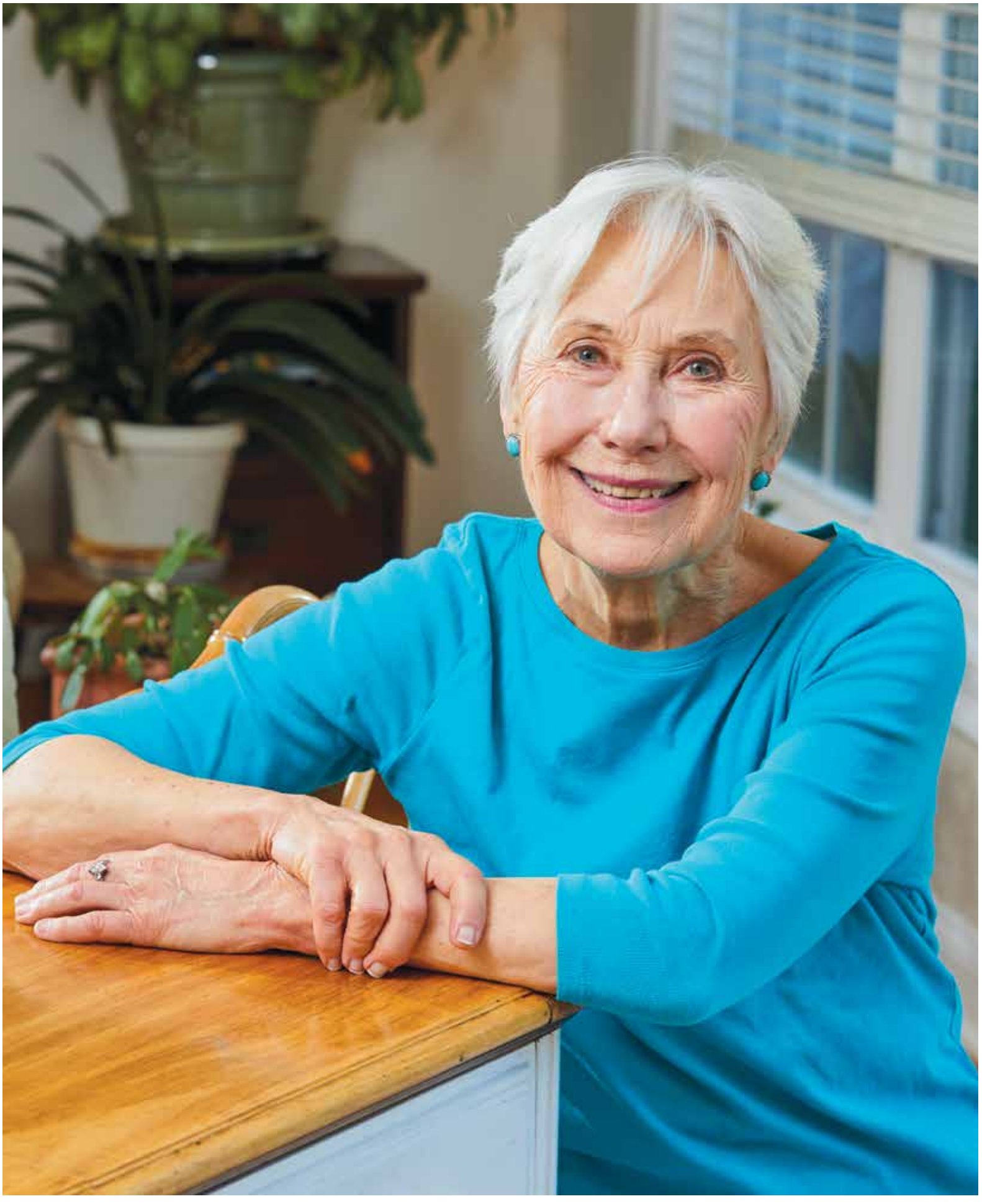
IN THE 1990s, geneticists hoped that mapping the human genome would provide a path to treating many seemingly incurable or poorly understood conditions; obesity, dementia, and cancer, to name a few. As understanding of genetics expanded and improved, however, scientists came to see the genome as just a first step in understanding a vastly more complex world of interactions within the body, one that extended to organisms that were not traditionally considered native or essential to humans—the microbiome.

Research at Yale focuses on a wide swath of relationships between microbes and humans, from the gut to DNA. According to the latest inquiries, the evolution of *Homo sapiens* is not just a tale of vertebrate mutations, in which genetic variation leads to useful adaptation, but a hyper-complex series of mutually beneficial arrangements between the human body and the many organisms that call it home.

In some cases, researchers are still attempting to establish a correlation between a given microbe and conditions in humans. This issue explores some of those possibilities in articles about diabetes, cystic fibrosis, and multiple sclerosis. In other cases where a correlation has been established, such as with *Clostridium difficile* infections, the question is not whether microbes play a role in human health, but the specific nature of that role.

One fact has become apparent in compiling this issue of *Yale Medicine Magazine*: the old idea of the human body as a self-sufficient entity constantly fighting hostile microbes is obsolete. We are collections of organisms working together to survive. At least on a cellular level, the concept of the heroic individual is not just anomalous—it is absurd, unworkable. Each person is a miracle of cooperation and altruistic mutual interest, a collective of creatures. Good health and evolutionary success are the products of alliances, not ruthless selfish competition.

MAYA SZATAI ILLUSTRATION



A SOPHISTICATED SYSTEM

How researchers at Yale are complicating the picture of human health.

BY STEVE HAMM | ROBERT LISAK PHOTOGRAPH

A long struggle with *Clostridium difficile* left Jane Norgren weak and emotionally despondent—until she underwent a revolutionary new therapy. Cured of the infection, she's eager to share her success story with others who may be suffering.

Jane Norgren was suffering terribly. A pernicious bacterium, *Clostridium difficile*, had taken up residence in her colon and refused to leave—no matter what antibiotics she took. As a result, she had bouts of uncontrollable diarrhea on and off for nearly four years. It was a miserable situation. She always had to be near a bathroom. "I felt like I was untouchable," she says.

Then Norgren's agony was over. That's because she was one of the first people in Connecticut to benefit from fecal microbiota transplantation (FMT). Most of the existing bacteria in her digestive tract were killed by a heavy dose of antibiotics and replaced by healthy bacteria from a fecal donor (her daughter). "I have been fine ever since," she says.

The procedure was performed by Paul Feuerstadt, MD, an assistant clinical professor of medicine at Yale School of Medicine. He says that more than 95 percent of the patients he has treated in this way through the Gastroenterology Center of Connecticut have recovered.

FMT is the first treatment that has emerged from a wave of research on the role of the microbiome in health. For years, most medical researchers treated microbes as a sideshow to the main event—the role of genetics in illness and medicine. Now, many are turning their attention to the impact on health of the trillions of bacteria, fungi, and other tiny organisms that colonize human digestive systems, lungs, nasal passages, skin, vaginas, and many other body parts and surfaces.

"For medical science, this is our next frontier. The better we understand our microbiome, the better we'll be able to potentially avoid diseases or treat them more successfully," says Feuerstadt.

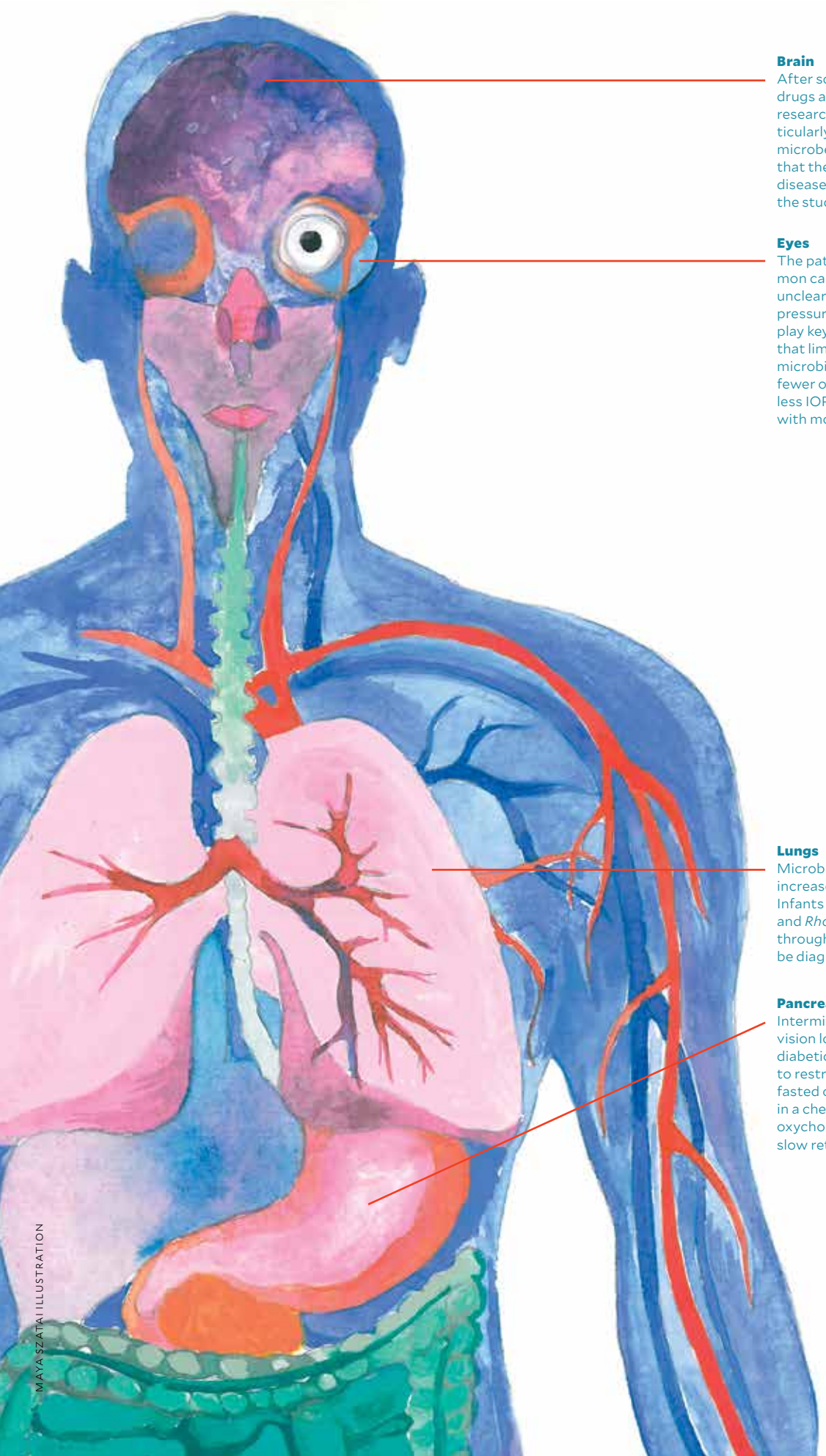
Researchers believe that the microbiome plays a role in a wide variety of human diseases and conditions, including inflammatory bowel disease, irritable bowel syndrome, Crohn's disease, lupus, chronic fatigue syndrome, fibromyalgia, cardiovascular disease, cancer, Parkinson's, diabetes, cystic fibrosis, asthma, autism, and some forms of mental illness.

At Yale School of Medicine, researchers from more than a dozen academic departments are studying the microbiome. Some focus on understanding the fundamental mechanisms whereby bacteria interact with each other and with our bodies. Others develop tools for sequencing and editing genes in bacteria. Still others are focusing on the effects of the microbiome on specific diseases.

While these are early days, it's already clear that Yale researchers are playing a key role in the microbiome revolution. For instance, Loren Laine, MD, professor of medicine and interim chief of the Section of Digestive Diseases, was instrumental in establishing the American Gastroenterological Association's Fecal Microbiota Transplantation National Registry, which helps researchers assess short- and long-term outcomes associated with FMT.

This wave of microbiome research has been gathering strength for about a decade. However, the history of such research began in the 1860s when the French chemist Louis Pasteur showed that microbes are present all around us and in our bodies, and that some are responsible for diseases. Ever since, medical scientists have been studying the microbiota in the environment, animals, and humans so that physicians can better combat infection. With the emergence of antibiotics in the 1930s and 1940s, many believed that infectious diseases would swiftly be eliminated. Sadly, it didn't happen. Now, resistance to antibiotics is a major concern.

Until a little over a decade ago, most research on the microbiome focused on which microbes played a role in causing infectious diseases, and how. Then came the Human Genome Project (HGP), launched in 1990 and completed in 2003, which provided the foundation of a better understanding of the genetic basis of such diseases as cancer. It was discovered that genes alone were often not sufficient to fully explain why complex



Brain
After screening over 1,000 non-antibiotic drugs against 40 gut bacterial strains, researchers found that several classes—particularly antipsychotics—prevented healthy microbes from thriving. The findings suggest that these drugs could influence neurological diseases via microbial interactions. However, the study's in vitro design is a limiting factor.

Eyes
The pathogenesis of glaucoma, the most common cause of blindness worldwide, remains unclear. Researchers know that high intraocular pressure (IOP) and overactive immune T-cells play key roles. A study earlier this year hints that limiting bacterial strains in the ocular microbiome might also be a factor. Mice with fewer ocular microflora strains experienced less IOP-related damage compared to those with more.

Lungs
Microbial communities in our gut might increase the likelihood of developing asthma. Infants with higher levels of the fungi *Candida* and *Rhodotorula* in their gut, detected through stool samples, were more likely to be diagnosed with asthma at age 4.

Pancreas
Intermittent fasting might help alleviate vision loss, called diabetic retinopathy, in diabetic mice. This phenomenon could be due to restructured gut microbiota. Mice who fasted on alternate days had an increase in a chemical chaperone called tauroursodeoxycholic acid, which has been shown to slow retinal degeneration.

MAYA SZATAI ILLUSTRATION

diseases occur or how therapies work. So researchers began to look more deeply into the genetic makeup of microbes and their interactions with each other and with human cells—both negative and positive.

In an effort reminiscent of the HGP, the U.S. National Institutes of Health in 2007 launched the Human Microbiome Project. The goal was to fund research and collect data about the genomes and interactions of all the microorganisms in or on our bodies. Research funded by the project provides today's scientists with a trove of data upon which to base their new inquiries.

One factor that makes this research so complex is that no two people have the same microbiome. While broad commonalities exist, each human has his or her own stew of bacteria and other organisms. In addition, while our personal microbiomes tend to be relatively stable, they change with the introduction of new organisms from the environment. So my microbes interact with my body differently than yours do with your body; and they interact differently today than they did six months ago.

And consider this: There are 150 times more genes in our microbiome than in our genome.

Yale faculty members say this complexity must be overcome. The ability to sequence and map human genomes has raised hopes that physicians will be able to understand an individual's body so well that they can deliver truly personalized medicine—custom-designed therapies and treatments that will work especially well for that individual. Yet it's becoming clear that understanding human genes and cells won't be enough. "To truly understand the signals that regulate the expression of both healthy and diseased genes, you need to understand the microbiome. Precision medicine will be fairly imprecise without this," says Gary Desir, MD, the Paul B. Beeson Professor of Medicine and chair of Internal Medicine.

Martin Kriegel

"This may become personalized medicine. We need to look at … human genes, and at the microbiome in the patient's gut and tissues. Based on these analyses, we should be able to decide on the best treatment for a particular patient in the future."

Scientists admit they are still at the beginning stages of understanding the role of the microbiome in health. "We aren't yet at the point where we can look at what is there in a microbiome and tell you much about what it can do. It's hard to identify a diseased microbiome if you don't know what a healthy one is," says Andrew Goodman, PhD, an associate professor of microbial pathogenesis.

Goodman is determined to change that. His lab on Yale West Campus focuses on deepening

understanding of how microbes in our digestive systems, the so-called gut microbiome, interact with each other and us. He and his colleagues have seen situations in which one microbe species uses a vitamin produced by another to survive in the gut; and others in which microbes fight each other to the death. On the microbe-to-host axis, the team is learning how gut microbes could affect how particular individuals respond to particular drugs.

So far, most of this experimentation involves mice—but not just any mice: germ-free mice. Only by using mice with no bacteria present can researchers introduce individual species or consortia of microbes and study the effects of their absence or presence. Although Goodman has a dedicated team of experts in these techniques, the med school also has a central germ-free mouse facility that all the scientists can access.

Another essential element of microbiome research is the tools that are used to read and analyze the genetic code within microbes and then to edit or even recode their DNA so that they interact with each other and our bodies in different ways.

Scientists employ the same tools for microbes that are used for human genetics research. The CRISPR/Cas9 technology has democratized gene editing by enabling scientists to cut and paste snippets of DNA code relatively easily. But researchers at Yale are some of the leaders in developing new approaches that don't involve breaking the double strands of DNA and killing cells.

One effort is led by Farren Isaacs, PhD, an associate professor of molecular, cellular and developmental biology. His lab produces and uses high-throughput gene engineering technologies. With these tools, the researchers can rewrite the genomes of human cells and bacteria on a large scale—introducing scores of precise edits without creating double-stranded breaks in the strings of genes. His team developed a technique called eukaryotic multiplex genome engineering (eMAGE) and used it to alter the genetic information in yeast. The team members hope this technique will be used eventually to alter disease-causing genes in human cells and microbes.

Earlier this year, Isaacs' lab pitched in on an effort aimed at engineering communities of gut microbes to help humans digest cellobiose, one of the most abundant disaccharides present in vegetables, which our digestive systems don't have the means to metabolize. If efforts like this pay off, we will be able to harvest more energy from the food we eat.

Across the spectrum of Yale academic departments, researchers are using germ-free mice and gene sequencing and editing tools to advance research on the role of the microbiome in a wide variety of diseases and body functions. Laypeople tend to think that bacteria in the digestive system stays put, but in fact, microbes migrate via the blood to a host of other body organs and systems, including the liver, the lymph nodes, and even the brain. Much of the research focus at Yale is on infectious diseases, the immune system, and autoimmune diseases.

Martin Kriegel, MD, PhD, FW '06, adjunct assistant professor of immunobiology, and of medicine (rheumatology), has been focusing on *Enterococcus gallinarum*, a bacterium that his team discovered can migrate from the gut into the lymph nodes, liver, and spleen in predisposed hosts—thereby producing an autoimmune response. Kriegel's research team found that they could suppress the response caused by *E. gallinarum* in mice with an antibiotic or vaccine. Research like this could help pharmaceutical companies produce antibiotics and vaccines that are particularly good at attacking specific bacteria.

"This may become personalized medicine," says Kriegel. "We need to look at the host predisposition such as the human genes, and at the microbiome in the patient's gut and tissues. Based on these analyses, we should be able to decide on the best treatment for a particular patient in the future."

Other labs are focusing on prevention in addition to cures. Li Wen, MD, PhD, FW '97, associate professor of medicine (endocrinology), is looking into the causes of type 1 and type 2 diabetes. Her team's research has shown that certain types of gut bacteria cause intestinal inflammation, which in turn promotes the development of type 1 diabetes. At the same time, the research shows that obesity and other factors associated with type 2 diabetes are more prevalent in patients with low diversity in the gut microbiome. Down the road, she believes, people with a genetic predisposition to diabetes may be able to fend off the disease by consuming customized probiotic cocktails.

"I think prevention is most important," she says. "It's the most effective and economical way to deal with diabetes."

While most of the research at Yale concerns the gut microbiome, a handful of faculty members are focusing on other body parts or systems. For instance, Barbara Kazmierczak, MD, PhD, a professor of medicine and of microbial pathogenesis, specializes in the lung microbiome—specifically the effects of bacteria on cystic fibrosis.

Much of the research being done at Yale, while promising, is not expected to deliver new treatments or drugs for many years. But some projects might be closer to the marketplace. For instance, two professors—Noah Palm, PhD, assistant professor of immunobiology, and Richard Flavell, PhD, Sterling Professor of Immunobiology—are co-founders of a startup company Artizan Biosciences, aimed at identifying harmful bacteria in the gut and targeting them for destruction. One of their first targets: inflammatory bowel disease.

"We found that when we take a healthy microbiota and add one microbe to the mixture, the mouse gets sick. On the flip side, if you're able to block the pathologic effects of that bug or eliminate it entirely, the mouse does not get sick," says Palm. The next step is figuring out how to attack the bad bug—with targeted antibiotics, small molecules, or perhaps even phages.

Elsewhere around the country, a number of medical schools are establishing major research initiatives focused on the microbiome. Among them are Harvard, University of Chicago, Stanford, University of Pittsburgh, University of Michigan, and New York University.

Several Yale researchers say they'd like to see a larger and more coordinated effort to foster and support microbiome research. Such an initiative might make it easier for them to secure funding and develop more multidisciplinary collaborations. Moreover, there would likely be benefits from expanding the variety of research done at Yale. Right now, most of the focus is on experimental science and the gut microbiome. They'd like to see more done in data analysis and in other microbiomes.

Goodman, who on his own keeps a web page (medicine.yale.edu/microbiomeresearch) tracking microbiome research at Yale, says, "I'd like to see it happen. There's a such a great base of people here. There's a lot of opportunity for really exciting things with more coordination and resources."

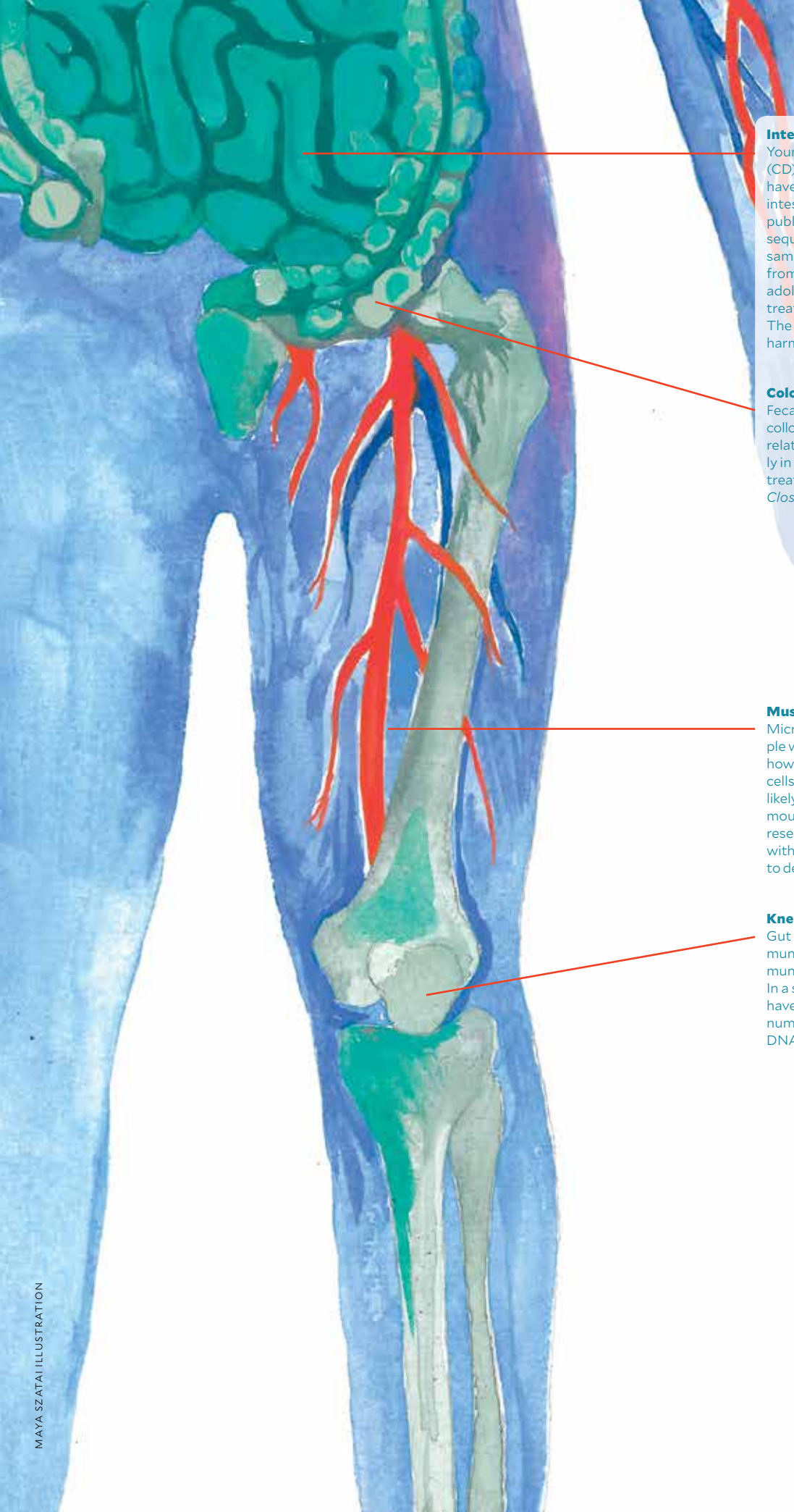
Meanwhile, local people who suffer from diseases related to the microbiome are cheering Yale researchers on. One of them, Shari Hoffman of New Haven, says, "This makes me optimistic that patients may one day receive better care and have better overall well-being."

Shari Hoffman

> "This makes me optimistic that patients may one day receive better care and have better overall well-being."

/yale medicine magazine

Steve Hamm is a contributor to Yale Medicine Magazine.



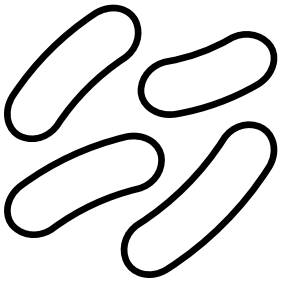
Intestines
Young people who suffer from Crohn's disease (CD), a chronic inflammatory bowel disease, have reduced levels of beneficial bacteria in their intestines, according to an oft-cited 2014 study published in *Cell Host & Microbe*. Researchers sequenced the genome of microbes in tissue samples taken from the large intestine and from fecal samples of about 600 children and adolescents. None of the patients had received treatment—usually antibiotics—for CD just yet. The researchers pointed to the likely further harm that antibiotics might wreak on their gut.

Colon
Fecal microbiota transplantation (FMT), known colloquially as a "poop pill," is the only microbiome-related therapy that has been studied extensively in clinical trials. It is an established effective treatment for difficult-to-treat or recurrent *Clostridium difficile* infections.

Muscles
Microbes in the gut that are often found in people with multiple sclerosis (MS) appear to change how white blood cells interact with the body's cells—including neurons—by making them more likely to attack, according to a study that used mouse models. Another study found that when researchers implanted gut bacteria from humans with MS into mice, those animals were more likely to develop the autoimmune disease.

Knees
Gut microbes may influence the adaptive immune response, which goes awry in autoimmune diseases like rheumatoid arthritis (RA). In a small 2016 study, RA patients appeared to have decreased gut microbial diversity and large numbers of *Collinsella* bacteria, according to a DNA analysis of stool samples.

MAYA SZATAI ILLUSTRATION



MYSTERIOUS MEDICINE

Research shows that probiotics can treat some ailments, but has not yet shown why.

BY JEANNA LUCCI-CANAPARI

Take a look up and down the supermarket aisles: probiotics, loaded with the "good bacteria" once relegated to yogurt and a few other fermented foods such as kimchi and pickles, have escaped the dairy cases. They appear in packaged foods now, with cereals, snacks, and even chocolate infused with these good bugs. Studies of the microbiome have provided an unintended boost to the market for probiotics, shedding light on their power and revealing some potential for therapeutic use beyond an occasional yogurt to boost digestion.

Though probiotics have become a multimillion-dollar cottage industry, much of the science behind them remains murky. "The idea certainly has scientific merit," says Ruslan Medzhitov, PhD, Sterling Professor of Immunobiology and a Howard Hughes Medical Institute investigator whose lab studies the microbiome's impact on diet and inflammation. "But the vast majority of claims surrounding probiotics are based on very loose connections and correlations. This is not to say that the idea is wrong, just that we don't know enough about the biology of commensal bacteria to start using them in this wholesale manner."

Still, those correlations are strong enough that probiotics are beginning a transition from general food supplements to medically valid treatments for serious diseases. Priti Kumar, PhD, associate professor of infectious diseases, is examining a role for probiotics in HIV treatment. One question that has long frustrated HIV researchers is why HIV patients on a successful regimen of antiretroviral therapy (ART) exhibit signs of early immunosenescence. Evidence, Kumar says, points to a change in the composition of the gut microbiome. Could probiotics be used to halt or reverse the premature aging process? Recent studies have examined introducing the bacterial genus *Lactobacillus*, which is commonly found in yogurt and other over-the-counter probiotics, into the diet of HIV patients. "Just introducing this single probiotic strain in the diet seems to really make a marked improvement, in bringing the immune system several steps toward normalcy," Kumar says.

While a potential success, this novel therapy also highlights a limitation of the use of probiotics as therapy. To maintain their healthy status, HIV patients must take ART for the rest of their lives. Probiotics must be used in the same way, because most of these

good bugs have not evolved to adhere to the gut, and they end up passing through the body very quickly. This finding poses another interesting question: "If something is good for us, then why didn't we evolve to hold on to it?" asks Medzhitov. "We are holding on to trillions of bacteria. Why are we not holding on to others that are good for us?"

Evolution may provide the answer. A recent finding revealed that some "bad" bacteria in the gut microbiome can promote obesity, which can lead to such metabolic diseases as type 2 diabetes, while other so-called "good" bacteria are associated with lean individuals.

"One is good and one is bad," says Medzhitov. "However, what we define as good and bad can be different than what would have been considered good and bad in our evolutionary ancestors." This observation can explain why so-called "good bacteria" are not stable in the human intestines. "From an evolutionary perspective, there is nothing good about them. They make you lean," says Medzhitov. "That's good if you are in Hollywood, but not if you are a caveman that can only eat every three days." Because human genes have not had the time to adjust to the drastic changes in modern life that have occurred only in the last few hundred years, including modern medicine, hygiene, and obesity-causing food abundance, they still operate under the assumption that what are now considered bad bacteria are actually good, and vice versa.

Medzhitov predicts that in the next 10 to 15 years, probiotics will make the leap to synthetic biology, which would incorporate engineering and gene modification in their design. "Once we know enough about how bacteria in the gut adapt to their environment, understanding what makes them stable or unstable in the host, or what makes them good or bad, and apply the tools of synthetic biology, which are increasingly sophisticated, one could theoretically create 'designer probiotics,' where we could introduce genes that encode specific proteins that would metabolize certain toxins, for example," he says.

This novel approach to probiotics would still have to pass muster with public opinion. Just as there is strong support for natural commercially available probiotics at the moment, there is powerful opposition to genetically modified organisms (GMOs) in food. Yet many of these next-generation probiotics by definition must be genetically modified. Jason Crawford, PhD, the Maxine F. Singer '57 PhD Associate Professor of Chemistry and associate professor of microbial pathogenesis, cites an example of a probiotic he is working on that has the potential to prevent colorectal cancer. "The challenges for this example are in the regulatory landscape, not the science," he says. "A neutralizing enzyme that we discovered protects humans from a particular toxin, but it needs to be secreted outside the cell as opposed to inside the cell. We need to change that single gene to have a secretion signal. But we can't easily do that with the current regulatory landscape. As soon as we modify that organism, then it's a GMO. That is a huge current barrier between research science and market potential."

Over-the-counter probiotics are not regulated by the Food and Drug Administration. Because other next-generation probiotics will be labeled as GMOs, "it's a different story," says Medzhitov. "There is an assumption that if they are genetically modified, there is something unnatural about them, as if all of evolution is not about genetic modification. Bugs exchange genes all the time, they are always being genetically modified. There is nothing unnatural about it."

As with all other discoveries, these probiotics of the future "would suffer from a certain amount of suspicion," says Medzhitov. "But over time, science will win."

Jeanna Lucci-Canapari is a frequent contributor to Yale Medicine Magazine.

INFECTION CONTROL

A dangerous hospital-acquired infection, *Clostridium difficile,* is now increasing in the community.

BY CARRIE MACMILLAN | ROBERT LISAK PHOTOGRAPHS

Marianne J. Davies, assistant professor of nursing at Yale School of Nursing, is familiar with *Clostridium difficile* (*C. diff*). She describes a healthy immune system as "checks and balances" and *C. diff* infections as opportunistic, occurring when already-weakened immune systems are thrown out of balance from, for example, prolonged antibiotic treatment of a particular illness or infection.

In the messy world of the gastrointestinal tract, good and evil can, at least temporarily, coexist. The gut is home to trillions of bacteria, fungi, viruses, and parasites. Most are helpful in obscure ways, assisting the body in carrying out its various vital functions. But some types of bacteria, including *Clostridium difficile* (*C. diff*), are nefarious and opportunistic.

In a perfect world, beneficial bugs in the microbiome keep the bad ones in check. But when normal bacteria are wiped out (most often by antibiotics or illness), *C. diff* flourishes and can cause a brutal infection characterized by violent, uncontrollable diarrhea. Sometimes, especially in frail, very sick patients, this infection leads to serious complications, even death.

"If there is a window to overtake a healthy environment, *C. diff* will find it," says Marianne J. Davies, DNP, APRN, an assistant professor of nursing at Yale School of Nursing. "The normal bacteria in your bowel maintain metabolism, break down food, and help with digestion. When you take antibiotics, you lower the normal flora that keep other pathogens out of the body. It's like routine checks and balances."

C. diff is the most common health care-associated infection in the United States, causing approximately 500,000 infections and 29,000 deaths in 2015, according to the Centers for Disease Control and Prevention (CDC).

And recently, for reasons researchers don't understand, *C. diff* infections acquired in the community (versus hospitals, where the rate is actually decreasing) have been on the rise.

"There are theories as to why this is happening. Are we seeing more aggressive or resistant strains because facilities have become more efficient and are discharging patients before *C. diff* has had an opportunity to demonstrate itself?" Davies asks. "Typically, the onset is after you've been on antibiotics for five to 10 days."

Preventive initiatives, such as limiting the use of antibiotics unless truly necessary, are imperative, Yale experts say.

NATURE'S BOUNTY

Commonly found in the air, soil, and water, *C. diff* is a bacterium that occurs naturally in the gut microbiome of about 5 percent of the population. But that doesn't make it benign.

"Healthy people with a hearty immune system may have *C. diff* in their intestinal tract, and they coexist with it," Davies says, noting, "But it's not what we call normal flora."

For patients in a health care setting, recent antibiotic use is the leading risk factor for contracting a *C. diff* infection. People on antibiotics are seven to 10 times more likely to get *C. diff* while on the medications and during the month after, the CDC reports. Antibiotics, which destroy and slow the growth of harmful germs, end up killing the good bugs too, explains Laura K. Andrews, PhD, APRN, an associate professor of nursing at Yale School of Nursing. This blanket effect gives *C. diff* room to multiply and crowd out any normal bugs that remain.

Once entrenched, *C. diff* releases toxins that inflame the protective lining of the large intestine. This causes *C. diff* colitis, which entails up to 30 watery stools a day, along with abdominal pain and fever.

"A mild case might mean taking oral antibiotics at home to treat it. For severe to life-threatening cases, you end up in the ICU and can even go into shock with multisystem organ failure," Andrews says. "Patients can become profoundly dehydrated in less than 24 hours. They are losing liters of fluid."

Other high-risk factors for *C. diff* infection include being over age 65 and/or taking immune-suppressing medications. Adding further challenges, *C. diff* can survive for months, is resistant to disinfectants, and can spread after contact with any contaminated surface.

"When you walk through a hospital, you see Purell and other alcohol-based sanitizers all over. These are a good reminder to staff and visitors that handwashing is important. Which is great, but these products are just an extra step. They will not kill *C. diff* spores. For

that, she explains "diligent handwashing with hot soapy water is essential." It takes bleach to kill the spores on surfaces and the friction of handwashing to rid hands of *C. diff*.

HAIR OF THE DOG

Fortunately, many infections respond to treatment with antibiotics. Typically, it takes a 10-day course, but some people may require more time or a course of IV antibiotics in a hospital.

"If you are harboring bacteria in your bowel, there is risk of recurring infection, so it's important to follow the prescribed course of antibiotics. Discontinuing antibiotics when symptoms decrease can contribute to antibiotic resistance," Davies says.

Serious or resistant *C. diff* infections may require more aggressive strategies. In some cases, a fecal transplant procedure (transferring bacteria from a healthy person's colon) may be necessary. For instance, surgery may be required to fix a perforated colon.

"Some strains are resistant to antibiotics, which is why we caution people not to self-medicate with antibiotics just because you have them," Davies says. "We, as medical professionals, are making concerted efforts to be good antibiotic stewards and not overprescribe, to minimize resistance to any strain."

Andrews agrees. "People get a cold and often go to the doctor demanding antibiotics, but a cold is a virus and antibiotics won't work. Taking them unnecessarily is causing virulence and resistance in many classes of microbes," she says. "By doing this, you are going to cause resistance five or 10 years down the line."

Researchers believe a particularly virulent strain of *C. diff*—NAP1—that emerged in 2000 was spawned by antibiotic overuse. This strain accounts for about 30 percent of all *C. diff* cases. "It's a big toxin producer. It can also be antibiotic-resistant and tends to recur," Andrews says.

Furthermore, there has been a slow rise of community cases, including those among people who don't fit the mold. "We are seeing it in a younger population, in those who aren't immune-suppressed," Davies says. "If a 19-year-old who is not on antibiotics or immune-suppressing medications comes into my office with significant diarrhea, *C. diff* is still something to think about."

Awareness of the threat posed by *C. diff* and similar infections has led to changes in prescription habits and that's a good thing, says Laura Kierol Andrews.

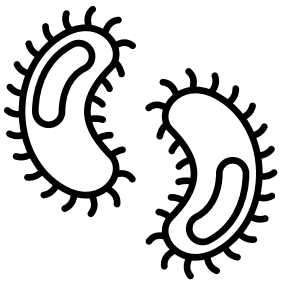
Yale School of Public Health is part of the Connecticut Emerging Infections Program, a collaboration between the Connecticut State Department of Public Health and the CDC. Its *C. difficile* surveillance program monitors all cases in New Haven County and is one of 10 sites throughout the United States monitoring *C. diff* infections in the population.

"One of the biggest trends we are looking at is from 2011 to 2017, when we saw the overall number of *C. diff* cases, as well as the hospital-acquired cases, go down. But the community-associated cases were going up," says Danyel Olson, MS, MPH, the program's surveillance coordinator. That trend continued until about 2015, Olson says, when the rates stabilized.

"The decrease in hospital infections could be from implementation of infection control practices, antibiotic stewardship, and new treatment guidelines," Olson says. "We are unsure why infections increased in the community."

Andrews, for one, is optimistic about the tide turning when it comes to the overuse of antibiotics. "I think half the battle is recognizing that this is a problem," she says. "*C. diff* infection rates may get worse before they get better, but I think it goes back to getting antibiotic prescriptions under control." */yale medicine magazine*

Carrie MacMillan is a staff writer for Yale Medicine, the clinical practice of Yale School of Medicine.



COSTS AND BENEFITS

Some parasites may be unlikely allies with human health.

BY JENNY BLAIR, MD '04

Hookworm, one of humankind's oldest foes, dwells in the ground, waiting quietly for its victims. This gape-mouthed parasite gains entry from warm, moist soils through bare feet; takes a trip through the lungs; and settles in the intestine to suck blood, often causing anemia, malnutrition, and stunted development. More than 500 million people worldwide are thought to be infected, mostly in Latin America, Africa, and Southeast Asia, and vaccination development and deworming solutions are underway.

But the hookworm and related parasitic worms, called helminths, may also have something to offer us. Infection can be protective in some circumstances, and Yale researchers are finding that the creatures can teach us how our immune systems self-regulate.

"These parasites have evolved over hundreds of thousands of years with their mammalian host. They understand each other extremely well," says Michael Cappello, MD, a professor of pediatrics, of microbial pathogenesis, and of public health, who studies how nutrition influences susceptibility to worm infection, as well as the efficacy—or lack thereof—of treatment.

The human-worm relationship may be an agreement of sorts, Cappello suggests. "'We'll allow you in as long as you don't cause too much disease and you don't overwhelm us,'" he says, adding, "I think that we have evolved to harbor light worm infections."

As evidence, Cappello explains that curing worm infections may not necessarily make a child healthier: "In some places, [mass deworming] has brought down the intensity of worm infections. But it's been less clear that those reductions are actually associated with improved health."

The worm might protect children from some of the worst effects of malaria. In 2007, Cappello studied anemia levels in Ghanaian children who were infected with malaria, hookworm, both, or neither. Having either one of the two infections rendered a child more likely to be anemic compared to uninfected children. With malaria, the anemia was especially severe. Paradoxically, though, having both infections at once does not multiply that likelihood, the team found. In fact, having both parasites resulted in less severe anemia than in victims suffering from just malaria.

"The combination of these two parasitic diseases is such that they actually in some ways kind of cancel each other out—and it may be that light hookworm infection blunts the response to malaria that leads to anemia," Cappello says. "This was a surprising finding. … but it does add some supporting evidence to the idea that light worm infections may be beneficial."

To be clear, that's *light* infection. Moderate and heavy infections seem to do more harm than good, so it's important to keep the worm under control. One major tool for doing this is mass drug administration, or deworming people en masse with a single dose of an antiparasitic drug like albendazole. But while this approach has been shown to reduce the prevalence of worm infections in some parts of the world, it doesn't always work as expected.

In West Africa, for instance, Cappello's team has found that mass drug administration has spotty efficacy.

"Some villages have a cure rate with albendazole that is 75 percent, whereas a few miles away a village showed a cure rate of zero," Cappello says. The reasons have to do with the child's nutritional status, the timing of treatment, and some worms' genetic resistance to the drug, he believes.

So current worm control strategies may need to evolve, and Cappello wants to be ready. "Our lab and a small number of other groups around the world are trying to develop tools so that resistance can be detected when it emerges," he says.

Hookworms are also chemistry wizards of sorts, manufacturing molecules that lead to profound effects in their hosts. They pump out anti-clotting molecules, for example, to keep their blood meals flowing (Cappello spent his early career purifying these molecules, one of which made it to human drug trials).

Perhaps more importantly, the worms also send molecular communications that regulate the immune system and ward off a strong attack. Carla Rothlin, PhD, is an associate professor of immunobiology and of pharmacology, who studies the immune system's brakes—which molecules and pathways signal that it's time to slow or stop an immune attack. One such brake is called the TAM receptor. The body can stimulate that receptor itself, but parasites can do it too. During an immune response to helminth infection, Rothlin's lab has found that immune cells begin making massive amounts of a molecule called IL-4. That leads to the creation of a molecule called protein S, which plugs into TAM receptors and starts a negative feedback loop that calms the immune system.

Piecing together interactions like this one may shed light on the hygiene hypothesis—a way of explaining why, as sanitation improves and people are exposed to fewer microorganisms, their rates of allergy and autoimmune diseases go up. Researchers believe the immune system has evolved to anticipate its parasitic foes and even to rely on their tools for tamping down the immune system. When the parasite and its moderating influence are absent, we turn on ourselves.

This is the idea behind helminth therapy, in which worms are deliberately ingested to treat autoimmune and allergic diseases. Pig whipworm eggs have been studied as a treatment for inflammatory bowel disease, for example. Unable to develop to adulthood in humans, the eggs nonetheless deliver molecular messages to the human immune system that seem to curtail its propensity to attack itself. Intentional hookworm infections have also been investigated for allergic rhinitis.

But Rothlin believes it may be safer to pinpoint which molecules the worms use to talk to the immune system, then mimic that communication with drugs. This approach could replace potentially risky experiments with parasite infection—a practice "I would argue … can be very dangerous," Rothlin says.

"Microorganisms are very good at this," she adds. "For millions and millions of years, they have tried to usurp the regulatory pathways that we have. We can now study them, identify which molecules [they use, and] know more about the regulatory pathway itself. Microorganisms are great tools to understand immunology."

Jenny Blair, MD '04, is a frequent contributor to Yale Medicine Magazine.

FROM BENCH TO BOOK

How research findings make their way to the classroom.

BY JOHN CURTIS | ROBERT LISAK PHOTOGRAPHS

Yale School of Medicine's Richard Belitsky, left, and Michael Schwartz work with faculty to shepherd the latest medical research from the pages of publications into the school's curriculum.

In a first-year course called "Attacks and Defenses," discussions of the microbiome make up part of the 17 immunology lectures.

One lecture covers "what the microbiome is known to do in the health and disease setting, everything from Alzheimer's to autism to obesity to cancer. It's a very broad stroke—there aren't enough lecture hours to get into specific areas," said Akiko Iwasaki, PhD, the Waldemar Von Zedtwitz Professor of Immunobiology, and Molecular, Cellular, and Developmental Biology, and a Howard Hughes Medical Institute investigator. "There's so much discovery going on in the microbiome field. I believe it's going to have to be expanded every year."

The new medical school curriculum, unveiled in the fall of 2015, anticipated exactly this kind of scientific advance.

"No matter what we define as the content of the curriculum, no matter what we decide to teach at any given point in time, as we are planning and implementing the curriculum, knowledge is continually changing," said Richard Belitsky, MD, HS '82, FW '83, deputy dean for education, the Harold W. Jockers Associate Professor of Medical Education, and associate professor of psychiatry.

With each advance, faculty and administrators gauge the breakthrough's importance and whether it's something medical students need to know. For each new finding, faculty must figure out how and who to teach it, and—there are only so many hours in the day—find space in the curriculum. "People who are teaching are always thinking about this," Belitsky said. "We rely on the expertise of our faculty to determine the key things our students need to know. We ask them to do it not independently of the curriculum, but coordinated with the rest of the curriculum."

Belitsky jokes that managing this constant pressure on medical education explains the large bottle of Tums on the desk of Michael L. Schwartz, PhD, associate professor of neuroscience and associate dean for curriculum. It falls to Schwartz to work such discoveries into the classroom. This integration happens in two ways, Schwartz said, the first of which involves faculty keeping tabs on what's happening in the various departments. "Things come in organically by virtue of the fact that our faculty are world leaders in their fields," Schwartz said, adding that course directors meet monthly, and faculty have an annual retreat for discussions of curriculum.

Then there is also structured process, as occurred with the opioid epidemic. In response to a growing national crisis, a task force was convened to examine what was being done to prepare future doctors. This review included assessing the curriculum, how well the related material was being taught and learned, and whether the curriculum had omitted any critically important information.

The curriculum integrates basic and clinical science across the four-year continuum. Students begin clinical training early in medical school and revisit the basic sciences during clerkships, which requires faculty coordination to avoid unintended repetition and to place new material in a useful context. "We have structures in place to continuously examine this," Belitsky said, "and it's a constant balancing act."

So far there has been no schoolwide effort to introduce the microbiome into the formal curriculum, but it is happening in some courses. Cyrus Kapadia, MD, FW '78, professor emeritus of internal medicine, is planning to introduce it in a first-year master course on energy and metabolism. First, he wants to find out what students are already learning about the microbiome. Then, he'll tap into faculty experts. "We have some people at Yale who are known nationally for their work on the microbiome," he said. "Not to use those people is a crime." Kapadia hopes to have a plan for the course by December.

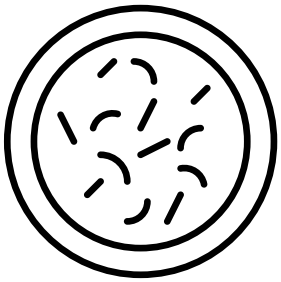
Kapadia pointed out that while there is enormous interest in the microbiome today, interest in gut flora among scientists began decades ago. One fascinating study published in 1934 examined the bacterial population at different levels of the intestines of dogs and monkeys. This work was done decades before Watson and Crick's paper in *Nature* on the structure of DNA,

The Yale School of Medicine curriculum is the product of an ever-evolving set of variables and inputs. Keeping it relevant requires constant input and balanced perspectives. From left, Richard Belitsky; Leigh Cromey, student services officer and manager of integrated curriculum; Michael DiGiovanna, co-director of integrated course curriculum; and Michael Schwartz review the curriculum changes.

and with access to only primitive microbiological techniques. It wasn't until the 1960s that more advanced microbiological methods enabled a quantitative assessment of the microbial flora at different sites in the intestines from duodenum to colon. Studies in the native population and in Peace Corps volunteers in the 1960s at such centers as the Christian Medical College in Vellore, India, further established the link between gut flora and small intestinal mucosal architecture.

The availability of DNA sequencing methods has brought the field to a higher level. "The big thing now," Kapadia said, "is that we are talking about the role of the microbiome in diseases affecting the mind, its role in diabetes and obesity, and its connections to cardiovascular disease and to cancer." Just as the medical curriculum is constantly changing, the hope among faculty is that students will appreciate that medicine requires lifelong learning. Kapadia reminds his preclinical students: "Your education won't stop when you get to the wards!" */yale medicine magazine*

John Curtis is a frequent contributor to Yale Medicine Magazine.



GOOD BUGS GONE BAD

Helpful in some places, bacteria can cause conditions like MS when they break through the body's barricades.

BY JENNY BLAIR, MD '04

In multiple sclerosis (MS), the immune system attacks the nervous system, causing nerve and brain damage. Yet the problem might actually originate in another place entirely: the gut. Yale researchers are among those teasing apart how MS and other autoimmune diseases may arise as a result of complex interactions among genes; the intestines' ability to maintain a tight boundary between its contents and the rest of the body; and the bacteria that live there.

To begin with, genetic mutations in MS "lead to changes in the interactions between the immune system and the microbiome in the gut," says David A. Hafler, MD, the William S. and Lois Stiles Edgerly Professor of Neurology and professor of immunobiology.

A renowned researcher responsible for a number of seminal discoveries in MS, Hafler was first to describe the immune cells that attack myelin in the nervous system. He has also identified MS-specific genetic variants—most of them related to immune genes—and unraveled signaling pathways that make potential targets for drug treatment. In 2013, he and his colleagues published the landmark discovery that sodium chloride can lead to autoimmunity in MS. He is preparing papers for *Science* and *Cell* that map out the disease's genetic architecture, a culmination of almost two decades' work.

Hafler is among a group of scientists who are uncovering genetic clues linking MS to the gut. In 2011, he co-authored a paper listing scores of culprit MS genes, one called *INAVA*, whose products show up in the gut. Researchers recently found that *INAVA* also plays a key role in Crohn's disease—a type of inflammatory bowel disease (IBD) that often accompanies MS. In a March 2018 paper in *Science*, a team at the Broad Institute of MIT and Harvard reported that the *INAVA* variant seems to loosen the integrity of the intestinal barrier, rendering it permeable to molecules that shouldn't be able to pass through.

That phenomenon is sometimes called "leaky gut." Findings like the Broad team's hint at the importance of the gut lining to autoimmune disease. The digestive tract is lined by epithelial cells that are tightly connected to one another, forming a barrier between the food being digested and the bloodstream. Abnormal permeability of that layer has been observed in people with IBD, as well as in mice suffering from a version of MS.

Though leaky gut has become a popular scapegoat in complementary medicine circles for everything from autism to acne, it likely constitutes a real link to inflammation, says Noah Palm, PhD '11, FW '15, assistant professor of immunobiology, who studies the links between autoimmune disease and the gut microbiome. His lab explores how communities of gut bacteria may influence not only the immune system, but also neurodevelopmental disorders like autism.

"There's a lot of suggestive evidence in the literature that at least some sort of barrier disruption co-occurs with a lot of these [autoimmune] diseases," Palm says.

Leaky gut seems to arise in a number of ways. In some cases, bacteria may drill down to the barrier and loosen it directly, Palm says.

Chronic high blood sugar can also do it, according to a team led by former Yale postdoctoral associate Eran Elinav, MD, PhD, now at Israel's Weizmann Institute of Science. Elinav's group linked leaky gut to obesity and to type 1 diabetes, an autoimmune disease, in a March 2018 paper in *Science*.

When the gut's barrier comes down, it can let in bad actors. In genetically susceptible mice, certain bacterial species can traverse the intestinal barrier; travel to the liver and lymph nodes; and trigger a lupus-like autoimmune disease, according to a group led by Martin Kriegel, MD, PhD, FW '06, adjunct assistant professor of immunobiology at the School of Medicine. The team members, who found the same bacteria in liver biopsies of human patients with lupus, also published their results in a March 2018 issue of *Science*.

There's strong evidence to suggest that bacteria are central to what goes wrong in MS and other autoimmune diseases.

"One of the things that we're doing very intensively is looking at the microbiome in MS," Hafler says. "We and others have found that there are clearly abnormalities."

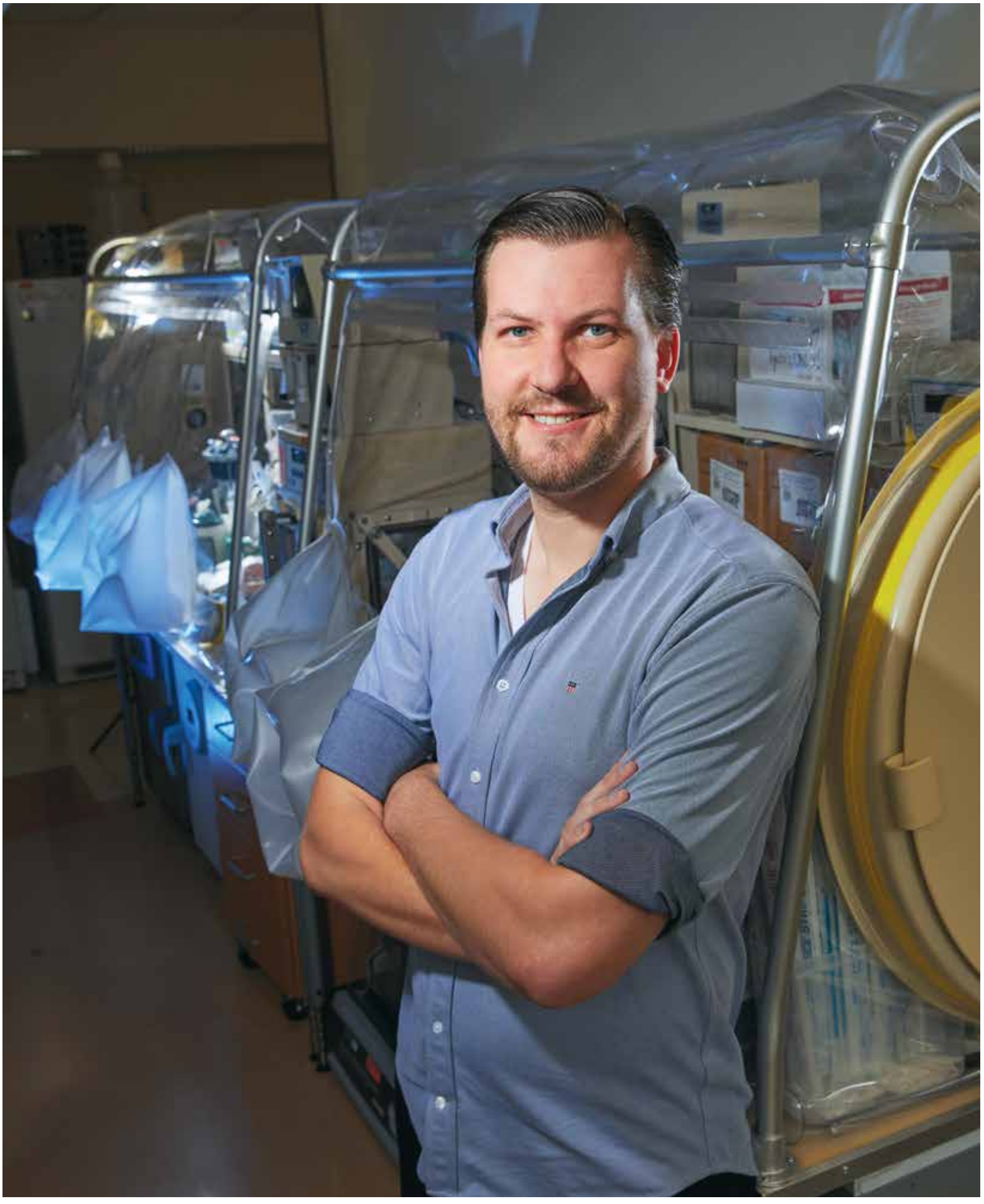
For instance, MS patients have a lower-than-normal abundance of *Lactobacillus* species—the kind found in yogurt—and a higher abundance of *Ruminococcus*, a group of bacteria that can break down resistant starches. Exactly how such differences translate into disease is still unclear. But in mouse models of MS, inflammatory cells involved with the disease have been observed to be influenced by gut bacteria.

Moreover, a microbiome "transplant" from MS patients into mice can actually provoke MS-like symptoms, according to two papers appearing last fall in *Proceedings of the National Academy of Sciences*. The patients' bacteria seem to alter immune T cells' behavior in the mice, leading to a type of encephalitis similar to MS.

Bacteria also seem to influence brain cells. Tryptophan is an essential amino acid found in protein-rich foods like meat, oats, and peanuts. It is converted in the body into the neurotransmitter serotonin and the sleep-related hormone melatonin. But in a March 2018 paper in *Nature*, a multinational group of researchers reported that molecules from bacteria that metabolize tryptophan were also controlling microglia cells in the brain that can stimulate astrocytes to produce an MS-like disease in mice. Such bacterial influence, the authors suggested, may help explain why problems with the gut microbiome can impair recovery from spinal cord injury—and why certain other species seem to help recovery instead.

"The most important questions are: What is the microbiome? And what metabolites is it making in relation to the genetic architecture of the individual?" Hafler says. "That's what I think it comes down to."

Jenny Blair, MD '04, is a frequent contributor to Yale Medicine Magazine.



EVOLVING ATTITUDES

How microbes are changing received wisdom.

BY JEANNA LUCCI-CANAPARI | ROBERT LISAK PHOTOGRAPHS

As researchers compile evidence of microbiome-related afflictions, faculty like Noah Palm help place discoveries in their proper contexts. In many cases, in which an effect has been measured, the cause remains unidentified.

Just as the ancient Greeks centered their understanding of the human body on its four humors, and later eras separately proclaimed the heart, the brain, and even the genome as the leading player, the microbiome is now taking center stage. This superorganism, as it has come to be known, has become a major force in the biomedical research marketplace, attracting substantial financial investment and taking up more and more column inches in publication space. It is also becoming equally clear that this young field still has a long way to go before it truly shifts the paradigm for understanding disease.

"There are a lot of microbiome evangelists out there who would tell you this has changed our world; it's changed it already and will continue to change it," says Noah Palm, PhD '11, FW '15, assistant professor of immunobiology. Palm heads the lab that seeks to understand the mechanisms by which the microbiome interacts with the human hosts' immune system, with the ultimate goal of using these interactions to combat disease. However, "so much is still in question, at a basic science level, that must be understood before research addresses how the microbiome can be used in therapies."

The impatience and an eagerness to take advantage of the resources brought by hype surrounding the microbiome, says Palm, means that there is pressure to fulfill the great promise of the microbiome too hastily. "You have one or two failures and everyone gives up on the whole thing. That's actually one of my major fears in terms of the whole field of biotech. I do believe there will be transformative, paradigm-shifting therapies that target the microbiome. But it's not going to be next year."

Rather than evangelism, Palm says a common view at Yale is a more "conservative, data-driven kind of perspective," he says. More conservative scientists say microbiome research must focus on establishing cause-and-effect evidence that the microbiome impacts disease on a molecular level, rather than just inferring causality through observation. According to Eduardo Groisman, PhD, the Waldemar Von Zedtwitz Professor of Microbial Pathogenesis, it is very difficult to locate a sure causal relationship between a microbe in the gut microbiota and a function in its host, but there are many undeniable correlations. "The underlying assumption of all these correlations, which is very intuitive, is that if you have an abundance of a particular type of bacteria from the microbiome, then that organism is responsible for a particular behavior," he says. Groisman studies bacteria, such as the gut-symbiotic *Bacteroides thetaiotaomicron*, in an attempt to find the mechanism behind how organisms know when and how to shut particular genes on and off.

"To a lot of scientists in mature fields, it's not causation until you have a level of molecular insight that makes you comfortable with how it's really working, not just that it works," says Palm. To them, causation means more than a presence or absence of particular microbes or groups of microbes in the gut that cause disease, proof of their function, and how they exert that function. The challenge of causation is further confounded by the vast diversity in the microbiome, which varies widely among both individuals and populations. "If you compare it to understanding, say, the function of human genes, it's of an intractable magnitude. There are 150 times more genes in your microbiome than in your own genome," says Palm. The microbiome is also intensely sensitive and can change within an individual even within a day.

Further, the expense of experimentation influences the research. Because of this, "there is a temptation to generate a lot of data," says Groisman. "What these correlations are providing is information. But one cannot equate information with knowledge."

Working alongside researchers like Richard Flavell, Palm looks for causal relationships between bacteria and health outcomes. Scientists have established promising correlations, but the mechanisms by which bacteria contribute to a healthy immune system remain elusive.

In the past 10 years, major strides have occurred in moving from correlation to causation in microbiome research, with investigators using animal models, particularly gnotobiotic, or germ-free mice, for proof. Palm's postdoctoral work with Sterling Professor of Immunobiology Richard Flavell, PhD, used immunoglobulin A to identify the bacteria in the microbiome that affect irritable bowel disease (IBD). Using these mice, who are born completely sterile, the team was able to isolate and identify a particular microbe that drives the disease. "To me that's causation," Palm says. "This bug is causing this disease."

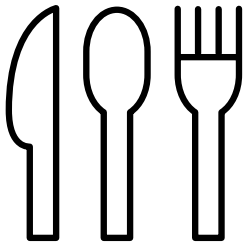
Groisman points to the most established use of the microbiome in therapy as an example: fecal material transfer, an FDA-approved treatment for the stubborn and potentially deadly *Clostridium difficile* infection, or *C. diff*. The science behind this therapy, which has been shown to work in the vast majority of *C. diff* cases and even save lives, is based on an observed correlation, not causal effect, says Groisman. It is a very recent development, with the long-term effects still unstudied. "How many of these correlations will hold over time? We will see."

When it comes to the microbiome, "there are still massive gaps in our fundamental knowledge," says Palm. Despite these growing pains, the field is making progress toward maturity, balancing the excitement over the potential of the microbiome with rigorous study. "I think we have at least the beginnings of this tool set to do the correlation-to-causation transition," says Palm. The tool set includes increasing improved DNA sequencing, as well as culturing techniques that allow annotation of the vast number of microbes that make up the microbiome. "The hope is that by leveraging cutting-edge tools and feeding the data we get into computational pipelines, you start to take bigger bites of the apple, even though the problem seems intractable at this time," says Palm. With careful use of the resources available, the hope is that all this information will eventually turn to true knowledge.

This young field is not just a flash in the pan. "The microbiome is not going away," says Palm. "Just like neurobiology is not going away. Nobody is going to stop studying the brain. Same thing with the microbiome."

/yale medicine magazine

Jeanna Lucci-Canapari is a frequent contributor to Yale Medicine Magazine.



AN END TO DIETING

Research on obesity may change approaches to nutrition.

BY JEANNA LUCCI-CANAPARI

"Consider the gut microbiome as the center of the world," says Li Wen, MD, PhD, FW '97, associate professor of medicine (endocrinology). At the center of a lined notepad, Wen draws a circle: this is the gut microbiome. Radiating out, she draws arrows that point to a wide span of human diseases, including cancer, problems with the body's circadian rhythm, and autism. Among them are diabetes and obesity. Yale researchers, including Wen, have been at the center of pivotal studies that elucidate the gut microbiome's connection to these disorders.

In a trial published in *Nature* way back in 2008, Wen drew a line connecting the gut microbiome and type 1, or juvenile, diabetes. Unlike type 2 diabetes, which is largely driven by such environmental factors as diet, type 1 is an autoimmune disease in which the body's innate immune system does not properly function and attacks its own insulin-producing beta cells. Using genetically modified diabetic mice, Wen and a team pinpointed a protein molecule, MyD88, that acted as a "master controller" of innate immunity. The mice bred without the MyD88 molecule in a pathogen-free environment did not develop type 1 diabetes. "We thought, 'Wow, we've got a molecule with the potential to translate into clinical use in humans,'" recalls Wen.

As is often the case in research, Wen encountered a complication: the mice, while diabetes-free, developed opportunistic bacterial infections. "We know that when there is an infection, it affects the immune system, so we needed to eliminate this possibility," she says. To do so, they performed the experiment with germ-free mice, which are bred to have no microorganisms of any kind living in or on them. Stunningly, the diabetes returned.

"Science is like a dog chasing its own tail," Wen says. To understand this development, the team contaminated those germ-free mice with gut bacteria. The diabetes rates in these mice dropped drastically. The team concluded that a combination of genetics and the commensal bacteria in the gut of the mice together halted the development of type 1 diabetes, and this combination would be critical in understanding how autoimmune diseases develop.

"Genes alone do not explain these diseases. Genetic shifts cannot occur as rapidly as immune

diseases have been rising," says Martin Kriegel, MD, PhD, FW '06, adjunct assistant professor of immunobiology and of medicine (rheumatology).

Kriegel, in a study published earlier this year in *Science*, discovered that gut bacteria in mice can break through the gut lining; travel to other organs; and trigger an immune response, with implications for the treatment of lupus, another autoimmune disorder. "Environmental factors also have to go through the so-called barrier organs—the skin, the lungs, the gut—that are covered with microbes. The combination of genes, environmental factors, and their influence on resident microbes contributes to disease onset."

Yale researchers have established a causal link between the microbiome and obesity, which is a driver of type 2 diabetes. Rachel Perry, PhD '13, FW '17, assistant professor of medicine (endocrinology), discovered through a series of experiments that the mice with high-fat diets produced high levels of acetate, a short-chain fatty acid, which increases insulin secretion and raises the drive to eat. This acetate, says Perry, is derived from the microbiome itself. The study, which she conducted with Gerald Shulman, MD, PhD, the George R. Cowgill Professor of Medicine (Endocrinology) and co-director of the Yale Diabetes Research Center, was published in *Nature* in 2016.

Much like Wen's discovery, "we got into this largely by accident, as happens with a lot of interesting science," says Perry. When conducting experiments that used acetate as a tracer, she and a team in Shulman's lab noticed that obese animals were producing higher levels of acetate. But they did not know where in the body it was being produced, or why.

"Surprisingly to us, these obese mice had a large increase in their plasma insulin concentration," Perry says. "Obese patients who are not yet diabetic have very high plasma insulin concentrations, and that is what is required to keep their blood sugars in the normal range. When we saw this increase in acetate, we thought maybe these two things are related."

The team discovered that acetate drives this increased insulin secretion through activation of the parasympathetic nervous system, leading the researchers to the gut microbiome as the source of that acetate. Shulman and Perry are now looking to identify the specific microbe or set of microbes in the microbiome that set off this reaction.

The ultimate goal of finding these types of links, says Wen, is to develop the ability to test for particular microbes and use them as biomarkers, essential for early prevention. The next step is to make the leap from animal to human studies, which is fraught with challenges. "I like to compare it to the human genome field two decades ago, which was very exciting but also very descriptive," says Kriegel. "Now the field has matured. A lot of insight is gained from animal studies, but these studies are not always translatable to humans."

The ever-shifting constitution of the microbiome is just one complication that frustrates inquiry. In their work, "we were struck by how quickly the microbiome changes," says Perry. "In rats, when we took food away for just 48 hours, there were drastic shifts in their acetate production, and, I suspect, in their microbial composition. It took only two days of not having anything to eat for that to change very drastically. And the challenge in humans will be, how do we know we are sampling what we think we are sampling?" This is the nature of transformative science.

"The more one studies," concurs Wen, "the more questions one has."

Jeanna Lucci-Canapari is a frequent contributor to Yale Medicine Magazine.

A heroic contribution to medicine

Joseph Marshall Flint's genius for wartime surgery

Jacqueline Rocheleau

Because Joseph Marshall Flint, MD, was trained as a research anatomist, many at Yale did not see him as their top choice for professor of surgery at the School of Medicine. When the administration offered Flint the position, other faculty and physicians complained: the doctor's only former surgical experience was during a sabbatical year in Germany and Austria in 1906, right before he arrived at Yale. Despite the controversy, Flint would prove his value to Yale during his 14-year career there, leading its mobile hospital unit in World War I and reforming surgical education.

Before he accepted the position as professor of surgery, Flint had conditions. He wanted laboratories, classrooms, and offices "in close contiguity with the hospital and dispensary," wrote Flint's Yale colleague, Samuel Clark Harvey, PhB 1907, MD 1911. In the early 20th century, medical schools did not usually have full-time faculty or resources dedicated to research and student training.

Around this time, however, a movement to institute these changes in medical schools was beginning. Flint joined the movement and helped restore Yale's waning reputation as a top medical school. For example, to make up for the fact that medical students could not work with

patients, Flint instituted a dog surgery course modeled after the one Harvey Cushing, MD, had pioneered at Johns Hopkins.

European conflicts interrupted Flint's practice as a professor. During the Greco-Bulgarian War in 1913, a precursor to World War I, Flint served as a surgeon in an Athens hospital. Once World War I began, Flint started volunteering on behalf of the French before the United States joined. He worked as a surgeon in a French military hospital in 1915 and wrote papers on military medicine. He also developed an X-ray photography method to locate foreign bodies and refined suspension methods used to treat fractures.

Flint took particular interest in French military hospital design. After five months volunteering there, Flint told the *Yale Daily News*, "Not the least interesting feature of military surgery is the organization of a military hospital."

In fact, according to an article in the *Yale Daily News*, Flint had pushed for Yale to join the war and provide a Yale Hospital for wounded European soldiers as early as 1914.

In 1917, a few weeks after the U.S. declared war on imperial Germany, Flint was asked to head the efforts to design and implement a mobile hospital for American soldiers in France. Flint's work with the French resumed as he studied their mobile hospitals to perfect the American counterpart.

From 1917 to 1919, Flint served as the commanding officer of Mobile Hospital Unit No. 39, the Yale Unit, of the American Expeditionary Forces. He designed the Yale Unit for maximum efficiency, modeling it after both French hospitals and Ford's factory assembly lines. If soldiers were the product along the assembly line, the staff members were the factory workers, staying in place to perform their assigned duty as the belt rolled along to maximize hospital efficiency.

According to Melissa Grafe, PhD, the John R. Bumstead Librarian for Medical History and head of the Medical Historical Library, Flint's design was efficient not only on paper but also in practice, lowering the average operating time per patient.

Because of the hospital's success, Flint was awarded the Distinguished Service Medal with a citation that, according to Harvey, read: "When placed in a position of great responsibility as commanding officer of Mobile Hospital No. 39 at Aulnois-sous-Vertuzey, France, he used extraordinary skill and sound judgment in the organization and operation of that unit, the first of its kind in the American Expeditionary Forces."

During his service as commanding officer, Flint contracted the Spanish Flu and never fully recovered. Throughout the rest of his life he experienced persistent pulmonary problems. In Yale's collection of his writings, several books are filled with hand-drawn medical charts, colored pencils and red ink tracing the trajectory of his health. Flint died in 1944, living long enough to see Mobile Hospital Unit No. 39 reinstituted in World War II.


Yale's Pioneer Mobile Hospital.

OPPOSITE PAGE Flint's "Mobile Hospital No. 39" was based on experiences with systems he had observed in the French military, and during volunteer work with the Greek alliance during the Second Balkan War of 1913.

LEFT Period publications were positively effusive in their praise for Flint's hospital, which incorporated the very latest in organizational theory.

BELOW A depiction of Flint's Mobile Hospital from a scrapbook in the George Milton Smith collection, made by his brother, J. Andre Smith, who served in WWI.

LEFT Overhead view of a 3-D architect's model built for presentation purposes. The library still owns a copy of the model, though it is maintained only as a historical curiosity.

COURTESY MEDICAL/HISTORICAL LIBRARY

Akiko Iwasaki and the Mighty Microbiome

IGA UENO CASTLE, ALSO KNOWN AS HAKUHO or White Phoenix Castle, is considered one of the more beautiful examples of an architectural style popular in Japan during its early modern period. Located in Mie Prefecture, Iga Ueno Castle was built to project political legitimacy during great civil unrest. The castle provides a visually striking reminder of a time in human history when stability was just a couple of bad harvests from breaking down, and a healthy country required tall, thick stone walls to have a chance of surviving. Without those great defensive bulwarks, feudal Japan's fledgling government might not have lasted to evolve into the form that it holds today.

Perhaps it is fitting, then, that a child of Iga should be among the world's foremost experts on biological defense—specifically, conceptualizing how the human body defends itself from illness. Yale's Akiko Iwasaki, PhD, the Waldemar Von Zedtwitz Professor of Immunobiology and of molecular, cellular, and developmental biology, and a Howard Hughes Medical Institute investigator, has dedicated her professional career to researching how the body perceives and responds to certain infections.

As someone who helped develop the field of antiviral immunology, Iwasaki often focused her inquiries on the microbiome. One recent example involved medical trials with mice raised in laboratories.

"We found a few years ago that when you treat mice with antibiotics, and you get rid of most of the microbiome, these mice become susceptible to influenza," says Iwasaki. She explained that the microbiome and the mouse's "natural" immune system work together to keep each other healthy and prepared for infection, and that when one is compromised the entire system falls apart. "It seems that the microbiome is important for the well-being of the immune system in general," Iwasaki says.

Scientists have known for some time that animals with germ-free guts are at higher risk of disease and defect. Iwasaki notes that these early observations from decades ago relied on culturing bacteria from stool samples with crude equipment, but that the technological advances of the last three decades have spurred a kind of categorical revolution in the field. "With sequencing technology, we can actually tell what type of bacteria live in a particular gut, even the ones one can't culture in a lab. We have the whole picture of what kinds of bacterial species are present in a healthy or unhealthy animal or, increasingly, person," says Iwasaki.

One portion of this equation that isn't understood yet is the mechanical relationships between body and microbe; which causes produce which effects. In part this difficulty is due to the

Akiko Iwasaki, center, is excited about the many recent technological and scientific advances that have helped break open the floodgates for insights into infection. Women's Health Research at Yale undergraduate fellows Haleigh Larson, left, and Rose Davis look on.

ROBERT LISAK PHOTO

sophistication of the microbiome. Another difficulty, according to Iwasaki, arises because the microbiome itself is far more complicated than is easily imaginable.

"Going past the microbiome, and the human genome, you have the metagenome, which includes all the phages or viruses that live within the bacteria, and other viruses that live inside our cells. So, we must consider the virome, too."

Another recent discovery is that the 90 percent of human DNA previously considered "useless junk" seems to have purpose, and may not be human DNA at all. "Retroelements occupy almost half of our genome," says Iwasaki, noting that this is "huge real estate compared to our coding sequence. And we have very little idea what they're doing, though they seem much more vital than originally envisioned."

Iwasaki finds the question of infection fascinating—why under some circumstances bacteria and viruses are able to coexist with the body in healthy numbers and may even be critical to its healthy function; while under different circumstances an imbalance can create conditions for discomfort or even death. Many recent scientific advances have been accompanied by an exponential expansion in the number and complexity of questions for laboratories.

After the period of civil unrest ended in Japan, White Phoenix Castle deteriorated and was allowed to fall into ruin. Later, though, it was rebuilt for its architectural beauty and historical significance. One might debate its utility as a defensive

ONLINE EXCLUSIVE

Patricia Nez-Henderson, the first Native American woman to graduate from Yale School of Medicine, spoke with Peter Salovey as part of the President's Women of Yale Series. She discussed issues like identity, displacement, addiction, and the power of perseverance.

For more on their talk, visit ymm.yale.edu/talk

structure necessary to the survival of Japan's government, but it and castles like it are significant in ways their builders may not have imagined. As it turns out, the health or illness of a system can be immensely complicated, not just on a microscopic level but on a national level as well.

—*Adrian Bonenberger*

From the killing fields to the halls of power

When *Yale Medicine Magazine* last checked in with SreyRam Kuy, MD, MHS '09, FW '09, it was in the aftermath of Hurricane Harvey last summer. Kuy, associate chief of staff at the Michael E. DeBakey Veterans Affairs Medical Center in Houston, was running the hospital's emergency response. She spent days on end making sure the hospital took care of its patients and staff, even taking a turn working the cafeteria's chow line.

Kuy has served the VA for nearly two decades, in roles spanning from Deputy Under Secretary for Health, overseeing a $14.5 billion-dollar budget, to operating on colon cancers and gangrenous limbs as a general surgeon. "In any capacity, it is an honor to serve these heroes," Kuy said.

She's also been named one of 10 recipients of the Women of Worth award by L'Oréal Paris and is a Daily Point of Light—the latest in a roster of awards that includes the Ford Family Foundation's Gerald E. Bruce Community Service Award and the American College of Surgeons' the Dr. Mary Edwards Walker Inspiring Women in Surgery Award. A common thread is her service to such vulnerable and underserved populations as veterans and mothers on Medicaid. Given her life story, said Kuy, "paying it forward" is nonnegotiable.

"I am a child survivor of genocide," she said. "To be able to live in America is a privilege I am very grateful for. I owe it to the generosity of strangers who saw value in helping me when I had nothing of value to give back and there was no reason to believe in me."

Kuy was born in Cambodia in 1978. This was three years after the Khmer Rouge took power and emptied the capital, Phnom Penh, at gunpoint. Kuy's father had a government job and her mother was a school teacher. The Khmer Rouge executed everyone with an education, Kuy's parents feigned illiteracy. With her older sister, they marched hundreds of miles to forced labor camps in the jungle. Kuy was born in one of those camps.

The family saw a chance to escape in 1979, when Vietnam invaded Cambodia. They walked by night and hid during the day until they reached a refugee camp in Thailand. Safety still eluded them, however. A rocket-propelled grenade landed on their tent, injuring Kuy and her mother. A Red Cross surgeon saved their lives.

Three refugee camps later, the family landed in the Philippines, where a Christian missionary helped them enter the United States as refugees. They settled in Corvallis, Ore., in 1981. Kuy's father worked as a janitor at Oregon State University and her mother was a housekeeper at Good Samaritan Hospital.

"My mom used to mop the floors of the operating room and now I work as a surgeon; my dad mopped the floors at Oregon State University, and that's where I graduated," Kuy said. "That is how amazing America is."

After college and medical school in Oregon, Kuy completed her surgery residency at the University of Texas Health Science Center at San Antonio and then applied to the Robert Wood Johnson Clinical Scholars Program that brought her to Yale.

"My journey as a health care public servant has been as a direct result of the skills I gained at Yale," she said. Biostatistics, public health, computer programming, and working with large data sets were important, she said, but she also learned "the courage to take on challenges."

In 2017, as chief medical officer for Medicaid in the state of Louisiana, Kuy's challenge was the opioid crisis. That year she was selected to the Presidential Leadership Scholars Program, a partnership among the presidential centers of Lyndon B. Johnson,

A child survivor of genocide, SreyRam Kuy has followed an extraordinary path into medicine. In Houston, she helped organize responses to the flooding brought by Hurricane Harvey.

RYAN SMITH PHOTO

George H.W. Bush, Bill Clinton, and George W. Bush that brings together mid-career leaders from diverse backgrounds.

The fellows met once a month for four-day workshops led by former presidents, cabinet secretaries, and other policy luminaries. Kuy sought ideas on the opioid crisis from her mentors and colleagues, and came away from each meeting with ideas that she brought back to Louisiana.

"I walk into the classroom and there's a judge, a lawyer, a teacher, a poet, a Marine, a nurse—each offering a perspective on how to mobilize stakeholders," she said. "I would come back from the class just energized."

Kuy organized town halls; held symposiums; and ran seminars for doctors, patients, and stakeholders. Her solutions included payment reform to reduce overprescription of opioids and increasing accessibility to naloxone, used to treat overdoses. "We reduced opioid prescriptions among new users by 40 percent," Kuy said.

Kuy's accolades extend beyond medicine and health policy. She is an accomplished writer with articles published in the *Los Angeles Times* and the *Washington Post*. Her novel, *The Heart of a Tiger*, is based on her family's experiences in the killing fields.

"My life is a miracle," she said. "It is a testament to the grace of God and the extraordinary human capacity for compassion."

—John Curtis

The immune system & acts of kindness

DAVID G. SCHATZ, PHD, chair of Yale School of Medicine's immunobiology department, can explain mind-bendingly complex processes of the human body's immune system in relatable terms. For instance, here is his description of a process that produces antibodies to fight viruses and bacteria as follows: "This immune system reaction treats the chromosome like a big long string. It comes in with molecular scissors, cuts the string, and then different enzymes come in and tie the string back together in a new configuration."

What Schatz just described is called the variable, diversity, and joining, or V(D)J recombination process, and it allows T cells and B cells to randomly assemble different gene segments. As a graduate student at MIT in the lab of David Baltimore, a virologist who shared the 1975 Nobel Prize in Physiology or Medicine, Schatz established an assay to detect V(D)J recombination activity. Then, in collaboration with another doctoral student, he used this assay to isolate and discover two key enzymes in this process called RAG1 and RAG2. That groundbreaking contribution to the field happened almost 30 years ago. Schatz never slowed his pace.

Earlier this year, Schatz, the Waldemar Von Zedtwitz Professor of Immunobiology and professor of molecular biophysics and biochemistry, was elected to the National Academy of Sciences in recognition of his biochemical insights into RAG function and evolutionary origins. He was also a Howard Hughes Medical Institute investigator between 1991 and 2017; has been elected to the American Academy of Arts and Sciences; and is a fellow of the American Association for the Advancement of Science.

Yale Medicine Magazine caught up with Schatz, who earned his BS and MS degrees in molecular biophysics and biochemistry from Yale University in 1980, to learn more about the intricate processes of the immune system and what he values most in colleagues.

Has public awareness about the immune system and immunology changed during your career? Yes. The central driving trend for growing awareness has been a recognition that the immune system is involved—often quite directly—in almost every human disease. That's particularly true for what we call the "diseases of modern society," like obesity, diabetes, and heart disease. There's also growing recognition of the process of inflammation and the role it plays in initiating or exacerbating diseases. Another major trend in awareness is within cancer immunology. Immunotherapy has revolutionized our thinking about cancer and how it can be treated.

How would you summarize your research focus now? I've gotten very interested in the question of how recombination processes evolved. They are so unusual that it immediately raises the questions: *Where did they come from? How did the human body come to have these processes?* We think we can trace the V(D)J recombination process to a piece of DNA known as a transposon. This is an autonomous, mobile piece

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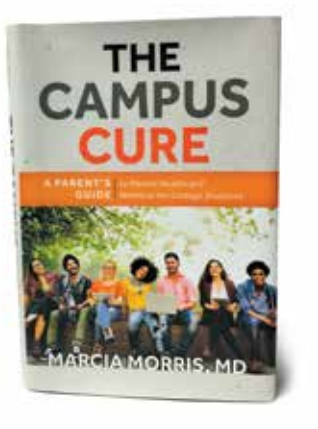
of DNA that encodes an enzyme that's able to bind to an element, snip it out of one location, float, and place it into another one. We believe that's how the immune system can make hundreds of millions of different antibodies. Our antibody genes are broken up into discontinuous bits and fragments of DNA, and the enzyme comes along and allows those fragments to join in new configurations. So, we owe our adaptive immune system to this mobile DNA element that gave us the capacity to snip and cut and rearrange our DNA.

What comes to mind when you think about the microbiome and immunology? The microbiome has come onto the stage with incredible speed. Much like the immune system itself, which influences almost every process in the body, the microbiome—we are learning—affects so many different processes. There is incredibly sophisticated intercommunication going on between the immune system and the microbiome. In our own department, Noah Palm, PhD, assistant professor, is studying how the microbiome affects health and disease states in an area that few people think about, which is the metabolites that bacteria produce. These are small organic molecules that bacteria either have on their surface or secrete. We know virtually nothing about what these tens of thousands of chemicals tell our body, what they signal our body to do or to think. Noah is just beginning to explore the diversity of those chemicals and their effects.

What message do you have for today's future scientists? Once, during a conversation with David Baltimore, I asked him what made a great leader. His answer was one word. "Generosity." That succinctly captures much of what I admire in the great leaders I've known. I would like to convey the message that respect and a humble eagerness to learn from one another are incredibly important parts of doing science and being a scientist. Acts of kindness, sharing, cooperation, collegiality—all of these have an enormous impact on atmosphere, and ultimately, the productivity of the whole scientific endeavor. The brilliant ideas that drive science forward can happen at any time from any one, so you just need to make people as free as possible from stresses and pressures. The other point I would like to convey is the excitement that comes from learning something or discovering something no one else has ever known before. I would love to pass on that deep love of making new discoveries.

TERRY DAGRADI PHOTO



Improving college students' mental health

By Cathy Shufro

It's a rare parent who doesn't feel a twinge of anxiety when dropping off a child at college. Although parents may worry most about drinking and sexual assault, more subtle disturbances can also hinder college students, according to campus psychiatrist Marcia Morris, MD '89. Recently, Morris has been seeing more students who feel extremely lonely or are obsessed with perfection.

Those are among the problems she addresses in *The Campus Cure: A Parent's Guide to Mental Health and Wellness for College Students*. Drawing on research and on 25 years as a psychiatrist at the University of Florida, Morris also discusses suicidal behavior, financial stress, eating disorders, struggles with sexual identity, and psychosis. "This is my way of trying to help parents prevent some of these problems, or to address things quickly," says Morris, the associate program director for psychiatry at the University of Florida's Student Health Care Center. Morris is also an associate professor at the university's College of Medicine and the mother of two recent college graduates.

In *The Campus Cure*, Morris explains how to recognize trouble. For instance, she advises parents to look at their children's grades each term; bad grades may signal problems that a student has managed to hide. For a family facing a crisis, Morris provides step-by-step guidance on how to proceed.

She confirms that unchecked drinking is commonplace in college. One recent study showed that a third of students had binged on alcohol during a two-week period. (Binging means four or more drinks in two hours for a woman and five or more for a man.) When parents warn their children against misusing drugs and alcohol, Morris advises them to focus on health, not morality. She notes that young people who observe that their parents moderate their drinking are likely to do the same.

Sexual predation is also widespread. By graduation day, one in 10 female students will have experienced forced penetration. Unwanted sexual contact affects one in four students who are transgender, queer, or nonconforming, and one in 20 men. Morris reminds parents not to blame a child who is victimized.

Although college social life may look appealing, Morris reports that many students feel lonely. One study found that one in four students had felt "very lonely" during the previous two weeks. Feeling isolated increases the likelihood of depression and suicide, whereas more robust social support correlates with higher grades. Morris points out that children who grew up on Snapchat and Instagram have missed some chances to practice face-to-face interaction.

She suggests that students seek friends by joining clubs, cultural groups, and religious organizations. A student might arrive early at class and then chat with a classmate, join a study group, or arrange to meet a potential friend for lunch. Group therapy can help young adults with social anxiety disorder, and Morris recommends *The Shyness & Social Anxiety Workbook*.

She has also noticed an increase in extreme perfectionism. Some people call it "duck syndrome": appearing to excel effortlessly while madly paddling just below the water line. "Parents should tell their child that they might get a C or even an F in a class, and help them recognize that sometimes we do fail at things," says Morris. External factors may contribute to an obsession with success, including the pressure to find a job with a salary sufficient to repay loans.

Although *The Campus Cure* addresses distressing problems, the book provides case studies and action checklists that can help parents and students weather difficulties. Morris sympathizes with parents of college students: "I want to make sure that when parents read the book, there's no sense of guilt. Raising kids is very challenging, and there's not one formula for it."

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OPPOSITE: ROBERT LISAK PHOTO

The end of an era

ON A BALMY MAY AFTERNOON, longtime Yale School of Medicine personality, beloved mentor, accomplished doctor, and dedicated physician Margaret "Peggy" Bia, MD, FW '78, stepped away from her official responsibilities. Surrounded by former patients, colleagues, friends, and well-wishers, like David Mulligan, MD, (with Bia, above). Bia was visibly moved as the group offered heartfelt thanks to her advocacy and leadership.

"Dr. Bia changed my life," said Marilyn E. McNee, a transplant recipient, when asked for her reflections. "It's been 13 years since my transplant, and she's always a phone call away."

Bia, a powerful advocate for increasing the number and roles of women in medicine, was also instrumental in emphasizing the importance of follow-ups after surgical operations and transplants to patient health. She leaves behind a more integrated and patient-focused system, one in which discharge from a hospital is not the end of care, but rather a new beginning.

—Adrian Bonenberger