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Winter 2020

Yale Medicine Magazine, Winter 2020

Yale University. School of Medicine

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yale medicine magazine

An anatomical illustration of a human torso, rendered in a dark brown silhouette against a lighter brown background. The internal organs, including the lungs, stomach, and intestines, are depicted in a lighter shade of brown. Several red and orange spots are scattered across the body, highlighting specific areas of interest. The text 'Short-term gains, long-term losses' is overlaid in white on the right side of the torso.

Short-term gains,
long-term losses

Winter 2020

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from the editor

Yale's Actions and Response to Coronavirus (COVID-19) website, covid.yale.edu, provides such information as clinical and laboratory research, patient care, resources to both track the spread of the virus and help cope during this crisis, COVID-19 news, and messages.

For many years, this section was a space for readers' feedback to a particular issue, or story. It is still that, and will continue to be so long as the U.S. Postal Service delivers mail.

But there's another world in which stories receive attention and feedback: online. And while *Yale Medicine Magazine's* physical circulation is around 22,500, online it receives around 25,000 unique visits per month.

Editing *Yale Medicine Magazine* is my primary responsibility, and both a joy and a privilege. I have a second job, though, which I created for myself: I plan, manage, and run

Yale School of Medicine (YSM)'s social media accounts. As readers are likely aware, social media is a proving-ground for ideas both small and great, and the social and scientific assertions and hypotheses of YSM faculty and researchers are no exception to that rule.

In the coming issues, we would like to offer up examples of conversations that happened online, that in the past may have made their way into this section via the postal service. These include posts on LinkedIn, Twitter, Facebook, or Instagram that the public found to be interesting or noteworthy.

Or ideas that were sufficiently resonant to capture my attention.

The three posts for this issue that stood out were, first, that announcing Nancy Brown's assumption of the deanship—our most read, shared, and commented-on post on LinkedIn of all time. The commentary was universally celebratory and positive in tone. Second, a post by Yale Orthopaedics commemorating International Women's Day with a callout to Rosie the Riveter. Third and finally, a post by Interventional Radiology technicians in the Department of Radiology & Biomedical Imaging was shared by CNN's Instagram page, where it received nearly a quarter of a million likes—a bit more than our more modest totals.

Many other subjects find air on social media. These were the three that jumped out from within YSM's community. To hop onboard a social media conversation, look us up online.

Adrian Bonenberger
Editor, *Yale Medicine Magazine*



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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.

Yale SCHOOL OF MEDICINE
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The road back to New Haven

JUST WEEKS INTO HER TENURE as the 19th dean of Yale School of Medicine, Nancy J. Brown, MD, found herself thrust into the center of a global pandemic. She shared her thoughts with Yale recently on the state of the school, and its efforts to help turn the tide against COVID-19.

How have Yale School of Medicine doctors responded to the influx of patients with COVID-19? Our response to COVID-19 has brought out the caring, collegiality, and creativity of our people. Clinical leaders are working hard to ensure that we have personal protective equipment, sufficient capacity in the hospital, and enough clinicians. Clinical Virology Laboratory developed testing for COVID-19 in-house, and this has made rapid testing available for health care workers.

Our critical care physicians have stood up and equipped hospital floors dedicated to the care of COVID-19 patients, with more space on the way. To decrease the number of ambulatory patients, our faculty have greatly expanded telehealth services. Clinical leaders have conferred with colleagues throughout the world to learn from their experience and strengthen our response.

What research is taking place around the virus? Epidemiologists across the health science schools have been modeling the pandemic to allow us to focus resources where and when they are needed. Our world-class immunologists have shifted their programs to understand how COVID-19 infects cells, the immune system's response, and how to interrupt that process. Our geneticists are exploring how patient factors determine outcome. Data scientists study outcomes in patients using electronic health records. We are sharing these methods with other institutions to facilitate effective research, and are leveraging the infrastructure of the Yale Center for Clinical Investigation to quickly initiate clinical studies of new therapies.

Other than moving to online classes, what is the effect on medical students? We had to interrupt the clinical clerkship training, which provides medical students with clinical experience. Students are valuable members of the care team, but with the decrease in ambulatory visits and elective surgeries, clerkships didn't make sense. Students are working with their advisors to develop individually tailored plans. Many have volunteered to conduct literature searches for our teams, just as they would on the wards. The students also suggested creating an elective on COVID-19 and pandemics. This is a trying time, but challenge can also mean opportunity.





Laying the groundwork

IN DECEMBER 2019, Merck received FDA approval for the Ebola vaccine trademarked Ervebo. Merck had distributed this vaccine for free in the Democratic Republic of the Congo over the last year and a half. The vaccine is based on a viral vector developed in the lab of John Rose, PhD, professor emeritus of pathology and senior research scientist in the Department of Pathology during an eight-year period in the 1990s. Rose is currently the director of Yale's Molecular Virology Program. The Ebola vaccine based on Rose's research has proven to be close to 100% effective in preventing Ebola infection.

"It's incredibly rewarding to know that one's efforts have made a tangible difference in the world," said Rose. "Merck has provided the vaccine for free to over 250,000 people."

Rose said that the project started out as a method to develop a general vaccine platform for viruses and other pathogens. His lab's work with this vaccine system focused initially on multiple viruses including HIV, a notoriously tricky and mutable foe. His laboratory also distributed the viral genetic system to over 100 other labs, including the one that eventually developed the Ebola vaccine.

The method relies on genetic engineering of a relatively benign animal virus called vesicular stomatitis virus (VSV) to express protein antigens from dangerous viruses or other pathogens. This system can be used to generate vaccines against multiple threats. For example, it can even protect against plague caused by the *Yersinia pestis* bacterium.

It can also protect against coronaviruses. Rose and colleagues published a paper in 2005 demonstrating a VSV-based vaccine that protects against SARS coronavirus in the wake of the SARS outbreak.

"A VSV vector worked for SARS, so almost certainly will for other coronaviruses like the 2019-nCoV," wrote Rose via email. "The recombinant vaccine could be made in a week, but approval for use could take

years. SARS was contained through public health measures, long before a vaccine could be tested and approved.”

While the legal mechanisms by which different vaccines are tested and approved for use are endeavors in their own right apart from research, the news is good: if the current outbreak of coronavirus were to intensify dangerously, researchers would have little difficulty in creating vaccines.

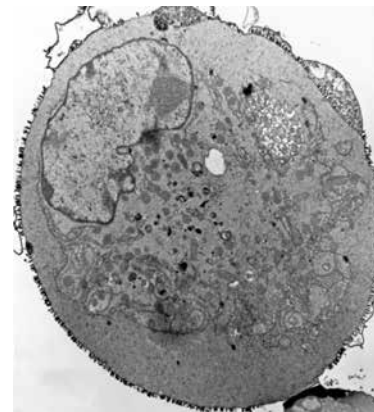
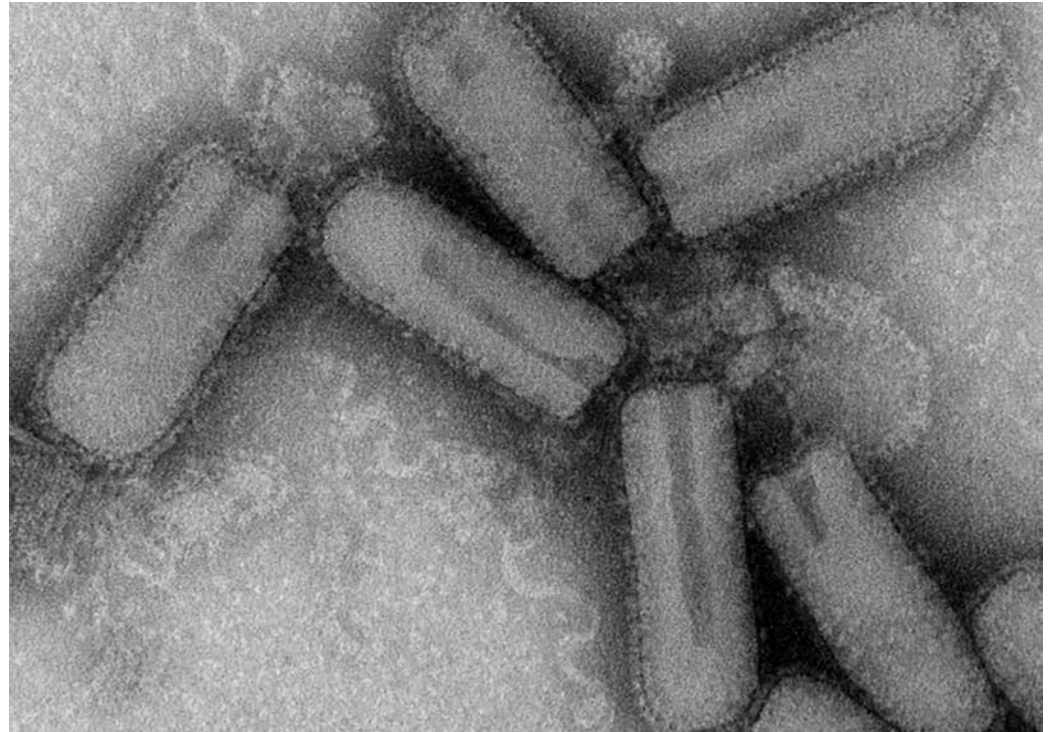
Vaccines for HIV and Zika using the VSV platform are still under development, but show great promise. And Rose is happy his team had an opportunity to work on a project of lasting importance. “The researchers who worked on this project are spread to the four winds, and many have their own labs now,” he said. “Knowing that we’ve made a significant contribution to humankind in terms of understanding how viruses work, and offering ways to combat them, is a very good feeling.”

—Adrian Bonenberger



Researching a clinical mystery

When Daniel Wong was overcome by seizures that struck out of the blue only two months after he graduated from Stanford in 2013, his doctors were alarmed. They could find no triggering event, no history of epilepsy, no explanation for his sudden prolonged seizures.



Electron micrographs of VSV particles, taken in the laboratory of John “Jack” Rose. They show (clockwise from above) the bullet-shaped “magic bullets” engineered to carry extra genes and make vaccines, an infected animal cell where thousands of VSV particles are budding from the cell’s surface, and, finally, an enlargement of the surface showing the budding bullets.



ONLINE EXCLUSIVE

Yale School of Medicine researchers such as Christopher H. Gottschalk, MD, and Deena Kuruvilla, MD, are looking at ways to stop migraine. They've found that certain medications work on the inflammatory cascade that plays a role in producing oftentimes debilitating pain for the patient.

For more on migraine, visit ymm.yale.edu/migraine

Doctors placed the 22-year-old Daniel in a drug-induced coma to protect his brain and tried numerous therapies to control his seizures. All treatments failed. Less than three months later, Daniel died without regaining consciousness.

At the suggestion of one of his doctors, Daniel's parents, Nora and Raymond Wong (both graduates of Yale College) met with Yale School of Medicine (YSM) neurologists Lawrence J. Hirsch, MD '91; Emily J. Gilmore, MD; and Nicolas Gaspard, PhD, at Yale New Haven Hospital in August 2014. The clinicians were planning a multinational, multi-center study to include patients like Daniel—who was thought to have a syndrome referred to as new-onset refractory status epilepticus or NORSE.

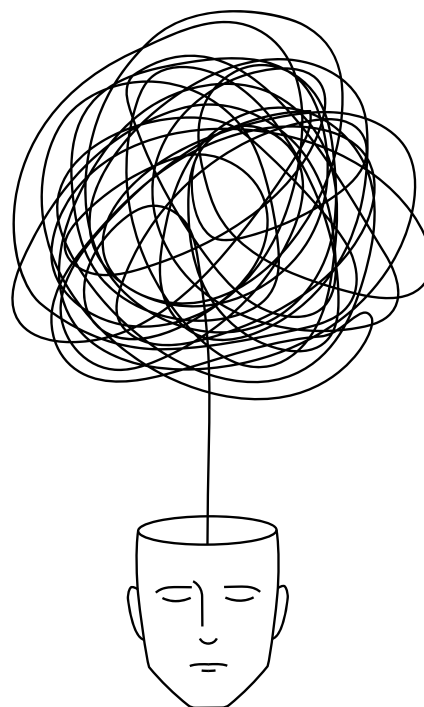
NORSE is described as a clinical presentation of prolonged seizures that are uncontrolled by at least two antiseizure medications, with the cause of the seizures remaining unidentifiable for 72 hours. NORSE tends to affect primarily healthy young adults and children with no previous history of epilepsy. The consequences of the disorder are devastating. There is significant short-term mortality (as high as 27%) and morbidity. Patients often survive with significant brain damage and develop chronic epilepsy. The Wongs created the Daniel Raymond Wong Neurology Research Fund at

YSM to support this prospective observational study that collects clinical data from NORSE patients and their biospecimens, both of which are banked at Yale.

With Hirsch and Gaspard as co-chairs of her medical advisory board, Nora Wong established the NORSE Institute (norseinstitute.org), a collaboration of NORSE families, clinicians, and basic scientists. In the past five years, the NORSE Institute has worked to raise awareness of this rare disorder. At Nora's request, Hirsch and Gaspard wrote the first description of NORSE issued on the rare disease websites hosted by the National Institutes of Health's Genetic and Rare Diseases

Information Center (GARD), the National Organization for Rare Disorders (NORD), and the Epilepsy Foundation.

To build a common language for the disorder, Hirsch assembled a group of international experts to develop consensus definitions of NORSE and a related syndrome termed FIRES (febrile infection-related epilepsy syndrome). "So far the NORSE Institute has developed, posted, and published a recommended diagnostic evaluation for specialists, readily available through the NORSE Institute website," said Hirsch. "One of the first challenges for a new disease is creating a name and consistent definition for it. The next is awareness—making sure everyone knows about the disease or the condition's definition." The NORSE Institute has been very successful in addressing these issues.



“NORSE shares some attributes with FIRES, now defined as a subset of NORSE, in which the patient has a prior infection with fever, usually a mild one,” said Hirsch. He added that although FIRES has traditionally been associated with children, it occurs in adults as well.

Through the Wongs’ support, the NORSE Institute sponsored the first international conference on NORSE in Salzburg, Austria, in 2017, where Hirsch and his group of experts met and later presented the consensus definitions. The definitions were published in *Epilepsia* in 2018 and are accepted as standard definitions worldwide. A roadmap of NORSE research was published in *Neurology* by Hirsch, Gaspard, and other members of the NORSE Institute medical advisory board. The institute sponsored multiple roundtable workshops with international researchers discussing the immunologic, genetic, and clinical aspects of NORSE, including ways to determine the best treatments. And in December 2019, the NORSE Family Registry was launched. This registry allows families to provide retrospective information about NORSE patients; it is intended to complement the ongoing prospective study of acutely ill NORSE patients. The NORSE family registry is supported through a gift to Yale by the family of Robert N. Kohn, who also died of NORSE.

—Adrian Bonenberger



Behind the scenes at “Diagnosis”

Twice a month, the “Diagnosis” column appears in *The New York Times Magazine*. In 1,300 words, Lisa Sanders, MD ’97, HS ’00, associate professor of medicine at Yale School of Medicine (YSM), untangles a case that has had doctors scratching their heads as they sort through a patient’s symptoms for clues to the diagnosis.

“I’m interested in the diagnostic process, how you get from puzzling symptoms to an important diagnosis,” said Sanders, who started writing the column in 2002.

Since then her column has spawned a TV drama, *House*, which aired from 2004 to 2012; provided material for her own books; and recently became a series on Netflix. At first, the column appeared once a month and Sanders did all the research and interviews on her own. But in 2016, when her editor asked her for two columns a month, “I realized I needed help,” Sanders said.

She turned to the Office of Student Affairs, which sent an email inviting medical students to apply for an interesting research opportunity. Sanders’s first hire was Fatima Mirza, a third-year student, who wrote for the *Harvard Crimson* as an undergrad and served as co-editor-in-chief of the *Yale Journal of Biology and Medicine*. A year ago, Sanders took on a second assistant, Aishwarya Vijay, a fourth-year student at YSM, who wrote for the *Yale*

Daily News as an undergrad. Mirza and Vijay make the first pass at story ideas that come in via email, at grand rounds, and through the grapevine.

Another YSM graduate who put heavy work into tracking down appropriate patient stories was Michael Gormally, MD ’19, PhD. “Michael helped me set up a system for me to keep track of the patients I am planning to write about,” said Sanders. “Not a week goes by that I don’t benefit from his smart system.”

With the column’s increasing popularity and the debut of the Netflix series in August, emails have poured in, Sanders said. “Right now, I get about 100 emails a day. Before, I got maybe 100 a month.”

How do Sanders and her assistants decide what makes the cut? First, there has to be a mystery.

Each column starts with symptoms ranging from the commonplace to the bizarre that stymie the patient’s doctor or doctors. They may order further tests or consult with colleagues as they seek a diagnosis. “You know it’s a weird case if it’s in my column,” Sanders said.

“Often, it’s a very rare presentation of a common disease, and you want to look at something that has a happy ending,” said Mirza. “If it doesn’t have a happy ending, there’s some sort of big lesson you can take from it that can help other patients.”

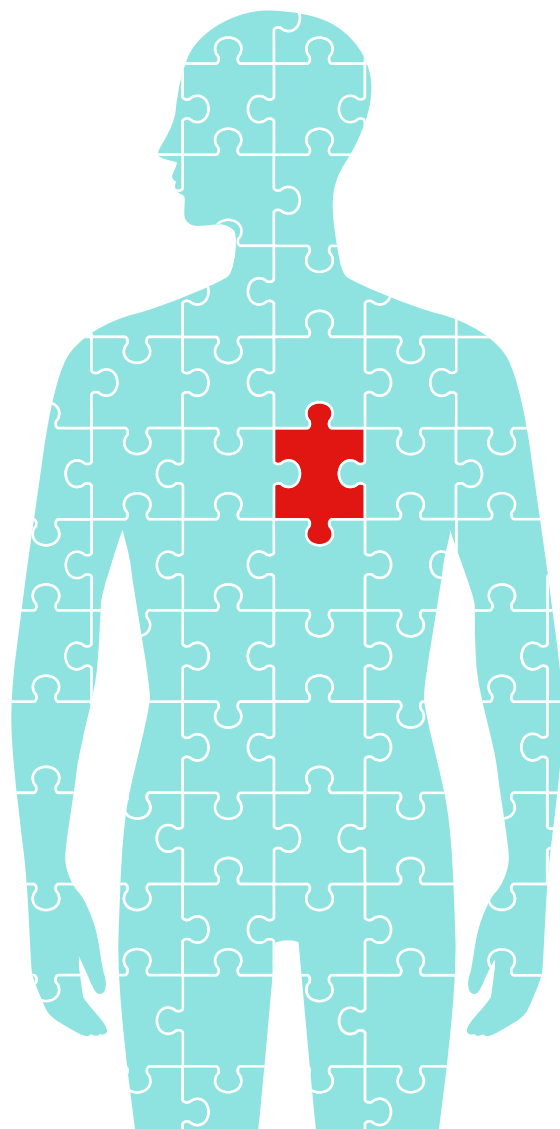
“It’s easier to have a case when there is one team or one doctor that made the decision



ONLINE EXCLUSIVE

Yale Journal of Biology and Medicine has, at long last, earned an Impact Factor. This means they'll be monitored to see how often their articles are cited by others, a huge coup for the only internationally recognized medical journal edited and published by students.

For more on YJBM, visit ymm.yale.edu/yjbm



and can really focus and give a full narrative,” Vijay added.

To find those cases, the team sorts through thousands of tips for the 24 that will make it into the column each year. Then they reach out to the doctor on a promising case and obtain a signed release to speak to the patient and obtain medical records. “Until you talk to them you never get the full story,” Mirza said. “You get a two- or three-sentence synopsis from their email and you don’t know if it’s a real diagnosis.”

The students then explain how the reporting and writing process will unfold. “The patients are usually ecstatic,” Vijay said. “They want to get the word out about what they struggled with.”

After initial interviews and a review of the medical records, Mirza and Vijay pass their suggestions on to Sanders. And they

note that there are often false starts. “Stories fall through all the time,” Vijay said. “We get halfway down the line and then the medical records don’t work out or the patient has decided that they don’t feel comfortable.”

The irregular schedules of medical students and a working physician, and the unyielding deadlines of a major newspaper make for odd working hours. Sanders and her two assistants are rarely able to meet in person, so they communicate by phone and email. And they’re usually multitasking. “We often have multiple cases and a bunch on the back burner,” said Vijay.

Once she’s chosen the cases for her column, Sanders reaches out to the patient and doctor for more in-depth interviews. There may be multiple doctors on the case, but Sanders usually interviews only the ones who made the diagnosis. Readers often ask how the doctors could have missed what seems in hindsight so obvious.

“Diagnosis is a process,” Sanders said. “You have to go through what everybody has before you can look at what nobody has.”

Sanders typically spends two days on her first draft, then goes over it twice more. Her columns reach the *Times* on a Monday; by Thursday of the following week they’re online; and by the next Sunday they’re in print.

“When I see it in the paper,” she said, “I know it’s time to write my next one.”

—John Curtis

round up

a collection of recent scientific findings



SCHOOLCHILDREN SHAPED BY TEACHERS' BIASES

A study co-authored by Yale sociologist Grace Kao, PhD, concludes that first grade teachers' racial and gender biases about the abilities of their students affects how those students perform academically, as well as how those students view themselves and their abilities.

Kao's study was published online in January in the *Du Bois Review: Social Science Research on Race*.



KETO DIET BETTER IN SMALL DOSES

According to the lead author of a recent study, the keto diet's effectiveness derives from its ability to trick the body into burning fat. Vishwa Deep Dixit, DVM, PhD, the Waldemar Von Zedwitz Professor of Comparative Medicine and professor of immunology, evaluated the mechanisms by which the body processes different types of food—in this particular case, a diet's low carbohydrate content—and made the unusual discovery.

Dixit warns, however, that the keto diet works for only a limited time period in mice, and that studies in humans are needed to find out whether humans can safely follow the diet for months or years.



BRIGHT START FOR YALE ALUMNI HEALTH NETWORK

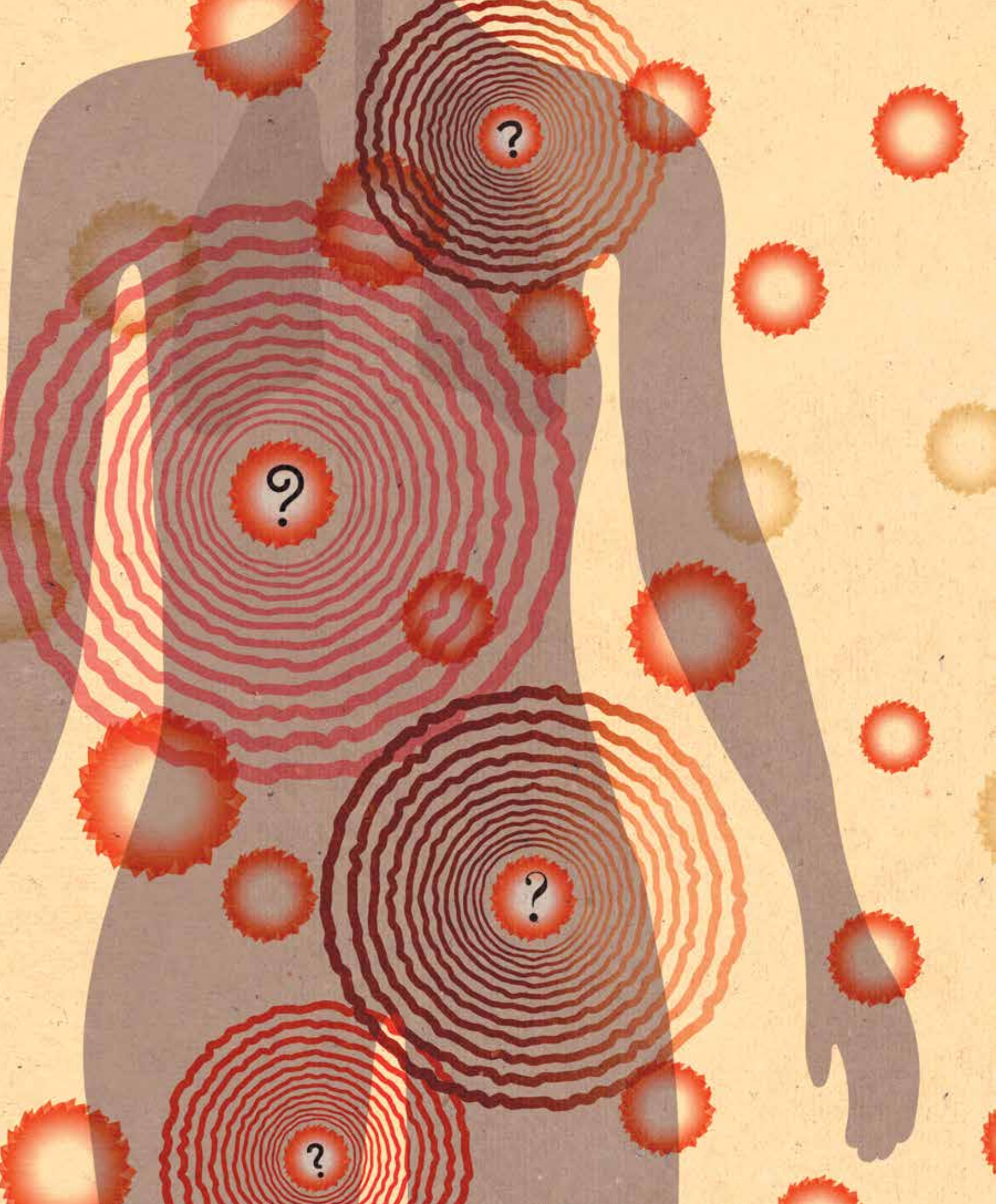
A new alumni health group, co-founded by Christine Walsh, MD '73, and Jamie Wells, MD, held its inaugural meeting at the Yale Club of NYC this winter. The Yale Alumni Health Network (YAHN) hopes to bring Yale alumni leaders together from all sectors that touch on health and health care: medical practice, academia, science, law, and finance.

Interested Yale School of Medicine (YSM) alumni can find YAHN on Facebook, Twitter, and LinkedIn.



MEDICAL ERRORS DON'T PLAY A ROLE IN MOST HOSPITAL DEATHS

Due to underlying disease, estimates of preventable deaths of hospitalized patients may be two to four times too high. The YSM and VA Connecticut study extrapolated likely numbers for the United States from results in European and Canadian hospitals. Benjamin Rodwin, MD, assistant professor of medicine, said that more studies are needed, but the notion that the quality of care in hospitals is better than previously assumed is indeed welcome news.



Short-term gains, long-term losses

IN THIS ISSUE, *Yale Medicine Magazine* covers research at Yale School of Medicine that extends the boundaries of what humankind knows about inflammation—the body’s response to threat or infection. Our writers explore the long history of physicians observing inflammation and also describe the physiology of inflammation—what current science understands about the process of inflammation, its energy costs, and the role it plays in wound repair and aging. Finally, we attempt to lay out the most current progress being made in understanding why immune systems work the way they do.

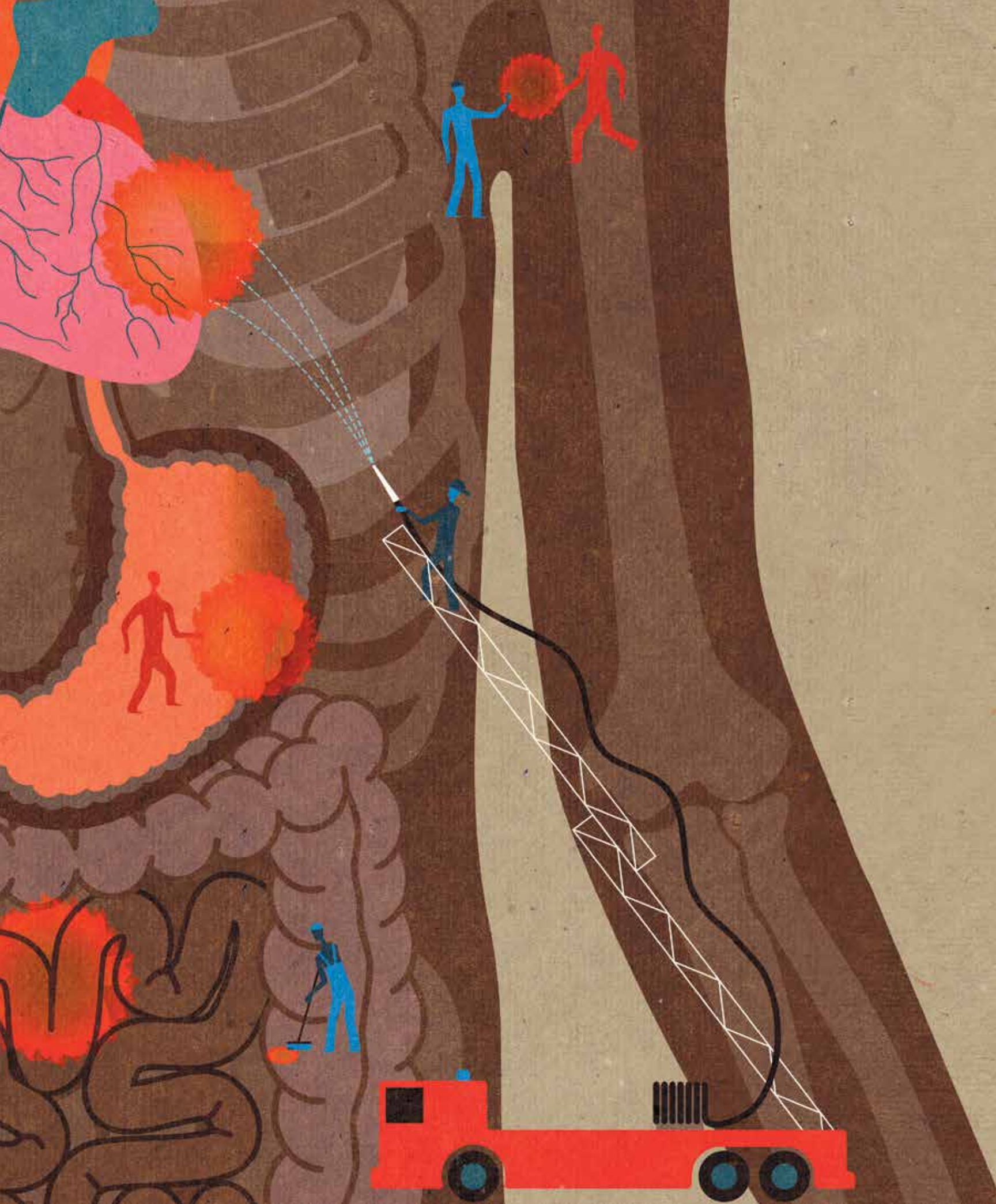
At stake is more than just the short-term benefits versus long-term costs of inflammation. Many diseases and conditions are either caused or influenced by malfunctioning immune systems—from lupus to Alzheimer’s disease to diabetes and many more. Understanding how the immune system works and the role inflammation plays will do more than answer esoteric questions about disease—it will improve the quality of life for people who are struggling every day with deadly ailments, and may even save or extend lives.

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Inflammation: part hero, part villain

BY CHRISTOPHER HOFFMAN | OTTO STEININGER ILLUSTRATION



The traditional approach to inflammation is that it's bad and should be suppressed, but recent findings offer a more nuanced view.

For many years, inflammation was considered one of medicine's chief enemies. Experts viewed it as a side effect of illness and injury, a negative byproduct of the body's efforts to heal. One managed and banished it whenever possible.

That view has undergone a major reassessment over the last decade. Inflammation, it turns out, isn't always bad. In fact, researchers increasingly believe that it plays a vital role in maintaining good health. Some even believe inflammation is so central to the body's proper functioning that our understanding of physiology must be rewritten.

"It (inflammation) is a very natural state," said David A. Hafler, MD, the William S. and Lois Stiles Edgerly Professor of Neurology, professor of immunobiology, and chair of the School of Medicine's Department of Neurology. "When you look at the immune system, it has multiple roles. The obvious one is fighting off infection. But the immune system has also been co-opted by nature

to be used in a number of different systems for homeostasis. Inflammation is more than about just fighting off disease."

Some examples: The immune system acts at times as a kind of cleanup crew that tidies up molecular messes. Elsewhere, it performs such functions totally unrelated to fighting microbes as pruning excess neurons in the brains of small children—an essential part of brain development. The immune system also helps regulate the function of many organs, including the liver and intestines. In doing all of these good things, it inevitably leaves residual inflammation.

A TWO-EDGED SWORD

While these insights recast inflammation as a more positive component of a person's health, they also raise intriguing questions about how it may cause illness later in life. Are such diseases as cancer, for example, triggered when the immune system's maintenance and regulatory duties go

awry, often in connection with a gene, and cause too much inflammation?

“The immune system is a two-edged sword,” said John MacMicking, PhD, an associate professor of microbial pathogenesis and of immunobiology, and a Howard Hughes Medical Institute (HHMI) investigator. “Some things help protect you. Some things put you in harm’s way. Researchers are looking for the right balance.”

Inflammation has already been identified as a culprit instead of just a side effect in many illnesses, including multiple sclerosis (MS) and other autoimmune diseases. We have also learned that it plays a role in so-called lifestyle illnesses and such conditions as heart disease, obesity, and diabetes, said Akiko Iwasaki, PhD, the Waldemar Von Zedtwitz Professor of Immunobiology, professor of molecular, cellular and developmental biology, and an HHMI investigator. It’s hard to think of any disease that does not involve inflammation, Iwasaki said. That fact has some researchers calling for a wholesale reassessment of inflammation’s role in the body’s functioning.

“We still think in terms of normal physiology and abnormal inflammation,” said the Sterling Professor of Immunobiology and HHMI investigator Ruslan Medzhitov, PhD, one of the world’s leading inflammation researchers. “That view is, I think, outdated. There’s no modern framework to replace that view.”

Medzhitov and his lab are hard at work building that scaffolding. He argues that inflammation is as central to understanding physiology as are hormones. Once the initial work is complete, the next stage will be to try to find ways to turn inflammation on and off to treat or forestall disease, he said. He estimates we are about halfway to mapping the basics but only 10% of the way toward fully understanding how inflammation works.

“It’s clear that inflammation is not just about infection,” he said. “It’s not just a response to injury. It has multiple other job descriptions, multiple other functions that are involved also in what we call normal physiology.”

In a pioneering step, the medical school has incorporated Medzhitov’s findings into its curriculum, teaching future doctors that inflammation is an integral part of both health and sickness, not simply a side effect. As research attaches ever greater



David Hafler says inflammation is more than a defense system to fight infection—it’s part of how a healthy body maintains homeostasis, such as when it prunes excess neurons in the developing brains of children, or when it occurs in the liver and intestines.

importance to inflammation, Yale is considering the establishment of an institute devoted exclusively to its study, according to Medzhitov and other researchers at the school. Understanding the role of inflammation in the body at the molecular level could pave the way for a new generation of pharmaceuticals and treatments. Because inflammation accompanies nearly every illness and disease, the potential for new developments is enormous.

“If you are infected, inflammation can even be a good thing, helping provide additional signals that alert the host to the presence of microbial pathogens and recruiting immune cells to the site of infection. However, you need to turn it off once the infection is resolved to avoid excessive tissue damage,” MacMicking said. “Is there a way to do that? Can I take a pill that helps reduce the inflammatory burden?”

THE ROLE OF CYTOKINES

On a basic level, our understanding of inflammation hasn’t changed, Iwasaki said. Inflammation from a broken ankle or a bronchial illness, for example, is the body’s way of summoning the immune system to restore homeostasis. Too much inflammation in and of itself can kill by, for example, flooding the lungs with fluid or causing dehydration.



Carla Rothlin wants to know about mechanisms that set or limit the magnitude of the body's immune response—how a body transitions from defense to wound repair, and why.

Now we understand that inflammation can be both a cause and an effect, Iwasaki said. Obesity and diabetes are examples, she continued. When people become overweight, their fat cells become bigger. Immune system cells called macrophages, whose job is to maintain homeostasis, sense something is wrong, and they deploy disease-fighting small proteins called cytokines against the cells, creating inflammation. While the tipping point remains unclear—it appears to vary from person to person—the resulting inflammation can lead to diabetes and heart disease. Exactly how that happens requires further study, said Iwasaki. “We just know that if we can block these macrophages from firing, we can prevent the disease from happening,” she said.

Another example is Alzheimer's disease, Iwasaki said. Research indicates that an immune reaction to amyloid plaques in the brain may contribute to the dreaded illness. According to the model, macrophages interpret crystal-like plaques in the brain as foreign objects and begin secreting cytokines that attack them, which leads to inflammation and destruction of neurons culminating in dementia. Ultimately, inflammation may also play a role in such behaviors as depression and suicide, she said.

Hafler, an expert on MS, cites yet another example of the double duty performed by inflammatory cytokines.

His lab compared spinal fluid from healthy medical students and patients with MS. Unsurprisingly, the fluid from MS patients was inflamed—but so was that of the healthy medical students. “We had a very hard time telling the difference between MS spinal fluid and normal spinal fluid,” he said. That's because cytokines, in addition to fighting disease, also help regulate the nervous system in relation to synaptic connections, fluid absorption, and other functions, he said.

KEEPING THE MICROBIOME HEALTHY

There's another potential source of sickness-inducing inflammation: the human gut. Researchers increasingly think that inflammation in the digestive tract may be the point of origin of a variety of diseases, including neurodegenerative illnesses like Parkinson's. They are also coming to believe that a healthy microbiome—the billions of bacteria in the gut that help us process food—may be key to avoiding that potentially disease-inducing inflammation.

Noah Palm, PhD '11, FW '15, assistant professor of immunobiology, and his lab team are probing the connections between the microbiome, inflammation, and disease. The microbiome is exquisitely sensitive, Palm said. Changes in diet, or even something as seemingly benign as living with a dog, significantly alter the teeming microbial communities that populate our guts, he said. As the Western environment has become more antiseptic and most people's diets contain fewer plants and more processed foods, the makeup of our gut microbiome has changed, and its diversity has declined significantly. At the same time, the incidence of certain inflammatory illnesses and conditions—allergies, obesity, heart disease, diabetes—has exploded. Is there a connection?

“In my lab, we are trying to make the transition from correlation to causation,” said Palm. He has already begun to establish potential causation in certain illnesses, specifically inflammatory bowel disease (IBD). He and his lab assistants have found that when microbiome material from an IBD sufferer is inserted into an otherwise healthy mouse, the mouse will develop a disease that looks similar to human IBD. While genetic factors may also be involved, these findings indicate that particular bacteria may trigger IBD in at least a

subset of patients. Palm's research has a long way to go, but it could ultimately lead to individualized treatments designed to maximize microbiome health and stave off disease-inducing inflammation.

A NEW APPROACH TO ANTIBIOTIC RESISTANCE

The expanded understanding of inflammation in the gut and how it is induced could also one day address one of medicine's biggest long-term challenges: antibiotic resistance. Jorge Galán, PhD, DVM, the Lucille P. Markey Professor of Microbial Pathogenesis, professor of cell biology, and chair of the Department of Microbial Pathogenesis, said his lab studies "in detail" intestinal tract diseases—especially salmonellosis. The long-held view was that the inflammation resulting from *Salmonella* infection, which makes you sick, was caused by the immune system's attacking the pathogen. But "we now know that this is not the case," Galán said.

Nutrients are scarce in the gut, Galán added. In order to make those nutrients available, *Salmonella* and similar pathogens must induce inflammation. That's not easy because the immune system is tamped down in the gut; otherwise recognition of the bacteria in the microbiome would trigger a chronic state of inflammation. "*Salmonella* needs inflammation," Galán said. "Its stomping ground is the gut. Now it's got a problem. It needs inflammation in a place where it's not easy to trigger it."

Salmonella meets this goal by injecting proteins that trigger inflammation, thereby producing the nutrients it needs to survive, Galán said. He has on a table in his office a clear block containing an image of the pathogen's microinjection device, a gift from his students. Most of the time, the resulting inflammation isn't enough to make a person sick because the pathogen uses its own mechanisms to turn it off; it's when inflammation gets out of control, which is rare, that one develops the classic symptoms of salmonellosis. "That is what is so cool about inflammation," Galán said. "There are so many ways to trigger it."

Galán's insight potentially creates a new treatment pathway. Instead of killing the pathogen with a classic antibiotic, you can try to formulate a targeted drug that simply shuts off the microinjection device inducing the inflammation, he said. "You gum up the



1980s data demonstrated that taking aspirin lowered the risk for cardiovascular disease. They expanded that research to include cancer, and determined that aspirin could lower mortality there as well, acting as a chemopreventative therapy, according to Charles Fuchs.

bacteria," Galán said. "You are preventing the bacteria from causing disease, which is a totally different concept. Certainly the evolutionary process that leads to antibiotic resistance would be slowed significantly."

The promise of a deeper understanding of inflammation and its roles in sickness and health is significant, potentially paving the way for individualized and less invasive treatments that work in harmony with the body, researchers say. It may well boil down to learning how to turn inflammation from on to off.

"Can we uncouple the beneficial from the harmful effects?" MacMicking said. "Find new molecular targets that mount effective antimicrobial responses but avoid the non-collateral damage. Cytokine signaling turns on hundreds of genes—is there a way to pick and choose downstream host responses we'd like to elicit and quieten those we wish to avoid?" MacMicking and his fellow Yale researchers are working to find out.

/yale medicine magazine

Christopher Hoffman is a frequent contributor to Yale Medicine Magazine.



Studying autoimmunity

Researchers hope that the Colton Center for Autoimmunity at Yale will yield results over the next 10 years.

BY JOHN CURTIS | OTTO STEININGER ILLUSTRATION

Throughout his career at Yale, Joseph E. Craft, MD, HS '80, FW '85, has studied autoimmunity, specifically systemic lupus erythematosus. Now he's heading a new project that will span the university, encouraging researchers from disciplines inside and outside medicine to seek ways to move existing knowledge about the more than 80 autoimmune diseases from the laboratory to the clinic.

"The goal is to take what we know about autoimmunity from our research at Yale and what we have learned from others and move those ideas into practical applications," said Craft, the Paul B. Beeson Professor of Medicine (Rheumatology) and professor of immunobiology. "Many of the proposals will come from immunologists, but by no means is it meant to be restricted to experts in autoimmunity, nor is it meant to be restricted to experts in immunology. We want the best ideas: things that may be novel, things that may be untried and untested, things that may be pie in the sky."

The Colton Center for Autoimmunity at Yale is an outgrowth of an initiative that began at NYU Langone Health in 2013. The Judith and Stewart Colton Center for Autoimmunity was launched to find new ways of diagnosing and treating autoimmune diseases. Although centered at NYU, the program has recruited researchers and clinicians throughout the scientific community. Creating a satellite center at Yale with Craft in charge was an obvious choice—he sits on the NYU center's advisory board.

The satellite center at Yale will receive funding for up to 10 years. In its first year, Craft said, he hopes to fund about eight proposals. "The idea is to use funds every year to invest in ideas to develop intellectual property," he said. "That's the first step to getting those into translatable initiatives."

Research proposals from across the university are welcome, Craft said. "You don't have to be an expert in autoimmunity to have a good idea. It could be from

engineering, the Faculty of Arts & Sciences, chemistry," he said, adding that faculty at all levels are encouraged to apply. "That only enhances the ability of the program to get things done. Biomedical engineering has been very successful in thinking about ideas on how to treat cancer. If they can bring those ideas to autoimmune disease, that would be great."

An advisory committee of four faculty in immunobiology, two academics from outside Yale, and three private sector members with experience in technology transfer and immune-mediated diseases will review grant applications. The committee will meet once each year in person and throughout the year in videoconferences.

The application process, Craft said, will be streamlined. "We would like to shorten that to a couple of months and make the hurdle for applying relatively simple," he said. "Putting the idea on paper ideally would be done in a day or two. Our goal is to eliminate the bureaucracy and eliminate the timing."

The new center also fits in with the University Science Strategy Commitment (USSC), said Michael C. Crair, PhD, the William Ziegler III Professor of Neuroscience, professor of ophthalmology and visual science, and vice provost of research for Yale University. He will serve as an ex officio member of the center's advisory board. The USSC will invest in strong areas of science at Yale, specifically inflammation, neuroscience, data science, energy science, and environment.

"Inflammation is one of the top areas where we'd like to build, and autoimmune is one of the pieces within the broad area of inflammation," Crair said. "We want to make sure that what we are doing in autoimmunity is coordinated with what we are doing in all the inflammation sciences." */yale medicine magazine*

John Curtis is a frequent contributor to Yale Medicine Magazine.





Ketostasis: nature's sweet spot

BY SONYA COLLINS | OTTO STEININGER ILLUSTRATION

Glucose plays a complex role in immune system health

For followers of popular science news—or of the latest diet craze—the term “intermittent fasting” is decidedly trending. Each new mention of the eating plan brings with it more revelations about the health benefits it could offer.

In the last six months alone, new studies have tied fasting to reduced risk of diabetes, heart disease, and a host of chronic inflammatory diseases. Periodic fasting may also improve symptoms of multiple sclerosis and inflammatory bowel disease. One study found that a 24-hour fast boosts regeneration of intestinal stem cells in aging mice.

But what's behind all these potential benefits of occasionally going without food? Yale research suggests that sugar deprivation gives fasting its many virtues. It may halt or mitigate inflammation that leads to or exacerbates numerous illnesses. And it could be that each of the potential health benefits of eliminating sugar is born of a different mechanism.

FEED A VIRAL INFECTION, STARVE A BACTERIAL ONE?

When colleagues Andrew Wang, MD, PhD, HS '13, FW '17, and Ruslan Medzhitov, PhD, were discussing how they feed their kids when they're sick, they started to wonder what was behind the old adage, “Starve a fever, feed a cold.”

“All animals—from worms, to flies, to dogs, to us—do this. When we get acutely infected, we lose our appetite, and people have wondered for a long time why that might be,” said Wang, who is an assistant professor of medicine (rheumatology) and of immunology.

The two wanted to find out the potential benefits of fasting during an illness. In their 2016 study, published

in *Cell*, when they force-fed an animal that was fighting listeriosis—a bacterial infection—the animal died. On the other hand, feeding an animal battling the flu—a viral infection—helped nurse it back to health.

When the researchers broke the food down into its key components—protein, fat, and sugar—they found that sugar is the active ingredient. Mice that had viral infections needed glucose to adapt to the stress brought on by antiviral inflammation and to prevent stress-induced cell death. In bacterial infections, however, glucose prevented ketogenesis, which was necessary to counteract the oxidative stress of antibacterial inflammation.

Still, Wang said, “As a doctor, I'm hesitant to simply say, ‘If you think you have a bacterial infection, starve yourself, and if you think it's viral, don't.’”

And Wang has good reason to hold off doling out that advice. The role of glucose in inflammation is far more complex. New research suggests that glucose deprivation before flu infection may in fact prepare the body to fight it. While glucose after flu infection promotes adaptation to inflammation, a November 2019 study in *Science Immunology* co-authored by Vishwa Deep Dixit, DVM, PhD, the Waldemar Von Zedtwitz Professor of Comparative Medicine and professor of immunobiology, suggests mice already in ketogenesis are better equipped to fight the flu once it hits.

In the study, mice that were on the high-fat, low-carbohydrate ketogenic diet when they contracted the flu were more likely to survive the illness than those on a normal high-carb diet. The extremely low-carb diet, the study found, activates a group of T cells in the lungs not

previously linked to the immune system's response to influenza. The T cells step up mucus production in airway cells and trap the virus.

While the studies point to opposing roles for glucose in viral inflammation, they also asked different questions.

"Our 2016 study," said Wang, "asks why animals eat less when they have the flu. So, we fed them after they were infected to see what impact that would have. [This new study] asks, 'If an animal is in a ketotic state, how does it affect response to flu infection?' I think what is clear from both studies is that the metabolic state of the organism in an infection—before and during, and probably during recovery—is a critical determinant of the organism's overall outcome in that infection."

Glucose has a role in parasitic infections, too. Wang and Medzhitov explored this relationship in a 2018 study published in *Proceedings of the National Academy of Sciences (PNAS)*. When they blocked glycolysis in mice with malaria, the mice didn't go on to develop cerebral malaria.

The glucose deprivation didn't make the mice resistant to malaria. In fact, in both groups, parasite burden, neuroinflammation, blood-brain barrier permeability, and anemia were the same. But, blocking glucose made mice more tolerant of the disease. Or maybe, the study authors suggest, glycolysis inhibition made the parasites themselves less harmful. Either way, fewer microthrombi (tiny blood clots) formed in the brains of those mice, preventing the spread of the infection to the brain.

BURN FAT, SLOW AGING

Of course, inflammation isn't only an acute reaction to a new infection. Ongoing inflammation is implicated in nearly all diseases of aging. If modulating glucose can change the course of acute infection, could it also interfere with the lifelong process of aging?

"Most of the cells in the body run primarily on glucose," said Dixit. "So, we wanted to know what happens when glucose is limited." The answer sheds more light on the various health benefits of fasting and low-carb diets like the ketogenic diet.

When the body doesn't have glucose for fuel, it burns fat for energy. This process occurs in fasting, starvation, and in endurance exercise after sugar stores are used up. It also happens on a low-carb diet.

The brain and heart are the biggest consumers of the body's energy. But when the body turns fat into long-chain fatty acids, they can't cross the blood-brain barrier. So, the body converts those into short-chain fatty acids, specifically a ketone metabolite called beta-hydroxybutyrate, for the brain's use.

When the body runs on fat for fuel, Dixit and his team wondered, what happens to immune cell function? Macrophages—mobile white blood cells that gather at infection sites—run on glucose when they are inflamed.

"If macrophages aren't seeing glucose," Dixit added, "but are exposed to alternate fuels instead, how would that affect their activation state?"

What Dixit and his team found was that beta-hydroxybutyrate can block an inflammatory protein complex called the NLRP3 inflammasome. Now, NLRP3 isn't all bad. It plays an important role in triggering inflammation in acute infection. But, Dixit explained, "If it remains chronically activated, it can lead to multiple chronic diseases and it's implicated in the overall process of aging."

When researchers gave beta-hydroxybutyrate to NLRP3-inflamed mice, the ketone metabolite blocked the inflammasome, and the mice did not go on to develop several age-related chronic diseases.

The findings may help explain why popular diets like intermittent fasting and keto bring health benefits beyond weight loss. "Because when one is fasting," Dixit said, "the body has to burn fat, and the metabolites that are increased in this process can potentially reduce inflammation."

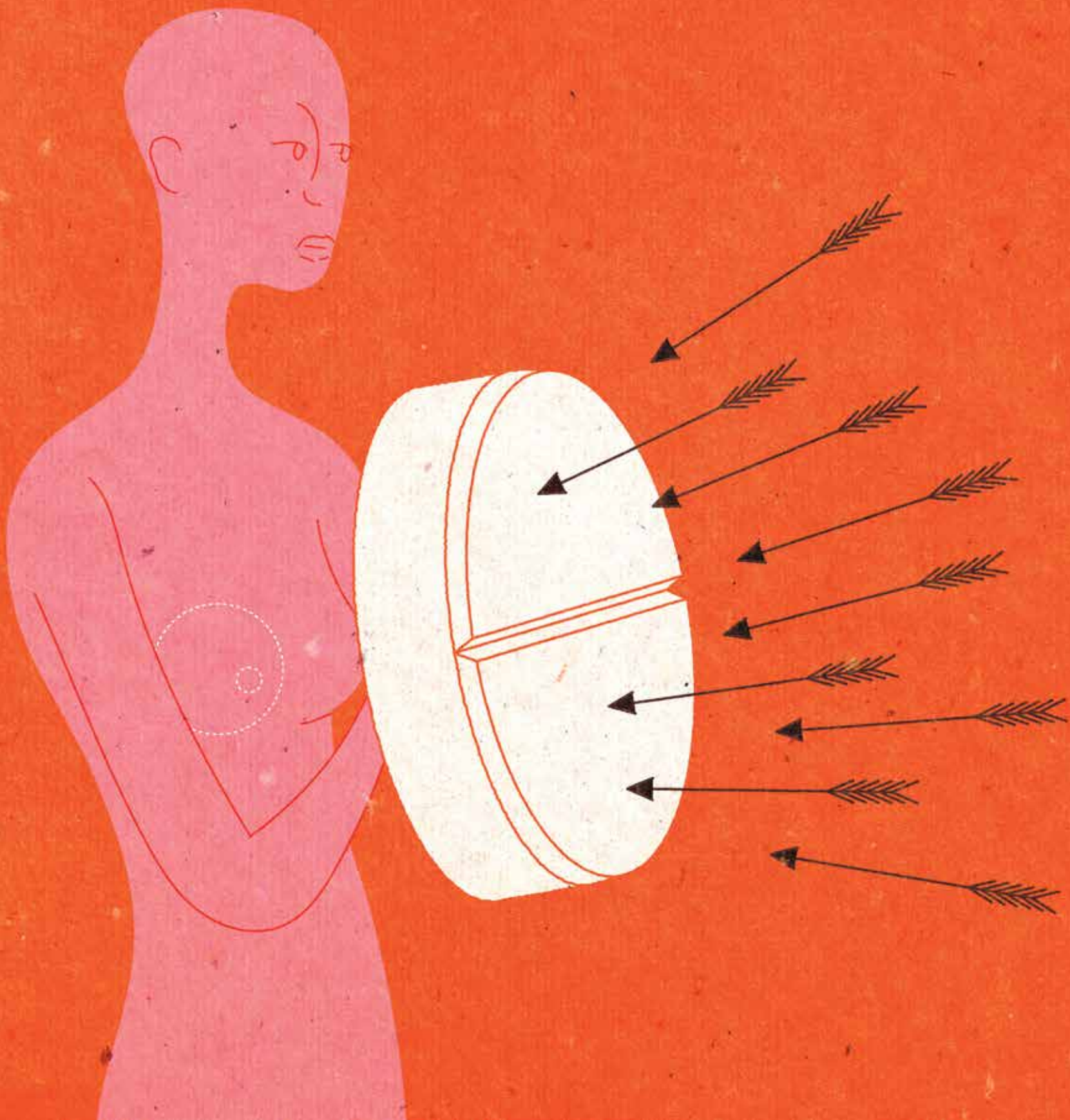
JUST A SPOONFUL OF SUGAR

This deeper understanding of sugar's role in inflammation could lay the groundwork for both dietary recommendations and medications that regulate glucose in various types of inflammation.

But that doesn't mean sugar is all bad. "The appropriate amount of everything is what we require," said Dixit.

There's not one diet that fits all. "Different types of inflammation require different things," said Wang. "So, you have a lot of moving parts, and figuring out the combination that gives you the best clinical results is not trivial." */yale medicine magazine*

Sonya Collins is a frequent contributor to Yale Medicine Magazine.



Another use for aspirin

A versatile remedy also a potential treatment for breast cancer.

BY JOHN CURTIS | OTTO STEININGER ILLUSTRATION

In ancient times physicians extracted from the bark of the willow tree a substance—salicylic acid—that reduced fevers, inflammation, and pain. By the mid-19th century, a French chemist had mixed the acid with acetyl chloride to form acetylsalicylic acid, the compound that Bayer marketed in 1899 as aspirin.

Over time aspirin transcended its original uses, and by the 1970s and 1980s it was seen as a treatment for stroke and heart disease. During the 1980s physicians and researchers also saw that it could fight cancer. By 1991, they'd found that aspirin lowered the risk of colorectal cancer, and subsequent studies linked it to a lower risk of other cancers.

Physicians at Yale are helping to figure out whether aspirin can keep breast cancer from recurring in women who have already gone through surgery, radiation, and chemotherapy.

“There’s an overwhelming amount of data that suggests that taking aspirin may be beneficial, and that aspirin is safe enough for the majority of people to take daily,” said Neal Fischbach, MD, assistant professor of clinical medicine (medical oncology), who’s leading the trial at Yale.

The Aspirin for Breast Cancer (ABC) Trial was launched in Boston, sponsored by Brigham and Women’s Hospital and Dana-Farber Cancer Institute. The study hopes to recruit 3,000 patients between 18 and 70 who have had breast cancer, haven’t used aspirin in the past month, and whose breast cancer has not recurred.

Previous studies, said Fischbach, have found a reduced risk of recurrent metastatic breast cancer in those who take aspirin. “Aspirin might not be preventing cancer,” he said, “but in those who get cancer, it may prevent cancer from spreading.”

Aspirin’s anti-inflammatory properties, Fischbach said, inhibit the enzyme cyclooxygenase. “That pathway is important in production of many inflammatory mediators which have a lot to do with cancer cell growth and metastasis,” he said. “For the same reason

that taking anti-inflammatories may be good to reduce joint inflammation and pain, they may also inhibit metastatic spread and growth of cancer cells.”

Among aspirin’s drawbacks are the risks of gastrointestinal bleeding and hemorrhagic stroke in some patients. And, Fischbach said, prior studies just aren’t robust enough to recommend aspirin to prevent the onset or recurrence of cancer. The only such recommendation to date came in 2015 when the National Cancer Institute said that in certain patients, aspirin could prevent colorectal cancer and cardiovascular disease.

Charles Fuchs, MD, MPH, the Richard Sackler and Jonathan Sackler Professor of Medicine (Medical Oncology), director of Yale Cancer Center, and physician-in-chief of Smilow Cancer Hospital, traced original studies of aspirin and cancer to the 1980s.

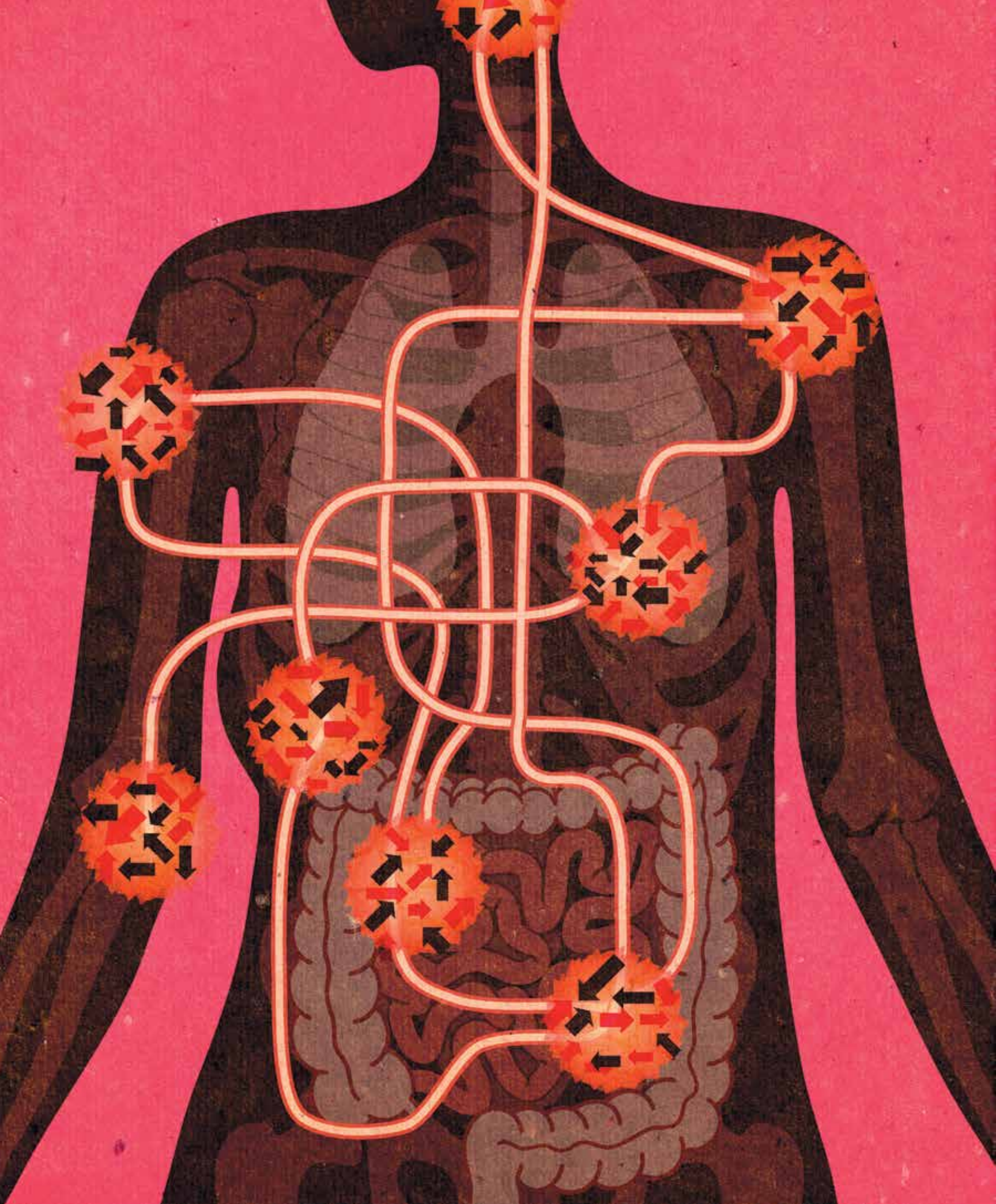
“That is when the data of aspirin and its ability to affect cardiovascular risk came to the forefront,” he said. “A lot of those studies that were designed to look at cardiovascular risk also started to look at cancer risk, finding that [aspirin] did reduce cancer mortality.”

Fuchs and colleagues found that aspirin could affect the growth of colon cancer cells in the lab. Clinical trials further found a link between taking aspirin regularly and a reduced risk of developing colorectal cancer. “That has led a number of policy-making organizations to conclude that aspirin is a chemopreventive therapy for colon cancer,” he said.

So far Fischbach has recruited 20 patients for the breast cancer trial. For five years, half will receive aspirin and half will receive a placebo that looks and tastes like aspirin. Ideally, Fischbach said, researchers would like to see a reduction in cancer recurrence of between 25 and 50%.

“We have detected a glimmer that aspirin may be good for cancer,” he said, “but we don’t have the really robust prospective studies.” */yale medicine magazine*

John Curtis is a frequent contributor to Yale Medicine Magazine.



Untangling the web of autoimmune disorders

When a person develops certain autoimmune disorders, others often follow in their wake. Figuring out why, and how to stop the deterioration, are top priorities for scientists.

BY STEVE HAMM | OTTO STEININGER ILLUSTRATION

Seven years ago, Fatiha began to experience joint pain and swelling of her hands. A doctor diagnosed her with Sjögren's syndrome, an autoimmune disease.

Three years later, the joint pain flared up and was accompanied by a severe rash and sudden hair loss. Fatiha, 32, who asked for her last name to be withheld, could barely walk. The diagnosis was lupus, another autoimmune disease.

Still later, she was diagnosed with rheumatoid arthritis. In spite of her illnesses, the Trumbull, Conn., resident works at a restaurant and is studying computer science at the University of Bridgeport. "I was never sick before in my life. Then one day everything changed," she said.

It is not unusual for people who develop one autoimmune disorder to experience one or more additional ones. Figuring out why this happens is challenging for clinicians and medical scientists. It's a tangled web of causes and effects.

But experts in the field believe that the knowledge they gain from treating such patients combined with advances in laboratory research will not only bring relief to countless people around the globe but will also help scientists better understand the fundamental mechanisms of inflammation and the immune system.

While tremendous progress has been made in treating some autoimmune disorders, doctors are

frustrated by the slow progress in treating other disorders and in cases where multiple disorders or unusual clusters of symptoms occur. "We have to understand the mechanisms, especially the immune mechanisms. But we also have to understand deeply what's going on with an individual patient. It's a form of precision medicine," said Insoo Kang, MD, an associate professor of medicine (rheumatology) at Yale School of Medicine, who is now treating Fatiha. "This is what we hope to accomplish over the next five to 10 years."

Autoimmunity occurs when the immune system loses tolerance of the body's own tissues and behaves as if they are infected with a pathogen. In addition, some researchers believe autoimmunity may occur when the immune system overreacts to a pathogen that has entered the body and attacks healthy tissues.

Typically, autoimmune diseases are treated with therapies that depress the immune system—an approach that leaves patients vulnerable to viruses, bacteria, and other pathogens. "The immune system can be protective or pathogenic. It's the classic metaphor—the double-edged sword," said Jordan Pober, MD '77, PhD '77, FW '78, professor of immunobiology, the Bayer Professor of Translational Medicine and pathology and dermatology.

Some of the more common autoimmune diseases include rheumatoid arthritis, which attacks the joints; lupus, which affects skin, joints, and kidneys; multiple sclerosis, which attacks the nervous system; and inflammatory bowel disease.

Autoimmune diseases are typically caused by mutations in multiple genes, but they can be triggered by environmental factors and stress. Inflammation is closely associated with autoimmune disorders. Most often, it's a symptom of the disorders, but sometimes it's a trigger. "Immune diseases are very complex. You can have the wrong genes but need also the wrong microbiome, diet, or environmental factors," said Martin Kriegel, MD, PhD, FW '06, an associate professor adjunct of immunobiology.

Tumor necrosis factor (TNF) blockers are being used successfully to treat rheumatoid arthritis and other autoimmune diseases, including psoriatic arthritis, ulcerative colitis, and Crohn's disease. However, lupus and some other diseases are not as well understood. People with lupus seem to be particularly susceptible to developing additional diseases.

Researchers believe that a malfunctioning thymus may cause some people to have multiple diseases, said Kriegel. The thymus is instrumental in the maturation of T lymphocytes (T cells), which are essential for fighting pathogens throughout the body. Sometimes, because of genetic defects, the T cells aren't taught how to distinguish between pathogens and normal cells. In other cases, researchers suspect that checkpoints in the lymph nodes and spleen, where immune responses are typically launched, are faulty, leading to patients having more than one disorder.

The causes and manifestations of autoimmune diseases are so complex that researchers struggle to find the best ways to discuss them. Kang describes a "rainbow spectrum" of disorders in which causes and effects overlap. Often, several gene mutations are shared by multiple disorders. Meanwhile, Andrew Wang, MD, PhD, HS '13, FW '17, assistant professor of medicine (rheumatology) and of immunobiology, refers to "constellations" of disease. "If we're honest with ourselves, we recognize that patients with complicated inflammatory diseases can't all be lumped together and all treated the same," he said.

One of his patients, Lois Walters, a retired postal worker in Hamden, Conn., was diagnosed with lupus more than a decade ago, yet her symptoms, including fatigue, joint pain, and skin rashes, didn't respond well to traditional therapies for lupus. After Wang became her clinician four years ago, he tried a different strategy. He recognized that Walters essentially suffered from her own personal version of lupus, so he broke from conventional therapies and treated each of her symptoms separately. It's working. "This is the best I've felt in a long time," said Walters.

Wang believes that a new approach will be required to address the complexities of autoimmune disorders. Today, many of the successful therapies target immune mediators, the signals that immune cells make to tell the body there's a problem. He believes that an alternative approach is to target the metabolic programs that support the immune cells.

Wang said research breakthroughs will be essential in dealing with these complex illnesses, but so will old-fashioned doctoring: "It's important to be mindful of the particular constellation that your patient might have, and it's important to listen to the patient because they'll tell you what's wrong with them." / ***yale medicine magazine***

Steve Hamm is a frequent contributor to Yale Medicine Magazine.

Getting warmer: thermoregulation and inflammation

The human body has a number of innate responses to infection that include heating the affected part of the body, or cooling it down. Yale School of Medicine researchers are looking hard at the causes behind both.

The body survives infection in one of two ways: resistance or tolerance. In resistance, the body uses its resources to mount an all-out war against the invading threat and eliminate it. In tolerance, rather than spending its resources on an attack, the body downshifts into “power-saver” mode where it rides out the infection.

During this time, trade-offs are made. Appetite loss in sickness, for example, allows the body to turn its energy away from food metabolism and conserve strength for weathering the illness ahead. And body temperature regulation, researchers are learning, may also be a key trade-off when surviving an infection is the body’s top priority.

“The idea of using temperature to modulate metabolism and affect immunity is not new, it’s just not understood,” said Andrew Wang, MD, PhD, HS ’13, FW ’17, assistant professor of medicine (rheumatology) and of immunobiology.

Ancient Egyptians used cryotherapy to treat inflammation as early as 2500 BCE. The Edwin Smith Papyrus, the oldest known medical text, dated 3500 BCE, mentions cold therapy multiple times.

More recent research has begun to disassemble the mechanism behind thermoregulation’s immunological success. “It turns out we have to spend a considerable amount of energy defending our body temperature,” said Wang. Saving that energy could help the body enter tolerance mode.

In a study published in *Cell* in 2019, Wang and his colleagues examined a hormone (growth differentiation factor 15 or GDF15) that further illuminates the role of metabolic regulation in infection tolerance. In mouse models of both bacterial and viral sepsis, GDF15 was crucial for survival—which suggested its value isn’t measured

by helping the immune system attack a specific type of invader. In fact, the hormone is triggered after the body launches an inflammatory response. The hormone didn’t reduce pathogen levels in mice compared to those in which GDF15 was blocked, either.

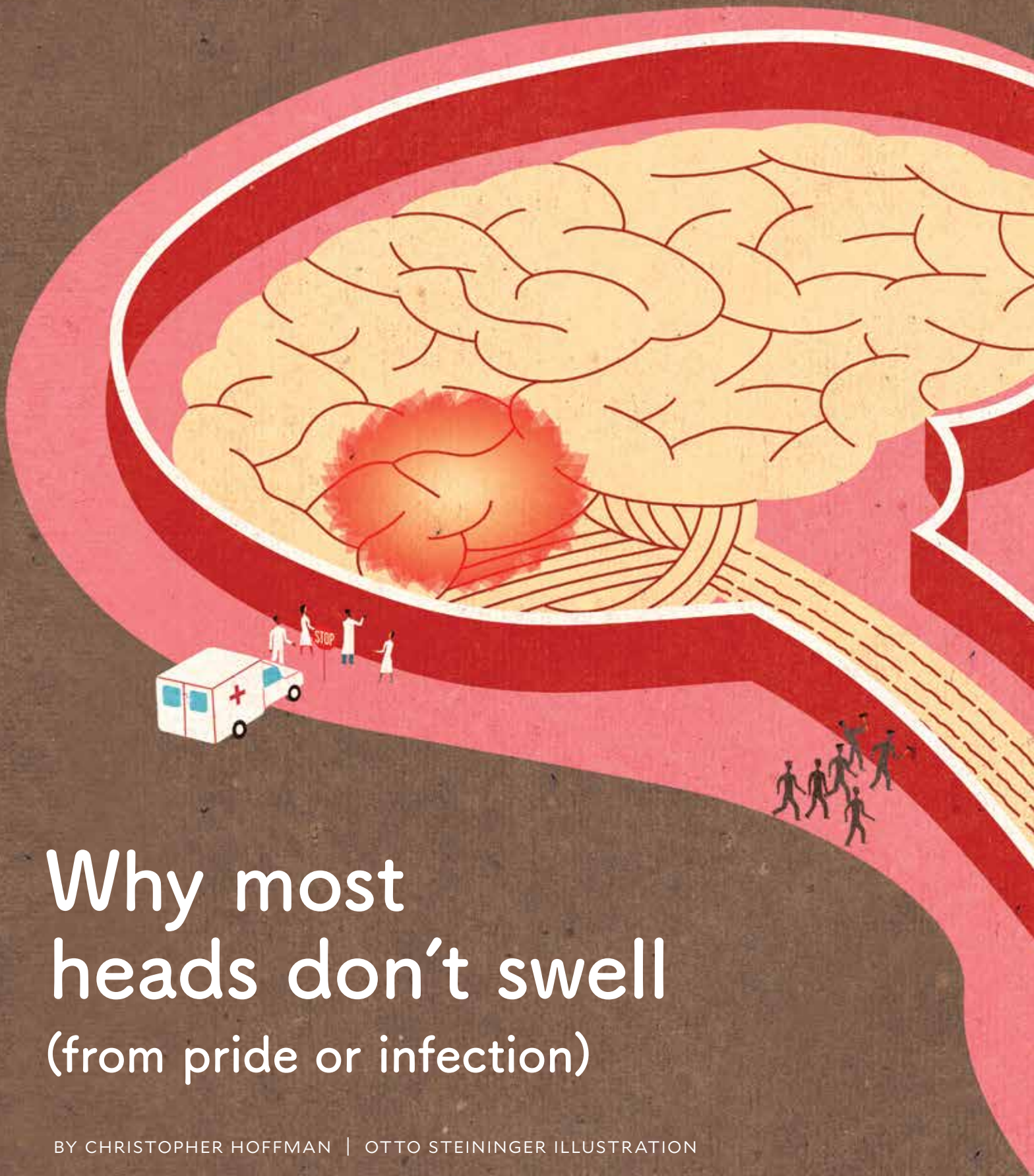
Researchers suspected that the hormone doesn’t help the body resist infection at all. Rather, it helps the body tolerate the inflammation that is necessary to fight it.

“In an overwhelming infection like sepsis, where inflammation becomes a big problem, the tolerance approach—rather than resistance—can be beneficial,” said Ellen Foxman, MD, PhD, FW ’15, assistant professor of laboratory medicine and immunobiology.

The researchers identified physiological changes that seemed to shift the mice into tolerance mode. For one, GDF15 protected the heart from injury in sepsis. It also maintained the body’s temperature. Mice in which the hormone was blocked suffered hypothermia—a serious problem in sepsis patients.

According to Wang, it will be very important to understand how metabolism is controlled to increase resistance to disease. Cryopreservation and other states of suspended animation are extreme examples of “power saver” modes that confer maximal tolerance to inflammatory insults. “Animals that hibernate are extraordinarily resistant to stress, trauma, infection, and most inflammatory injuries,” said Wang. “There’s tremendous interest in seeing how that works.”

—Adrian Bonenberger



Why most heads don't swell (from pride or infection)

BY CHRISTOPHER HOFFMAN | OTTO STEININGER ILLUSTRATION



Some places in the body don't suffer from inflammation as a response to intrusion.

The brain and spinal cord are among them.

When it comes to inflammation, not all organs are created equal.

Some—including the brain and the spinal cord—are privileged. By that immunologists mean that it is very hard to produce inflammation in them. Why? Because these organs have very few immune cells. It's difficult for them to get in, and the organs have inhibitors that turn off immune cells that do manage to gain entry.

"There may be limits to immune invasion and having immune cells migrate en masse into them [privileged organs] even though they can enter in small numbers as part of ongoing immune surveillance," said John MacMicking, PhD, associate professor of

microbial pathogenesis and of immunobiology at Yale School of Medicine, and a Howard Hughes Medical Institute investigator.

On one level, this exclusion of immune cells makes sense. The brain and spinal cord, unlike skin or the liver, cannot regenerate themselves. Plus, there is no backup system for the brain and the spinal cord, unlike, for example, the kidneys. Once brain cells are gone, they are gone forever. The last thing you want is the body's powerful immune system rampaging through the brain, triggering neuron-destroying inflammation as it fights infection.

"In one sense, cells of the brain like neurons may be less well equipped to deal with some of the

toxic products generated during inflammation,” MacMicking said.

The good news is that it’s difficult for diseases to get into the brain and the spinal cord. But what happens when it does? Even worse, what if that disease is cancer? This is one of the reasons that treating brain carcinoma is so challenging.

As if that isn’t bad enough, doctors face another challenge with brain tumors: the blood-brain barrier. It’s a thicket of cells that screens out immune cells as well as microbes, said Lieping Chen, MD, PhD, the United Technologies Corporation Professor in Cancer Research and professor of immunobiology, of dermatology, and of medicine (medical oncology). The blood-brain barrier is a good thing in that it keeps illness out of the brain, but once again represents a double-edged sword, Chen said. The barrier also makes getting cancer medication into the brain difficult, said Chen, the co-leader of cancer immunology at Yale Cancer Center.

“There’s a block,” Chen said. “It protects the brain from most trouble, but it also makes it more difficult to treat brain cancer.”

The blood-brain barrier, however, is not rigid and unchanging. It can contract or expand. Researchers have learned to trick it to expand, increasing the amount of administered medicine that gets through to as high as 40%, Chen said.

Once medicine is inside the brain, clinicians confront an additional challenge: keeping inflammation as tamped down as possible to avoid damaging delicate neurons, Chen said. “If you overdo it a little, you damage the brain,” he said. Understanding and one day learning to control inhibitors that block immune cells will help make treatments more effective, he said.

Recent research, meanwhile, has shown that the blood-brain barrier is not as absolute as once believed, according to MacMicking. “Immune cells do get into the brain and look around,” he said. “The idea of an impermeable, unforgiving physical structure is more of a conceptual model than a functional one.” That does allow the cells to initiate inflammatory responses to disease, including cancer, he said.

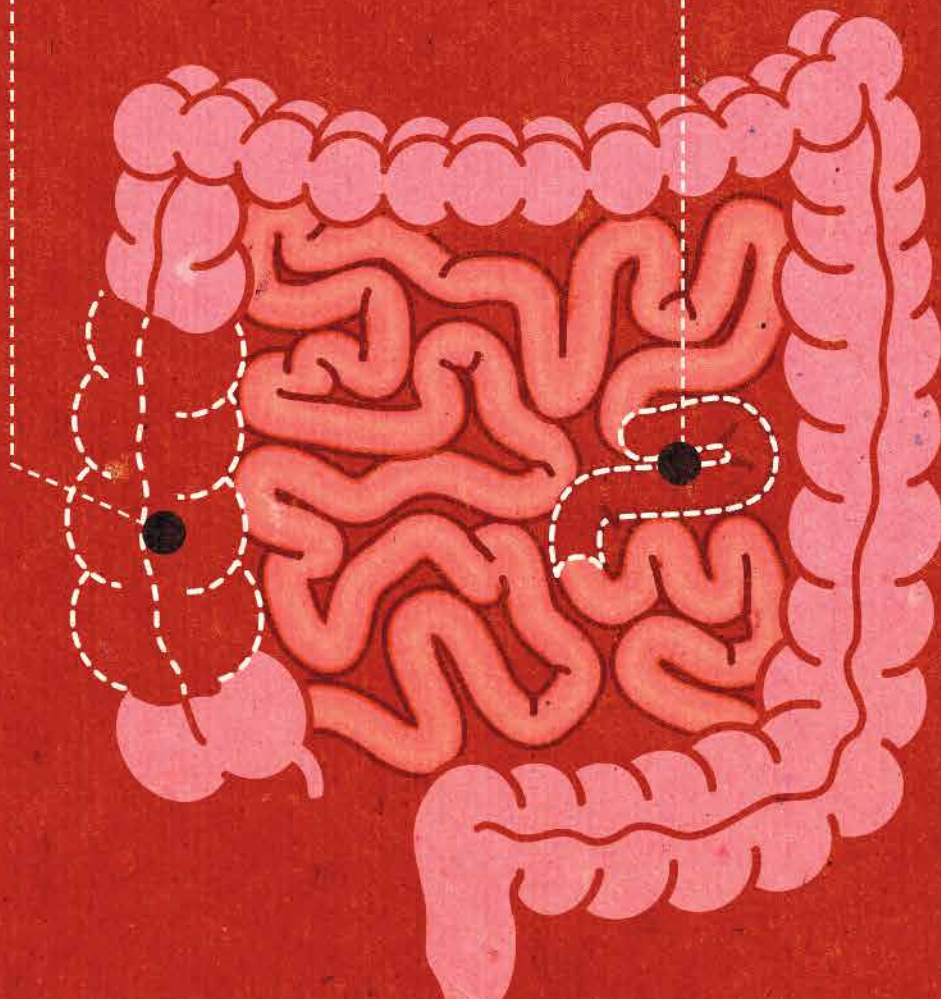
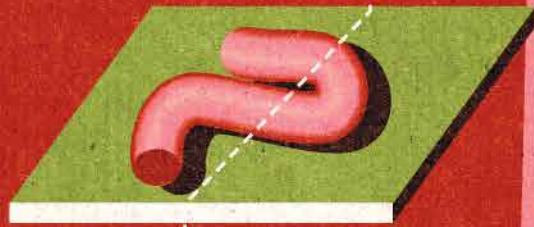
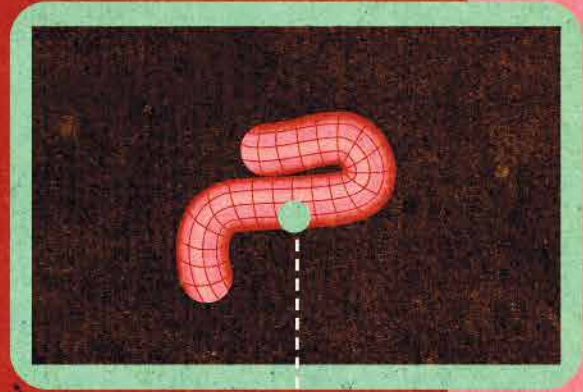
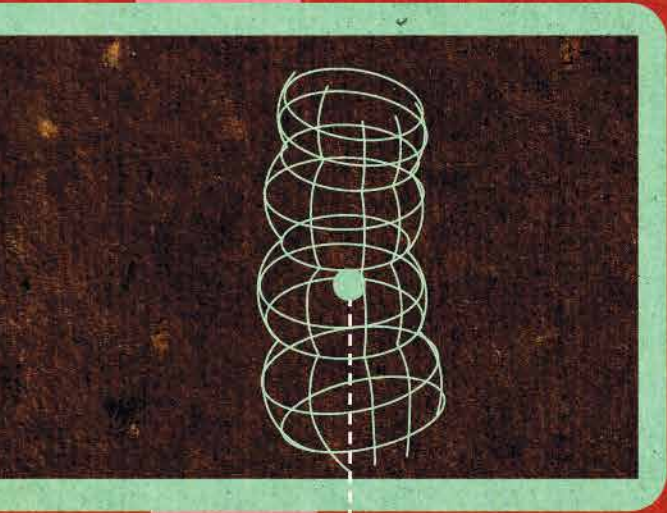
Spinal cancers, meanwhile, are very rare and inflammation likely plays a role in them as well, MacMicking

and Chen said. “We know that inflammation, along with genetics, is an underlying cause of another central nervous system disease, multiple sclerosis [MS],” said David Hafler, MD, chair of the Department of Neurology, the William S. and Lois Stiles Edgerly Professor of Neurology, and professor of immunobiology. An overly robust autoimmune response leads to inflammation when B cells tell T cells to attack the nervous system, Hafler said. This process causes inflammation predominantly in the white matter of the brain and spinal cord. The result is somewhat akin to the insulation being stripped from an electrical wire.

“If you deplete the B cells, you stop the disease,” said Hafler, an MS expert.

As Yale researchers close in on a better understanding of inflammation (or a lack thereof) in the brain and spinal cord, conditions like MS and other nervous system disorders or diseases may soon be diseases of the past. */yale medicine magazine*

Christopher Hoffman is a contributor to Yale Medicine Magazine.



A new dimension to intestinal surgery

One doesn't often think of the intestines when thinking about how 3D printing can assist with surgery or medicine. John Geibel is looking to change that.

BY ADRIAN BONENBERGER | OTTO STEININGER ILLUSTRATION

Long considered one of the worst abdominal injuries, intestines damaged by trauma or illness are almost impossible to heal, and the injuries are fatal under certain circumstances. New technology may change that: 3D printing intestines from a subject's own cells is fast approaching commercial viability. And John Geibel, DSc, MD, MS, FW '88, professor of surgery (gastrointestinal), of cellular and molecular physiology, vice chair of the Department of Surgery, and director of surgical research, is at the forefront of efforts to bring 3D-printed intestines to market.

"Imagine, God forbid, you've been stabbed, or shot, as often happens during war, or you develop some condition that damages your intestines [radiation treatment, traumatic injury, or genetic abnormality that reduces functional intestine]. Soon, we'll be able to fix that," said Geibel.

Fixing pieces or lengths of intestine using 3D printing was something Geibel had considered, but it wasn't until he partnered with a company called Organovo that he had the equipment to begin trials. Initial testing was promising, with lengths of intestine holding up well to volume and pressure, so he decided to push the limits, and developed a procedure capable of printing intestines even faster.

"The key to commercial viability with this process is being able to make durable pieces of intestine that won't rupture, in a short enough timeframe that the patient can benefit from it quickly. We think we have such a procedure," said Geibel.

Drawn to the intestine partly because of his surgical focus on gastroenterology, Geibel said that focusing on

printing this particular organ provides another advantage to people looking to bring it online quickly as a therapeutic option: its relative simplicity.

"The heart has seven cell types with multiple chambers, multiple valves. The kidney has 26 different cell types and 2 million nephrons, not counting connective tissue and vasculature. The intestines have seven cell types," Geibel said. "Furthermore, if you implant a piece of intestine grown outside the body, that intestine will actually integrate into the rest of the system, so it can absorb nutrients and be more than just a length of flexible tubing."

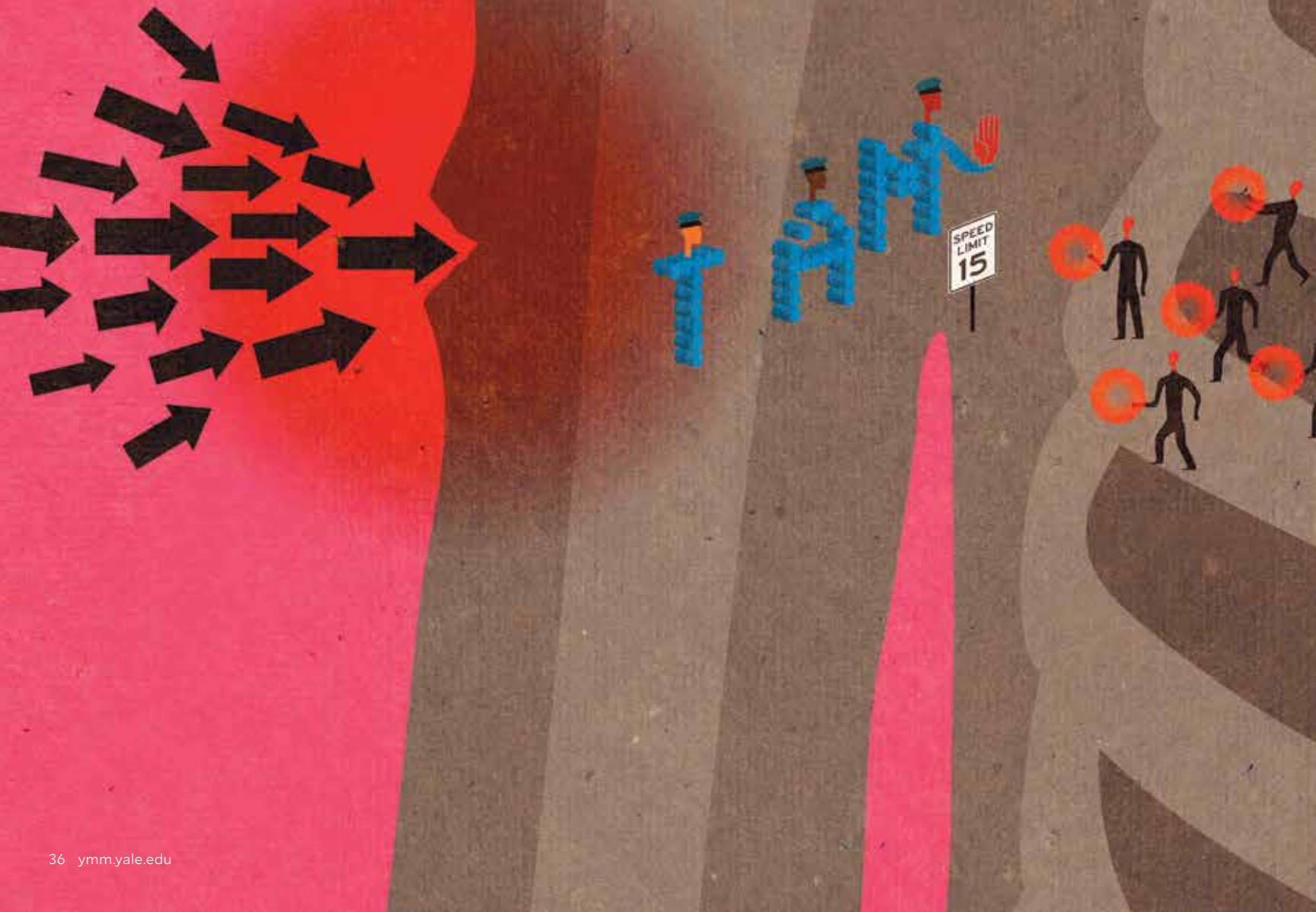
The absorption of nutrients is one of the key difficulties for people suffering from diseases, conditions, or injuries that affect the intestine. Initial trials have been very promising, and 3D-printed intestinal sections that have been implanted to plug holes or cuts made in healthy intestines in a laboratory setting have been successful in animal models.

Although there are troubling technical aspects to forming viable lengths of intestine, Geibel feels that his technique addresses all concerns. Now, he's working with ways to print the intestine faster while also strengthening the printed organ so that it can endure the vast amounts of liquid, salts, nutrients, and waste products it will be expected to carry. The final step will be to test it in people. Geibel is eager to advance to this point, and to give people who are suffering from life-altering health complications hope for a viable replacement that can restore functionality to damaged tissue. */yale medicine magazine*

Adrian Bonenberger is editor of Yale Medicine Magazine.

Exploring the frontiers of immunity and healing

BY KATHERINE L. KRAINES | OTTO STEININGER ILLUSTRATION





Researchers at Yale are aware of how wounds know to heal.

Now they want to know why.

During a 1989 lecture at the Cold Spring Harbor Symposium on Quantitative Biology, Yale School of Medicine professor Charles Janeway, MD, hypothesized the existence of an innate immune system and special receptors on immune cells (currently known as toll-like receptors) that trigger the body's response to infection. Janeway's research later confirmed his insights, providing the foundation of future endeavors exploring the intricacies of the human immune response. New discoveries continue to reveal an exquisitely tuned immune system in which inflammatory responses and healing are initiated and regulated by known and unknown mechanisms.

Carla Rothlin, PhD, the Doris McConnell Duberg Professor of Immunobiology and professor of pharmacology, and co-leader, cancer immunology, Yale Cancer Center; and Sourav Ghosh, PhD, associate professor of neurology and pharmacology, run Yale's Rothlin Ghosh Laboratory. "We focus on mechanisms that set or limit the magnitude of the immune response," said Rothlin, "as well as mechanisms that signal the shift from a pathogen-defense mode following successful immune defense to resolution and

wound repair." The team is also studying the different types of inflammation that occur as part of the immune response and are examining immune mechanisms that play a role in the healing process.

Rothlin and Ghosh's partnership began as postdoctoral fellows at the Salk Institute for Biological Studies, where they started to understand the role of three cell receptors: Tyro3, Axl, and MerTk, known as the TAM receptor tyrosine kinases. While found on other cells, these receptors are primarily expressed on the plasma membrane of innate immune cells known as macrophages and dendritic cells. Continuing their investigations at Yale, Rothlin and Ghosh found that the TAMs are also essential to the healing process.

"Our lab discovered that the TAM receptors serve as innate immune checkpoints in regulating the magnitude and duration of the immune response by working to negatively regulate the response. In other words, they operate as brakes on the inflammatory response," Rothlin said. "The goal is to mount an adequate response to fight the bacteria, virus, or parasite and not kill you. This process must also regulate the immune response to bring the body back to baseline.

The TAM receptors play a pivotal role in the homeostatic regulation of the immune system.”

The immune or inflammatory response is a finely tuned classical feedback loop that begins with toll-like receptors, located with the TAMs on macrophages, reading the presence of a pathogen and activating inflammation. The TAM receptors are downstream of this positive signal and are activated to tell the toll-like receptors to slow down the inflammatory response so it is not overdone. Once the pathogen is gone, the TAMs identify a type of dead cell associated with the transition to resolution of inflammation and induction of tissue repair, and start the healing process by triggering macrophages to eat the cells and produce growth factors to make new ones. “What is beautiful is the immune system can kill invading pathogens and repair the damage after inflammation, and we have found that that is contributed to, in part, by the TAM receptors,” said Rothlin.

Together the TAMs serve as negative regulators of the immune response, but each receptor has selectivity of function related to the kind of inflammation that occurs. Some TAM receptors function better as brakes on a bacterial or viral infection, and others are more effective with an allergic response. “Key to understanding the role of TAMs is knowing that there are different types of inflammation,” Rothlin said. “Being infected with a virus is different from mounting an allergic response. We discovered that the “T” in TAM—Tyro3—is a negative regulator of type 2 inflammation, which is an allergic response.”

The immune system has an amazing ability to recognize invading microorganisms, react, and eliminate them, and to coordinate healing. Yet healing is not only dictated by the macrophages, but also by the location of the damage. “Different tissues have different capacities to recover,” said Rothlin. “Our skin and mucosa are in touch with the environment and heal better because they are more likely to be damaged. However, the brain and heart are not that good at healing. You cannot easily make more neurons or cardiomyocytes.”

Much is still unknown about the immune mechanisms in autoimmune diseases or cancer. Current drugs to treat autoimmune diseases suppress the

response, but Rothlin noted that the resulting inflammatory damage still requires healing. “Autoimmunity is complex and is a result of many, many changes happening together,” she said. “Targeting the TAM receptors might help healing by allowing us to put the brakes on chronic inflammation or to release the brakes to allow the immune system to persist in a sustained way against something like cancer.”

Moving forward, understanding the transition from inflammation to tissue repair is going to be very important. “We have medications that reduce inflammation, but we have nothing to induce healing,” said Rothlin. “Studying what these receptors can do may allow us to develop therapeutics that not only limit inflammation but also promote tissue repair.” *yale medicine magazine*

Katherine L. Kraines is a frequent contributor to Yale Medicine Magazine.

The intricate history of a long-familiar companion of tissue injury

Inflammation has captured the interest of generations of distinguished clinicians and researchers.

By Jenny Blair, MD '04 and Rebecca Frey, PhD '99

Rubor, calor, tumor, dolor: Dating from the early first century CE, these Latin words form an incantation that medical students recite to this day. They come from the Western world's first known description of inflammation, authored by one Aulus Cornelius Celsus, a Roman who observed that the condition manifests as redness, heat, swelling, and pain.

The Romans weren't the first to mention the phenomenon, though. The ancient Egyptians wrote about pus collections and

ulcers, while in the fifth century BCE, Hippocrates repeatedly brought up inflammation in connection with such ailments as hemorrhoids, superficial skin infections, and ulcers. For patients with leg wounds, the great Greek physician made this chatty recommendation (one that suggests he may not have taken deep vein thrombosis into account): "If a person ... at first betakes himself to bed, in order to promote the cure, and never raises his leg, it will thus be much less disposed to inflammation, and be much sooner well, than it would have been if he had strolled about during the process of healing."

Hippocrates' suggested herbal treatments included

boiled mullein, fig and olive leaves, and "linseed ... moistened with the juice of strychnos [the source of the poison strychnine] or of woad, and applied as a cataplasm."

Galen, a Roman medical authority and personal physician to Emperor Marcus Aurelius, who was revered for over a millennium after his death in 216 CE, believed inflammation allowed blood to escape the arteries. His many misconceptions were taught until the Renaissance. Eventually, though, anatomists began

to glimpse the actual inflammatory process thanks to the invention of the microscope.

The Dutch medical professor Herman Boerhaave (1668–1738) peered at blood vessels in inflamed tissue, decided they were too small to conduct blood, and proposed that *calor* arises from the blood's generating friction. His German-born student Hieronymus David Gaubius (1705–1780), whom history will also remember as the discoverer of menthol, correctly linked inflammation to coagulation.

The Scottish surgeon John Hunter (1728–1793), another careful observer, wrote a book (published by a colleague in 1794) comprising detailed discussions of inflammation and its connections to such colorful ailments as "putrid and jail-distempers," gout, and ringworm.

Henri Dutrochet, a French botanist and physiologist, watched white cells escaping through vessel walls in 1824; and Rudolf Wagner, a German anatomist, described leukocyte rolling in 1839—processes by which inflammation delivers cells to the site of injured tissue. In 1867, the pathologist Julius Cohnheim realized that changes in vessel walls

allow white cells to cross, alliteratively describing a typical cell as a “colorless, matte-shining, contractile corpuscle.” Ilya Ilyich Metchnikoff in 1893 described different white cell types and observed that the engulfment of harmful agents by amoeba-like phagocyte cells is central to the process of inflammation. He shared the 1908 Nobel Prize in Physiology or Medicine for his work on immunity.

In an irony that persists today, battlefield experience increased the West’s understanding of infection, inflammation, and healing. Surgeons in the Roman army—the first army to have a dedicated medical corps—emphasized the importance of keeping surgical instruments clean and promptly evacuating wounded men. In 16th-century France, an era when gunpowder weapons complicated traumatic inflammation and even minor wounds could lead to tetanus, Ambroise Paré challenged prevailing Galenic notions after engaging in an accidental experiment. One day in 1537, after running out of the usual gunshot-wound dressing—excruciating and injurious boiling oil—Paré applied a soothing ointment to such wounds, to

far better effect. He went on to be known as the father of military surgery.

Dominique Jean Larrey, a surgeon in Napoleon’s army and the inventor of field triage, broke with a tradition of delayed amputation by performing it promptly to reduce the risk of inflammation and infection; in 1809 he amputated the shattered leg of one of Napoleon’s marshals in less than two minutes. His technique for treating abdominal gunshot wounds also avoided the inflammatory complications that had beset those of his predecessors. Larrey also insisted on retrieving wounded men and tending to them behind the front, reviving the long-defunct Roman practice. Trailblazing, trousers-wearing American Civil War surgeon Mary Walker clashed with her colleagues against the overuse of amputation, arguing that it is often unnecessary. These surgeons contributed to a move away from indiscriminate amputation of wounded limbs on the grounds that the practice increases the risk of inflammation rather than lowering it.

In the 19th-century, to the classical list of inflammation’s four signs was added a fifth sign—*functio*



laesa, or loss of function of the affected body part—by Rudolf Virchow, the 19th-century German pathologist. (Legend has long held that Galen did so, but in his 1991 book *The Healing Hand: Man and Wound in the Ancient World*, physician-historian Guido Majno argues persuasively that it was Virchow.) Far ahead of his time, Virchow also linked inflammation to atherosclerosis.

The 20th-century saw repeated milestones in the study of inflammation, and

we now understand the basic steps of the process. Blood vessels dilate, leading to redness and heat; they become leaky, causing swelling as fluid and cells cross their walls; and pain arises from pain receptors in the inflamed tissue.

Today, researchers believe subtle, chronic inflammation contributes to many diseases of modernity, including heart disease, obesity, depression, cancer, and even dementia. Even the gradual attenuation of bodily functions that accompanies growing older is thought to be powered in part by inflammation, a process called “inflamm-aging.”



Inflammation was one of the first symptoms of injury or infection noticed by ancients. As science has advanced over the years, doctors have come to understand far more about the mechanisms governing how the body inflames, and under which conditions. Some of Peter Parker’s patients in 19th-century China bore conspicuous evidence of the phenomenon.



Around the world in six years

GROWING UP IN LA RIOJA, SPAIN—wine country—Judith Jimenez Sainz, PhD, was surrounded by people involved with the production of its famous red. Her grandfather made wine; both of her uncles own vineyards; and as a little girl, she picked grapes from the vines.

In high school, though, Jimenez Sainz decided on a path a long way from viticulture. Her teachers, glimpsing a talent for science and research, advised her to explore those fields. And although her first thought as a young woman was that science is for men, she trusted her mentors. When it came time for college, they encouraged her to find the best institution to feed her curiosity.

“I’m very grateful to my teachers for helping me challenge myself,” said Jimenez Sainz. “They were instrumental to pushing me to seek out opportunities in research.” Jimenez Sainz decided to study at the University of Valencia,

where she took her PhD. She also spent a year in the United Kingdom at University College London, broadening her research capabilities and her professional network. But her journey was just beginning.

“I am a biochemist and molecular biologist who focuses on breast and ovarian cancer in women, and ways to identify, prevent, and (I hope) cure it,” said Jimenez Sainz. “I ended up in New Haven because that’s where I had the best feeling about my PI [principal investigator].”

Jimenez Sainz had heard of Yale—“Of course, everybody knows about the Ivy League in Europe”—but hadn’t realized it is in New Haven, Conn.—a place unfamiliar to her. Originally set on working in a big city “like Boston or New York,” Jimenez Sainz was ultimately drawn to the research possibilities at Yale, the academic culture, and sense of optimism she felt about her lab. Now, she is an associate research scientist with the Jensen Lab in the Department of Therapeutic Radiology.

It didn’t take long for Jimenez Sainz to adapt to New Haven. And while she was adjusting to the United States, she dove headfirst into her research and also into the community, becoming involved with the E-visibility program (of which she is now director) and Españoles Científicos en USA (ECUSA: Spanish Scientists in the United States). She is also a



Judit Jimenez Sainz's research brought her from her native Spain to England, and now, to the United States. Her advocacy for gender equality in science and medicine will bring her to Antarctica this fall.

strong advocate of women in science, which is how she came to participate in a program called Homeward Bound that will send her to spend three weeks in Antarctica later this year.

“Homeward Bound is an international leadership, scientific, and visibility initiative that aims to bring 1,000 STEMM [science, technology, engineering, math,

and medicine] women across the globe in 10 years,” said Jimenez Sainz. Part of the cohort HB5, Jimenez Sainz discusses the program and fundraising for it on her webpage.

Why leadership? “Just like I had to learn how to do experiments properly, I need to learn more about the craft of leadership,” she said. “I hate to say it, but growing up, it didn’t even occur to me that I could be a scientist, let alone a department head or a dean. I thought, to be honest, that these were jobs for

men. I have a lot of catching up to do with leadership training.”

Hence the culminating three-week trip to Antarctica. “Until 1969, women were forbidden from Antarctica. Not because of any laws—there is no government in Antarctica. Just because with a very small number of exceptions, they weren’t brought on scientific



ONLINE EXCLUSIVE

After graduating from Yale School of Medicine, Howard Koh served as Commissioner of Public Health for the Commonwealth of Massachusetts and the Assistant Secretary for the United States Department of Health and Human Services under President Barack Obama. He shares some of his insights into how to achieve lasting success in life.

For more on lasting success, visit ymm.yale.edu/success

expeditions or military operations. The prohibition was, from a certain perspective, self-imposed: women thought that it would be impossible for them to go to Antarctica, that they had nothing to contribute to such an expedition. *Homeward Bound* helps foster leadership, and self-starting is part of that,” said Jimenez Sainz. “I’m looking forward to what the future holds.”

—Adrian Bonenberger



**Paying it back:
Kristina Brown’s quest**

Chronic disability casts a shadow over the lives of people who live with it. One can never be sure when the condition or illness will flare up or be permanently exacerbated. Even when times are good, it’s difficult to focus fully on long-term projects like career or education, knowing that a setback could be just around the corner.

Kristina Brown’s mother’s multiple sclerosis was under control for much of Brown’s childhood, and her family was financially healthy. That changed when Brown was a teenager and her mother’s disease worsened to a debilitating level. Her mother’s need for home care required Brown to devote significant time each day when she was still just in high school. Her parents divorced when Brown was in college, further reducing resources available for care. Only Brown and one of her sisters

acting as caregivers kept their mother alive.

So it was that when Brown was accepted to Yale School of Medicine (YSM), normally among the happiest days in a young student’s life, she was faced instead with a terrible choice: continue caring for her mother at home, foregoing a career in medicine, or pursue her dream and accept major financial risk and indebtedness by taking out student loans to not only pay for her education but also for the care of her mother.

Luckily for Brown, for YSM, and for the United States, she took the latter path. Now a fourth-year student at YSM, she has a lot to say on the subject of equitable treatment of individuals with disabilities as well as fair compensation for caregivers. “We have a health system that is full of gaps, where entire groups of people are routinely overlooked,” said Brown. “And we have an economic system where caregivers go into debt and make unthinkable sacrifices taking care of loved ones. It doesn’t have to be this way.”

The gap to which she refers, and which is referenced in an op-ed she published in the *Washington Post*, has to do with health insurance coverage. Her mother made too much money to qualify for Medicaid, a health care system that covers the poor, but her private insurance did not cover home health care for such daily needs as bathing

and personal hygiene. And in any case, private insurance did not leave Brown’s mother with enough money to pay for home care along with a mortgage and all other expenses. Medicare, the health system that covers elderly patients, kicks in only when one reaches 65. What is a middle-aged, middle-class disabled person to do?

Brown wrote about the dilemma. Titled “My family faces an impossible choice: caring for our mom, or building our future,” the article took months of drafting and energy, as well as some assistance from a writing mentor, Anna Reisman, MD. When the *Washington Post* published the article, it went viral, and Brown received an invitation to testify in front of Congress a week later. She did so at a hearing in honor of National Alzheimer’s Disease Awareness Month and National Family Caregivers Month. “It was a great honor to get to speak in front of Congress,” she said.

Hopeful about the potential for future reforms, Brown said that extended disability is something that everyone should care about. “If you’re in the middle class, it can happen to you,” she said. “Imagine your son or daughter donating hours of their lives to your care out of financial necessity. That’s the reality many Americans live with today.”

The article has had two outcomes that give Brown great hope: first, responses by people

in her position who have said the op-ed inspired them and made them realize they aren't alone; and second, opportunities to cover expenses while she's still in New Haven and unable to give her mother the necessary assistance.

One such source of assistance is a GoFundMe page that Brown set up with the goal of raising \$80,000 for home care for her mother. As of this writing, she has raised \$14,339 of the total needed—a not-inconsiderable sum, though short of her goal. “I thought about leaving medical school before the piece came out, to return to caregiving for my mother,” said Brown. “I had explored and applied for every option for financial assistance, and without any forthcoming, I felt trapped and desperate. The community has responded so well, it's amazing.”

Brown's next stop will be residency at UCLA, in Medicine-Pediatrics. She hopes this will help her to grow as an advocate for individuals who through no fault of their own lack voices; those with disabilities; and those systemically disenfranchised by dysfunctional political institutions.

—Adrian Bonenberger

Kristina Brown published an op-ed with the *Washington Post* in 2019 about the difficulty of being a caregiver for her mother, who suffers from MS. The piece resonated deeply with other Americans, and was widely read and shared, landing Brown an opportunity to testify in front of Congress the following week. Now she's carrying that advocacy work forward with her.



The machinery of immune systems

FROM A YOUNG AGE, Joseph Craft, MD, FW '85, the Paul B. Beeson Professor of Medicine (Rheumatology) and professor of immunobiology, adopted a problem-solving approach to chores on his childhood 300-acre farm in rural North Carolina. If a piece of farm machinery shuddered to a stop in the middle of a cornfield, Craft inspected every piston, rod, and washer in the engine to diagnose the problem. If one of his calves fell ill, he needed to find out why. "You develop a curiosity about all kinds of things," Craft said.

In college, Craft honed his curiosity in chemistry, which laid the groundwork for a career devoted to understanding the immune

system—particularly antibodies. Antibodies are proteins formed to bind to and attack antigens—structures located on the surface of invading viruses, bacteria, and other foreign molecules that can trigger an immune response.

Chemical interactions form an important part of the antigen-antibody relationship.

When Craft was a first-year medical student, he

helped care for a patient with systemic lupus erythematosus (SLE), an autoimmune disease that has no cure as of 2020. Craft decided then that he wanted to understand immunology through lupus. "It was a very mysterious disease at the time," Craft said. "It still is, but we know a lot more about how it works."

Since he arrived at Yale in 1980, Craft's immunology research has focused on how lupus develops, along with different aspects of the immune system's response to foreign pathogens and vaccines. He directs the Investigative Medicine Program for physicians who earn a PhD while gaining experience in the lab or in-patient research. In 2004, he won Yale's prestigious Charles W. Bohmfalk Prize for teaching in the basic sciences and is a fellow of the American Association for the Advancement of Science.

Yale Medicine Magazine discussed antibodies and inflammation with Craft, as well as follicular B helper T cells (T_{FH}), which his laboratory also studies, and which could play a future role as a therapeutic target for lupus.

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

Lupus is an autoimmune disease. Briefly, what's going on in the immune system when it develops?

Our immune system produces antibodies, proteins that circulate in the blood, that protect us against infections. The cells that make antibodies are called B lymphocytes. When you get a flu vaccine, for example, the vaccine initiates production of antibodies by B lymphocytes, which lead to protection against flu infection. This is a well-regulated process, and vaccines are quite safe. In patients with lupus, however, the immune system is not regulated properly, and patients with lupus develop antibodies against DNA and RNA, which are in every cell. Antibodies directed against components of one's own cells are called autoantibodies. Autoantibodies bind to the individual's tissues, damaging organs, especially the skin, joints, and kidneys in lupus. As a consequence, the majority of patients with lupus have skin and joint inflammation, and about half of patients will have kidney disease.

How does inflammation figure into this?

Autoimmunity is a response of the immune system against itself. If not properly regulated, autoimmune attacks lead to tissue inflammation and ultimately damage, if not properly treated.

How do follicular B helper T (T_{FH}) cells figure into this process?

We are trying to understand how T_{FH} cells contribute to inflammation in lupus and what drives chronic inflammation. T_{FH} cells largely function in your spleen and lymph nodes. B lymphocytes' production of protective antibodies, after flu shots for example, absolutely requires help from a second T helper lymphocyte. The latter are called follicular helper T cells, as they reside in special areas of the spleen and lymph nodes, the follicles where B lymphocytes also reside. An analogy would be if you are lifting a sofa, you can lift one end, but you'll need help with the other end. Now we are trying to understand the basic biology of T_{FH} cells—how they function and

survive, as well as how they help B lymphocytes make antibodies. We've identified how they are activated and new ways to characterize them.

In lupus, T follicular helper cells are also required for production of tissue-damaging autoantibodies.

Would T_{FH} cells be a good target for a potential new drug for lupus?

We have shown that targeting T_{FH} cells could help symptoms of lupus, but we are trying to determine which mechanism of T_{FH} cells to target, and how to do this effectively and safely.

What stands out in your more than 30 years here at Yale?

Yale is a special place to do research and care for patients because of the dedication, expertise, and intellect of the students, staff, and faculty. I've learned so much from these colleagues, shaping how I care for patients and do science. What is most impressive are the students and trainees. Their intellect, capacity for work, their curiosity—it's just mind-boggling. One can't help but make contributions in an environment like this.



Permission to feel

By Cathy Shufro

Our vocabulary for emotion is impoverished. We're stressed or we're good; we're bummed or we're okay. The meagerness of this lexicon tells us something about ourselves, according to psychologist Marc Brackett, PhD: It shows how hazily we perceive our feelings.

And physicians on average may be particularly undiscerning. It's an occupational hazard: As doctors rush from patient to patient, they can't take time to reflect on feelings. And when they witness the suffering caused by illness and death, one way they cope is to drive emotions underground.

Except suppression doesn't work, said Brackett, director of the Yale Center for Emotional Intelligence and professor in the Child Study Center. When doctors habitually suppress their feelings, they burn out, even get sick. And patients view emotionally blank doctors as heartless. On the other hand, patients don't benefit from seeing their physicians sobbing uncontrollably.

"You don't want other people to think they need to take care of you," said Brackett.

In his new book, *Permission to Feel: Unlocking the Power of Emotions to Help Our Kids, Ourselves, and Our Society Thrive*, Brackett helps readers find an emotional equilibrium, or a "best self." That self is at once collected and compassionate, Brackett writes. Using stories of deprivation and distress from his own childhood, Brackett provides a method for realizing that best self: recognizing and regulating emotions, and learning to express feelings judiciously in accord with the situation. Acknowledging feelings, he said, "prevents emotions from having undue influence over our actions."

The best self shows sympathy not only for others but also compassion for the self. For instance, when a patient dies, a doctor might tell himself or herself, "You really did everything possible to support this person." Brackett also recommends giving priority to self-care. "My workouts and yoga sessions are in my calendar," he

said. Recently, he's begun using meetings to take walks.

Groups of colleagues will also fare better if they share feelings. For instance, at a casino where Brackett served as a consultant, workers quit frequently because they were worn down by being around gamblers who were drunk or angry about losing money. Scheduling time for the workers to talk over the emotional toll of their work reduced turnover. Brackett suggests that group medical practices schedule time for meetings whose sole aim is to "provide time and space to just process."

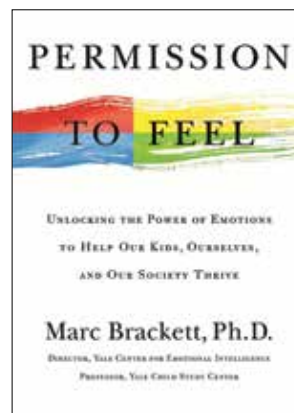
Checking in with one's emotions also prevents a reaction to one situation from coloring the next interaction. "If you name it, you can tame it," Brackett said. "Once you attribute that emotion to its source, it no longer will have a subconscious influence on how you interact in that second setting."

Understanding the emotions of another person, he writes, "requires the use

of our storytelling ability, perspective-taking skills, and pattern-seeking to piece together the concatenation of feelings and events that led to the current situation. It begins with being an emotion scientist, not a judge."

Just as understanding emotions requires listening, so does finding the best way to help someone in distress. Brackett suggests asking such open-ended questions as, "What do you need right now? How can I support you?"

Brackett teaches a course at Yale College called Emotional Intelligence that draws hundreds of students. Sometimes a student will tell him, "I didn't need emotional intelligence to get into Yale, so why is it so important?" And doctors have said, "I've gotten here without those skills." Brackett's answer: "What about the quality of your relationships? What about your physical health? What about your mental health? It's a narrow definition of success." Real flourishing, he argues, for the individual and for society, will arise when we give ourselves—and others—permission to feel.



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Hail and Farewell

ON ONE OF THE COLDER EVENINGS of an unusually warm winter, dozens of faculty, faculty emeriti, and department chairs gathered in Yale School of Medicine (YSM)'s Medical Historical Library to shake hands with the new dean and raise their glasses to the former dean.

The affair was comfortable and familiar, with Nancy J. Brown, MD, the Jean and David W. Wallace Dean of Medicine and C.N.H. Long Professor of Internal Medicine, mingling and chatting with her new colleagues. She said she begins her journey as dean with YSM in “an incredible place, due largely to the leadership of Bob Alpern.” Robert J. Alpern, MD, Ensign Professor of Medicine and professor of cellular and molecular physiology, partook in the festivities, basking in the glow of 15 years' efforts successfully handed over to a capable and competent successor. With that, one era was over, and another began.

—*Adrian Bonenberger*