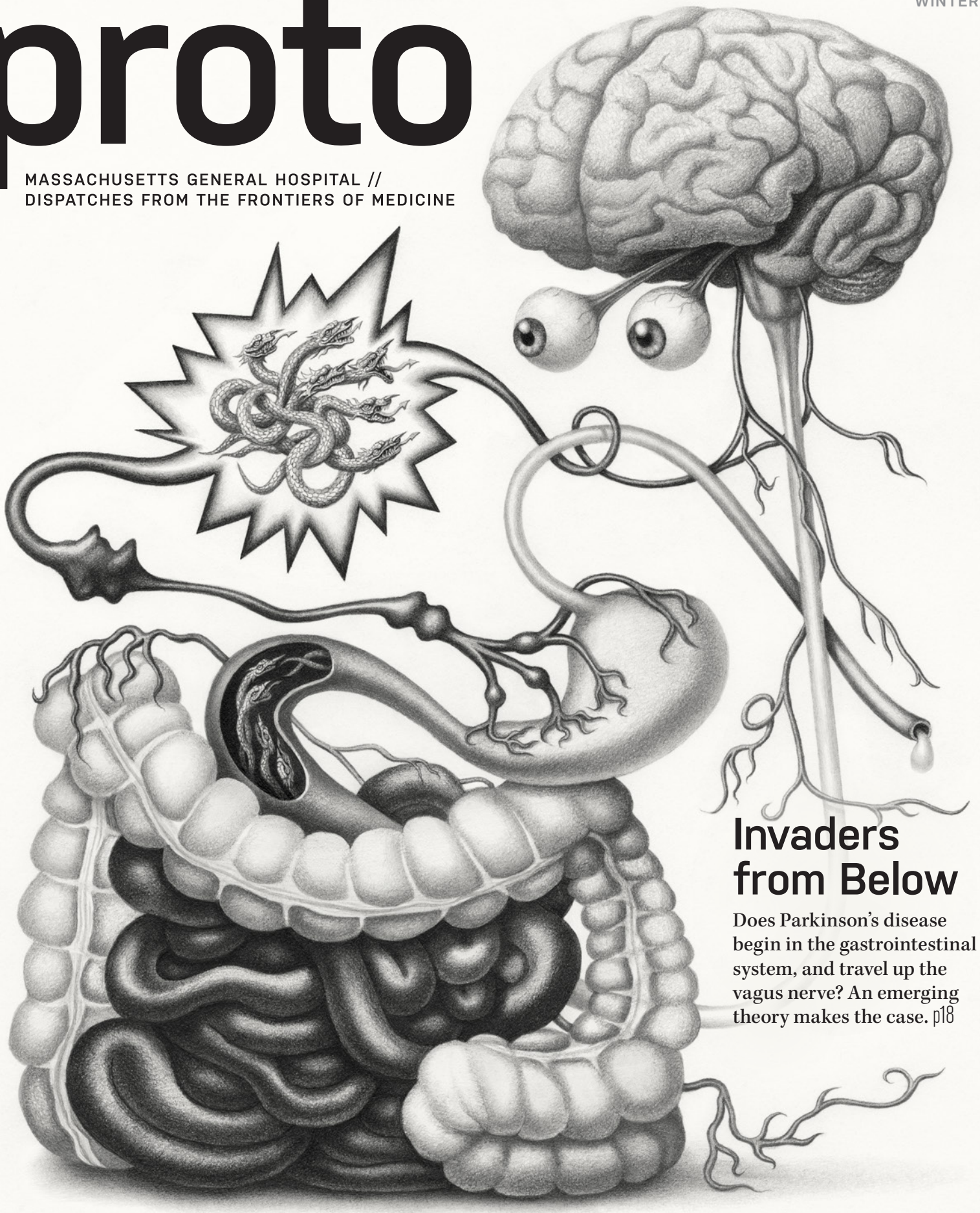
WINTER 19

proto

MASSACHUSETTS GENERAL HOSPITAL //
DISPATCHES FROM THE FRONTIERS OF MEDICINE



Invaders from Below

Does Parkinson's disease begin in the gastrointestinal system, and travel up the vagus nerve? An emerging theory makes the case. p18

contents

WINTER 2019

STAT

POST-OP

FEATURES

on the cover

Understanding where idiopathic Parkinson's begins could lead to earlier detection and new treatment options. Now some believe that the gut may play a major part. // Illustration by Armando Veve

proto: a prefix of progress, connoting first, novel, experimental. Alone, it conjures an entire world of the new: discoveries, directions, ideas. In taking **proto** as its name, this magazine stakes its ground on medicine's leading edge—exploring breakthroughs, dissecting controversies, opening a forum for informed debate.

proto

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Founded in 1811, Massachusetts General Hospital is a 1,000-bed academic medical center located in Boston. It is a founding member of Partners HealthCare and is the original and largest teaching affiliate of Harvard Medical School.

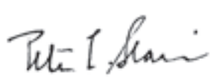
ON THE AFTERNOON OF November 19, shots rang out in the emergency room of Chicago's Mercy Hospital & Medical Center. Four people died, including a first-year pharmacy resident and an emergency room physician. The outpouring of grief and outrage from the medical community was swift, less because the attack came as a surprise than the fact that, by now, such an incident feels inevitable.

Those who practice medicine are no strangers to violence. Clinicians treat people in their most vulnerable moments, and many patients have been underserved by mental health care and social services. But violence in hospitals is on the rise, as "When Healers Get Hurt" relates. And when violence happens, clinicians too often feel pressure to brush it off and assume it's part of the job. They are trained to think of patients' needs first, and so a culture of tolerance for such incidents has been building, not for years, but decades.

Silence is not the answer, however, and neither is complaisance. At Massachusetts General Hospital, we have built a series of protocols to be prepared for any situation. The Center for Disaster Medicine has worked through active shooter scenarios and taken the entire hospital through a drill that included Boston Police and Boston EMS. We have equipped work stations with panic buttons. We have invested in strategies that help us spot troubled people before they cause harm.

Above all, we have become students of how to de-escalate tense situations. Behavioral psychologists have made strides in establishing techniques that can manage aggressive behavior. Staff members can take part in seminars to learn how to respond. We are committed to doing everything we can to help keep patients from hurting themselves and others.

A recent conversation about this topic has trended on Twitter under the hashtag #silentnomore. It is indeed time to break the silence. It is our job as a profession to listen to one another and make sure that hospitals remain a safe place for patients and their healers.



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stat

FOCUS

Using an infrared camera, photographer Gray Hutton spent last winter on the streets of London capturing the lives of homeless people and the extreme conditions they face. A report released in March 2018 revealed that homelessness is on the rise in every European country except Finland. Hutton hopes that his photos, which show the heat signatures of his subjects against the frigid outdoors, will shed light on this epidemic in a way that the eye otherwise cannot see.

Medical records for the homeless pose special problems, as these patients are often in transit and unable to communicate their complete histories. One of the earliest systems was designed in 1994 by engineers at Massachusetts General Hospital for the Boston Health Care for the Homeless Program. Recently a nonprofit for the homeless in the United Kingdom created a "template" that works on the U.K.'s leading electronic health records platform. It houses data about these patients' clinical histories, mental health and addiction issues and information about housing and financial status. The template uses national clinical coding to help keep track of homeless people as they travel from place to place and provider to provider.

GRAY HUTTON

INTERVIEW

Medicine and the Makers

Roderic Pettigrew is training a new hybrid specialty—half physician, half engineer.

BY WYATT MARSHALL

Growing up in the Deep South, Roderic Pettigrew remembers making his first bow from the limb of a chinaberry tree and a strip of rubber from a bike inner tube. His career in medicine has been marked with a similar curiosity about how things work, leading to a master's in engineering and a Ph.D. in applied radiation physics in addition to his M.D.

Pettigrew is a member of both the National Academies of Medicine and Engineering, in part because of his research and inventions in magnetic resonance imaging. He also served as the founding director of the National Institute of Biomedical Imaging and Bioengineering. But his latest project is to bring his own cross-disciplinary experience to a new generation.

As executive dean of the new Engineering Medicine (EnMed) program at Texas A&M University College of Medicine in Bryan, Pettigrew will help students earn degrees in engineering and medicine within a blended four-year graduate program. A mind immersed in both the physical and life sciences, says Pettigrew, can provide expertise the twenty-first century desperately needs—the realm of the "physicianeer."

Q: How is EnMed different from a traditional medical school?

A: Our students will earn two degrees in four years. But EnMed is much more than that. We are training people to be intellectually and conceptually fluent in multiple languages across the whole landscape of science. The idea is that our graduates will have an integrated engineering and medicine mindset, with the tools to find and solve big problems.

Q: What kind of problems?

A: Here's a good example. We don't have a vaccine for HIV, a virus that's been around since the 1980s. But what if you bring teams together from very different fields and ask them to come up with an integrated approach to mobilizing and controlling the immune system? Recently the NIH had a workshop focusing on this question for the first time and brought together the bioengineering and vaccinology communities.

Or what if you wanted to send flu vaccines in the mail that people could apply themselves? There are teams working on projects like that. A materials science engineer, a biologist and a vaccinologist produced a vaccine embedded in microneedles so tiny that they don't cause pain. It is about the size of a dime and you place it on the skin. Microneedles penetrate the dermis and deliver a form of this vaccine that doesn't require refrigeration.

Now imagine if we trained students to do that kind of integrated-discipline thinking from the start. They would be uniquely suited to build the next generation of discoveries. That is the goal of EnMed.

Q: Are there any unusual requirements in EnMed?

A: We want these students to solve problems and to be invention-minded. To anchor that in a practical way, we ask all our students to invent something transformational during their time here. It's not a hollow requirement, something that you toss out there to students and say, "Have at it!" The curriculum will be designed to train them in this unusual skillset and guide them through the inventing process.

Q: Are there things you wish you had learned at the outset of your career?

A: I wish I had gotten an earlier understanding of even more scientific fields. The concepts of different disciplines really help you sort though problems, because the cross-talk is synergistic. As a simple example, the body is often described biologically and physiologically on the scale of an organ. But it is full of tiny mechanical, fluid mechanical and electromechanical systems—levers, circuits, electrochemical, physical and shear stress gradients. These systems even occur at the molecular and cellular levels and are integral to genetic expression, which guides how we develop and function. These basic biological systems are actually easier to understand if you have the context of engineering. So that's really what we're trying to do—create a person with a new type of mindset to work at those intersections.

MICHAEL STARGHILL FOR *PROTO*

DIEGO NAIVE FOR THE NOUN PROJECT

BY THE NUMBERS

COFFEE

191

Species of medicinal herbs documented by German physician Leonhard Rauwolf during his sixteenth-century travels through the Middle East. One curious bean was made into a drink called *chaube*—"as black as ink, and very good in illness, chiefly that of the stomach." It is the first European description of coffee.

56

Pounds of coffee bequeathed to the London College of Physicians in 1657 by William Harvey. He was the first physician to describe the circulation of blood and one of England's earliest devotees of coffee, saying: "This little fruit is the source of happiness and wit." Harvey also had chronic insomnia.

70.1

Percent of pre-clinical medical students in a 2017 study who consumed coffee during their second year. Sleep deprivation during this study-intensive time was correlated with hazardous driving and mental health problems.

400

Milligrams of caffeine are recommended to stay alert during an overnight shift, according to the 2009 Fatigue Risk Management System Resource Pack for hospitals in Queensland, Australia. This is equivalent to five or six cups of coffee.

70,772

Cups of coffee consumed by physicians in one Swiss hospital in 2014. Whereas 84% of doctors drank coffee at work, significant differences among the specialties became clear. Orthopedic surgeons drank the most (189 cups), while anesthetists drank the least (39 cups). Across specialties, the more senior the physician, the more coffee consumed.

INFOGRAPHIC

Anatomy of a Hashtag

Public health messaging online yields beautiful—but sometimes worrying—data.

About two in five people make health care decisions based on information from social media. This could be good news for public health organizations, who have at their fingertips a way to reach billions of users. But a message launched on social media doesn't always follow a predictable path.

A team from the Royal College of Surgeons in Ireland set out to graph a handful of public health topics on Twitter. They focused on hashtags, words marked with the # sign that help users navigate by topic. "We wanted to see who the influencers really were," says Richard Arnett, director of psychometrics at RCSI and a creator of the project.

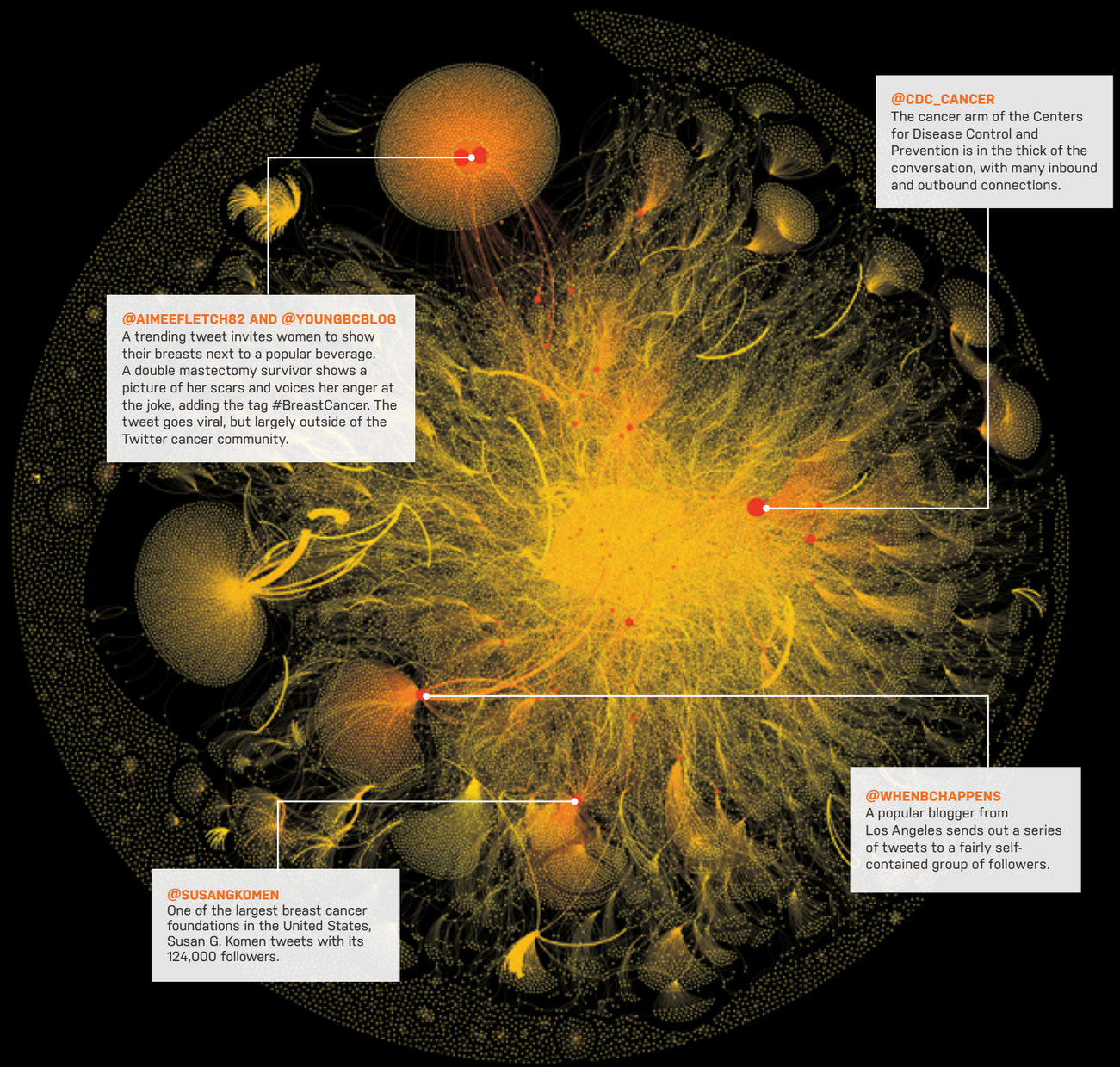
Nearly 50 million tweets a year touch on cancer. In the study shown here, the RCSI team mapped 90,000 posts tagged with #BreastCancer sent over the course of eight weeks. While many were part of awareness and screening campaigns, others were hijacked for unrelated discussions.

On other divisive topics, such as vaccination or abortion, the images show conversations diverging into two or more separate camps, with messages being shared only among like-minded people. "There was an awful lot of noise and a potential for messages to get bent out of shape," says co-creator Eric Clarke, a lecturer in health informatics.

The team hopes that these maps help demonstrate that social media outreach carries benefits and risks. "It's only one instrument in the toolbox to reach individuals," says Arnett. "But it is increasingly an important—and unpredictable—tool."

#BREASTCANCER

- Every dot represents one user tweeting about #BreastCancer.
- Larger dots have more followers and greater influence.
- Every line represents a connection between two users.



@AIMEEFLETCH82 AND @YOUNGBCBLOG
A trending tweet invites women to show their breasts next to a popular beverage. A double mastectomy survivor shows a picture of her scars and voices her anger at the joke, adding the tag #BreastCancer. The tweet goes viral, but largely outside of the Twitter cancer community.

@CDC_CANCER
The cancer arm of the Centers for Disease Control and Prevention is in the thick of the conversation, with many inbound and outbound connections.

@WHENBCHAPPENS
A popular blogger from Los Angeles sends out a series of tweets to a fairly self-contained group of followers.

@SUSANGKOMEN
One of the largest breast cancer foundations in the United States, Susan G. Komen tweets with its 124,000 followers.

DATA VISUALIZATION BY ERIC CLARKE, RICHARD ARNETT AND JANE BURNS

MEDUCATION

Singular Exceptions

Should primary care physicians be trained to spot unusual, medically important cases? BY PETER SMITH

A man arrived at Bicêtre Hospital in Paris with a curious symptom. His mind was lucid, but he could speak only a single word—*tan*. Doctors cared for and carefully observed "Tan" from 1840 to 1861. After he died, an autopsy revealed a lesion in his brain's left frontal lobe, which his physicians believed was connected to the loss of language. This led to a major advance in neurology, confirming that parts of the brain had specialized functions.

Many discoveries start at the bedside of an unusual patient, when clinicians not only provide care but also ask questions about the medical unknown. That kind of research by physicians is becoming less common, however, at a time of increasing patient loads and a pile up of administrative duties. To spark a revivial and foster scientists on the lookout for medically significant cases, one program is looking to residents who will be on the front lines of care.

The Pathways service at Massachusetts General Hospital is an elective rotation during a three-year residency program in internal medicine. In a recent case, for instance, a patient arrived via medevac with blue fingers and lungs filled with fluid, and was immediately put on advanced life support. After the patient recovered, he voiced a suspicion that he had a rare reaction to hydrochlorothiazide, a common blood pressure drug that has been safely taken by millions.

Pathways participant C. Lee Cohen explored this and other possibilities, and enlisted the help of specialists in immunology and pulmonary and vascular biology. Cohen and her colleagues are working on a case report that considers a possible mechanism of action and could offer clues for better diagnosis and treatment of pulmonary edema.

Katrina Armstrong, physician-in-chief at MGH, helped found the Pathways program and notes that the current system of training doctors divides care of a patient among specialties, which sometimes makes it difficult to spot, treat and research medical anomalies. "A resident may call a kidney doctor, a heart doctor and a lung doctor," she says. But even after all of them see the same patient multiple times, an underlying problem may remain unresolved. "Nobody's really digging down and saying, 'What's at the root of all these problems?'"

Pathways, on the other hand, encourages residents to "shine a spotlight on what we do not know," as Armstrong put it in a recent article in *The New England Journal of Medicine.* The program connects medical residents with academic and industry researchers across specialties to help residents make diagnoses, and facilitates the complex logistical arrangements needed to approve research in a clinical setting. Pathways also helps doctors gain access to new and investigational drugs.

The goal is to end up with physicians who not only are good diagnosticians, but also scientists who play a critical role in research. "The ability to think this way is what drove the pediatrician who discovered the Flint water crisis," says Armstrong. "It's the ability to put things together. It's seeing the world differently because you're asking the right question."

POLICY WATCH

Sins of the Past

The California Death Certificate Project is finding the physicians associated with opioid overdoses. Is it justice or a witch hunt?

BY ANITA SLOMSKI

Medical authorities have struggled with how to atone for the opioid crisis, in which the industry played such a pivotal role. Efforts to curb opioid prescribing have proliferated, but punishing the physicians who overprescribe has been a more delicate topic. One of the more controversial efforts, launched by the Medical Board of California in 2015, is the California Death Certificate Project. It set out to find the physicians whose scripts directly contributed to the death of their patients.

When a state medical board disciplines a physician, it's generally responding to an outside complaint or lawsuit. In California, however, the board has taken on the detective work itself. It requested all of the state's death certificates between 2012 and 2013 in which prescription opioids were implicated as a cause of death. Looking at 2,700 cases, and helped by a prescription drug database, the board identified 450 cases in which there were excessive prescriptions for opioids within the last three years of a patient's life. The board has closed 100 of these cases, but the rest are still under investigation.

So far, the board has seen accusations filed against 23 physicians. Sanctions can include the revocation of a medical license, public reprimand or a range of other penalties. One physician was prohibited from practicing for 30 days and permanently barred from prescribing any controlled substance, and also required to perform 100 hours per year of non-medical community service and take courses on prescribing procedures. He has since stopped practicing medicine.

Many California physicians have taken issue with the board's actions. "Looking back to 2012, when guidelines for opioid prescribing were very different than they are today, is not an appropriate way to help physicians modify their opioid prescribing," says ophthalmologist David Aizuss, president of the California Medical Association. Aizuss notes that in 2001 the California Legislature mandated that every physician in the state take 12 hours of continuing medical education on appropriate prescribing for pain "because physicians were thought to be under-treating patients for pain."

Andrew Kolodny, executive director of Physicians for Responsible Opioid Prescribing, also notes that in the earliest days of the epidemic, and until recently, "doctors got a lot of misinformation telling them that opioids were safer than over-the-counter analgesics and that the risk of addiction was less than 1% on long-term opioids. These messages came not only from drug companies, but also from pain specialists, medical societies and state medical boards."

Retroactively disciplining physicians for aggressive opioid prescribing in 2012 isn't fair, agrees Kolodny. "But if a doctor in 2018 escalates an opioid dose and that patient dies, there should be an investigation," he says.

As word began to circulate that the California board was sending notification letters to doctors, telling them that they were under investigation, many began referring their patients to pain specialists. Some of those specialists, in turn, have been overwhelmed by the demand for their services and are sending patients back to primary care physicians—who no longer want to manage their patients' pain. "Patients are becoming pawns in the middle of this dragnet," Aizuss says.

There may be another way. In a recent study published in *Science*, a team led by Jason Doctor, chair of the Department of Health Policy and Management at the University of Southern California, brought the past to bear in a less threatening way. Physicians who had a patient die from an opioid overdose in the previous year received a personal letter from the county medical examiner telling them of that finding.

"The letter was empathetic and designed to help doctors see the real risks of opioids in terms of the outcomes their patients are experiencing," says Doctor. "Physicians know excessive opioid prescribing is a huge problem nationally, but many think that it's other doctors who prescribe too much. By giving them feedback about their own patients, we let them know it is occurring in their practice too."

Word began to circulate that the California board was sending notification letters to doctors.

The 404 California clinicians who received the letter, which included the latest CDC guidelines on safe opioid prescribing, reduced their opioid prescriptions by 10% within four months. That was in contrast to a control group of 447 clinicians who received no letter and slightly increased their opioid prescribing. Those who received the letter were also less likely to start a new patient on opioids and wrote fewer high-dose prescriptions.

Stopping physicians who prescribe too many opioids is an important goal. But for Kolodny, the people whose lives are ruined by these prescriptions should remain the highest priority. "We really have to deal with the victims," says Kolodny. "We need to treat their addiction." The process of bringing someone back from an opioid addiction is slow, uncertain and expensive. "We have begun to mobilize outpatient programs to help people who are addicted to opioids," he says, "but we don't have nearly enough of them."

CHRIS GASH

SECOND OPINION

A Holy Grail for HIV

About 12 years after the discovery of the human immunodeficiency virus (HIV) as the cause of AIDS, combination antiretroviral therapy made its grand debut in the mid-1990s. These miracle drugs fundamentally altered the natural history of AIDS, transforming a disease that carried an almost certain death sentence into a chronically manageable condition. But many would falsely conclude that the threat of HIV/AIDS is over.

While progress has been great, it is important to remember that millions of infected people remain untreated. Antiretroviral drugs immensely improve the quality and quantity of life for most infected people, but these drugs are not curative—they must be taken every day for life. New approaches are urgently needed, as outlined in "An Endgame for an Epidemic" (Fall 2018).

An effective HIV vaccine has long been regarded as the holy grail of HIV research. In contrast to many pathogens, progress toward an HIV vaccine has been haltingly slow. One limiting factor is that the key types of immunologic responses required for protection remain poorly defined. It is too early to predict which vaccine approach will ultimately cut this current Gordian knot, but it is imperative that a broad-based search be undertaken.

Warner C. Greene // Director, Gladstone Center for HIV Cure Research, Gladstone Institutes, San Francisco, Calif.

Medicine in Deep Space

"140 Million Miles From Home" (Fall 2018) provides a succinct survey of physiological and psychological challenges men and women will face on a space mission to Mars. It also addresses some of the currently available and newly emerging strategies and countermeasures to mitigate biomedical risks associated with long-duration human spaceflight.

Prolonged effects of reduced gravity, solar radiation, isolation, confinement and distance from the Earth are all stressors to human health. Risk is inevitable and solutions are needed to ensure crew safety and health, as well as mission success.

Gazing forward, astronauts venturing beyond low-Earth orbit for extended periods of time will require capabilities that—compared with the systems and approaches utilized today aboard the International Space Station—are more compact, integrated and sustainable, and allow for increased autonomy and personalization to that astronaut. In preparing for innovations that define the future, space biomedical research will benefit enormously from advances in science, medicine and engineering. Reciprocally, ambitious human space endeavors will drive discovery, inspire humanity and yield benefits that enhance life on Earth.

Jeffrey P. Sutton // Founding Director, Center for Space Medicine, Baylor College of Medicine, Houston, Texas

MISSED THE LAST ISSUE?
All stories from *Proto*, Fall 2018, are available at protomag.com.

WHAT'S YOUR TAKE? **Send your comments or suggestions for future topics to protoeditor@mgh.harvard.edu.**

Health care workplaces are among the most violent, and incidents of aggression are on the rise. Is personal risk just part of the job?

WHEN HEALERS GET HURT

Allysha Shin clearly remembers only the first kick and punch to her face. “Everything happened so fast,” says Shin, a neuroscience nurse at Keck Medicine of USC in Los Angeles, who was attacked by a patient on a December night two years ago. Hours into her graveyard shift in the intensive care unit, Shin was working alone at the bedside of a female patient who had suffered a hemorrhagic stroke. The condition led to bouts of agitation requiring restraints on her feet and wrists—not only to protect those attending her, but also to ensure she couldn’t pull out the wires and tubes that were keeping her alive.

The patient became suddenly fierce, twisting and breaking free of the restraints and delivering multiple blows to Shin’s face, chest and stomach. “If I’d been knocked out and unable to call for help, she could have killed me,” Shin says. It took four nurses and several other staff members to wrestle the patient into a chair, and she continued to spew threats until she was finally sedated.

“I was in shock, but the attitude around me was that this was all in a day’s work,” says Shin. She completed her shift that night, realizing how much pain she was in only after the adrenaline wore off. Bruised and sore, she called in sick the next two nights.

In health care settings around the country—especially in emergency rooms and psychiatric units—dealing with such attacks is increasingly common. Violence in

By Linda Keslar //

Photographs by Danny Kim

hospitals, havens of care and compassion, is an underreported and sometimes daily threat to nurses, physicians and other providers, who risk both verbal and physical harm. Hospital employees are hurt by violence at more than four times the average rate for workers in all other private industries, according to the U.S. Bureau of Labor Statistics, and most hospital security directors polled for a survey by the International Association for Healthcare Security and Safety (IAHSS) and the American Society for Health Care Engineering (ASHE) said they had seen an increase in violence against their staffs during the most recent year.

Some incidents make headlines. In November a gunman at Mercy Hospital in Chicago killed a physician, a pharmacy resident and a police officer before shooting himself. A Long Island hospital patient kicked his physician unconscious, punched a security guard and set his bedsheets on fire; a patient in Cleveland pinned an emergency department nurse against the wall and sexually assaulted her; a disgruntled supply worker at an Alabama hospital fatally shot a nursing supervisor and wounded another employee before shooting himself; a prominent Houston cardiologist was killed by a man whose mother had died under the doctor's care 20 years earlier.

Workplace violence in health care is "underreported, ubiquitous and persistent."

Yet less newsworthy acts of violence are far more common. Caregivers routinely deal with patients who lash out by spitting, hitting, pulling hair, biting, choking or throwing things. There's also verbal abuse, threats and harassment. In one recent survey, 71% of nurses and 47% of physicians said they had been harassed by patients through stalking, persistent attempts at communication and inappropriate social media contact, among other threatening actions.

SOURCE PHOTOS: GETTY IMAGES

"Violence occurs throughout the hospital," says Judith Arnetz, a professor and associate chair for research in the Department of Family Medicine at Michigan State University in Grand Rapids, who studies the topic. Nurses, nursing aides and behavioral health staff members suffer the highest rates of abuse and violence, she says, and physicians, particularly in the emergency room, are also at high risk.

Hospitals and health care systems spent an estimated $1.1 billion on security and training to prevent violence in 2016, with an additional $429 million put toward medical care, staffing, compensation for lost wages and other costs related to violence against employees, according to a report by the American Hospital Association.

Amid a human and financial toll that is obvious and increasing, more and more academics, health care workers, medical and industry associations and hospital leaders are pushing for solutions. Some hospitals have begun to step up their efforts to curb workplace violence, while unions, regulators and lawmakers, among others, advocate sweeping reforms that could break the cycle of violence.

• • • •

The numbers underscore that this is a large and escalating problem. Three-quarters of the nearly 25,000 people reported assaulted at work each year have jobs in health care or social services, according to the Occupational Safety and Health Administration (OSHA), and a Government Accountability Office report in 2016 found that health care workers experience five to 12 times more violence than other workers do. Other studies have shown that few hospitals, clinics and nursing homes have avoided violent incidents.

One in four nurses has been physically assaulted on the job, and about half have been physically or verbally threatened, according to the American Nurses Association; roughly one-third of approximately 3,500 emergency room physicians polled recently said they had been physically assaulted by patients within the past year, and seven in 10 said violence had increased in the past five years. Asked about their experiences with patients in a single week, more than half of about 7,000 ER nurses said they had been abused verbally, and more than one in 10 reported physical violence. A 2016 *The New England Journal of Medicine* review of medical literature on workplace violence in health care summarized the problem as "underreported, ubiquitous and persistent"—and largely ignored.

Most violent incidents fly under the radar, says Gordon Lee Gillespie, a professor at the College of Nursing at the University of Cincinnati. A registered nurse who has worked in hospitals for more than 15 years, Gillespie has suffered two serious assaults and more than 100 cases of other physical and verbal abuse from patients. "I never thought much about it—it seemed a normal part of the day," he says. When several nursing colleagues of his filed a lawsuit against a patient for assault, the judge threw out the case, saying that violence was just part of their line of work.

Scenario

An elderly woman with mild respiratory complaints is told, after a preliminary exam in the emergency department, that she'll have to wait to be seen. She becomes increasingly agitated. "When am I ever going to see a doctor?" she shouts, then throws a box of tissues at the registration nurse.

Gordon Lee Gillespie, a professor at the College of Nursing at the University of Cincinnati: The triage nurse who examined the patient initially should talk to her and explain the ED is doing its best to find a bed. The nurse might do a quick re-exam to reassure the patient her vital signs remain stable. If acting out continues, we call security personnel, who can de-escalate the situation. As in all such conflicts, caregivers should make sure they have a clear path to an exit and alert the ED station desk if they're attending the patient alone. If the patient becomes violent despite our efforts, she may be restrained.

Multiple studies show that most health workers don't report incidents because of time

constraints, cumbersome reporting mechanisms and fear of reprisal. "Nurses tell me if they wrote up every event, they'd have no time to take care of patients," Gillespie says. "There's also the worry that reporting something will be held against you in your evaluation. And if you report a lot of it, the hospital is going to find a way to get rid of you—because you'll be blamed for causing the problem."

Many nurses also fail to report violence because they believe nothing will be done, according to a 2014 study, "Nothing Changes, Nobody Cares: Understanding the Experience of Emergency Nurses Physically or Verbally Assaulted While Providing Care," published in the *Journal of Emergency Nursing*. Another study found that in most cases, nurses who did notify security personnel or a supervisor about attacks received no response from the hospital.

Yet a lack of reporting does nothing to diminish the impact of assaults on health care workers. Victims of this violence sometimes suffer symptoms of post-traumatic stress disorder, according to several studies, and they may be prone to absenteeism and to patient safety errors and lower patient satisfaction. A survey of workplace violence by the Emergency Nurses Association found that one in four nurses considered going to a different ED or to a non-emergency department. Violent incidents also contribute to high burnout rates of ER physicians, says Paul Kivela, managing partner of Napa Valley Emergency Medical Group in California and president of the American College of Emergency Physicians. "Our job is stressful enough without the threat of being assaulted on a regular basis," he says.

• • • •

But why is violence in hospitals and other health care settings so frequent and persistent? In 2015 OSHA identified more than a dozen risk factors, including overcrowded waiting rooms, unrestricted public access and poor lighting in hallways and other areas. Violence in hospitals can also spill over from gang activity and other crime in surrounding communities. "What happens in health care settings is a reflection of what happens in society," says IAHSS president-elect Alan Butler.

Scenario

In intensive care, a man with a history of antisocial behavior is recovering from surgery after being shot in a domestic incident. He curses at nurses and doctors and threatens to kill them if they don't provide more painkillers.

Lance Clemsen, chair of the Disruptive Patient and Visitors Program at the University of Iowa Hospitals and Clinics: In our system, the man is immediately reported as a safety risk, and a temporary red flag may be added to his electronic health record. I discuss the flag with the patient and he is urged to correct his behavior. If the patient disagrees, he has the option to appeal. I might also explain that an increase in aggression will cause a change in color-coded cards on the white board at his bed—from green to yellow to red—and may cause staff to withdraw. Given these warnings, we hope that he calms down so that the red flag can be removed from his record.

Several trends—federal spending cuts on mental health programs, the deinstitutionalization of patients with psychiatric problems and an epidemic of substance use disorders—have made hospital emergency rooms especially dangerous, says Terry Kowalenko, chair of emergency medicine for Beaumont Health System in Michigan and a researcher on ER violence. "ERs are more crowded, patients face long waits and there's no question violence is a growing problem," says Kowalenko. "Intoxicated patients and those with psychiatric illnesses are also more likely to perpetrate violence on staff."

Patients in pain or cognitively impaired because of dementia, addiction or intoxication are likelier to lash out, according to research. And words can sometimes do as much damage as physical violence. An encounter with a patient who threatened Kowalenko late one night after he refused to write an opioid prescription remains seared in his memory. "'Your shift is almost over and I'll be waiting for you in the doctor's parking lot,' he told me," says Kowalenko. "I found every reason to stay later than usual and I had security walk me out at 1 a.m. He wasn't there, but of all the violent acts by patients that I've witnessed or been part of, that's the one that affected me most."

To help keep health workers safe, OSHA has long provided guidelines for preventing workplace violence, and in 2015, in response to rising rates of attacks, the agency updated its guidance for health care and social service workers. Yet even as violence has increased, just about three-fifths of hospitals have bumped up their security budgets, according to a recent survey. "There's still a lack of understanding of security and safety by some hospital leaders; some budgets are increasing but there's also immense pressure to contain costs," says Tom Smith, president of Healthcare Security Consultants in Chapel Hill, N.C., who notes that although many hospitals are spending more on staff training, technology and other security measures, they may still resist hiring additional security personnel.

Still, there is a growing trend of arming existing security staff or having officers carry batons or pepper spray, despite questions about whether weapons deter violence. "Introducing weapons raises the risk of escalating violence because people tend to react to a weapon with a bigger weapon," says Chris Van Gorder, president and CEO of hospital system Scripps Health in San Diego, who has worked as a police officer and a hospital security officer. "As an alternative to having our officers carry guns, we're providing better training and giving them bulletproof vests and Tasers."

Other hospitals are adding video surveillance of patients, visitors and staff and installing metal detectors and requiring identity badges or key cards for authorized personnel. They're also improving lighting in parking lots, hospital corridors, stairwells and elevators, and providing panic buttons that staff members can use to call for help.

Because much of the violence involves fists and feet rather than guns or other weapons, training clinicians how to deter or respond to an attack can be crucial. In the recent IAHSS/ASHE survey of hospitals, most respondents had plans to train personnel to watch for early signs of agitation and aggression in patients by reading body language, facial expressions or behavioral cues such as pacing or rapid speech. Providers are also taught tactics for easing the tension and ways to protect themselves—for example, always having a quick exit route.

> "Our job is stressful enough without the threat of being assaulted on a regular basis."

Since Massachusetts General Hospital began offering staff members access to training and videos that teach de-escalation techniques, violent incidents requiring physical restraint of patients or visitors have fallen by as much as 80%, says Bonnie Michelman, executive director of MGH's Police, Security and Outside Services. Michelman also handles security planning and operations for Partners HealthCare, a system that includes MGH and nearly a dozen other hospitals. Although reporting rates have risen, the number of reported incidents overall hasn't increased at the hospitals, she says, and fewer cases of verbal abuse now escalate to physical assault.

OSHA, the Joint Commission (an accrediting organization for hospitals) and other regulators

are encouraging hospitals to create comprehensive workplace violence prevention plans, and in 2016 the AHA launched a campaign, Hospitals Against Violence, that grew out of an earlier meeting of the organization's board of trustees, says Laura Castellanos, an AHA associate director. "There was a lot of emotion because of some recent mass shootings," Castellanos says. As part of the campaign, case studies, fact sheets and webinars on education, training and workplace violence prevention are now available on the AHA website.

In a related effort, the first randomized, controlled, large-scale study of a standardized approach that hospitals might use to combat violence was published in the *Journal of Occupational and Environmental Medicine* in 2017. The project was designed to help develop a possible blueprint for future efforts, says Michigan State's Judith Arnetz, who led the four-year effort involving 41 units of seven hospitals in the Detroit Medical Center. Twenty units functioned as controls, operating as usual, while teams at the 21 intervention units were encouraged to experiment with solutions. They were given three years of data on past violent events and injuries specific to their work areas and were asked to devise action plans. Those units implemented physical changes—bedside alarm buttons and better lighting in parking lots—as well as administrative changes, such as increasing staffing levels. They also taught providers how to deal with aggressive patients. The interventions significantly reduced the risk of violent events as well as the risk of violence-related injuries.

In its attempt to head off violence, the Veterans Health Administration, the largest health system in the country, has created pop-up alerts in the electronic records of certain patients. Before someone may be identified in this way, however, a multidisciplinary team at each facility conducts a rigorous review of the patient's medical history and behavior, says Lynn M. Van Male, director of the VHA Workplace Violence Prevention Program. Caregivers are given a "safety action plan," and some of these may contain restrictions—how and where health care can be delivered, for example. In the case of these retrictions, the patient is notified and offered the opportunity to appeal. Often patients are willing to meet with providers to discuss options, which may include different care management strategies. Some patients may interact with providers from home using tablet computers rather than coming into a facility in which they may get anxious and be more likely to act in unsafe ways, Van Male says.

Training clinicians how to deter or respond to an attack can be crucial.

Modeling its program on the VHA effort, the University of Iowa Hospitals and Clinics created its own system that included health record-flagging five years ago, and in 80% of cases that were flagged, there have been no additional violent incidents, says Lance Clemsen, a social work specialist at UIHC and chair of the hospital system's Disruptive Patient and Visitors Program. For the other 20% of cases there was a sharp decline in "code greens," situations in which a security team gets involved. Overall, however, reported violent incidents in the hospital increased 25% in 2017 over 2016, says Doug Vance, director of the UIHC Department of Safety and Security, an uptick he believes is tied to the hospital being at high capacity all year.

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With relatively few federal protections for health care workers against violence, several states are making efforts to address the problem. For example, legislators in Massachusetts are considering Elise's Law, named for an emergency nurse who was stabbed and almost died on the job in 2017, which would set certain state standards around health care violence prevention. Seven other states now require hospitals to offer workplace violence prevention programs, while more than 30 states have made it a felony to assault health care workers or emergency medical personnel. And California legislation that took effect in 2017 requires the state's health care employers to report and maintain records of workplace violence, information that will be published in January 2019, and to develop comprehensive prevention plans.

Last March, Ro Khanna, a Democrat from Silicon Valley, introduced national legislation in the U.S. House of Representatives modeled after the California law. The Health Care Workplace Violence Prevention Act defines wokplace violence as both acts and threats and requires all health care employers to adopt measures similar to the California regulations, emphasizing reporting, prevention, adequate staffing, training and worker participation.

The bill has attracted bipartisan support and more than two dozen co-sponsors. Still, Khanna acknowledges that the Trump administration's anti-regulatory push is an obstacle. "These regulations will have to be well crafted," he says. "But I don't understand why anyone would oppose legislation to make the workplace safer for health care workers, particularly nurses."

Scenario

A gang member follows a gunshot victim for 20 miles to a hospital and then fires his gun in the parking lot.

Scott Strauss, assistant vice president of corporate security at Northwell Health, a health care network in the New York City metropolitan area: The shooting, coupled with other acts of violence, made us fast track a program to explore arming our security personnel—an unusual move, but one that we felt was called for. These armed officers go through a vetting system and receive training in 'shoot/don't shoot' scenarios. They are then issued the same 9 mm handguns used by the New York City Police Department. We expect the arming of our officers will help deter violence, but have made sure they are aware of the sensitivities of being armed in a health care setting.

Others, however, question whether a national standard on staffing levels or violence prevention could work when there are such wide disparities in the kinds of hospitals and the patient populations they serve. "A one-size-fits-all approach ignores hospitals' individual needs," says Lawrence Hughes, assistant general counsel for the AHA. The hospital association would prefer to have OSHA conduct additional research into approaches that could be tailored to specific circumstances.

Looking back now, Allysha Shin emphasizes that her attack occurred even with preventive measures that were in place at Keck Medicine of USC. The health system provides de-escalation training for staff and has protocols for dealing with agitated patients that Shin followed. Moreover, a staff member who responds to the needs of difficult patients was working with Shin, but she had been called to another room before Shin was assaulted.

Shin, who did file a report with the hospital and continues to work at Keck, has testified before government agencies as an advocate for workplace violence prevention. "No one should have to go through what I experienced," she says. "We're at the point of: How many more nurses or health care workers have to die before this issue is front and center?"

DOSSIER

"Workplace Violence Against Health Care Workers in the United States," by James P. Phillips, *The New England Journal of Medicine*, April 2016. An emergency medicine physician discusses violence in health care and the challenge of finding solutions.

"Preventing Workplace Violence: A Roadmap for Healthcare Facilities," by the Occupational Safety and Health Administration, December 2015. This report outlines five core components of violence prevention programs and real world examples of how hospitals have implemented policies to protect staff.

"Preventing Patient-to-Worker Violence in Hospitals: Outcome of a Randomized Controlled Intervention," by Judith Arnetz et al., *Journal of Occupational and Environmental Medicine*, January 2017. This study examines data-driven interventions that showed significant differences in incident rates of violent events inflicted by patients.

Some researchers now believe that a misfolded protein in the gut, traveling up the vagus nerve, may kick-start the destruction of neurons that leads to Parkinson's disease. How solid is their case?

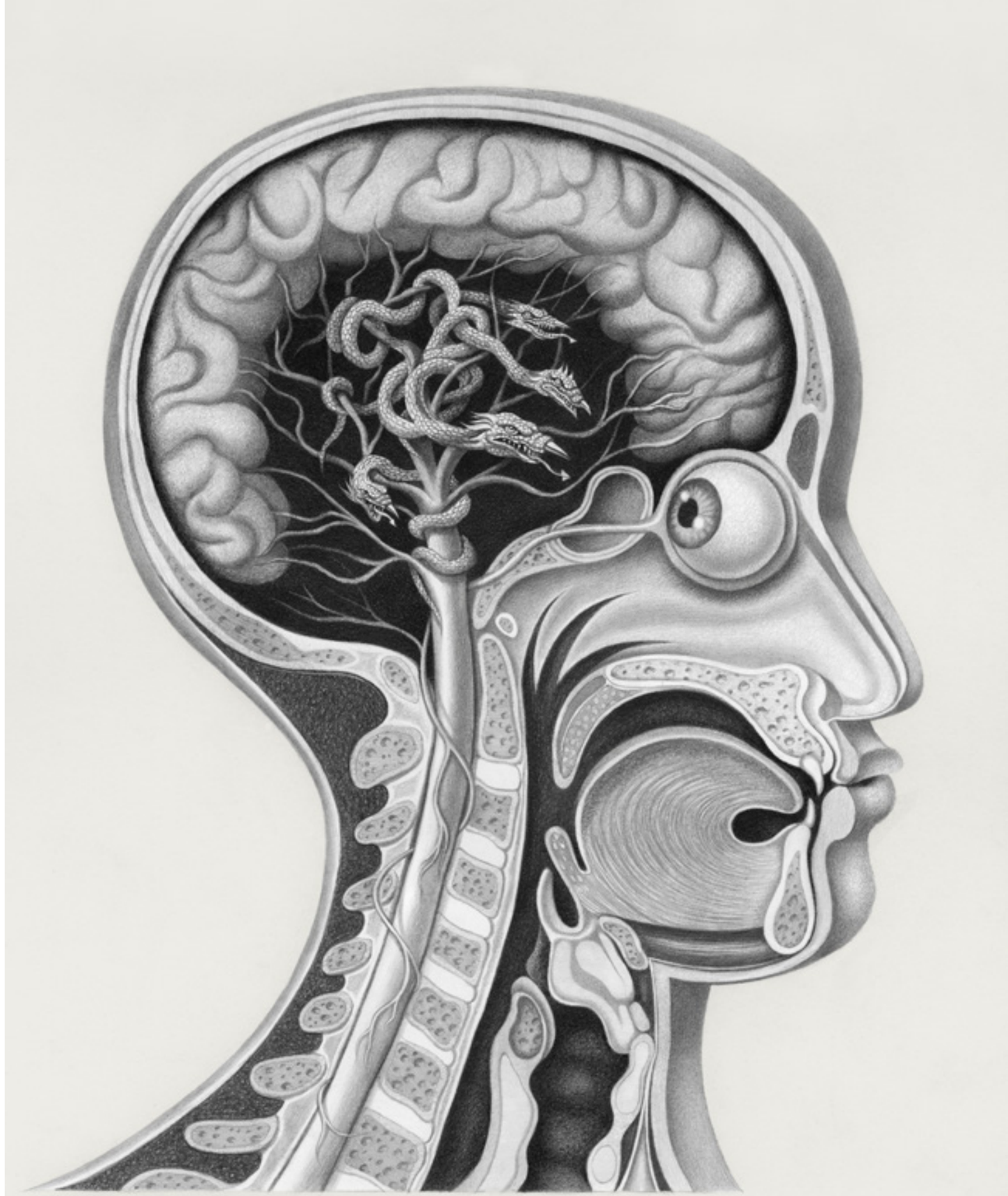
THE Gut HYPOTHESIS

In May 2008, doctors at the Centre for Digestive Diseases in Sydney, Australia, began treating a 73-year-old man for severe constipation. They gave him strong antibiotics and anti-inflammatory drugs, and within weeks, his constipation abated. But something strange—and surprising—also happened: The symptoms of the man's Parkinson's disease largely went away. In a report published in *The American Journal of Gastroenterology*, the doctors called the man's relief from his neurological disorder "unexpected and dramatic."

The incident added to a growing body of evidence to support a curious hypothesis—that Parkinson's disease, unquestionably a disease of the brain, may in some cases begin in the gut. According to this theory, the disease starts with certain proteins misfolding in the gut, which then leads to a chain reaction of aberrant proteins traveling up a nerve to the brainstem. From there, the damage spreads to the rest of the brain.

Although this model of Parkinson's disease has been kicking around for almost 15 years, recent discoveries have led researchers to consider it more seriously. Epidemiological evidence increasingly points to a link between gastrointestinal (GI) disorders and the risk of Parkinson's disease, while animal studies are helping researchers understand how, physiologically,

by Anil Ananthaswamy // illustrations by Armando Veve



the connection between gut and brain might occur. Although the hypothesis remains controversial, some scientists consider the accumulating findings difficult to ignore. "It really divides Parkinson's researchers into believers and nonbelievers," says Per Borghammer of Aarhus University in Denmark.

If the believers are right—and most cases of Parkinson's disease do begin in the gut, in advance of any neurological symptoms—there could be enormous implications. If clinicians had an early start on detecting the disease, they might be better able to slow it, and perhaps prevent the pathology from reaching the brain in the first place.

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Parkinson's is the second most common neurodegenerative disease, second only to Alzheimer's. There is some confusion about how to categorize it—is it a disease, with a singular cause, or a syndrome of similar symptoms that have different pathological underpinnings? Either way, most researchers agree that its main feature is the appearance of motor symptoms that may include tremors, muscle stiffness and slowness and rigidity of movement. A small portion of cases arise from known genetic mutations that run in families. But the form of the disease that has no known cause, the idiopathic version, is much more common, accounting for 80% to 90% of Parkinson's cases worldwide.

A CHAIN REACTION OF ABERRANT PROTEINS TRAVELS UP A NERVE TO THE BRAINSTEM.

No objective test, such as blood biomarkers or telltale signs in brain scans, can detect the disease, so clinicians diagnose Parkinson's based on the appearance of the motor symptoms. Autopsies of patients who died of Parkinson's, however, have shown that the disease likely begins well before those symptoms show up, with the appearance of protein aggregates in the brain called Lewy bodies and Lewy neurites. Named after Friedrich Lewy, a German-born American neurologist who in 1912 discovered these protein deposits in a patient who had died of Parkinson's disease, Lewy bodies and neurites are primarily made of abnormal forms of a protein called alpha-synuclein. The faulty proteins clump together and are thought to damage neurons in the brain, particularly in a region called the substantia nigra, a tiny cluster of neurons near the top of the brainstem. Especially vulnerable are cells that produce the neurotransmitter dopamine, a lack of which leads to the characteristic motor symptoms.

Those facts about Parkinson's are largely undisputed. Less certain is where damage to the neurons begins—in the brain or somewhere else. In 2003 a team of neuroanatomists, then at the J.W. Goethe University in Frankfurt, Germany, proposed an entirely novel hypothesis, suggesting that the formation of Lewy bodies and neurites, and hence the harm to neurons, originates in the gut and olfactory bulb. They based this theory on their examination of the brains of 168 people. Of those, 110 had either been diagnosed with Parkinson's disease or had deposits of Lewy bodies or neurites in various regions of their brains. The other brains served as controls.

Comparing the brains suggested that the disease progressed in stages, with the earliest signs of damage occurring in two areas. The first site was in the olfactory bulb, in the front of the brain, which has led one camp of researchers to wonder if toxins or pathogens in the adjacent nasal cavity might be a factor in Parkinson's. The other site of damage was in the vagus nerve's dorsal motor nucleus, a clump of neurons at the bottom of the brainstem. The neurons in this area send and receive signals via the vagus nerve, which extends down into the GI tract and reaches other internal organs.

Early damage to neurons in those two brain areas spread into other parts of the brain, eventually reaching the substantia nigra, the cerebral cortex and the neocortex. But the neuroanatomists found that lesions in the olfactory bulb were less likely to extend into other brain areas than were those in the dorsal motor nucleus of the vagus nerve. This prompted them to wonder whether the disorder might be caused by an as yet unidentified pathogen that enters the GI tract, then creeps up the vagus nerve into the brainstem and deeper into the brain.

The first part of their conclusion—that the disease progresses in stages within the brain—was immediately accepted as a major finding, says Borghammer. For years, however, there was much more skepticism about the second notion. That has changed recently. "Those latter ideas have really picked up speed, and they're talked about more and more," he says.

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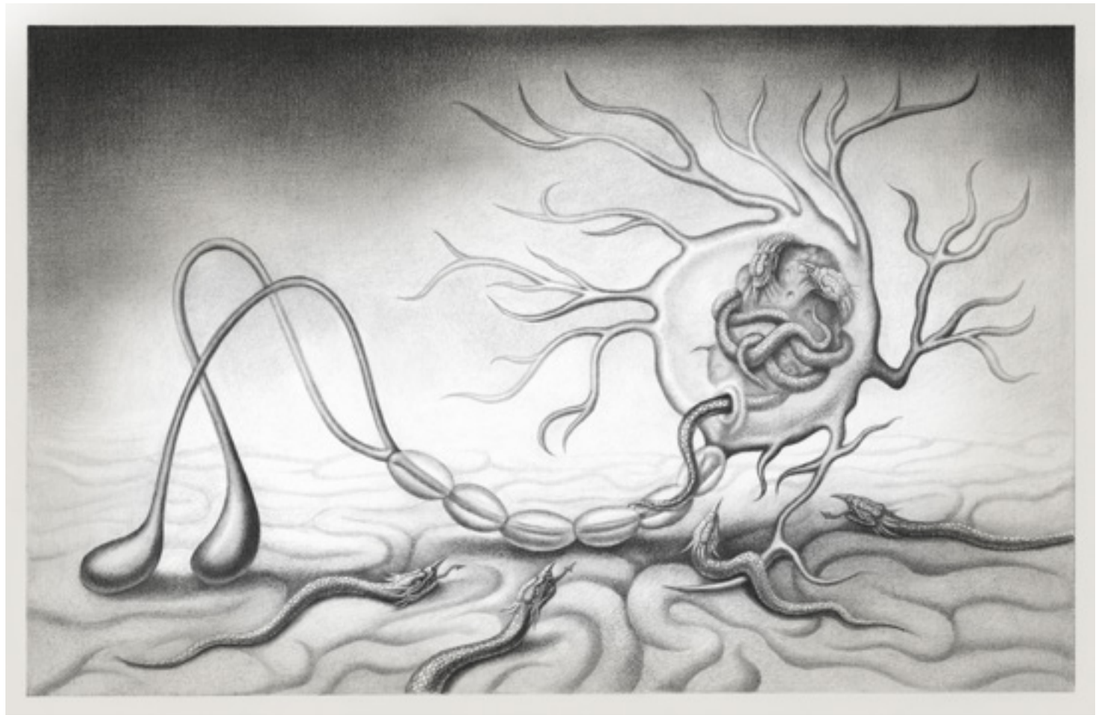
The gut hypothesis offers an explanation for one of the more puzzling aspects of Parkinson's, namely that patients also suffer from constipation and other GI disorders that are governed by involuntary muscles, in addition to the voluntary muscle disorder more characteristic of the disease. The Lewy pathology found in patients' brains is also found in neurons in the gut and could explain the impaired motility of the GI tract. "Constipation often shows up far earlier than the motor symptoms of Parkinson's," says David Sulzer, a neuroscientist who studies the basic neurobiology of Parkinson's at Columbia University Medical Center in New York.

Further support for the gut-brain hypothesis has come from epidemiological studies. Borghammer's team, among the first to think of approaching the question in this way, started with the simple notion that if the vagus nerve is a pathway for Parkinson's disease to go from the gut to the brain, there should be a lower incidence of Parkinson's disease in people whose vagus nerve had been severed for some reason.



It turned out that many people, decades ago, had undergone just such a surgical procedure—vagotomy—to treat serious peptic ulcers. The vagus nerve stimulates the production of stomach acid, and cutting it was an effective, if drastic, treatment.

In 2015 Borghammer and his colleagues used the Danish National Patient Registry to find all patients who had undergone vagotomy between 1977 and 1996. Analyzing data from more than 11,000 of those patients—as well as from 127,211 people who hadn't undergone such surgery—they discovered that "if you had a full truncal vagotomy, your risk of Parkinson's disease was more or less cut in half," says Borghammer.

A report published in 2017 by a team from the Karolinska Institute in Stockholm used similar data from Swedish medical registers. The researchers identified 9,430 patients who had undergone vagotomy, of which nearly 3,500 had had their vagus nerve fully severed. The dataset was cleaner than the one in the Danish registry, which had muddied the distinction between certain partial vagotomies and full vagotomies. The Swedish researchers matched these patients by age and sex with 377,200 people from the general population. "They found more or less exactly the same thing we had," says Borghammer: The risk of getting Parkinson's disease was cut almost in half in people who had undergone a truncal vagotomy. But he points out that even with truncal vagotomy, the risk is not entirely eliminated, suggesting that there may be other pathways for the disease.

Taking a different approach, Inga Peter and her colleagues at the Icahn School of Medicine at Mount Sinai in New York City identified 144,018 U.S. patients who were diagnosed with inflammatory bowel disease (IBD). When those people were matched with 720,090 control patients, the researchers found that patients with IBD were 28% more likely to develop Parkinson's. "This is indirect but very strong evidence" that disturbances of the gut and Parkinson's disease are linked, says Peter. "I'm a big believer that that's the case." Several other studies have shown similar results, including a September 2018 meta-analysis that found that the overall risk of Parkinson's in IBD patients was significantly higher (95%) than in control groups.

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To find more evidence of that link, researchers have tried to reproduce parts of this hypothetical process in animal models. Virginia Man-Yee Lee, a neuroscientist at the University of Pennsylvania Perelman School of Medicine in Philadelphia, wanted to know whether Lewy bodies could spread from one region of the nervous system to another. She led a team that injected abnormal forms of the alpha-synuclein protein into different locations in the brains of mice.

In 2012 they reported that just one injection in one spot of the brain was enough to induce a cascade of reactions, resulting in the appearance of Lewy bodies and neurites elsewhere in the brain. That, in turn, led to the loss of dopamine-producing neurons in

the substantia nigra and loss of motor coordination in these mice—a pathology similar to Parkinson's disease.

Their work showed that abnormal alpha-synuclein proteins can induce aberrations in normal forms of the protein, and that those problems can spread. One explanation is that these complex molecules may have the properties of a prion, a type of abnormal protein that acts as a "bad apple," passing its own malformations on to normal proteins in connecting neurons, which causes a slow-and-steady chain reaction through the nervous system.

To investigate whether such a cascade might travel all the way from the gut to the brain, a team led by Staffan Holmqvist at Lund University in Sweden took brain tissue from a patient with advanced Parkinson's disease and "homogenized" the tissue in a blender. They prepared a solution containing both normal forms of alpha-synuclein and clumps of misfolded alpha-synuclein and injected the solution into the intestinal walls of adult rats. In examining the animals 12, 48 and 72 hours after the injection, the team detected human alpha-synuclein along the vagus nerve in a pattern that suggested various forms of the protein were being taken up and transported via the vagus nerve to the brain. This was yet another piece of the puzzle: Not only do misfolded alpha-synuclein proteins cause normal proteins to misfold, but the misfolded proteins can be transported inside the long axons of neurons.

IF A GUT CONNECTION WERE ESTABLISHED, THE IMPLICATIONS FOR PREVENTING PARKINSON'S COULD BE ENORMOUS.

When the researchers injected rats with a different protein—bovine serum albumin, from cows—it didn't progress up the vagus nerve, suggesting that alpha-synuclein is uniquely capable of making that trip.

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The hypothesis that Parkinson's begins in the gut is not without its skeptics. Charles Adler, professor of neurology at the Mayo Clinic College of Medicine in Scottsdale, Ariz., thinks that even if misfolded proteins sometimes do travel along the vagus nerve, it is probably far more common for the disease to begin in the brain, perhaps in the olfactory bulb, and then travel down the vagus nerve. "We believe that it's a top-down progression," he says.

The evidence for this alternative theory comes from more than 600 whole-body autopsies done by the Arizona Study of Aging and Neurodegenerative Disorders. Because Parkinson's develops gradually, if the gut-to-brain hypothesis were correct, you would expect to find Lewy bodies in the gut of some people but not yet in their brains, Adler notes. But he and the other researchers found no cases in which alpha-synuclein pathologies were present in the nervous system in the GI tract but were absent from the brain. While this seems to refute the Parkinson's-begins-in-the-gut theory, the autopsies are not conclusive, since the progress of the pathology hasn't been studied in a living person.

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If a gut connection were established, however, the implications for detecting and perhaps even preventing Parkinson's disease could be enormous. For example, a biopsy of the colon in patients who have been diagnosed with IBD might detect protein abnormalities, such as alpha-synuclein aggregates, that could lead to Parkinson's. That has proven difficult so far, in part because all older patients are likely to have some Lewy bodies and neurites in their colons, even though not everyone will get Parkinson's. But this research continues as a possible avenue for early diagnosis.

Or perhaps Parkinson's could be prevented. Inga Peter's epidemiological study, which found a 28% higher incidence of Parkinson's in patients with IBD also found that the incidence of Parkinson's was 78% lower in IBD patients who took anti-inflammatory drugs to treat their IBD.

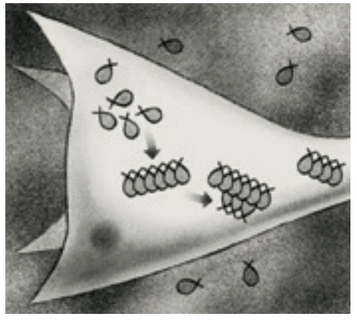
Their medications, called anti-tumor factor necrosis drugs, aren't supposed to affect the brain directly because they can't cross the blood-brain barrier. But the fact that they do seem to have a therapeutic effect could mean one of two things, says Peter. It could be that reducing inflammation in the gut lessens the risk of Parkinson's disease. It's also possible that IBD patients, whose gut linings are known to be compromised, may have a leaky blood-brain barrier that lets the anti-inflammatories reach the brain. "We are trying to investigate both of these possibilities," says Peter.

For Denmark's Per Borghammer, these are all enticing avenues to explore. Treating the gut to prevent Parkinson's—perhaps with a drug designed to disrupt the formation of Lewy bodies and neurites in the gut in the first place—would be far simpler than treating Parkinson's once the pathology enters the brain, Borghammer suggests. "The beautiful thing is that you could take such a drug in very small doses," because it would only need to be absorbed into the gut wall, he says. That's in contrast to a drug meant to prevent Lewy bodies in the brain, which would have to be considerably stronger to get across the blood-brain barrier and might be toxic to the rest of the body at that dose.

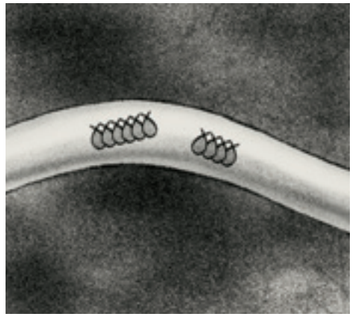
Some researchers, however, advocate continued caution about a gut-brain connection for Parkinson's. The basic reason to continue to question this model is that researchers have looked only at animal models and at patients who have died of Parkinson's, says Sulzer. "We have not yet followed this theoretical progression—from a pathogen in the gut, up the vagus nerve, and then through the neurons in the brain—in a single person to see whether it actually occurs."

Nonetheless, the community of Parkinson's researchers is becoming serious about the gut's role in the disease. "It's gaining more and more impetus," says Borghammer.

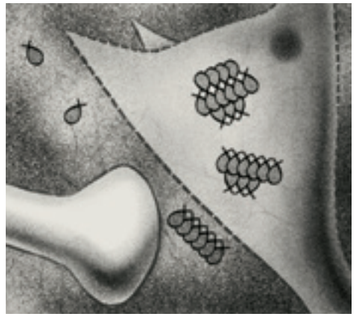
Tangled Proteins on the Move



1 *Alpha-synuclein (α) is found in neural cells and in the space between cells. The protein can become misfolded and form short, rodlike fibrils or can clump together to form amorphous protein aggregates (Lewy bodies). Sometimes the cell can clear these, but not always.*



2 *Neurons have a system to transport important cellular elements along the long, narrow axon, which in the vagus nerve can stretch in a single cell from the base of the brain to the abdomen. Alpha-synuclein aggregates are caught up in this transport system and carried toward the brain.*



3 *At the terminal, the aggregates can be released by one neuron and taken up by another. If there are too many of these abnormal aggregates inside a neuron, they can lead to that cell's death.*

DOSSIER

"The Concept of Alpha-Synuclein as a Prion-Like Protein: Ten Years After," by Jennifer A. Steiner et al., *Cell and Tissue Research*, July 2018. This paper reviews the current knowledge about prion-like behavior of the aberrant proteins associated with Parkinson's.

"The Enteric Nervous System in PD: Gateway, Bystander Victim, or Source of Solutions," by Kathleen Shannon et al., *Cell and Tissue Research*, July 2018. This article looks at findings that either support or confound the hypothesized gut-brain connection in Parkinson's.

"Does Parkinson's Disease Start in the Gut?" by Arthur Lionnet et al., *Acta Neuropathologica*, January 2018. Researchers use autopsy data to cast doubt on the hypothesis that Parkinson's disease originates in the gut.

HEAR THIS

Millions of people suffer from hearing loss. But a promising wave of research advances—using stem cells, gene therapy and new drugs—may turn up the volume.

By Lauren Arcuri // Illustrations by Katrin Rodegast

THE SENSATION OF SOUND, like all phenomena that make up the human experience, depends on an intricate relay of biological cells and signals running between the outside world and the brain. Human hearing begins when sound waves enter the outer ear and travel to the eardrum. There, sound waves are converted into vibrations and funneled to tiny bones in the middle ear, which amplify the vibrations and send them into the cochlea, a fluid-filled structure that resembles a snail shell. As the fluid in the cochlea vibrates, pressure variations move an internal membrane studded with bristly hair-like tufts, which belong to remarkable "hair cells" that can translate motion into an electric signal that runs along the auditory nerve to the brain.

Every step in this process plays out millions of times as people navigate the noise of daily life. But the modern world is much louder than the one of our human ancestors, and over decades, the many moving parts along the path from ear to brain may

become damaged and deteriorate. Some 466 million people worldwide, and more than 37 million in the United States, have lost part or all of their ability to hear. Roughly one in three adults between ages 65 and 74 is affected, as are half of those over 75, and one in five veterans of the wars in Iraq and Afghanistan has lost some ability to hear because of bomb blasts and other battlefield noises.

While some lose their hearing because of exposure to loud noises, others are affected by faulty genes, head trauma, a mother's infection during pregnancy or complications after birth. About three out of every 1,000 U.S. children are born with a detectable level of hearing loss, and some children who can't hear well during infancy may not achieve functional speech and language, because the first two years of life are particularly important for developing communication skills.

With no single cause of hearing loss, no current approach can treat everyone, and even the most successful interventions have problems. Conventional hearing aids, for example, can help many people, yet they're used by just one in five who might benefit, says Brad Welling, a neurotologic surgeon and chief of otolaryngology at Massachusetts General Hospital and Massachusetts Eye and Ear. They're often rejected because they increase the volume of sounds but fail to convey clarity, making it difficult to distinguish speech from background noise.

Cochlear implants, considered miraculous when they were introduced in the mid-1980s, are the primary option for people who are profoundly deaf. These devices bypass damage in the ear itself and directly stimulate nerves in the inner ear. Yet cochlear implants are worse than hearing aids in their ability to provide anything close to natural hearing. They generate a digital sound within a very limited range of frequencies, fail in noisy environments and can't help people properly hear music or other complex sounds. For some people, including those whose cochlear nerve is damaged or missing, the devices are no help at all.

Recent advances offer some improvement, with researchers approaching the problem along several fronts. They continue to expand what they know about the basic biology of hearing and how hearing loss develops in the hopes of finding new ways to repair and strengthen the signal as it travels to the brain. Gene therapy and CRISPR genome editing, so promising in other fields, may hold the key for treating genetic forms of hearing loss, and new kinds of drugs, as well as treatments involving stem cells, may regenerate or repair hair cells and nerves. Together, they offer hope that an epidemic of hearing loss may be coming closer to effective treatment.

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The biological process of hearing is still being decoded, step by step. For example, while researchers have known since the 1970s that hair cells transmit sound with the help of a crucial protein, it wasn't until 2018 that they were finally able to identify that protein with certainty. In a paper published in *Neuron*, co-senior authors David Corey, professor of neurobiology at Harvard Medical School, and Jeffrey Holt, professor of otolaryngology and neurology at Harvard Medical School, showed that transmembrane channel-like 1 (TMC1), a protein discovered in 2002, is what converts sound vibrations into the electrical signals to the brain. What's more, says Holt, "we think this protein underlies hearing in all vertebrates."

Mutations in the gene TMC1, which produces the protein, are responsible for several kinds of genetic hearing problems and loss, says Holt. While the study focused on a basic science question, "TMC1 is interesting from a therapeutic perspective as well," he says. Holt's lab has been studying mice that are deaf because they lack functional TMC1, mimicking a form of human deafness. The researchers have been able to use gene therapy to reintroduce a functioning version of the TMC1 gene into the mice's ears—a solution that has been quite effective, says Holt. "We can restore the ability of cells to convert sound waves into electrical signals," he says.

This kind of gene therapy typically utilizes a virus or other vector to infect a cell and deliver a working copy of the target gene, with the vector modified so that it won't cause disease or other unintended harm. But delivering it effectively to the ear, and in fact to most places in the body, remains a work in progress. For instance, adeno-associated viruses (AAVs) have often been tried as vectors, but because AAVs are quite common, the immune system tends to recognize and destroy them before they can carry their genetic cargo into the right place.

AN EPIDEMIC OF HEARING LOSS MAY BE COMING CLOSER TO EFFECTIVE TREATMENT.

Luk Vandenberghe, director of the Grousbeck Gene Therapy Center at Mass. Eye and Ear, set out to generate a kind of AAV that would escape detection by the immune system while retaining the mechanical properties that make AAVs appealing. To do that he sought to recreate ancestral forms of the virus, using computational tools to predict how their structures may have evolved and reconstructing earlier generations. The most remarkable upshot of that work may be an AAV called Anc80, which has transferred genes efficiently to the cochlea in mice. "The ability of this virus to target the outer, in addition to the inner, hair cell in the cochlea is unique," says Vandenberghe. That particular landing spot is important because the outer hair cell senses sounds and amplifies them, helping people distinguish very soft sounds and to focus their hearing in noisy, complex environments, such as a loud party.

Vandenberghe is a founder of Akouos, a biotech startup working on gene therapy treatments for patients with genetic hearing loss. His approach is similar to a pioneering gene therapy from Spark Therapeutics that was approved last year by the U.S. Food and Drug Administration to treat another kind of sensory disorder, a rare inherited form of blindness.

Gwenaëlle Géléoc, a researcher in neurobiology and otolaryngology at Boston Children's Hospital, recently explored the Anc80 vector as a therapy for Usher syndrome, a devastating genetic disorder that causes profound deafness and blindness as well as balance issues. The results in mouse models were striking. The balance of the animals was restored and formerly deaf mice could hear sounds as soft as a whisper. The damaged hair cells in the mutant mice were repaired by the gene therapy, and their hair bundle structures became similar to those of normal mice. "Our results were very visual," says Géléoc. "Mice with the Usher syndrome mutation would twirl and circle really heavily because of their balance defect. But the treated mice did not circle at all."

In a related approach, David Liu, a chemical biologist at the Broad Institute of MIT and Harvard, and Zheng-Yi Chen, a researcher at Mass. Eye and Ear, have used a version of CRISPR-Cas9, a genome-editing system, to alter the genetic mutation in the TMC1 gene that causes progressive genetic hearing loss in humans. In CRISPR, a piece of RNA ushers an enzyme (Cas9) to the proper location in the genome, where it cuts out the mutated part of the target gene. Liu, Chen and their colleagues encapsulated these two pieces inside fatty molecules called lipids that are able to cross cell

membranes. When they injected the lipid particles directly into the cochleae of the mice, the hair cells took up the lipids, and the Cas9 enzyme stripped out the mutated copy of the gene, improving the hearing of the mice.

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Not all forms of hearing loss are natural targets for gene therapy or genome editing. The most common type of acquired hearing loss—sensorineural, which encompasses a range of afflictions to the inner ear and auditory nerves—is often brought on or made worse by environmental and lifestyle factors.

The conventional wisdom has been that acquired sensorineural hearing loss is largely caused by the gradual degeneration of cochlear hair cells, which aren't replaced when they die. "One reason we've focused on hair cells is that there is really clear evidence for their demise," says Sharon Kujawa, director of audiology research at Mass. Eye and Ear. Once people start to lose outer hair cells, their threshold for hearing increases—meaning that sounds must be made louder to be detected. That's a change that can be charted on a hearing test audiogram, which shows the limits of pitch and volume that a person can hear in each ear.

Yet many cases of hearing loss follow a different pattern. Patients complain of not being able to understand speech in difficult listening conditions, yet their audiograms indicate they are hearing sounds at a perfectly normal level. Research by Kujawa and Charles Liberman, who directs a series of labs dedicated to the study of hearing and deafness at Mass. Eye and Ear, may help explain this disorder. Kujawa was studying mice exposed to loud noise early in life that seemed to recover from the damage it caused—their audiogram thresholds were normal. But when the mice aged, the researchers noticed a "massive neural loss."

It turned out the early noise had hurt the synapses that connect inner hair cells to the cochlear neurons. "That happened almost immediately after noise exposure," says Kujawa. Up to half of the synapses were silenced, even while hair cells remained intact. Over time, the cell bodies of the neurons also died. "We've seen this in every animal model we've studied, in terms of noise exposure and age-related hearing loss," she says.

This phenomenon—cochlear synaptopathy—has also been dubbed "hidden hearing loss" because it doesn't show up on audiograms until roughly 80% of neurons are gone. And although the synaptic connections between cochlear neurons and hair cells may be destroyed immediately when they're exposed to loud sounds, other parts of the nerve cells often survive for years or even decades. Kujawa doesn't yet know how widespread this phenomenon is in humans, but it could be a major factor in age-related and noise-related hearing loss. A recent study from Liberman confirms evidence in humans of this synaptic decline.

"HEARING LOSS IS HETEROGENEOUS, AND THERE WON'T BE ONE APPROACH THAT HELPS EVERYONE."

Because parts of the cochlear sensory neurons survive for years, there appears to be a long therapeutic window for treating the lost connections. Liberman is studying one potential therapy involving neurotrophin-3, part of a family of proteins that help neurons develop, grow and survive. His work in mice has shown that neurotrophin-3 can be delivered directly to the inner ear via a gel placed on the "round window," a membranous connection between the middle and inner ear. The treatment has regenerated hair cell synapses and restored neural function after noise exposure.

David Jung, an otolaryngologist and neurotologist at Mass. Eye and Ear, has taken Liberman's approach a step further. He worked with Michael McKenna, a neurotologist at MGH, to develop a way to deliver a drug called bisphosphonate to the inner ear without damaging hearing. Bisphosphonate is currently under investigation as a way to treat a common inner ear disorder called cochlear otosclerosis. Jung then wondered whether he could attach a drug, such as a neurotrophin, to a bisphosphonate molecule and deliver this combined therapy to the bone of the cochlea—since bisphosphonate binds to bone with high-affinity—to help restore destroyed synapses. This "hybrid molecule" approach, still being studied, could perhaps be used to deliver other treatments to the cochlea.

Lost synapses may cause some age- and noise-related hearing loss, but hair cells themselves also die, and efforts to replace or regenerate them are another urgent line of investigation. One possible route is the use of stem cells. Researchers have been studying how hair cells develop in an embryo to better understand the "recipe" for coaxing stem cells to become hair cells—allowing them to make what are essentially hair cells in a dish. If they are able to master that, they might then get those cells to develop and function in a human inner ear.

Albert Edge, director of the Tillotson Cell Biology Unit at Mass. Eye and Ear, began working with just a few stem cells isolated from the cochleae of mice and has been developing drugs to stimulate gene expression and molecular signals that can push these dormant stem cells to become new hair cells. Thus far, his recipe is working well, and Edge and his team have created mature, functional mouse hair cells. Karl Koehler, assistant professor of otolaryngology at Indiana University School of Medicine, has been working along similar lines and has created an entire "inner ear in a dish" that includes vestibular hair cells, responsible for balance, as well as inner ear neurons. This organoid could be used to help understand the connections between various parts of the inner ear, such as the synapses between hair cells and neurons. It could also be used to test gene therapy, drug treatments and other potential therapies for hearing loss.

The understanding of why and how hearing loss happens has made great advances in recent years. But it has become even more clear that the causes are just that—causes, plural. "We know that hearing loss is really heterogeneous, and there won't be one approach that helps almost everyone," says Sharon Kujawa of Mass. Eye and Ear. "That's the exciting part of all this—we're beginning to see how to translate some of this research. A lot of people are working on different approaches because everybody sees a different part of the elephant—but in the end, all of those different things being studied happen in the ear, and in the brain, and in the whole person—and they do all have to be addressed."

DOSSIER

"TMC1 Forms the Pore of Mechanosensory Transduction Channels in Vertebrate Inner Ear Hair Cells," by Bifend Pan et al., *Neuron*, August 2018. This study provides evidence that the TMC1 protein is a significant factor in the process of transduction, whereby vibrations become electrical signals that are carried to the brain.

"Cochlear Synaptopathy in Acquired Sensorineural Hearing Loss: Manifestations and Mechanisms," by M. Charles Liberman and Sharon G. Kujawa, *Hearing Research*, June 2017. This review of research on acquired sensorineural hearing loss demonstrates how ears exposed to loud noises show "exaggerated synaptic and neural losses" as they age.

"Treatment of Autosomal Dominant Hearing Loss by *In Vivo* Delivery of Genome Editing Agents," by Xue Gao et al., *Nature*, January 2018. Researchers use a genome-editing approach to ameliorate hearing loss in a mouse model of genetic hearing loss.

DANGER IN THE SHEETS

Rates of sexually transmitted diseases have hit record highs. Why now, and how to reverse the trend?

The battle against the "enemy in your pants"—as cheeky World War II-era posters referred to syphilis and gonorrhea—is as old as medicine itself and has a long history of mixing moral judgment with medical solutions. Beginning in 1917, social hygiene crusaders in the United States would identify and forcibly examine prostitutes and other women thought to be spreading "venereal diseases," sometimes even throwing them in jail. During the Depression, a positive syphilis test could disqualify a job applicant, and until the 1980s, negative syphilis tests for a prospective bride and groom were required before a marriage license could be issued.

The sexual revolution may have changed how public health leaders think of sexually transmitted diseases (STDs), yet the problem of how to curb their spread hasn't gone away—and may, in fact, have gotten worse. With the incidence of STDs surging to nearly 2.3 million reported cases in 2017, according to the Centers for Disease Control and Prevention, the United States has the highest rate of infection among industrialized countries. Over the past four years, reported cases of syphilis have increased by 76%, gonorrhea by 67% and chlamydia, the most prevalent STD, by 22%. And those figures don't count those who haven't sought treatment or don't know they're infected.

There has also been a 153% rise since 2013 in congenital syphilis in babies born to infected mothers, with 918 cases reported in 2017. This form of the disease is devastating, killing four of

By Anita Slomski //

10 infected offspring in the womb or shortly after birth, and those who survive often have deformed bones, are blind or deaf and may have other long-term problems. "In the past, a positive syphilis test in a pregnant woman was considered an emergency and everything was done to make sure she got treatment," says Jeffrey Klausner, professor of medicine and global health at UCLA Fielding School of Public Health and former director of STD Prevention and Control Services at the San Francisco Department of Public Health. But over the past 15 years, state and local STD programs have had to contend with a 40% cut in federal funding. "Today, public health departments are so short-staffed and underfunded that there may be no follow-up at all for that woman," Klausner says.

With the rise in the number of STDs comes other problems. "Because there is more syphilis around, we're seeing rare complications more frequently," says Kevin Ard, an infectious diseases specialist at Massachusetts General Hospital and medical director of the National LGBT Health Education Center at the Fenway Institute in Boston. "I've seen patients with hepatitis caused by syphilis; ocular syphilis, which can cause blindness; and syphilis in the brain."

Curbing the boom in the big three STDs will take ingenuity and clever epidemiology.

With gonorrhea, the challenge is to outwit a wily organism that has become resistant to each of the seven classes of antibiotics used to treat it since 1938. It may be gaining resistance to the current drug regimen, and a handful of recent cases have resisted all antibiotics that are normally effective against the organism, responding only to antibiotics of last resort. "If drug-resistant gonorrhea spread in this country, it would be a catastrophe," says Ard, who notes that MGH has been part of a national surveillance project that monitors gonorrhea strains for microbial resistance.

Yet while treating some cases of gonorrhea may be complex, most STDs respond to uncomplicated and effective therapies. In other words, curing these diseases isn't the most vexing problem. The challenge is locating an ever-shifting population of infected people and providing treatment quickly enough to slow the spread of disease in an expanding network of partners who are also infected. Curbing the boom in the big three STDs will take ingenuity, clever epidemiology and, perhaps, innovations in diagnosis and treatment.

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The picture was not always so grim. In 1999 the CDC predicted that syphilis could soon be eliminated in the United States—that is, there would be fewer than 1,000 new cases reported nationally each year. There were just 5,979 reported cases of primary and secondary syphilis (the infectious stages) in 2000, an all-time low. But syphilis began to rise again, mostly in men who sleep with men, or MSM, who in 2017 accounted for about 68% of syphilis cases.

Men have experienced the sharpest rise in gonorrhea, with the number of reported cases up 86.3% from 2013 to 2017, another sign that infections are on the rise in the gay, bisexual and MSM communities. Two-thirds of chlamydia cases are in people 15 to 24 years old, and that infection is found more often in women than in men, largely because clinical guidelines call for women under the age of 26 to be screened for chlamydia during annual gynecological checkups. But the overall number of cases of chlamydia is thought to be vastly underreported. "Only 40% of young women are being screened," says Edward W. Hook III, an infectious disease specialist at the University of Alabama at Birmingham. Adds Klausner, "The CDC estimates that there are almost three million cases of chlamydia annually, which means we're finding fewer than half of them."

The advent of hookup apps—social networking sites that connect adults with willing sexual partners in their area, often with a degree of anonymity—is one part of the changing landscape. "Syphilis has really found a home in people who use phone apps to find nearby sexual partners," says Bradley Stoner, associate professor of medicine at the Washington University School of Medicine in St. Louis and former chief of STD Services for the St. Louis County Department of Public Health. Most health departments have active partner notification programs for those infected by syphilis or human immunodeficiency virus (HIV), which can cause the most serious and lasting effects. "But syphilis has gotten a boost with these apps, because people don't know their partners and can't get in touch with them when an infection is diagnosed," he says.

A rise in all of these diseases at once can have a compounding effect, as co-infections often make STDs harder to treat. "Gonorrhea inhibits the immune system, so people who are also infected with chlamydia have a harder time clearing the infection and tend to get reinfected repeatedly," says Toni Darville, division chief of pediatric infectious disease and vice chair of pediatric research at the University of North Carolina School of Medicine in Chapel Hill.

A particular problem for MSM is the added risk that they'll acquire HIV, the virus that causes AIDS. "Half of MSM who are diagnosed with syphilis are found to have HIV as well," says Kyle Bernstein, chief of the epidemiology and statistics branch in the Division of STD Prevention at the CDC. "An MSM with syphilis is probably involved in a high-risk sexual network in which there is a lot of HIV," he says. But there may be biological as well as behavioral reasons for co-infection. Inflammation from an STD recruits the immune system's CD4 cells to the site of the infection. "These are the very cells that HIV uses to gain entry into the body," says Stoner.

MSM who are HIV-positive also tend to acquire more STDs than those who don't have the virus. Compromised immunity from HIV may be to blame, but one group of researchers believes antiretroviral therapy for HIV could reduce immune responses so that people become more susceptible to syphilis.

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Condoms effectively prevent STDs—witness Nevada brothels, which have cut HIV infection rates to zero by requiring all men to use them. And during the 1980s, when fear of HIV scared many people into scrupulously using condoms, that helped control other STDs as well. But the advent of effective antiretroviral therapy in the mid-1990s made HIV a manageable chronic disease, reducing anxiety about getting the virus and increasing the prevalence of condomless sex.

And just as the numbers of STD infections have risen, funding cutbacks have shortchanged efforts to control the epidemic. With budgets squeezed, health departments have had to get creative. "They've become savvy about using the hook-up apps to do public health work, including contact tracing and STD messaging, which might include information about outbreaks or a link to get a confidential home-testing kit for free," says Amanda Dennison, director of programs and partnerships at the National Coalition of STD Directors. Some health departments send vans to nightclubs and bars, offering free STD screening, while other states offer recurring shipments of free mail-order condoms to at-risk people who request them. In some states, clinicians can practice expedited partner therapy, providing patients diagnosed with chlamydia or gonorrhea prescriptions or medications to give to their partners.

"The hottest innovation today is sexual network analysis," says Kari Haecker, program manager for HIV/STD Prevention and Control Services in Clark County, Wash. In Haecker's previous job as field operations supervisor for the STD control program in Indianapolis, she faced the challenge of controlling STDs in a city that had the highest rate of syphilis per capita in the world in 1999 to 2000. "We had 407 cases of primary and secondary syphilis that year, which was related to an epidemic of crack cocaine," Haecker says.

Using the information they had on file about the sexual practices and partners of those treated for syphilis, Haecker created a map of about 200 gay men connected in a high-risk sexual "network" of those likely to have sex with each other. When one person in that group tested positive for syphilis, public health workers immediately began knocking on the doors of those in the network who

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hadn't recently been screened for STDs and offered them a syphilis blood test on the spot. "You're not making enough of an effort unless you're drawing blood on someone's porch or in their kitchen," says Haecker. One meth user in the network even offered his home as a screening venue.

The network map helped the health department predict where the next cluster of infections might occur and take steps to prevent an outbreak. Still, as effective as this approach can be, conducting the necessary personal interviews requires considerable resources, says Haecker.

A more pragmatic approach may be to focus screening on people who have had repeated STDs. When Katherine Hsu, medical director of the Division of STD Prevention and HIV/AIDS for the Massachusetts Department of Public Health, examined all cases of syphilis, gonorrhea and chlamydia reported in her state from 2014 to 2016, she found that 6,999 people—just 0.14% of a population of almost five million people ages 13 to 65—accounted for more than one-quarter of STDs reported during those two years. (Names of those infected are routinely reported to health departments, to help them find and notify sexual partners.)

"We can identify people at high risk of getting and transmitting STDs by looking at how many previous STDs they've had," says Hsu. Health systems have an opportunity to help control STDs in their communities by urging patients who have had multiple STDs to get screened every few months, she says. "Now we need some automated way, such as robo-texting, to get high-volume repeaters back to the clinics."

There's also an urgent need for quicker, easier STD screening. Someone who has been tested—in a clinic or using a home test for gonorrhea or chlamydia—may not get the results for a week or more, a delay that leaves time for additional sexual partners to be infected. A clinical trial is evaluating rapid screening tests that provide results in 20 minutes in a clinic. But Klausner wants instant, over-the-counter screening tests, similar to home pregnancy tests, that could speed the way to treatment. "There's no scientific reason not to develop an over-the-counter STD test, just a lack of resources and political will," says Klausner.

To combat congenital syphilis, all but six states require pregnant women to be screened for syphilis, and 14 states penalize clinicians who fail to test their patients. But screening for syphilis at the first prenatal visit, which most states require, misses women who are infected later in their pregnancies. And many women, including undocumented immigrants and those who use drugs or are homeless, shun prenatal care and are never screened—a problem that some health departments are trying to address. "Pregnant women who use drugs may feel judged or fear losing custody of their children if they seek prenatal care," says Emalie Huriaux, STD program manager at Washington State Department of Health. "We can alleviate the stigma by screening these women where they are."

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Once STDs are diagnosed, treating syphilis and chlamydia is straightforward and effective. That's not the case with gonorrhea. "It has developed resistance to every new antibiotic since the first sulfa drugs were introduced in the 1930s," says Alabama's Edward Hook, who studies new therapies for STDs and laments that the pharmaceutical industry shows little interest in developing new treatments. Even so, a few new classes of antibiotics are currently in clinical trials to test their effectiveness against gonorrhea.

SOURCE PHOTO: URBAN POSTER MOCKUP/CREATIVE MARKET; POSTER ART: FRANCESCO CICCOLELLA

One older drug—Cipro—may make a comeback. In 2007 the CDC advised against using the drug to treat gonorrhea because of increasing resistance. But according to research by Klausner at UCLA, 70% of gonorrhea in the United States still responds to Cipro, which is inexpensive and safe, and a rapid test he developed to identify whether a patient is likely to benefit is now in clinical trials.

Still, while effective diagnosis and treatment are essential, a vaccine to prevent STDs could make an even greater impact in reducing infection. But no research on a syphilis vaccine has ever advanced to a clinical trial, and trials for three gonorrhea vaccines have failed since the 1960s. To spur new research, the National Institutes of Health announced in 2018 it plans to award up to $9 million annually for five years to vaccine researchers, and even in advance of that support, the outlook has become more promising.

After people in New Zealand received a meningitis vaccine during an outbreak in the early 2000s, researchers noticed from medical records that teens and young adults who were vaccinated were 31% less likely to get gonorrhea than those who weren't vaccinated. "The gonorrhea and meningitis organisms are closely related," says Peter Rice, professor of medicine at University of Massachusetts Medical School in Worcester, who is in the late stages of developing his own gonorrhea vaccine. "GlaxoSmithKline, which makes the meningitis vaccine, is considering a clinical trial to evaluate whether its already proven vaccine is also effective against gonorrhea," he says.

"We need an automated way, such as robo-texting, to get high-volume repeaters back to the clinics."

Chlamydia, meanwhile, poses other challenges. Unlike gonorrhea, which invades the body by attaching to cell surfaces and multiplying, chlamydia goes inside cells, where the pathogen hides as it replicates and produces inflammation. To neutralize chlamydia within the cells, an effective vaccine must create a robust T-cell immune response, a task that has been made easier in the past decade by the development of adjuvants—molecules that can be given with a vaccine to stimulate the immune system. Toni Darville in North Carolina is developing two chlamydia vaccine approaches—one that can be used intranasally and another that uses a disabled virus to deliver chlamydia antigens into cells. She says researchers are also anxiously awaiting published results from a Swedish clinical trial testing the safety of a novel chlamydia vaccine.

But even the most effective vaccines will need to be used, and vaccine researchers worry that the stigma of STDs and the country's sexual mores will limit acceptance of a vaccine. Half of STDs occur in adolescents and young adults, so the target age for vaccination would be in the preteen and teenage years. And the experience with a very effective vaccine against the sexually transmitted human papillomavirus (HPV) is not encouraging. According to a 2016 CDC report, only half of 13- to 17-year-old girls and more than a third of boys have had the recommended two HPV vaccines to protect them from the virus, which can cause cancers of the cervix, vulva, vagina, penis and anus. "The HPV vaccine is amazing and lifesaving, but some parents are reluctant because they think giving it to their kids will lead to them having more sex, which isn't the case," says Darville.

Sexually transmitted diseases have plagued people for centuries and researchers seem undaunted in responding to today's record-breaking numbers of cases. "We are now much more sophisticated in our understanding of these pathogens and how to control them than we were even a few decades ago," says Kevin Ard at MGH. "I am optimistic about our ability to control STDs in the long term by combining tried-and-true approaches with new ones."

DOSSIER

"Characteristics of Cases With Repeated Sexually Transmitted Infections, Massachusetts, 2014–2016," by Katherine K. Hsu et al., *Clinical Infectious Diseases*, July 2018. This study suggests that those with a history of repeat STDs should be the main target of prevention efforts.

"Sexually Transmitted Infections in the Era of Antiretroviral-Based HIV Prevention: Priorities for Discovery Research, Implementation Science, and Community Involvement," by Jeanne M. Marrazzo et al., *PLOS Medicine*, January 2018. The authors argue that it's time to rethink how STDs are managed, now that effective HIV prevention and treatment have resulted in the use of fewer condoms.

"Post-Exposure Prophylaxis With Doxycycline to Prevent Sexually Transmitted Infection in Men Who Have Sex With Men: On Open-Label Randomized Substudy of the ANRS IPERGAY Trial," by Jean-Michel Molina et al., *Lancet Infectious Diseases*, December 2017. Researchers discuss the benefits of taking an antibiotic after sex to combat rising STDs in high-risk groups.

FIRST PERSON

Lies I've Told My Doctor

BY MELISSA PETRO

1. I'm 14 years old. My mother and I sit in the emergency clinic. We don't have insurance, but it burns when I pee and I can't ignore it any longer so my mom's taken the day off work. When the doctor asks me if I'm sexually active, my mother laughs and says, "She's too young!" Maybe I've never done "it," but the truth isn't so black and white. I say no.

2. Five years later, my doctor asks if my boyfriend and I use protection, and I tell her the truth—we don't. "Do you want to get pregnant?" I shake my head. "Do you want a disease?" I'm here for a physical, I think, not a lecture. The pill is too expensive and it makes me feel nauseous, and I don't like condoms. But she never asks why. Before I leave, I ask if she can prescribe me something for my acne. She looks at me as if I am an idiot and says, "Yeah, the pill." Her little zinger has the desired effect. I walk out without a prescription, and for years—if doctors ask—I just say I use condoms.

3. I'm 24 and the doctor asks how much I drink. I say, "Maybe a glass of wine or two every so often." I don't drink every day—not even every weekend—but when I do, I start with wine, followed by a real drink, followed by two or three or four more. The binges are followed by distressing behavior, physical hangovers and regret. Truth is, I'm too ashamed of my drinking to bring it up.

4. I tell my therapist that nothing is working. The Seroquel, in particular, only makes me feel worse. "I feel like an elephant that's been shot with a dart," I say, plus I'm convinced the pills make me gain weight, which the doctor says isn't a side effect. I don't believe him, and I leave out the part about how I've stopped taking them.

5. I'm 37 years old, more than 10 years sober. My husband and I are expecting our first child. Our first prenatal visit, I sit down and tell the doctor my medical history—all of it. I say I'm proud of keeping myself healthy, and I'm eating right and exercising regularly. At my 12-week visit, she chides me for gaining weight, telling me to "go easy on the carbs." Then she tells me I shouldn't be strength training. Everything I read online says that moderate strength training is OK. From then on when she asks, "Do you have any questions?" I tell her I don't. Instead, I go home and Google it.

6. Now the pediatrician is giving us sleep training advice that we have no intention of using. She assumes we're compliant with her previous direction not to sleep in the same bed as our baby. I can't imagine telling her the truth. And in that moment it seems so absurd, and a lifetime of lying to my doctors comes to a head.

Why do I do it? Maybe I've never felt they were on my side. Maybe my own shame kept me from telling them the truth. Frankly I don't know, but I'm done with it.

As we walk out of the office, I tell my husband that I don't want to lie anymore. We'll find different doctors if we need to, ones we can be honest with. And I ask him to help me stand up for myself. I'm a grown woman, I say. They're trained professionals. And it's time that everyone—me included—stops being so uncomfortable with the truth.

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