NYU PHYSICIAN

THE MAGAZINE OF NEW YORK UNIVERSITY SCHOOL OF MEDICINE

SPRING 2015

DANGEROUS RHYTHMS

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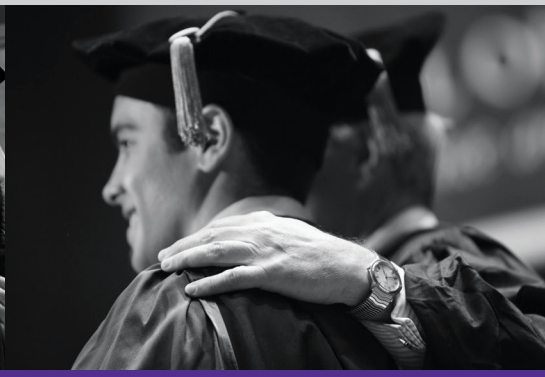

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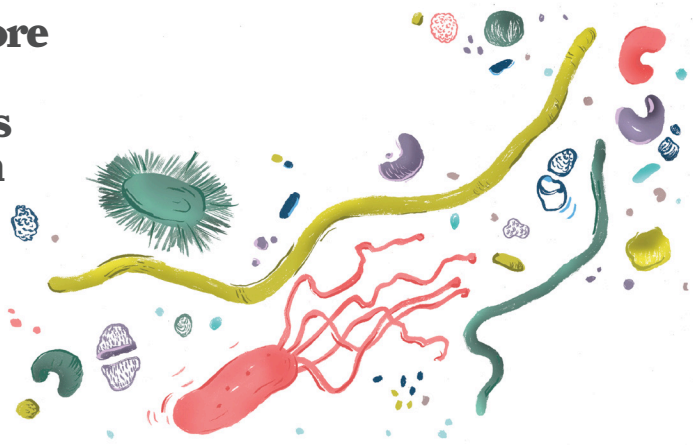
A new center will explore how the microbiome may provoke the body's immune system to turn against itself.



COVER STORIES

DEPARTMENTS

ILLUSTRATION BY ANDREA ROSSI

NYU School of Medicine
NYU LANGONE MEDICAL CENTER

The Versatile Heart

I've always been amazed by the heart. This mighty muscle works continuously to send oxygen-rich blood to cells. Every minute about 11 pints of blood are sent through the lungs and around the body. In the course of a lifetime, the heart beats over 3 billion times. When the beat goes awry, the consequences, of course, can be life threatening. Today, due to the revolution in genetic testing, it is possible to identify in infants and children congenital mutations that dramatically raise the risk of fatal cardiac arrhythmias. To prevent sudden death, they can be fitted with an implanted cardioverter-defibrillator (ICD).

In this issue of *NYU Physician* magazine, the stories of some of these young patients and their families are brought to light. Under the care of Dr. Frank Cecchin, a remarkable physician who is director of pediatric and congenital electrophysiology, these young patients learn to adapt to life with an ICD and to appreciate the lifesaving technology that enables them to lead normal lives. I hope you enjoy reading about him and his patients.

Other stories highlight discoveries from our laboratories that will one day affect children's health, from epilepsy to familial dysautonomia. Finally, our faculty conversation with Dr. Bernard Dreyer, president-elect of the American Academy of Pediatrics, underscores our unswerving commitment to children's health and well-being.

I'd like to end this letter with a note about the newest member of our family—Lutheran Medical Center, an acute care teaching hospital in southwest Brooklyn, now known as NYU Lutheran Medical Center. Our unprecedented alliance creates a clinically integrated healthcare network that provides access to our vast array of specialty and surgical care. In turn, NYU Lutheran gives us the opportunity to extend our expertise to a larger number and broader spectrum of patients. This is an exciting chapter in our history.

DEAN & CEO ROBERT I. GROSSMAN, MD

PHOTOGRAPH BY
JOHN CARNETT

NEWS FROM MEDICINE

SPRING 2015

ADVANCES IN BREAST CANCER RESEARCH, THE MICROBIOME, EPILEPSY AND MORE

ILLUSTRATION BY
STUART BRIERS

AGNEL SFEIR, PHD

SLOWING *BRCA* TUMORS

A glitch in a molecular repair tool may offer a way to halt some breast cancers.

A WOMAN'S LIFETIME risk of developing breast cancer in the U.S. is about 12 percent. But if she carries inherited mutations in the *BRCA1* and *BRCA2* genes, which account for 5 to 10 percent of all breast cancer cases, her risk is dramatically higher—anywhere from 40 to 90 percent, depending on individual risk factors.

In a recent study published in *Nature*, and funded partly by the Breast Cancer Alliance, researchers at NYU Langone Medical Center describe a new way to potentially slow or halt the growth of cancers linked to *BRCA1* and *BRCA2* mutations. In healthy cells, the *BRCA* genes encode proteins that reliably repair damaged DNA. In mouse and human cells with *BRCA1* or *BRCA2* mutations, however, the researchers discovered that a backup repair strategy takes over. This much less reliable mending kit employs an error-prone enzyme called polymerase theta, encoded by the *POLQ* gene, which may fuel cancerous growth.

But a cancerous cell is still a living cell. From the cell's vantage, this backup polymerase strategy is potentially lifesaving as it helps stave off full-blown genetic havoc. Agnel Sfeir, PhD, an investigator at the Skirball Institute of Biomolecular Medicine and a member of the Laura and Isaac Perlmutter Cancer Center, says this observation suggests an entirely new way to target *BRCA* cancers. "One way to kill cells with *BRCA* mutations is to block this enzymatic pathway and deplete *POLQ*," she says.

The finding stems from what Dr. Sfeir describes as a "simple" question about basic biology. The tips of our chromosomes, called telomeres, contain multiple repeats of the DNA letters TTAGGG and are normally protected by protein caps that act like the plastic nibs on shoelaces. If left unprotected, however, the telomeres can decay or fuse together, sometimes leading to massive DNA rearrangements like those seen in cancer. Which DNA letter, Dr. Sfeir wondered, appears at the precise junction between two abnormally fused telomeres? "You answer the question, and you don't know where the science will take you," she says.

In healthy cells, the *BRCA* genes encode proteins that reliably repair damaged DNA. In mouse and human cells with *BRCA1* or *BRCA2* mutations, a backup repair strategy takes over.

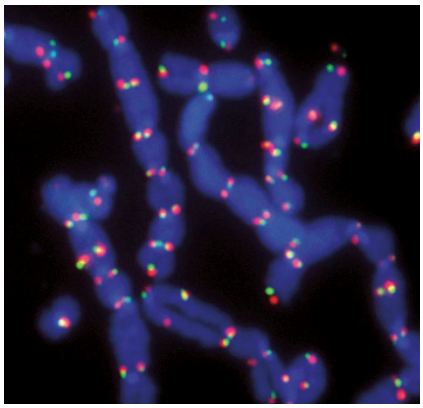
When the researchers sequenced the DNA at multiple telomere fusions, they unexpectedly found that many of the

PORTRAITS BY THEA BRINE. ILLUSTRATION BY STUART BRIERS

junctions contained randomly inserted DNA letters instead of the TTAGGG repeats. The random insertions suggested the activity of an error-prone polymerase. After testing several kinds of polymerase, the collaborators found that knocking out the *POLQ* gene for polymerase theta significantly reduced the propensity of dysfunctional telomeres to stick together, suggesting that the enzyme might actually promote the phenomenon. In particular, the data suggested that this polymerase plays a key role in the highly unreliable DNA patching service that may trigger both chromosomal fusions and wholesale rearrangements in cells with *BRCA* mutations.

Together with collaborators from The Scripps Research Institute in La Jolla, California, and the University of Texas at Austin, Dr. Sfeir's lab found that blocking the activity of *POLQ* in cells lacking the *BRCA* genes, meaning those deprived of *both* DNA repair mechanisms, led to chromosomal chaos and markedly reduced survival. Her lab is now testing whether the same *POLQ*-targeting strategy can inhibit tumor formation in mouse models of breast cancer.

A simple question and observation, Dr. Sfeir says, has since opened the door to an entirely new line of scientific inquiry. "There are many types of cancers that have altered DNA repair, and this polymerase theta seems to be up-regulated in many tumor cells," Dr. Sfeir says. "So why? What is it doing? Why is it up-regulated? All of these are important questions. We're going to be busy for the next 10 years or so." ● *—BRYN NELSON*



The tips, or telomeres, of these mouse chromosomes have become dysfunctional, causing individual chromosomes to fuse together in long tangled strands of DNA.

SCIENCE IMAGE: AGNEL SFEIR

MARIA DOMINGUEZ-BELLO, PHD

UNPRECEDENTED MICROBIAL DIVERSITY REPORTED IN REMOTE AMAZONIAN TRIBE

New findings shed light on the human microbiome.

IN 2008, a helicopter spotted an uncharted village of Yanomami Indians in the remote Amazonian jungles of southern Venezuela. The clan had subsisted for hundreds of generations by hunting and gathering, and up until that moment, its members had lived in total seclusion from the outside world, as a medical expedition would later learn.

For biologists, the unbroken isolation of the tribe offered a rare window on a seemingly ancient human microbiome, the trillions of bacteria that live in and on the body and that are increasingly seen as vital to our health. Most human microbiome studies have focused on Western populations. Now, a multicenter team of U.S. and Venezuelan scientists, led by researchers from NYU Langone Medical Center, report in the journal *Science Advances* that the villagers possess the most diverse collection of bodily bacteria ever documented. By comparison, the microbiome of people living in industrialized countries is about 40 percent less diverse, the scientists estimate.

"We have found unprecedented diversity in fecal, skin, and oral samples collected from the Yanomami villagers," says senior author Maria Dominguez-Bello, PhD, associate professor of medicine at NYU Langone. Science is only just beginning to understand the significance of diversity in the human microbiome. But the results bolster a growing body of data suggesting a link between, on the one hand, decreased bacterial diversity, industrialized diets, and modern antibiotics, and on the other, immunological and metabolic diseases such as obesity, asthma, allergies, and diabetes, which have dramatically increased since the 1970s. "We believe there is something environmental occurring in the past 30 years that is driving these diseases," adds Dr. Dominguez-Bello. "We think the microbiome could be involved."

In the study, the researchers analyzed bacterial samples collected and preserved from 34 of the 54 Yanomami villagers.

Among the volunteers, 28 gave skin and oral swab samples, while 11 gave fecal samples. Their bacterial DNA was then compared to samples from populations in the United States, as well as samples from the Amazonian Guahibo Indians in Venezuela and residents of rural Malawian communities in southeast Africa. The latter communities represent tribal populations with more exposure to the outside world than the Yanomami.

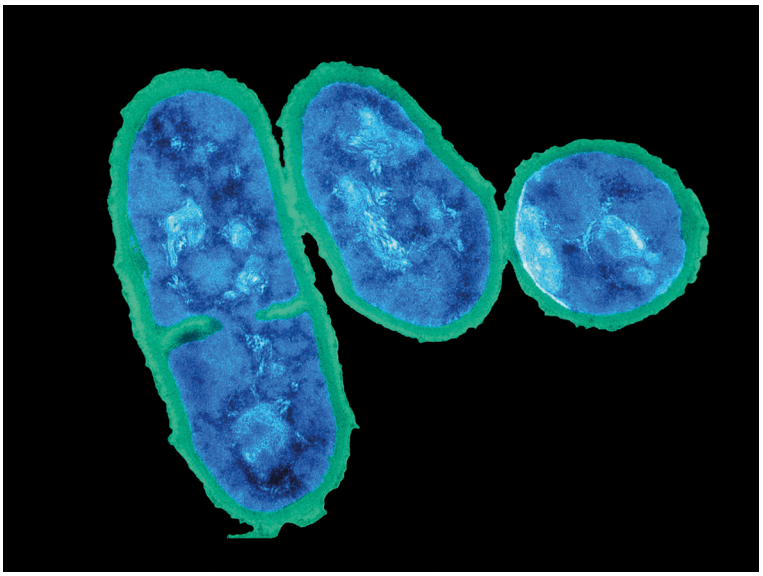
"There is a gradient of diversity in feces and skin that is inversely proportional to exposure to antibiotics and processed foods," says coauthor Jose Clemente, PhD, of the Icahn School of Medicine at Mount Sinai. "Even minimal exposure greatly decreases diversity and removes potentially beneficial bacteria from our microbiome."

Among the Yanomami skin samples, the researchers found no single dominant taxonomic group of bacteria, in contrast to the U.S. skin samples, which showed lower diversity and relatively high proportions of *Staphylococcus*, *Corynebacterium*, Neisseriaceae, and *Propionibacterium*.

In another intriguing finding, a genetic analysis of gut and oral bacteria revealed that the Yanomami villagers had bacteria containing genes that code for antibiotic resistance. The bacterial genes confer resistance not only to naturally occurring antibiotics found in the soil for millennia, but surprisingly, to synthetic antibiotics as well. The presence of resistance genes in microbiota unexposed to modern antibiotics may help explain the rapid rate at which bacteria develop resistance to new classes of antibiotics. "This shows that you don't need exposure to modern antibiotics to possess antibiotic-resistant genes," says Dr. Dominguez-Bello.

The researchers hope their insights will lead to new therapies that will rehabilitate disease-causing imbalances within the human microbiome. ●

—NICOLE DYER



No single group of bacteria dominated the Yanomami's skin samples. By contrast, relatively higher proportions of some microbes dominated U.S. skin samples, including *Propriobacterium*, shown here in a colorized electron photomicrograph.

SRIPAL BANGALORE, MD

NEWER STENTS, LESS RISK

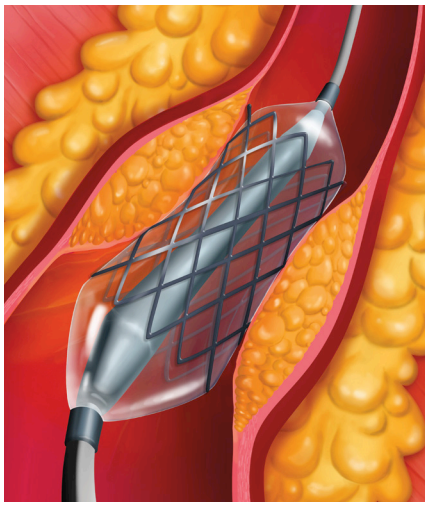
The latest generation of stents are compared to bypass surgery.

CORONARY STENTS or bypass surgery? Although commonly used to treat acute heart attacks and narrowed arteries, stents—the scaffolds used to hold blood vessels open—can promote inflammation and scar tissue growth, causing vessels to constrict again.

The technique for inserting a stent—called percutaneous coronary intervention, or PCI—however, requires a much shorter hospital stay than traditional open-heart bypass surgery, with faster recovery times, and is much less likely to trigger strokes. Though stents are less risky for patients in the first month or so after the procedure, they are more risky—with a greater chance of heart attack and death—in the years following.

These observations stem from studies

PORTRAITS BY THEA BRINE. KWANGSHIN KIM / SCIENCE SOURCE



Stents are tiny scaffolds that prop open clogged blood vessels. Newer stents are coated with drugs that inhibit inflammation and tissue growth.

The analysis should make it easier for "patients and their physicians to choose more wisely between stents and bypass surgery."

of older-generation stents, says Sripal Bangalore, MD, associate professor of medicine at NYU Langone Medical Center, who points out that newer stents are designed to be more compatible with living tissue and less likely to cause clots, inflammation, and tissue growth.

In a study published recently in *The New England Journal of Medicine*, Dr. Bangalore and colleagues compared some of the newer-generation stents to bypass surgery. They found that stents coated with the drug everolimus, an inhibitor of inflammation and tissue growth, didn't cause greater longer-term mortality than bypass surgery. Dr. Bangalore says that the findings about comparable mortality should make it easier for "patients and their physicians to choose more wisely between stents and bypass surgery."

The study is based on observational data from the New York State cardiac registries. It compared outcomes of patients who had bypass surgery with those who had everolimus-coated stents implanted. The stent group, as expected, fared better in the first 30 days with lower risk of death and stroke, but in contrast to earlier studies of older stents, the stent group didn't fare worse in the longer term for death. In the long run, the numbers of deaths in the two groups were not significantly different. Patients in the stent group had about 50 percent more heart attacks during the period compared to the bypass group, but for those patients whose stents successfully opened all of their diseased arteries, there was no significant increase in heart attacks.

Although this latest study does not settle the question definitively because it is based on observational data and not on the gold standard of a double-blind clinical trial, Dr. Bangalore says "the decision between stenting and bypass surgery should be based on weighing the up-front risk of death and stroke with bypass surgery, with the long-term need for repeat procedures with stenting."

The study was funded by Abbott Laboratories, which makes one of the two everolimus-coated stents now on the market. ● *—JIM SCHNABEL*

JEFFREY S. BERGER, MD

LINKING DIRTY AIR AND STROKE

Air pollution appears to affect the arteries feeding the brain.

ANALYZING DATA from tens of thousands of ultrasound tests of the carotid arteries, which supply blood to the brain, NYU Langone Medical Center researchers found a worrisome relationship—air pollution may increase the risk of stroke. They report in a new study that long-term exposure to a form of air pollution called PM 2.5, or fine particulate matter smaller than 2.5 microns in diameter, is associated with a greater chance of narrowing in the carotids. "Findings like these point to the possibility that lowering levels of fine particulates, which originate mostly from combustion engines, would reduce the risk of carotid artery stenosis and stroke," says coauthor Jeffrey S. Berger, MD, assistant professor of medicine.

The study, published in a recent issue

of the *Journal of the American Academy of Cardiology*, is based on ultrasounds performed on over 300,000 New York, New Jersey, and Connecticut residents from 2003 to 2008. Segregating the data by patients' zip codes and adjusting for demographic and socioeconomic factors, the researchers found that those people in the quartile of zip codes with the highest average PM 2.5 levels during the testing period were about 24 percent more likely to have stenosis—defined as a narrowing by at least half—in either of the two internal carotid arteries that supply the brain.

The analysis also showed that even a modest increase in the average PM 2.5 level, by just 10 micrograms per cubic meter, was associated with a near doubling of carotid stenosis risk.

"If you're in very good health, the levels of air pollution that we see in most of the U.S. probably don't pose a significant risk, but for the very young, the elderly, and people with other health problems like diabetes, air pollution might be a very important source of risk," says NYU Langone cardiologist Jonathan D. Newman, MD, MPH, the lead author of the study. ● —*JIM SCHNABEL*

NYU Langone Medical Center researchers found a worrisome relationship—air pollution may increase the risk of stroke.

RUBEN I. KUZNIECKY, MD

A NEW TREATMENT TARGET EMERGES FOR SEVERE CHILDHOOD EPILEPSIES

Researchers are focusing on the synapse.

THE SYNAPSE, a mere wisp of a structure at the junction where neurons communicate, may hold the key to novel therapies for a group of debilitating and sometimes fatal childhood epilepsies. New research by an international consortium of investigators has, for the first time, uncovered distinct anomalies in genes that help regulate synapses among children with these epilepsies.

"I think this finding is going to offer a new view of the kinds of interventions that could help patients with these disorders," says Ruben Kuzniecky, MD, professor of neurology, codirector of the NYU Comprehensive Epilepsy Center, and a member of the research consortium. Some 2 to 3 million people in the U.S. have epilepsy. Severe forms of the disorder, such as West syndrome, which affects some 2,000 to 2,500 infants each year in the U.S., are less common.

Children with epileptic encephalopathies have frequent seizures and experience progressive cognitive impairment, leading to lifelong disability. Pre- and perinatal infections and other complications, and inherited gene mutations are among the known causes. In recent years, teams of epilepsy researchers have been investigating another culprit: de novo (new) mutations that are found in children's genomes but not in their parents' genomes. Such mutations typically arise from spontaneous mutations in sperm or egg cells.

PORTRAIT BY THEA BRINE. ILLUSTRATION BY STUART BRIERS

The new findings, based on DNA samples gathered worldwide from 356 patients and their parents, were published recently in *The American Journal of Human Genetics*. By comparing children's DNA with that of their parents, the researchers found evidence that a substantial proportion—some 12 percent—of the children with no known cause of epilepsy harbored de novo mutations. Surprisingly, 75 percent of these mutations were in genes encoding proteins believed to help regulate synapses, the communication ports used by neurons to send chemical messages to one another. Most previous genetic studies have implicated a different nerve-cell process.

The de novo mutations occurred most frequently in a synaptic gene called *DNM1*, which codes for a protein named dynamin 1 that allows neurons to recycle some of the tiny capsules, or vesicles, used to send neurotransmitters across synapses to other neurons. This recycling process, called endocytosis, is essential for proper neuronal signaling.

"The *DNM1* mutations that we've detected appear to impair endocytosis," says Dr. Kuzniecky. The research, he says, also suggests that the gene defects mainly impair activity in inhibitory circuits that ordinarily restrain neuronal firing. Thus, such defects remove the breaks that prevent the excessive firing associated with seizures. Other researchers reported in 2010 that a mutation in *DNM1* leaves mice with a severe epilepsy-like syndrome, but until now, *DNM1* mutations haven't been implicated in human forms of epilepsy.

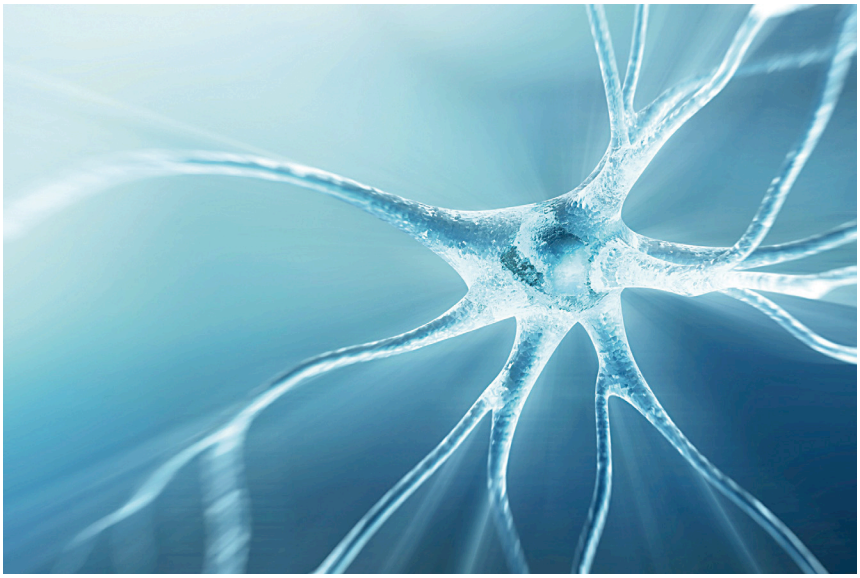
Nearly all previously reported mutations that cause childhood epilepsies were in genes coding for ion-channel proteins. These pipelike proteins, which form tiny channels in the outer membranes of neurons, allow passage of sodium, calcium, chloride, and potassium ions. The movement of the ions, in turn, regulates the general excitability of nerve cells—the readiness to fire bursts of neurotransmitter molecules to other neurons. A mutation may leave an ion channel stuck open or closed in a way that makes cortical neurons too excitable and thus prone to seizure activity.

The new study indicates that mutations in synaptic genes are another major underlying cause of seizure disorders. The *DNM1* gene and its protein are likely to come under particular scrutiny as potential drug targets. "Reversing or circumventing this *DNM1* deficiency will be an interesting challenge," Dr. Kuzniecky says.

The new study was a collaborative effort by the Epi4K Consortium, the EuroEPINOMICS-RES Consortium, and the Epilepsy Phenome/Genome Project, which Dr. Kuzniecky codirected. ●

—JIM SCHNABEL

Mutations in synaptic genes appear to be another major underlying cause of seizure disorders.



PASIEKA / SCIENCE SOURCE

Computer artwork of a nerve cell, showing long branches of dendrites emanating from the nerve cell body. Dendrites collect information from other cells.

DANGEROUS RHYTHMS

BY KENNETH MILLER • ILLUSTRATION BY JAMES STEINBERG

For children with dangerous cardiac arrhythmias, implantable defibrillators can be lifesaving. Yet for active children, these devices pose special challenges. Dr. Frank Cecchin has developed a nuanced approach to the problem of risk in his young patients—one informed by clinical studies showing that safety and flexibility are not always incompatible.


A
D
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A few months ago, Jake Baxter decided to get rid of the device that had protected him for a decade from the cardiac disorder that killed his sister. Jake was born with a genetic mutation that could send his heart into a rapid arrhythmia—ending in cardiac arrest—at any time. As a teenager, he was surgically fitted with an implantable cardioverter-defibrillator (ICD), designed to detect dangerously irregular heartbeats and deliver a shock to set the rhythm back on course. However, he'd never actually experienced a cardiac event, and the business card–size gadget had never been activated. Now he was 24, and he wanted it out of his chest.

THE REASON WAS PURELY PRACTICAL: He'd set his sights on a career as an electrical lineman, and after passing a series of grueling exams, he'd been accepted into the union. Then he learned that anyone with an ICD was disqualified from working with power lines, because electrical interference could cause the device to malfunction. For a worker 50 feet up a utility pole, a jolt from a misfiring defibrillator could have disastrous consequences.

Frustrated, Jake went to see Frank Cecchin, MD, director of pediatric and congenital electrophysiology at NYU Langone Medical Center, who had overseen his ICD's maintenance since implanting it in 2005. From previous conversations with the doctor, the young man knew that for patients with his condition, the risk of cardiac arrest may decline after age 20. "I don't really need this thing anymore," he pleaded. "Can't we just chuck it?"

"Maybe we can," Dr. Cecchin (pronounced "check-*een*") told him. "But before we move ahead, let me do a little more research."

• • •

For children at risk of fatal cardiac arrhythmias, an ICD can greatly improve the odds of long-term survival. First introduced in 1980, the devices were used almost exclusively in adults until the 1990s, when advances in electronics and computing allowed them to be made small enough to fit inside a child's chest. The basic version consists of a titanium box, or generator (containing computer circuitry, a capacitor, and a battery), and a wire known as the lead. In most patients, the generator is implanted in the left side of the chest, under the skin or muscle, and the lead is threaded through a vein into the chambers on the right side of the heart. Sensors relay heart rhythms to the ICD's microprocessors. If potentially life-threatening tachycardia or fibrillation persists for too long, the generator interrupts these very chaotic, fast rhythms by sending a surge of energy to an electrode in the right ventricle.

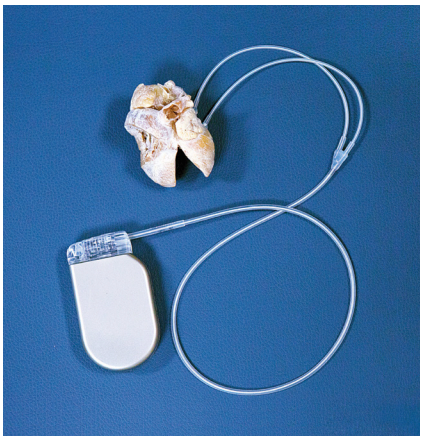
ICDs are used for two broad purposes: primary prevention, which means warding off sudden cardiac arrest in high-risk patients, and secondary prevention, which means avoiding a recurrence in those who've already endured such an episode. Newer ICDs can also double as pacemakers, delivering pulses of low-voltage electricity to keep the heart from beating too slowly. The device can be implanted in infants as soon as a few weeks after birth. In these patients, the generator is implanted in the abdomen, where there's enough space to accommodate it, and the leads are routed to the outside of the heart. In patients like Jake, who may experience sporadic arrhythmias, an ICD can function like a sprinkler system, kicking in if a biochemical glitch ignites a cardiac inferno.

An ICD has never prevented Jake Baxter from pursuing his passion—mountain biking. He has been racing since 2006.

PHOTO BY PAULETTE MERTES


KTM
Troy Lee Designs

Yet ICDs are difficult to live with. Batteries run out every five years or so, requiring surgery to replace the device. Leads can wear out or fracture, sometimes triggering a painful and terrifying storm of shocks. Even when an ICD does what it's designed to do, zapping a runaway heartbeat into submission, the sensation is scary—a kick in the chest that can leave even a strong man reeling. For children, there are additional challenges. Their higher activity levels and growing bodies put more stress on the hardware, necessitating more frequent equipment changes and posing a greater potential for complications. If a lead creates scarring in a vein, for example, it must be rerouted. After several such operations, a child can run out of viable pathways.



An ICD and a cast of an infant's heart.

• • •

The most daunting downside for pediatric ICD patients may be psychological. "You're completely dependent on that device functioning properly," observes Dr. Cecchin. "That knowledge affects all age groups, but it can have a huge impact on kids." Several studies show that children with ICDs have far higher rates of anxiety than healthy kids. According to a paper he coauthored in the journal *Pediatrics*, incidence rises with children's age at implantation and the severity of the disorder under treatment. "It's enormously stressful for the parents as well," notes nurse practitioner Sharda McGuire, who often recommends counseling for both patients and family members.

The devices and the doctors who prescribe them can sometimes reinforce recipients' sense of insecurity. More than 20 percent of pediatric ICD patients experience inappropriate shocks, whether due to a broken lead or to misidentification of a harmless arrhythmia. Many cardiologists add to young patients' angst by forbidding activities that could hypothetically damage the implant, such as sports in which collisions or falls are common. They may retain the ICD's factory settings, which program it to fire the moment a ventricular tachycardia (an arrhythmia originating in the heart's lower chambers) reaches 160 beats per minute. Better to suffer an unnecessary shock, goes the thinking, than to risk ventricular fibrillation, in which the rhythm becomes so rapid and disorganized that the heart stops pumping altogether.

Over his 20 years as a pediatric cardiac electrophysiologist, Dr. Cecchin has developed a more nuanced approach to the problem of risk in his young patients—one informed by

▼

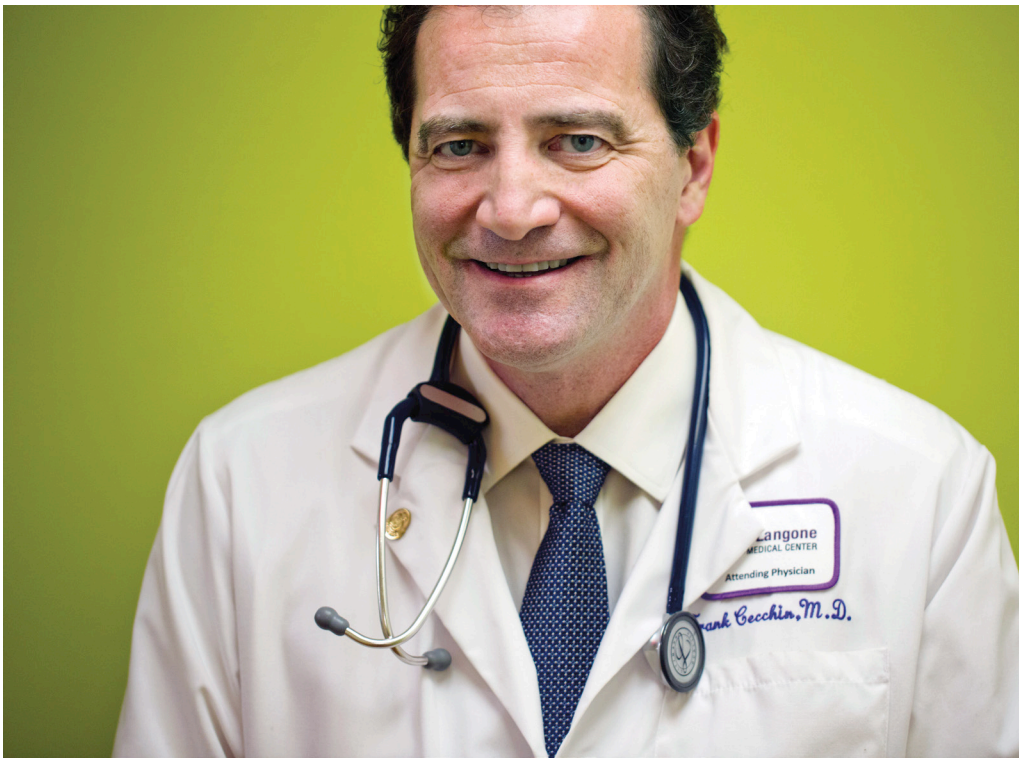
HUNZA MIRZA

AGE 14/BROOKLYN, NY

Hunza was three years old when he was diagnosed with hypertrophic cardiomyopathy, a genetic disorder that causes part of the cardiac muscle to thicken. At first, his only symptom was a heart murmur. "I kept praying that it would go away, but that's not how it worked out," says Hunza's mother, Katherine. As a kindergartner, he tired easily and was often short of breath, and his condition worsened with each passing year. By sixth grade, he could barely climb a flight of stairs. Because the disease can trigger a sudden, fatal arrhythmia, his doctor referred him to Dr. Cecchin at NYU Langone Medical Center.

At age 11, Hunza received an ICD, which doubles as a pacemaker to keep his heart from beating too slowly. His mother and three of his four brothers also tested positive for the disorder, and though only one sibling shows signs of illness, the others are being carefully monitored. Amid these worries, Hunza's ICD allows him and his family some precious peace of mind. "Sometimes it feels weird, but I'm really glad I have it," he says. "I might not be here today if I didn't."

"I tell children that this device is not there to stop you from doing anything. It's there to enable you to do things safely."



clinical studies showing that safety and flexibility are not always incompatible. In programming ICDs, he says, "we've learned not to be too aggressive. In children, a lot of arrhythmias are short-lived and resolve themselves. We wait for the maximum time possible to deliver a shock." Thanks to that strategy and improved computer algorithms, he reports, none of his patients has experienced an unnecessary shock in at least two years. Nor have their devices failed to fire when truly needed.

Rather than issue blanket bans on strenuous exertion, Dr. Cecchin carefully considers each patient's condition, discusses the possible dangers, and leaves the decision up to the individual. "If I say, 'You can't do this,' they get angry, and they usually do it anyway," he explains. "But if I give them an open door, they usually make the right choice."

In fact, he points out, recent studies show that even rough sports seldom cause damage to ICDs. Except in rare cases, he encourages patients to be as active as they can. "I tell children that this device is not there to stop you from doing anything. It's there to enable you to do things safely. If something happens, we'll deal with it. The bottom line is that you have to enjoy life."

If, in some cases, that might mean removing an ICD, he's willing to consider it.

DISHITA AGARWAL

AGE 9/SYRACUSE, NY

One morning in 2008, Dishita was playing with her twin brother when she crumpled to the living room floor. "I picked her up, and she was not breathing," recalls her father, Dhruv. Her parents pumped her chest frantically, and the two-year-old revived by the time paramedics arrived. At a local hospital, she was diagnosed with long QT syndrome—a common cardiac rhythm disorder affecting about 1 in 5,000 people. Although most cases are inherited and can be confirmed by gene sequencing, Dishita tested negative for all known genetic markers.

Dishita was referred to Dr. Cecchin, who implanted her with an ICD. (To mute her heart's response to emotional stresses, a cardiac surgeon also severed nerves in the chest that relay impulses from the brain to the sympathetic nervous system.) The device first saved her life at age four, shocking her heart out of an arrhythmia during a swimming lesson. It rescued her again recently, as she climbed stairs at home.

Yet the emotional toll is heavy. "It's scary when I get shocked," Dishita says tearfully. "My head hurts. Everything is buzzing." Her parents try their best to allay her anxieties. "We tell her, 'The ICD is protecting you,'" says her mother, Ruchi. "But the uncertainty has become a part of all of our lives."

PHOTOS BY BÉATRICE DE GÉA

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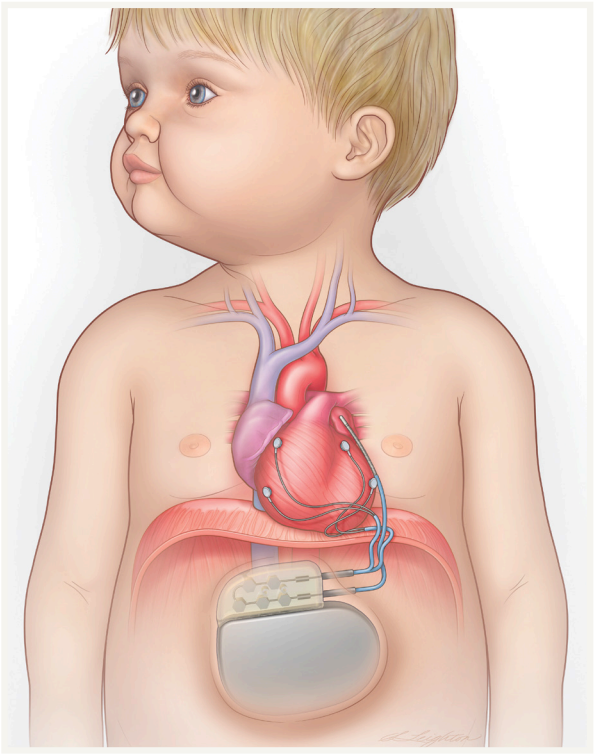
Jake Baxter is fair-haired and athletic, and the name of his late sister is tattooed over his heart. Rebecca was 13 in July 2000, the second of three children born to a pair of science teachers. She'd just finished eighth grade at Mansfield Middle School in Storrs, Connecticut, where she'd played basketball, softball, and soccer. She was a strong swimmer, too. So when she drowned in the shallow end of a public pool, her family's grief was accompanied by bafflement. The autopsy revealed that the cause of death was sudden cardiac arrest. "It was a mystery," recalls Jake, who was nine at the time. "We were all just blindsided."

There was one clue, however: Rebecca's father, Ed, had lost two brothers to drowning, both before they turned 18. A physician friend, suspecting that an inherited electrophysiological disorder might be the culprit, referred the Baxters to Dr. Cecchin, who was then practicing at Boston Children's Hospital and whose own family had been touched tragically by cardiac disease.

The son of Italian immigrants, Frank Cecchin grew up in The Bronx and Long Island, where his father worked as a tile setter. His parents never made it past sixth grade, and they were fiercely proud of their high-achieving son. But his dad died of a heart attack during Frank's first year of medical school. That event influenced his choice of specialties and helped shape his attitude toward his patients. "Dr. Cecchin is very warm and welcoming," says Jake. "He makes you feel like he has all the time in the world for you." Adds Jake's mother, Judith: "He's incredibly persistent. He wouldn't give up until he figured out how to help us."

Over the next two years, Jake and his sister Sarabeth, then 21, traveled to Boston for countless stress tests meant to spur a telltale arrhythmia. None of them yielded an abnormal graph line. Dr. Cecchin even immersed the siblings' faces in ice water (which Jake recalls enjoying), but the electrocardiogram remained unperturbed. Then, at a professional conference, he met a Mayo Clinic scientist who found their way to Dr. Cecchin. "He was the first doctor who talked to us about the course of treatment all the way to adulthood," recalls Rebecca. Dr. Cecchin also exchanged Cameron's original ICD for one with a safer and more effective design. Genetic tests showed that Mark was at risk, as well, and after his brother died of an arrhythmia at 45, he, too, received an implant.



An illustration of an ICD implanted in an infant's abdomen.

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CAMERON KNOWLES

AGE 14/ROCHESTER, NY

When Cameron was seven years old, his parents went to wake him for school and found him in cardiac arrest. Rebecca, a nurse, and Mark, a firefighter, saved his life using CPR. Diagnosed with long QT syndrome, Cameron was implanted with an ICD. A few months later, the family

Recently, Cameron enjoyed his first roller coaster ride. He joined an Explorer Scout troop that teaches firefighting skills, and though he may never be able to run into burning buildings, he plans to major in fire prevention in college. "At first, I was a little angry about needing an ICD," he says. "I thought my life was over. But when you look past the limitations, you see all the opportunities that are out there."

Dr. Frank Cecchin and nurse practitioner Sharda McGuire with a young patient.

was researching rare mutations in genes governing cardiac cells. Dr. Cecchin sent him a tissue sample from Rebecca's autopsy, and blood samples from Jake, Sarabeth, and their father. In June 2004, the results came back. All the specimens showed a mutation that causes a rhythm disorder called catecholaminergic polymorphic ventricular tachycardia (CPVT).

CPVT stems from a defect in the body's calcium channels, proteins that control the passage of certain electrochemical signals—carried by calcium ions—between cells. (Other rhythm disorders, such as long QT or short QT syndrome, involve different types of ion channels.) It's believed to affect about 1 in 10,000 people, and to be responsible for 15 percent of unexplained sudden cardiac deaths in youngsters. Warning signs may include dizziness or fainting in response to intense exercise or emotional stress. In some cases, however, the first symptom is cardiac arrest.

To prevent that from happening, Dr. Cecchin offered two choices: an ICD or a lifetime of exercise restriction and beta-blockers, which prevent tachycardia by blunting the heart rate. Jake's father opted for the medication. Jake—an avid mountain biker and snowboarder—chose the device. So did Sarabeth, and so did several of their aunts and cousins after they tested positive for CPVT.

Jake was 13 when he received the implant. Although he agreed to give up swimming, he soon returned to his other rugged pursuits. At 15, he joined a downhill mountain-bike team and began racing every weekend. By the time he finished high school, he'd competed on single tracks from Canada to California. He went on to junior college, earning a certification in sustainable energy. Then, he began studying to become an electrical lineman.

Meanwhile, in 2013, Dr. Cecchin moved from Boston to NYU Langone, lured there by Achiau Ludomirsky, MD, the Andrall E. Pearson Professor of Pediatric Cardiology and director of the Division of Pediatric Cardiology, who'd been his fellowship adviser at Texas Children's Hospital. "I'd been trying to recruit him for ages," says Dr. Ludomirsky. "I consider him one of the best pediatric electrophysiologists in the country, maybe the world."

After Jake visited his office last winter, Dr. Cecchin set to work trying to determine whether it was safe to remove the young man's ICD. Although the odds of sudden death from CPVT fall sharply in adulthood, he knew that different variants of the disorder could follow different courses. He began combing through the literature in search of other patients with the precise mutation shared by Jake and his relatives.

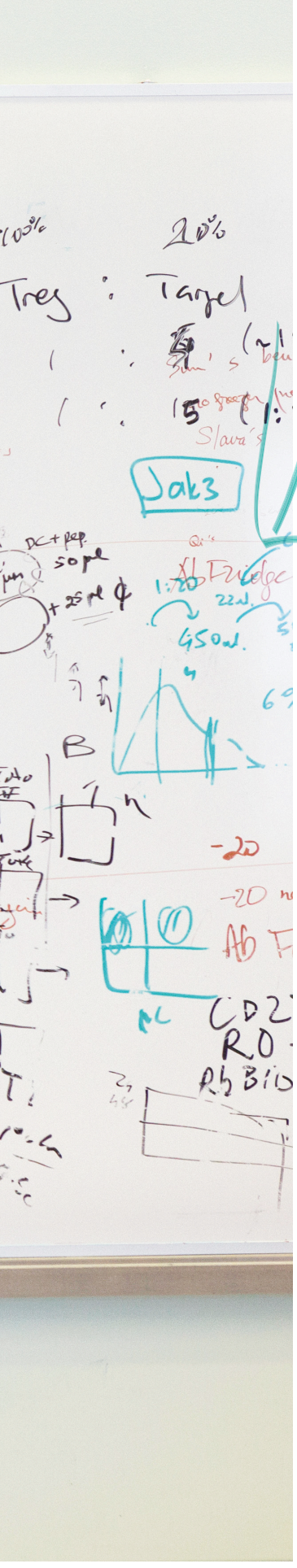
No one else turned up with that particular glitch, but there were a few cases of mutations on DNA base pairs just a rung or two away on the ryanodine receptor gene. Some of those patients, Dr. Cecchin discovered, had died of cardiac arrest in their 30s.

When Jake got the news, he came to a new decision: the implant would stay in; working on power lines was out. He would keep his current job, driving trucks for the department of public works. But he didn't surrender to the status quo. Instead, he turned his energy to another project, a small industrial-prototype business that he'd founded with a friend. The startup aims to specialize in developing prostheses for bike riders with disabilities.

"My defibrillator has never held me back from what I love to do," Jake says, "and it's good to know that someday, it just might save my life." ●

ILLUSTRATION BY SCOTT LEIGHTON. PHOTO BY BÉATRICE DE GÉA

Dr. Bo Shopsin (left) and Dr. Michael Phillips are working to find an effective solution to hospital-acquired infections.



Confronting an Ever-Present Threat in Hospitals

A new surveillance system at NYU Langone Medical Center aims to track healthcare-associated infections in real time, providing an early warning for potential outbreaks.

BY BRYN NELSON • PHOTOGRAPH BY BÉATRICE DE GÉA

AN UNWASHED HAND, an uncovered cough, inadequately sterilized instruments. In a hospital, any breach, small or large, can set off a chain reaction of deadly infections. The margin for error is so small that 1 in 25 patients in the United States battles at least one infection acquired during hospital care, known as a nosocomial infection. Because hospitals care for the nation's most gravely ill patients, they regularly encounter a range of tenacious bacterial, viral, fungal, and parasitic infections that can readily incubate and spread among other patients if not aggressively countered. Consequently, nosocomial infections are among the nation's leading causes of death, killing an estimated 75,000 every year.

Simple measures such as improved sanitation can help, but the more complex challenge is tracking infections in real time and tipping off healthcare providers before pathogens spread. Most hospital surveillance systems are geared toward identifying past infections. To flag potential hospital outbreaks, they rely on human beings to identify patterns in complex data sets and on cumbersome rules. One such rule calls for a follow-up investigation only after three infections appear within two weeks on the same unit. "By the time you figure out that the cluster has occurred, weeks and months have gone by and your opportunity for action has vanished," says Michael Phillips, MD, medical director of Medical Epidemiology and Infection Control at NYU Langone.

Dr. Phillips has devoted his career to studying the transmission of infectious diseases, ranging from multidrug-resistant bacteria to hepatitis C, and he is the Medical Center's leading expert in tracking the international stew of viruses and bacteria swirling around New York. He also assisted with the complex logistics of safeguarding staff and patients from possible exposure to the Ebola virus during Bellevue Hospital's successful treatment of a physician who had contracted the disease while volunteering in Africa.

Now he's partnering with Bo Shopsin, MD, PhD, assistant professor of medicine and microbiology, on a faster, more effective solution for fighting nosocomial infections. "Traditionally, infection control in hospitals has been done really ad hoc," says Dr. Shopsin. "We're creating a more systematic way of identifying clusters and outbreaks."

In late 2013, the doctors introduced a new infection-surveillance system at NYU Langone Medical Center's Tisch Hospital and the Hospital for Joint Diseases that leverages the booming fields of big data and genomics. The system combines classic shoe-leather epidemiology with advanced data mining and biomolecular analysis, allowing scientists to source hospital pathogens at unprecedented speed. With the ability to slice and dice vast amounts of information culled from electronic medical records and hospital databases, and then interrogate pathogen samples in the lab with painstaking detail, scientists at the Medical Center are challenging common assumptions about how pathogens spread.

Dr. Phillips recalls a case of two patients sharing a room who both tested positive for the superbug methicillin-resistant *Staphylococcus aureus*, or MRSA. On the surface, the infections looked like a simple instance of cross-contamination, likely due to a lapse in hand washing. But a deeper look at the molecular profile of the MRSA samples indicated two unrelated bugs. Such information, revealed only through savvy biomolecular sleuthing, radically redirected the investigation as well as hospital efforts to contain the infections.

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The first step in any hospital surveillance effort is to determine who might be carrying infectious pathogens on their skin or in their gastrointestinal tract. Since microbes can colonize a patient before symptoms emerge, and asymptomatic patients can still pass on disease-causing microbes to others, the Medical Center screens certain high-risk patients for infectious disease.

The problem is that this screening process generates a daily avalanche of laboratory data. The task of scouring it for telltale patterns and suspicious clusters traditionally falls to a handful of infection-control practitioners, typically nurses with advanced degrees in public health. It's painstaking, time-consuming work that diverts resources away from other important tasks such as education, observation, and prevention planning, says Tania Bubb, RN, PhD, a researcher in infection control and prevention. In fact, one study found that nonelectronic surveillance and analysis accounts for an average of 45 percent of the total time in infection prevention.

Under the new surveillance system, computers do the tedious work, analyzing data in a fraction of the time that it would take a human. At NYU Langone, electronic surveillance pivots around an open-source software program called WHONET, which was originally designed by researchers at Harvard University to help the World Health Organization track antibiotic-resistant microbes in developing nations. WHONET's chief value is its ability to merge and manage large volumes of disparate data, from laboratory results to patient information. Researchers at NYU Langone work closely with the Harvard developers to continually customize the software for the Medical Center's evolving needs.

WHONET alone cannot spot potential outbreaks, so the researchers rely on a second, complementary software tool called SaTScan. "WHONET structures the data, SaTScan analyzes it," explains Dr. Phillips, who first encountered the electronic tracking

system in 2004 during a Centers for Disease Control and Prevention fellowship at the New York City Health Department, where it was being used to flag signs of bioterrorism at city hospitals. "It really opened my eyes to newer, electronic ways of tracking infection," he adds.

Together, the software systems automatically comb through and compare hundreds of electronic medical records, pharmacy records, lab results, and other data, flagging potential clusters of infections that would be unlikely to occur by chance alone, such as three similar infections in the same unit within a few days, instead of a few weeks.

Churning through the neatly packaged WHONET data, SaTScan can track 15 kinds of nosocomial bacterial infections at lightning speed, grouping potential clusters of infection into low-, medium-, and high-risk categories. Sean Cloonan, MD, an instructor in the Division of Infectious Diseases and Immunology, oversees this data analysis, then reviews the results. In high-density cities like New York, where visitors have introduced microbes from around the world, multiple strains of resistant superbugs like MRSA and *Klebsiella pneumoniae* Carbapenemase, or KPC, can appear nearly identical at first blush. So whenever the software and Dr. Cloonan's analysis point out a suspicious cluster of cases, Dr. Shopsin and his team step in to determine if the infections may be linked.

Researchers rely on several tools and techniques to do this job. One, known as an antibiogram, assesses the sensitivity of the swabbed microbes to a range of antibiotics. Identical sensitivity patterns between two bacteria of the same species might suggest a high degree of relatedness and point to a common source. Another tool is strain typing. This technique identifies genetic differences within a single gene or among a defined set of them, allowing researchers to differentiate pathogenic microbes and determine whether a bacterial strain in one patient likely originated in another or in a source beyond the Medical Center. For more difficult cases, Dr. Shopsin's team may sequence and compare the entire set of genes, or the genome, of similar strains in collaboration with NYU's Genome Technology Center.

"The key is to get all of these data organized and automated so that the analysis and interpretation can be done by anyone."

Strain typing is a particularly powerful technique in the fight against nosocomial infections. In 2011, a highly virulent strain of KPC spread from one patient to 17 others over a six-month period at the National Institutes of Health Clinical Center in Bethesda, Maryland, a premier research hospital. Strain typing eventually revealed that a lung transplant patient had passed the same KPC strain on to three other patients, initiating a transmission chain that eventually killed six patients. The vital information showing that the infections were linked finally helped the hospital contain the outbreak. As part of its counteroffensive, the hospital physically separated infected patients from others, tested every patient in the hospital, and set up a strict protocol that barred the sharing of most hospital equipment and staff between infected and noninfected patients to prevent the further spread of the microbe.

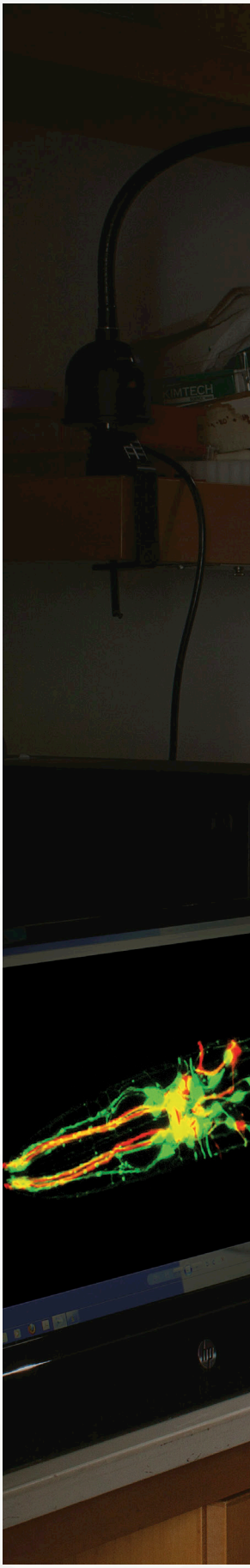
At a recent infectious diseases conference, Dr. Cloonan offered an early glimpse of strain typing's potential at NYU Langone. He described a case study in which the Medical Center's electronic surveillance system had identified a cluster of three infections that would have been overlooked otherwise. Dr. Shopsin's team followed up by sequencing the genomes of all three bacterial isolates, which were multidrug-resistant versions of an important hospital pathogen called *Pseudomonas aeruginosa*. Fortunately, the results showed that all three strains were unrelated. It was a false alarm.

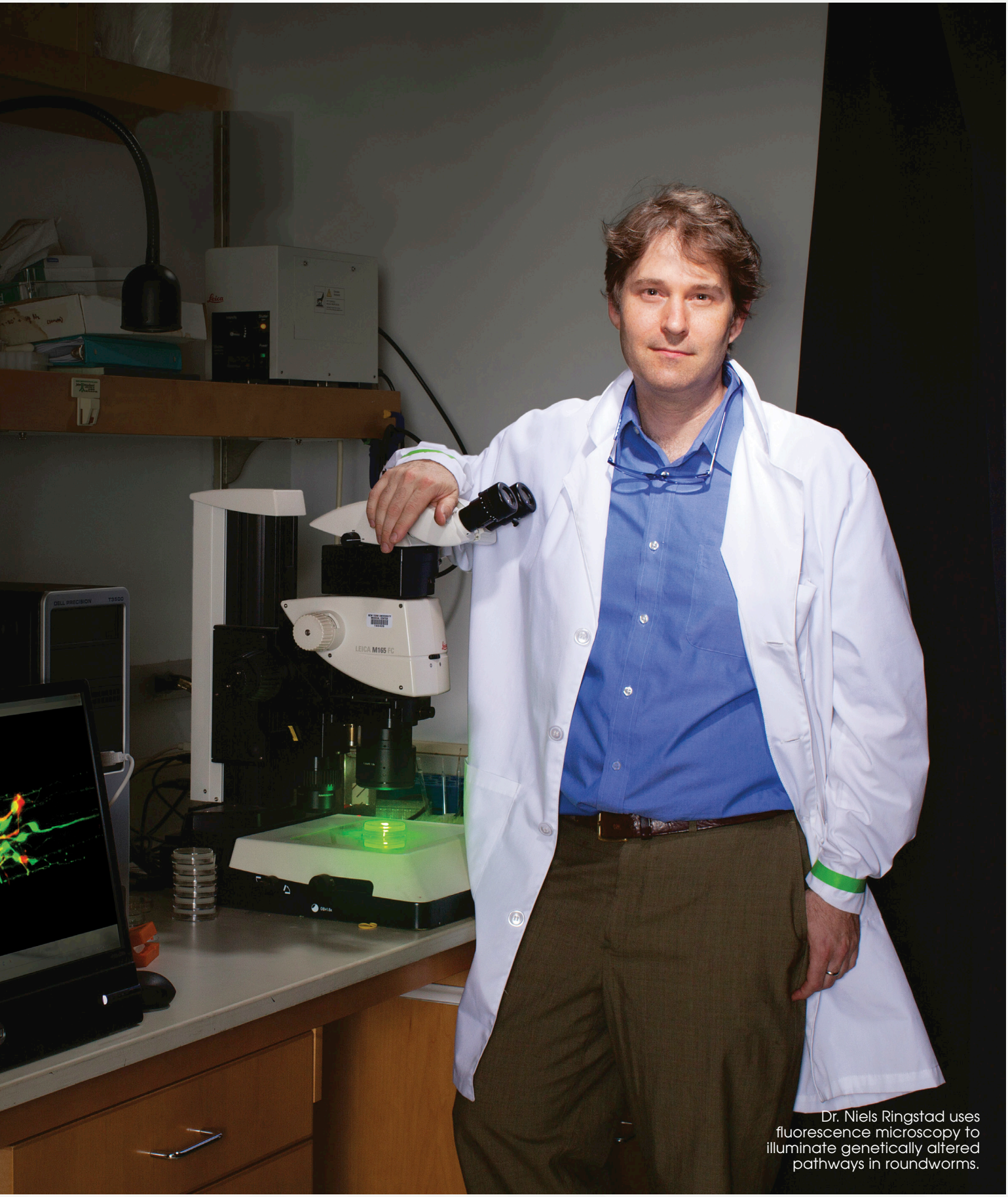
As NYU Langone's electronic surveillance system becomes more sensitive, Dr. Cloonan says, it will help inform critical decisions about whether and how to step up containment precautions, such as isolating infected patients and requiring anyone who enters their room to wear gown, gloves, and other personal protective equipment. Eventually, Dr. Shopsin adds, the team hopes to set up a more highly automated process that can quickly and cheaply collect and analyze the most relevant clinical data culled from patients' lab tests and electronic medical records. "The key is to get all of these data organized and automated so that the analysis and interpretation can be done by anyone," he says. ●

A WINDOW ONTO THE BRAIN

The unassuming roundworm captivates cell biologist Niels Ringstad, PhD, whose studies of the tiny worm are yielding surprising insights into psychiatric disorders and familial dysautonomia, a rare genetic condition among children.

BY NICOLE DYER
PHOTOGRAPH BY JOHN CARNETT





Dr. Niels Ringstad uses fluorescence microscopy to illuminate genetically altered pathways in roundworms.

THE DIRT-DWELLING ROUNDWORM is hardly the pinnacle of animal evolution. A grain of sand could crush its boneless body like a boulder. Its brain—if you can call it that—consists of a mere 302 neurons, about 100 billion shy of the number in a human brain. It has neither heart nor lungs, and its lifespan is only nine days.

Yet, after a decade of studying this modest creature—known formally as *Caenorhabditis elegans*, or *C. elegans*—Niels Ringstad, PhD, assistant professor of cell biology at NYU Langone Medical Center, believes he has only just begun to scratch the surface of its biochemical complexity. For scientists, the worm's outward simplicity is its greatest asset. Its translucency offers a convenient window onto a compact nervous system, which functions, cell to cell, in much the same way that ours does. Only instead of a chaotic universe of 100 trillion cellular junctions, or synapses, it has just 8,000, all of which have been neatly mapped. Perhaps no organism has been more examined than *C. elegans*, and yet there is so much more we can learn from it.

This simple fact is the engine that propels Dr. Ringstad's research. Since opening his laboratory at the Skirball Institute of Biomolecular Medicine in 2009, when he joined NYU Langone, the scientist has spent countless hours peering into a microscope, examining the neurons of *C. elegans* for clues to the cellular underpinnings of psychiatric disorders like depression and schizophrenia, for which there are desperately few treatment options. His latest discoveries, including genetic mutations that disrupt the brain chemicals serotonin and dopamine, build on a body of work conducted as a postdoctoral researcher at the Massachusetts Institute of Technology. There, he studied under the tutelage of H. Robert Horvitz, PhD, a leading authority on *C. elegans*, who shared the Nobel Prize in Physiology or Medicine in 2002 for his discovery of programmed cell death in *C. elegans*.

Dr. Ringstad helped discover a new family of chloride channels that open and close quickly, serving as an express route to the nervous system. Such channels, if they exist in humans, could point to novel treatments for neuropsychiatric conditions like addiction and mood disorders. "Dr. Ringstad is an unusually impressive scientist," says Dr. Horvitz. "He is hungry for knowledge, reads the literature avidly and broadly, and is fearless, yet practical, in defining his scientific vision and in incorporating new approaches and technologies into his experimental efforts."

"A lot of people wonder what the connection is between a little worm laying eggs and depressed humans."

Much of Dr. Ringstad's current work focuses on signals that govern serotonin, known for its salubrious effect on mood. In worms, however, the brain chemical is better understood for its role in reproduction. "A lot of people wonder what the connection is between a little worm laying eggs and depressed humans," says Dr. Ringstad, whose laboratory houses hundreds of millions of roundworms. "It's serotonin. It turns out that a lot of serotonin signaling in the human brain is conserved over a billion years of evolution."

Serotonin became a household word in the 1990s, when doctors began writing more than 2.5 million annual prescriptions for Prozac, which boosts serotonin levels in the brain. It's a remarkable phenomenon, considering that so little is understood about how serotonin actually influences mood. "For more than 50 years, we've known that levels of serotonin in the brain are correlated to mood," says Dr. Ringstad. "But we still don't know a lot about how the brain regulates serotonin signaling. That's what motivates us to look at this very tiny organism."

That simple question—How does serotonin work?—led Dr. Ringstad to an unexpected discovery that has taken his research in a new direction. In trying to understand the tangle of signals that regulate serotonin and underlie so many psychiatric problems, he set upon a mysterious neuropeptide that binds to serotonin neurons and shuts them down. The finding raised two important questions: Where did the protein come from, and what's the purpose of an on/off switch for serotonin?

In a paper published in November 2013 in *The Journal of Biological Chemistry*, Dr. Ringstad and his colleagues describe a series of genetic experiments in which they trace the source of the protein to a set of novel sensory neurons, dubbed "BAG cells" because they have structures that resemble big, floppy bags dangling off the end of a long stalk. The cells cluster near the worm's nose, where they function as carbon dioxide detectors. Dr. Ringstad believes BAG cells may let worms sense

the carbon dioxide emissions of pathogenic bacteria. Too much carbon dioxide triggers the release of the serotonin-blocking neuropeptide and shuts down egg production. From an evolutionary perspective, the mechanism makes good sense. Why would a worm lay eggs only to watch its offspring be killed by pathogens?

"As soon as our studies of simple behaviors in the worm led us to carbon dioxide–sensing neurons, we got completely captivated with the problem of how a neuron detects carbon dioxide," Dr. Ringstad explains. "No one knows how this happens in mammals on a molecular level, and we didn't know how it happened in worms."

The finding challenges the prevailing theory of how brain cells detect carbon dioxide. When carbon dioxide reacts with water, it generates carbonic acid. The long-held belief is that neurons indirectly detect carbon dioxide by detecting this acid. "People say, 'Well, neurons are acid sensitive. So the way that carbon dioxide regulates any cell is by generating acid, '" Dr. Ringstad notes. "But what we found violates that dogma."

"We think that this simple worm model can help us understand how the nervous system monitors carbon dioxide and transduces it into a signal that the rest of the nervous system can interpret."

Dr. Ringstad's research shows that BAG cells detect carbon dioxide directly. Again, this makes sense evolutionarily: If you huff and puff and generate a lot of carbon dioxide, at some point you will generate too much acid, your blood pH will drop, and your entire body will suffer. So the sooner your brain detects rising carbon dioxide levels, the better. "It would be stupid to design a system that monitors the buildup of carbon dioxide but only sounds the alarm when levels become so catastrophically high that your blood pH starts to fall," explains Dr. Ringstad. "At that point, the house is on fire, and you're already in a world of pain."

For the worm, carbon dioxide sensing is a lifesaving adaptation. The question is whether a similar mechanism could be at play in humans. Surprisingly, little is understood about how brain cells monitor carbon dioxide levels in the blood and help regulate breathing. "We think that this simple worm model can help us understand how the nervous system monitors carbon dioxide and transduces it into a signal that the rest of the nervous system can interpret," says Dr. Ringstad.

Lucy Norcliffe-Kaufmann, PhD, and her colleagues at NYU Langone's Dysautonomia Center confront this problem daily. The center is one of only two clinics in the world that treat familial dysautonomia, a rare genetic condition that afflicts children. The disease impairs the body's autonomic nervous system, including sensory neurons that monitor carbon dioxide in the blood. "These kids lose their ability to control blood-gas homeostasis," explains Dr. Norcliffe-Kaufmann, assistant professor of neuroscience and physiology. "Many times, they lack the drive to breathe, so carbon dioxide levels in their blood can get very high, and they can die in their sleep."

Dr. Ringstad and Dr. Norcliffe-Kaufmann are eager to learn whether any of the molecules and mechanisms that Dr. Ringstad's laboratory uncovers might inform the work of the Dysautonomia Center. "Dr. Ringstad's research is extremely important because for people with rare diseases, there aren't many therapies," says Dr. Norcliffe-Kaufmann. "A discovery like this, which enables you to understand the properties of the nerve cells, gives you a chance to think about new therapies that can enhance breathing."

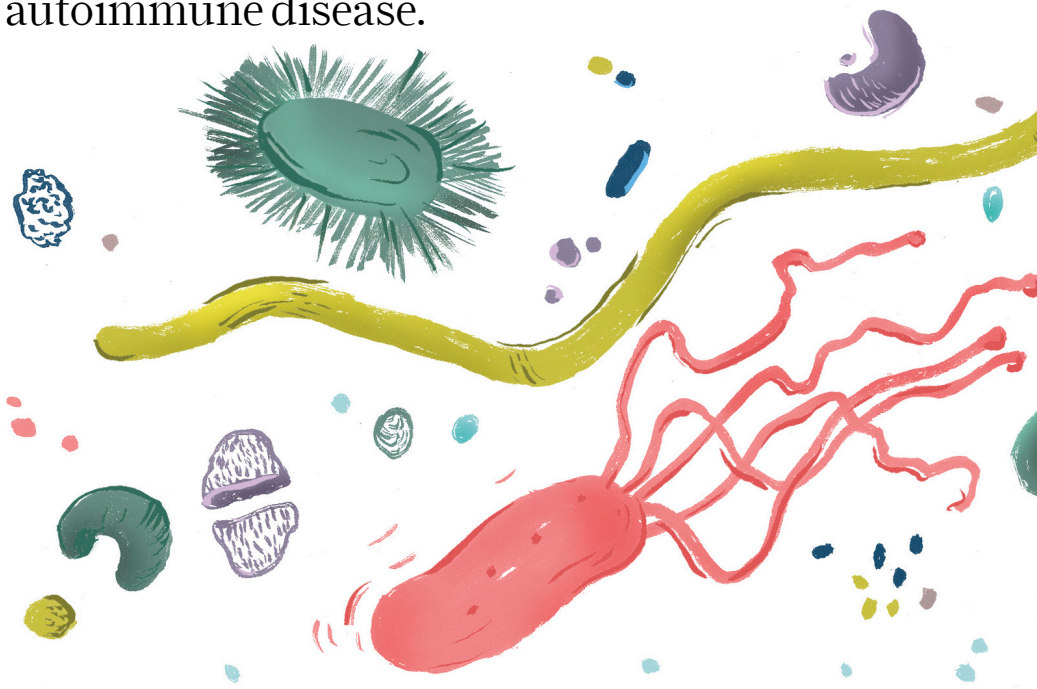
Among the books that sparked Dr. Ringstad's interest in biology were *The Lives of a Cell* and *The Medusa and the Snail* by Lewis Thomas, MD, who served as dean of NYU School of Medicine from 1966 to 1969. Dr. Thomas's award-winning books discussed basic biology through the lens of his clinical experiences. "I didn't appreciate it at the time," Dr. Ringstad acknowledges, "but when I think about those books now, I see the trajectory of basic knowledge turning into an understanding of how the world works, of changing the way people experience the world, and making the world better."

Dr. Ringstad recalls that back then, he thought cells were "cool little machines," and he wanted to understand how they worked. That hasn't changed much. He's still captivated by the mysteries of the cell, and grateful for a tool as powerful as the roundworm to explore them. "You realize that there are simple questions for which there are no satisfying answers," he says. "As basic scientists embedded in the medical community, our job is to run with those questions." ●

AT THE COLTON CENTER FOR AUTOIMMUNITY, THE MICROBIOME IS KEY

The new center will explore how the vast collection of microbes living on and in us may trigger autoimmune disease.

BY BRYN NELSON



BY SOME ESTIMATES, 50 million Americans suffer from lupus, rheumatoid arthritis, or one of the more than 80 other kinds of autoimmune disease identified so far. Although scientists have linked many of these diseases to genetic mutations, emerging research suggests that environmental factors may trigger much of the dysfunction that turns the body's immune system against itself.

A $10 million gift by philanthropists Judy and Stewart Colton to establish the Colton Center for Autoimmunity will allow researchers at NYU Langone Medical Center to explore whether a major culprit lies hidden within the human microbiome, the vast collection of microbes living on and in us.

"The microbiome has opened a whole new opportunity for discovery and for addressing this question in ways that we were never able to do," says Steven Abramson, MD, senior vice president and vice dean for education, faculty, and academic affairs; chair of the Department of Medicine; and director of the new center.

Our gut-dwelling microbial residents supply nutrients, help us digest food, and regulate our metabolism. More unexpectedly, some have been linked to the maintenance of a healthy immune system and to immune dysfunction when disrupted. Faster, cheaper, and more sophisticated molecular tools are now allowing researchers to identify these largely unknown bacteria in unprecedented numbers.

NYU Langone is a leader in microbiome research, and the Colton Center will bring together its immunologists, microbiologists, and rheumatologists to investigate how the microbiome interacts with specialized T and B immune cells to provoke autoimmunity. During its first phase, the Colton Center's researchers will identify and characterize the gut microbiome in patients with rheumatoid arthritis, lupus, and antiphospholipid syndrome (APS). During its second phase, the center's scientists and physicians will focus on translating the new discoveries into badly needed diagnostics, therapies, and preventive strategies.

The Colton family's ties to the Medical Center date back to the 1960s. Judy's uncle was eminent NYU Langone surgeon Lester Breidenbach, MD, in whose honor they established a loan fund for medical students, and Stewart has been a long-time patient of Philip Moskowitz, MD, the Mamdouha S. Bobst Associate Professor of Internal Medicine.

Previously, the Coltons also donated $1.5 million to support an asthma research program led by Joan Reibman, MD, director of the NYU-Bellevue Asthma Clinic, in honor of a daughter-in-law. Their latest gift again holds special meaning because one of their sons has battled a range of autoimmune diseases.

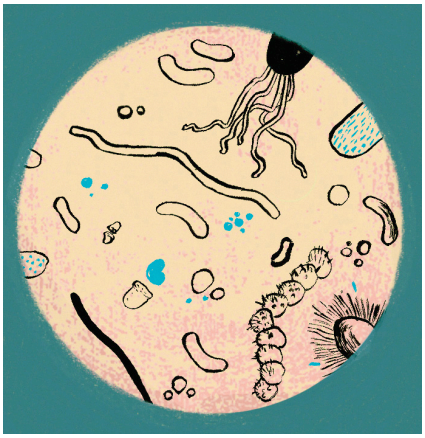
"We're pleased to be doing this, and we would love for it to nudge the field, hopefully sooner rather than later," Stewart Colton says.

As part of their donation to establish the new Center for Autoimmunity, the Coltons have funded a professorship that will allow the recruitment of another expert in autoimmunity and will continue the Colton Scholars program, established three years ago to support the research of early career physician-scientists. "This gift not only allows very targeted, focused discovery, but it also creates a hub that people studying other diseases can interact with," Dr. Abramson says. Research at the center, he explains, will help inform parallel investigations probing the potential links between the microbiome and diseases such as inflammatory bowel disease and diabetes.

At its core, though, the autoimmunity center will help NYU Langone researchers better understand a concept called preautoimmunity. "In other words, when does the process start?" says Jill Buyon, MD, one of the Colton Center's investigators and director of the Division of Rheumatology and the Lupus Center at NYU Langone. Some people, she says, have self-targeting antibodies circulating in their blood that are characteristic of lupus or rheumatoid arthritis, yet they remain symptom free.

"Our question is, can you find an environmental factor in the microbiome that explains why people have circulating antibodies but no disease?" says Jose Scher, MD, assistant professor of medicine and director of the NYU Microbiome Center for Rheumatology and Autoimmunity. Dr. Scher will coordinate the Colton Center's research with NYU Langone's rheumatoid arthritis patient population.

One of the center's main projects will be led by Dan Littman, MD, PhD, the Helen L. and Martin S. Kimmel Professor of Molecular Immunology and a Howard Hughes Medical Institute investigator. Dr. Littman's lab found that a gut microbe known as segmented filamentous bacteria, or SFB, might shape the immune system by influencing the development of specialized T cells. In collaboration with Dr. Abramson and Dr. Scher, his lab also found that a bacterial species called *Prevotella copri* is disproportionately common in patients with newly acquired rheumatoid arthritis.



"The microbiome has opened a whole new opportunity for discovery and for addressing this question in ways that we were never able to do."

Could *Prevotella* and other microbes activate specific T cells that promote inflammation and provoke autoimmune disease? The Colton Center's researchers plan to look for them among a larger group of rheumatoid arthritis patients using Dr. Buyon's SAMPLE (Specimen and Matched Phenotype-Linked Evaluation) biorepository for all patients with autoimmune or rheumatologic diseases.

Gregg Silverman, MD, professor of medicine and pathology, will lead another main project. His team will examine how gut microbes might trigger autoimmunity in lupus and APS patients through an abnormal activation of the immune system's B cells. "We want to characterize the fecal microbiome in at least 30 patients who have clinically defined lupus and APS, and compare them to controls," Dr. Buyon says.

The researchers plan to compare the microbiome patterns in patients with differing disease severities and levels of antibody production. Their findings may identify the warning signs of a disease flare-up. Eventually, such microbiome-associated biomarkers of disease could let doctors intervene before a troubled immune system becomes its own worst enemy. ●

ILLUSTRATIONS BY ANDREA ROSSI

"Love Your Children"

An Interview with Benard Dreyer, MD, President-Elect of the American Academy of Pediatrics

By Anastasia Toufexis

FOR MORE THAN FOUR DECADES, Benard Dreyer, MD, professor of pediatrics at NYU Langone Medical Center and director of the Department of Pediatrics at Bellevue Hospital Center, has tirelessly tended to children. "At an early age, I just fell in love with children and the magic of childhood," recalls Dr. Dreyer. Now, as president-elect of the 63,000-member American Academy of Pediatrics, he is set to become an ardent advocate for changes to policies that affect children's health and well-being. "One in five children in the U.S. lives in poverty," he notes, "and for those in the earliest years, the figure is one in four. This has an impact not only on children, but on their families and the nation." Dr. Dreyer recently shared his hopes for his tenure, as well as what he's learned from his years of practice.

PHOTO BY SASHA NIALLA

Why did you become a pediatrician?

I remember when I was 12 or 13 visiting one of my cousins, a 4-year-old girl, and being amazed and intrigued by how her mind worked—her imagination and language, and the way she viewed the world around her. I suppose that is when I began to view childhood as the "magic years" and wanted to be part of it.

Some physicians start out wanting to be pediatricians, but they can't bear to see children suffer. How do you deal with seeing children in distress?

I know that I can ease their suffering and help their family, as well, because a pediatrician is not only a child's doctor, but a family's. I find that very fulfilling. You know, people tend to view pediatricians as soft and mushy. But in fact, in my opinion, we're actually stronger and more rational than many other physicians. Pediatricians are very loving, but we also understand that children suffer and sometimes die.

It's often said that children are not small adults. In what ways do children need a special kind of care?

Well, there's the size difference, so the same concentration of toxins—say, from breathing polluted air—is just more toxic to them. The diseases that afflict them are also different. For example, children tend to have type 1 diabetes and adults type 2.

Pediatricians must "speak out in unison and declare that childhood poverty is unacceptable."

But childhood is a stage of continual change, which, of course, complicates care. There's this whole developmental trajectory on top of whatever the problem is. Managing a child with diabetes is very different from an adult doing self-management. You're working with a family that has to manage the child. But as the child gets older, his or her needs change. You involve the child more and more. Ultimately, the child is an adolescent who has to be taught to manage the disease herself.

Which health issues affecting children concern you most?

One of the problems right now is parents choosing not to immunize their children. It's the result of a number of things. The success of vaccines means that today's parents don't see many diseases. When I was a child, people were eager to get their kids immunized for polio or measles or anything because they saw the diseases. Now, we've pretty much eradicated those diseases, so parents are not afraid of them. They're more afraid of the vaccines. Most of that is due to science illiteracy. Parents don't understand science enough to understand what science shows us. We live in a society where there's access to a lot of information, so parents feel empowered to make their own decisions. That isn't bad, but you can't just pick and choose what you want to believe. You have to be able to tease out facts from emotions to make sound decisions. The recent measles outbreak in Disneyland is a lesson we need to learn from.

To what extent are many childhood illnesses the product of poverty?

Almost all childhood problems, including infant mortality, low birth weight, prematurity, and obesity, are related to poverty. Moreover, many chronic diseases are more frequent and more severe in poor children. If you look at kids who get admitted to the hospital with asthma, for example, they're almost never middle-class children. Poor children often live in environments that are more toxic, and their families are less educated, have less access to healthcare, and have fewer resources to manage chronic diseases. These children also have problems with academic achievement. By the time low-income children get to school, they're two to three years behind their middle-class peers, on average. The first two years of life are the most critical in terms of brain development—700 synapses form every second, and the brain triples in size. Children reared in poverty are more likely to drop out of high school and get into trouble with drugs, alcohol, and crime.

As the birthplace of modern pediatrics, how does Bellevue enrich pediatrics there and at NYU Langone?

These days we talk a lot about the "medical home." That's a pediatric concept invented in the early 1970s that has now become very important in healthcare reform. It means you don't just see patients for specific complaints, you take care of all their problems—medical, educational, and social. It's particularly important in managing chronic disease. We've employed that holistic model at Bellevue for many years, and NYU Langone will be expanding it with the construction of the Hassenfeld Children's Hospital within the new Kimmel Pavilion. The idea is to provide access to medical staff virtually 24/7 for all the needs of the child and family.

When your term as president of the American Academy of Pediatrics begins, what do you hope to accomplish as your unique and lasting contribution?

My big focus will be trying to do something in early childhood to help poor kids. There are good studies that show that we know what to do. We're just not doing it. The War on Poverty really worked. In the 1960s, childhood poverty dropped from 27 percent to 14 percent. We just didn't continue it.

Do you have specific goals you hope to meet while leading the academy?

Yes, I've laid out five. First, to mobilize pediatricians to speak out in unison and declare that childhood poverty is unacceptable. Second, to form coalitions with child advocacy organizations to promote change. Third, to advocate for the federal and state governments to better fund programs, such as food stamps and early childhood programs, which have been shown to help. Without these resources, instead of 20 percent of children living in poverty, it would be 33 percent. I'd also love to see an expansion of tax credits that affect children. A fourth goal is to enrich the education of medical students, residents, and fellows so that they gain a more in-depth understanding of the social determinants of childhood health. Finally, I'd like to see changes in the pediatrician's office, which is a great place to educate people on becoming better parents. One national program I'd like to see expanded is Reach Out and Read. We give books to parents at every well child visit up to five years of age. Four million children are now getting books from pediatricians, and studies show that it advances language development.

After so many years in practice, what is your best advice?

That's simple! Love your children every day, in every way. ●

Dr. Danny Reinberg Is Elected to the National Academy of Sciences

DANNY REINBERG, PHD, the Terry and Mel Karmazin Professor of Biochemistry and Molecular Pharmacology and a member of the Laura and Isaac Perlmutter Cancer Center, has been elected to the prestigious National Academy of Sciences.

Dr. Reinberg, who also is a Howard Hughes Medical Institute investigator, has spent three decades studying how the constituents of chromatin—DNA, RNA, and protein—impact gene expression. Among his notable achievements, Dr. Reinberg has isolated the mechanism that allows RNA polymerase II, the enzyme that transcribes genes, to move along DNA unobstructed by histones, the proteins that help DNA spool into a tight coil.

He and his collaborators were also the first to sequence the complete genomes of two ant species as part of a broader effort to understand the molecular machinery that turns genes on and off, and influences protein expression. These so-called epigenetic changes, Dr. Reinberg's lab has found, account for many of the striking differences in longevity and behavior among different castes of ants. A queen ant, for example, can live for 25 years, depending on its species, while a worker ant might die within 2 years.

Dr. Reinberg's insights into epigenetics hold promise for therapeutics that could potentially silence disease-causing genes and proteins.

Dr. Reinberg was inducted into the American Academy of Arts and Sciences class of fellows in 2012. He was also elected into the Institute of Medicine and has received an NIH Merit Award and a Faculty Research Award from the American Cancer Society. He has authored or coauthored more than 230 scientific papers and coedited an authoritative textbook on epigenetics.

Dr. Martin Blaser Makes *Time* Magazine's List of Most Influential People

FEW RESEARCHERS HAVE DONE more to expose the dangers of antibiotic overuse than Martin J. Blaser, MD, the Muriel and George Singer Professor of Medicine and director of NYU Langone Medical Center's Human Microbiome Program. This year, in tribute to his pioneering research on the role of bacteria in human health and disease, *Time* has named Dr. Blaser among its top 100 most influential people.

"Blaser's work is a stunning dose of reality in an environment flooded with corporate-agenda-fulfilling pseudoscience," Congresswoman Louise Slaughter, the lone microbiologist on Capitol Hill, wrote in *Time*. Slaughter calls Dr. Blaser "an incredibly important voice" on the alarming rise of bacterial superbugs and the link between antibiotics and modern plagues such as obesity, asthma, allergies, and diabetes.

In the past three decades, Dr. Blaser has tirelessly advocated for better bacterial stewardship, bringing to light the hidden ecosystem of bacteria that maintains the health and balance of our bodies. At a time when scientists were calling for the eradication of *Helicobacter pylori*, a gut bacterium that causes peptic ulcers and gastric cancer, Dr. Blaser's research suggested that *H. pylori* prevents disease as well as causes it. Children without *H. pylori*, he found, were more likely to develop asthma, hay fever, or skin allergies. More recently, Dr. Blaser has shown how excessive antibiotic use in childhood increases the risk of obesity and type 2 diabetes, as well as inflammatory disorders such as type 1 diabetes, asthma, psoriasis, and skin infections.

Dr. Blaser is a member of the Institute of Medicine, a fellow of the American Academy of Arts and Sciences, and author of *Missing Microbes: How the Overuse of Antibiotics Is Fueling Our Modern Plagues.* ●

PHOTO BY MIKE WEYMOUTH; PHOTO BY ANDREW NEARY

OBITUARY

Joseph Herbert, MD

JOSEPH HERBERT, MD, 65, professor of neurology and founder and director of the Multiple Sclerosis (MS) Comprehensive Care Center at NYU Langone Medical Center, died January 2, at home surrounded by family, after a 10-year battle with cancer.

Beloved for his kindness and gentle manner, Dr. Herbert built the MS center over two decades. A model of patient-centered care, today the center provides medical, nursing, physical therapy, and psychosocial support for 2,500 MS patients annually while maintaining an active and vigorous research program.

"He had a dream of a multidisciplinary MS center with everything under one roof," recalls Lisa Laing, RN, the center's nurse coordinator. She began working for Dr. Herbert 20 years ago, after he established an inpatient neurorehabilitation unit at the Hospital for Joint Diseases, before it became part of NYU Langone Medical Center.

Always interested in the social and emotional well-being of his patients, Dr. Herbert asked how they spent their days and taught staff to ask, says Laing. "I once had a patient tell me she watched TV or counted the tiles on the ceiling. When you hear someone say that, you realize you need to do more than just take care of the immediate needs of MS—you need to make referrals and get that patient out of the house."

Ilya Kister, MD, assistant professor of neurology, who started with the center in 2006 as a fellow of Dr. Herbert's, says, "MS was not part of his initial focus, but he was encountering a lot of MS patients on the wards. It's one of the leading causes of disability in young people." Always an innovator, Dr. Herbert tried various strategies, combining treatments, using whatever he thought would work. "He was very interested in patients and their stories, very empathetic, and they responded to that," says Dr. Kister. "He was just very level with patients, and that's how he was with colleagues and trainees."

Born in South Africa, Dr. Herbert immigrated with his family to Israel, where he graduated from the Hebrew University Hadassah Medical School in Jerusalem and served as a physician in the Israel Defense Forces. He moved to the United States to pursue a neuropathology fellowship at Harvard Medical School and then took a research position at Columbia University. His work on transthyretin, a transport protein produced in small amounts in the brain's choroid plexus, won him the 1986 S. Weir Mitchell Award for young researchers from the American Academy of Neurology.

Even after becoming a full-time clinician, Dr. Herbert never lost interest in research. He received the Research Award of the National Association of Rehabilitation Facilities for the study of desmopressin, or DDAVP, in the management of nocturia in MS. (DDAVP is the synthetic replacement for vasopressin, the hormone that reduces urine production.) Recently, he was engaged in implementing the MS Severity Score as a clinical tool, investigating ethnic variability among people with MS, and developing a new bedside disability scoring system for MS, among other projects.

A founding member of the New York State MS Consortium in 1994, Dr. Herbert served on its executive finance and scientific review committees. In 2006, he joined the International MSBase Registry, maintained in Australia, and became a member of the MSBase Scientific Leadership Group in 2012.

Joseph Herbert, MD

Clinically, he focused on refining the use of FDA-approved MS treatments, and under his leadership, the center participated in a wide variety of national and international multicenter clinical trials of experimental treatments.

Only a handful of his colleagues and patients knew he was ill. Ten years ago, he underwent successful treatment for colon cancer, but it returned at the five-year mark. "It meant that he was on chemo almost all of the last five years," Laing says. "He came to work with a port and a chemo bag in an inside pocket. The patients never knew." He continued to see patients up until last July.

Dr. Herbert is survived by his wife, Bette; their children, David, Shira, Adina, Adam, Joshua, and Elana; and six grandchildren. ● *—AUBIN TYLER*

Preparing for Ebola in Ghana

BY SARI SOGHOIAN, MD

"EBOLA SHOULDN'T COME," they said. "If it comes, we will run away." As the clinical coordinator for emergency medicine at Korle Bu Teaching Hospital in Accra, Ghana, a major hospital in West Africa, it was my job to mobilize our departmental response in advance of a potential Ebola outbreak here. The task was overwhelming. We lacked space for individual patient isolation, equipment for personal protection, reliable systems to investigate and monitor suspects, and staff who were willing to participate in training or the effort to organize. The situation made everyone fearful, and for many, it was unthinkable that we should manage a case.

In the last week of July 2014, just after Nigeria reported its first Ebola case, we heard that a much-loved physician who recently finished training at our hospital had died of the disease in Sierra Leone. Suddenly the epidemic felt very close to home, geographically and emotionally. That evening, we admitted a man for hematemesis [vomiting blood] after several days of fever, diarrhea, and abdominal pain. The team on duty panicked. Staff fled the male ward, abandoning all 10 patients there overnight.

The next day, I asked the patient how he was doing. "I'm embarrassed," he said. We had isolated him in the male ward pending Ebola test results, and no one wanted to enter the room. (The results turned out to be negative.) He was still sick and in pain, but stigma was his chief complaint. I asked our head nurse how the staff was doing. "We're embarrassed," she replied. The fear was still there, but now also a deep sense of failure. I learned that day that emergency preparedness with limited resources involves not only the technical challenge of identifying and managing potential cases, but also—and just as important—building support for staff to maintain their professional ethics in the face of fear, uncertainty, and personal risk.

Many of our team members are the sole breadwinners or primary caretakers for their families. None have disability or life insurance. No hazard pay or facilities for self-quarantine were being offered. "I am a widow. I have two young children. What will happen to them if I get Ebola?" asked one nurse. Others expressed concerns about receiving care if they were exposed. "Our experience is that we come to work every day, but when we get sick, hospital management doesn't make any provision for us."

These fears and a widespread sense of demoralization were compounded by an ongoing cholera epidemic that overwhelmed the health system and affected more than 20,000 patients in the capital, Accra, alone from June to October 2014. "If we can't handle cholera, how can we be prepared for Ebola?" staff members asked.

To address the epidemic, faculty from NYU's Global Institute of Public Health, NYU School of Medicine, and NYU's Center for Technology and Economic Development convened a roundtable at the NYU Accra campus last October. Our purpose was to identify what is needed to protect healthcare workers and the public in Ghana, a nation without Ebola cases but where the risk is high. Since then, we have made progress. Donations of personal protective equipment from NYU, Henry Schein, Inc., and the mining company Newmont, for example, have provided a measure of security and allowed us to conduct training in donning and doffing procedures.

Innovations have appeared. We wrap cloth blood-pressure cuffs in washable plastic covers, create hand-washing stations out of garbage cans, mixing stronger bleach solutions. Staff volunteer to manage cases and give input on protocol design.

Of course, even with the crisis waning, there is much work yet to be done. Staff needs more practical training and oversight to solidify changes in infection-control practice. Supply chains and financing for gloves, masks, and other materials must be developed. Interruptions in power and water are still routine, and 70 percent of Accra's population still has no access to plumbing. We still have our fear.

It will take considerable and long-term commitment to raise standards of hygiene in healthcare facilities and communities, build mechanisms for better collaboration, and engage stakeholders in creating the needed local solutions. The Ebola epidemic crystallizes and provides an unprecedented opportunity to support progress on these long-standing issues of critical importance to local and global health. ●

Sari Soghoian, MD, assistant professor of emergency medicine at NYU School of Medicine, has been working in Ghana for three years.

Dr. Harris with some of his tutorial students.

Jon Simon

Changing the World

Compulsory government service in a postwar Korea M.A.S.H. unit interrupted the NYU/Bellevue residency of Matthew Harris, MD, but it also ended up bringing the talented young surgeon "home."

"I was having doubts about continuing my residency," says Dr. Harris, "but then John H. Mulholland, MD, the legendary chair of NYU Langone's Department of Surgery arrived—he was a U.S. Army Inspector General. It was a serendipitous moment. Dr. Mulholland convinced me to return to my residency."

MATTHEW N. HARRIS, MD

Dr. Harris became a highly respected NYU School of Medicine (NYU SOM) professor and surgical oncologist. Though now retired, he continues to teach a second-year student surgical tutorial. A scholarship student when he attended medical school, Dr. Harris is also dedicated to helping today's students complete their educations.

This grandfather of six and his wife, Frances, have contributed an IRA rollover and made a bequest in their estate to fund the Matthew N. Harris, MD, Scholarship Fund at NYU SOM. Says Dr. Harris, "So many well-qualified students are hampered by lack of funds, and it's up to us to make sure they have the opportunities they have earned."

You, too, can also help today's bright young students become the physicians they were meant to be with a planned gift to support scholarships or other programs at NYU School of Medicine. For more information, contact Marilyn Van Houten, senior director, Office of Development and Alumni Affairs, at 212-404-3653 or Marilyn.VanHouten@nyumc.org.

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