NYU PHYSICIAN
THE MAGAZINE OF NEW YORK UNIVERSITY SCHOOL OF MEDICINE
FALL 2014

A FRESH START

Fecal microbiota transplants may help desperately ill patients reclaim their lives.

PLUS

KETAMINE FOR SEVERE DEPRESSION?
SLEEPING FRUIT FLIES
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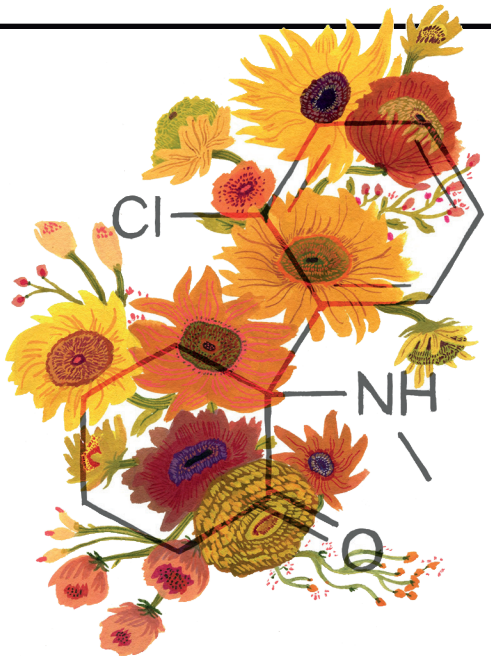
FALL 2014

NYU PHYSICIAN

ON THE COVER:
ILLUSTRATION BY
JOHN TOMAC



Ketamine was developed as a fast-acting general anesthetic in the early 1960s.

COVER STORIES

DEPARTMENTS

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ILLUSTRATION BY BECCA STADTLANDER

Paradigm Shifts

Among the elderly who are sick and worn down by antibiotics, *Clostridium difficile* remains a deadly threat.

One of the most common infections in hospitals and other healthcare facilities nationwide, the bacterium wreaks havoc on the gastrointestinal system, causing violent diarrhea and inflammation of the colon. It kills some 14,000 people annually. Unfortunately, it is now making alarming inroads among younger, healthy people who have not been exposed to healthcare facilities.

This issue of the magazine examines a promising therapy for severe and recurring *C. diff* that is so counterintuitive that it borders on the preposterous. Yet fecal microbiota transplants are yielding astoundingly high cure rates. The therapy has also inspired heated interest in the notion of "dysbiosis," disease caused by the disruption of the normal microbiota within the colon. Although it is still early days, and much testing and careful study is certainly needed before victory is declared, the cure for *C. diff* and a host of other diseases might very well lie in the restoration of the teeming microbial populations in our bodies.

This is potentially paradigm shifting, a term coined by science historian and philosopher Thomas Kuhn to describe how revolutions in science occur. He once wrote that scientists, led by a new paradigm, "see new and different things when looking with familiar instruments in places they have looked before. It is rather as if the professional community had been suddenly transported to another planet where familiar objects are seen in a different light and are joined by unfamiliar ones as well."

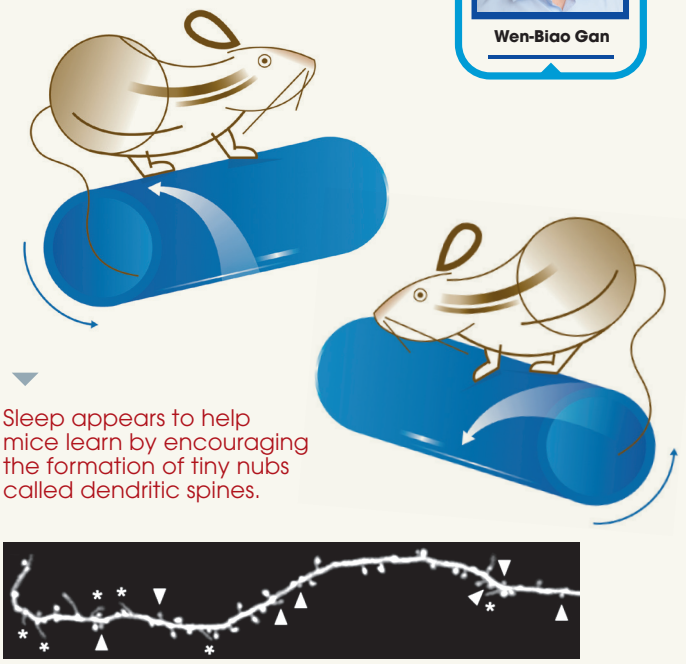
It seems as if such a transformation is occurring today in the treatment of *C. diff* and, possibly in the years ahead, many other diseases. Only time will tell.

DEAN & CEO ROBERT I. GROSSMAN, MD

PHOTOGRAPH BY
JOHN CARNETT

A Window onto the Slumbering Brain

A new study reveals why sleep improves memory, at least in mice.



Sleep appears to help mice learn by encouraging the formation of tiny nubs called dendritic spines.

MICROSCOPY IMAGE COURTESY OF DR. WEN-BIAO GAN

Why does a good night's sleep sharpen our memory and make us better learners, and a bad night's sleep render us dull as a butter knife. What happens inside the brain when we sleep—or don't sleep—that affects our cognitive powers during the day? In a study published in June in *Science,* Wen-Biao Gan, PhD, professor of neuroscience and physiology; Guang Yang, PhD, assistant professor of anesthesiology; and colleagues at NYU Langone Medical Center's Skirball Institute of Biomolecular Medicine offer an exciting new clue.

Peering inside the brains of slumbering mice, the researchers discovered that sleep after learning encourages the growth of specific dendritic spines. These tiny protrusions from brain cells connect to other brains cells via synapses, the junctions at which brain cells meet, and facilitate communication. Lack of sleep, on the other hand, inhibits the formation of these connections.

Their findings offer the first direct evidence that sleep stimulates connections between brain cells in the motor cortex, a brain region responsible for voluntary movements and motor memory. "Some people believe that sleep down-regulates synapses, and neurons get pruned," says Dr. Gan, the study's senior author. "But our evidence shows just the opposite. Sleep actually helps neurons form very specific connections that may facilitate long-term memory."

Documenting structural changes in the brain cells of living animals is a challenge, but Dr. Gan's laboratory has surmounted that challenge with a technique called transcranial two-photon microscopy. It uses infrared lasers to peer deep into the brains of mice genetically engineered to express fluorescent proteins. In the new study, motor cortex dendrites were tagged with yellow fluorescent proteins. When viewed with the microscope, these proteins glow, allowing the scientists to track and image the growth of dendritic spines along individual branches of dendrites.

The imaging was performed before and after mice learned how to balance on a spinning rod, a test of motor learning and memory. In one experiment, the researchers trained two sets of mice on the rod. The first group trained for an hour and then slept for seven hours. The second group trained for the same amount of time but stayed awake for seven hours. The scientists found that the well-rested mice experienced significantly more dendritic spine growth than the sleep-deprived mice.

Intriguingly, they also found that the type of task learned determined on which dendritic branches spines would grow. Running forward on the spinning rod, for instance, produced spine growth on different dendritic branches than running backward on the rod. Dr. Gan likens this growth to a tree that sprouts leaves (spines) on one branch but not another. "Now we know that when we learn something new, a neuron will grow new connections on a specific branch," says Dr. Gan.

Previous studies in the hippocampus, a brain region critical for memory, have established that tasks learned during the day replay during a stage of deep sleep known as slow-wave sleep, when brain waves slow down, and rapid eye movement and dreaming stop. This nocturnal replay is believed to consolidate and strengthen memories. The NYU Langone researchers confirmed that this same phenomenon occurs in the motor cortex and that disrupting it prevents dendritic-spine growth. "Our data suggest that neuronal reactivation during sleep is quite important for growing specific connections within the motor cortex," says Dr. Gan.

On the practical level, it's also quite important for anyone aspiring to learn a new move, whether it's a dance step or a tennis swing. Practice won't make perfect. Practice plus sleep does the trick. ● *—NICOLE DYER*

ILLUSTRATIONS BY **LEANDRO CASTELAO**

Power in Numbers

The bacterial hordes in our gut may shape the immune system.

Dan Littman

The roughly 100 trillion microbes that live within our intestinal tract, or our resident microbiota, help digest food, ward off dangerous pathogens, and most intriguing, hone the immune system.

Researchers have known for several years that a certain immune specialist called a T-helper-17 (Th17) cell protects the lining of the gut from invasion by disease-causing bacteria. However, this immune cell also has a decidedly insalubrious dimension. It can promote inflammation, spurring autoimmune diseases such as rheumatoid arthritis, psoriasis, Crohn's disease, and even multiple sclerosis. "How our microbiota can influence that autoimmunity is really the big mystery," says Dan Littman, MD, PhD, the Helen L. and Martin S. Kimmel Professor of Molecular Immunology and a Howard Hughes Medical Institute investigator.

A recent study in *Nature* by Dr. Littman's lab has revealed some important new clues. The research in mice details how the presence of a specific gut microbe known as segmented filamentous bacterium, or SFB, impels precursor immune cells to become Th17 cells. "SFB are generally beneficial or harmless microbes that can shape the specificity of the cells of the immune system as well as the function of the cells of the immune system," Dr. Littman says. Other researchers have found evidence of SFB colonization within the human gut as well, particularly in infants, and other microbes may use similar mechanisms to influence immune development.

Rod-shaped *E. coli* bacteria are a normal part of the gut's microbiota.

Understanding how SFB and these other gut-dwelling microbes exert their influence could allow researchers to similarly manipulate the immune system in ways that strengthen defenses or prevent inadvertent autoimmune attacks.

Dr. Littman's lab first linked the bizarre-looking SFB, which sports long hairlike filaments, to Th17 activation in mice in a 2009 study. Although the normally benign bacterium may be able to sense the local microbial flora within the small intestine and warn the immune system of disruptions, the lab's research suggested that it can also trigger an excessive inflammatory response that leads the body to attack its own tissues.

In the new study, the researchers found that most Th17 cells carry receptors that specifically recognize proteins, or antigens, studded across the outer surface of SFB cells. Other specialized immune cells, called T-helper-1 cells, failed to recognize these SFB antigens but did respond to surface proteins on *Listeria monocytogenes* bacteria.

The type of bacterium producing the antigen, in other words, likely determines the eventual identity of immune cells, a potentially paradigm-shifting observation. "This is showing us that there are commensal bacteria that basically have a dialogue with our immune system and can tell the immune system, 'OK, make a T-cell response against my bacterial antigen,'" Dr. Littman says.

Other microbes may have a similar effect. Dr. Littman and colleagues recently found that a bacterial species called *Prevotella copri* exists in the gut flora of about 75 percent of patients with newly acquired rheumatoid arthritis, but only in about 21 percent of healthy volunteers. One hypothesis, he says, is that this microbe may behave like SFB by activating specific T cells that promote inflammation and provoke autoimmune disease.

Researchers can now ask whether people with a predisposition to autoimmune diseases have a subset of inflammation-causing T-helper cells that have been goaded into action by specific gut microbes. If so, scientists might be able to design drugs that prevent the development of these T cells, potentially blocking their ability to spur autoimmunity throughout the body. ●

—BRYN NELSON

SPL / SCIENCE SOURCE

Amyloid-Reducing Compound Shows Promise

A pill a day to keep dementia at bay?

Martin J. Sadowski

Clinical trials of drugs to delay the progression of Alzheimer's disease by reducing the amount of amyloid beta in the brain have failed to stop or even significantly slow the course of dementia. Other processes that destroy brain cells are now seen as the main culprits in the final inexorable slide into dementia, which helps explain why reducing amyloid beta at that late stage is ineffective.

"The key is to prevent the disease process from getting to that late stage," says Martin J. Sadowski, MD, PhD, associate professor of neurology, psychiatry, and biochemistry and molecular pharmacology. The ideal way to do that, he believes, is with a daily amyloid-reducing drug, like the cholesterol-lowering statin drugs now used to lower the risk of heart attacks and strokes.

In a recent report in *Annals of Neurology*, Dr. Sadowski and his colleagues identify a promising molecule from a library of compounds provided by a company called Aria Neurosciences, based in Hamden, CT. The compound, 2-PMAP, reduced levels of amyloid in the brains of transgenic mice by 50 percent. "It's nontoxic in mice, gets easily into the brain, and lowers the production of amyloid beta and associated amyloid deposits," he says.

Dr. Sadowski's team found that the compound inhibits the production of amyloid beta's mother protein, known as amyloid precursor protein (APP). The APP molecule can be cut by cellular enzymes in different ways; one leaves amyloid beta as a fragment. Dr. Sadowski's team found that 2-PMAP, even at low concentrations that show no trace of toxicity, reduced amyloid levels by 50 percent or more in test cells and in mice engineered to get an Alzheimer's-like condition. Just four months of treatment blocked most of the insoluble amyloid deposits and prevented the cognitive deficits that are normally seen in such transgenic mice as they age.

Aggregates of amyloid beta accumulate slowly over decades before clinical symptoms of Alzheimer's appear. Modestly lowering its production in middle age, some researchers argue, may prevent or at least minimize deposits and thus prevent or delay dementia. An apparent proof of this concept emerged in 2012 from a study of a large sample of elderly Icelanders. Those carrying a gene variant that halved amyloid beta production experienced a slower cognitive decline in old age, lived longer, and had almost no risk of Alzheimer's even into their 90s.

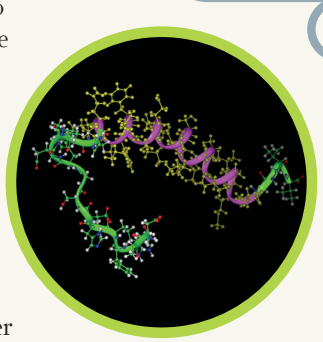
The results of trials using therapies to reduce amyloid in dementia patients with dense deposits have been dismal. Antibodies targeted to the protein, for example, have caused inflammation and brain swelling. Drugs designed to block enzymes that produce the protein have been plagued by undesirable, off-target effects on other proteins. A clinical trial of one such enzyme inhibitor was halted in 2010 after it appeared to worsen dementia and cause a higher incidence of skin cancer.

"What we want is a drug that modestly lowers amyloid beta and is also safe for long-term use," Dr. Sadowski says. Alzheimer's disease, the most common form of dementia, currently afflicts more than 5 million Americans, and the prevalence is expected to triple by 2050 unless preventive drugs or treatments are developed.

Other NYU Langone Medical Center researchers contributing to the study were lead author Ayodeji A. Asuni, PhD, research assistant professor of neurology and psychiatry, who performed most of the experiments; Maitea Guridi, MSc; Joanna E. Pankiewicz, MD, PhD; and Sandrine Sanchez, PhD.

A patent was recently issued for 2-PMAP to NYU School of Medicine and Aria Neurosciences. The School has licensed its interest in the patent to the company. ●

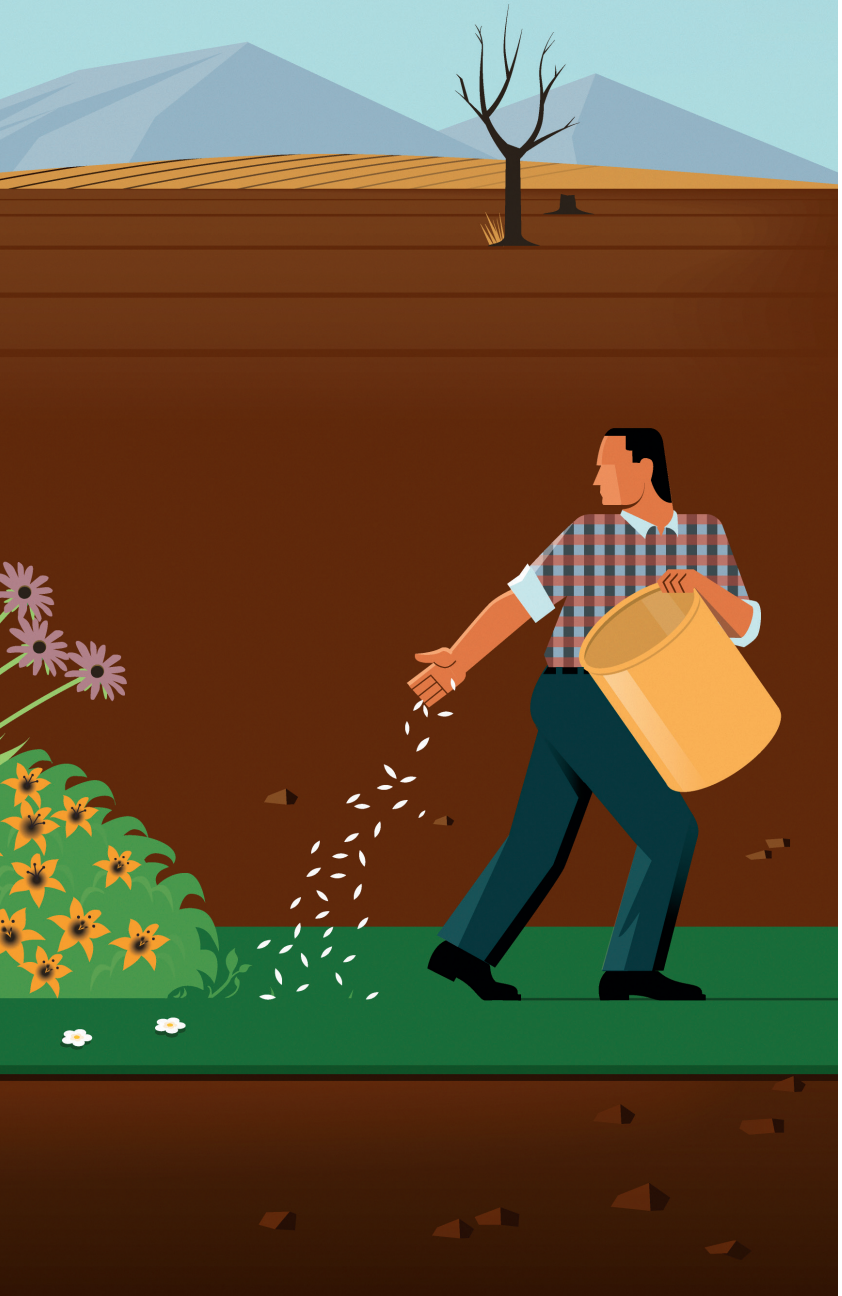
—JIM SCHNABEL



Amyloid beta accumulates in the brain years before symptoms of Alzheimer's appear, but isn't always linked with the disease.

LEONARD LESSIN / SCIENCE SOURCE

A FRESH START



WHEN ANTIBIOTICS MOW THROUGH THE HUMAN GUT, FECAL MICROBIOTA TRANSPLANTS CAN SOW NEW SEEDS, RESTORING WHAT'S LOST.

BY NICOLE DYER
ILLUSTRATION BY JOHN TOMAC

SHALOM LEVY WAS AN EASY MARK FOR THE DEADLY BACTERIUM *CLOSTRIDIUM DIFFICILE.* THE 87-YEAR-OLD GREAT-GRANDFATHER WAS ALREADY WEAK FROM A PROLONGED BATTLE WITH ORAL CANCER AND HAD STOPPED EATING SOLID FOODS AFTER RADIATION MADE HIS TEETH FALL OUT. THEN, IN THE WINTER, HE CONTRACTED PNEUMONIA.

"They pumped him full of antibiotics to get rid of it," says his son and caretaker, Ilan Levy, who lives with his father in Flushing, Queens. The medication, though successful, was debilitating. Shalom, a former jewelry repairman and designer, now spent much of his time in hospitals and rehabilitation facilities—places where *C. difficile* thrives.

Levy was at his most vulnerable when he contracted *C. difficile* that following July, possibly during another stint in rehab. The pathogenic bacterium preys on an estimated 3 million people in the U.S. every year, most of whom are too sick and worn down by antibiotics to fight off an otherwise innocuous bug. "*C. difficile* is a competitively weak organism and doesn't cause disease most of the time," says Ilseung Cho, MD, MSc, assistant professor of medicine at NYU Langone Medical Center and an expert on gut bacteria and human pathology. Yet there's nothing weak about it once it gains a foothold: *C. difficile* kills about 14,000 people annually. Levy dropped from 150 pounds to 120 pounds in two weeks, withered by constant and violent diarrhea. Though his dementia made communication difficult, "he could tell me when he was in pain," his son says. "And he was in a lot of pain."

The first round of antibiotics did nothing. So his doctors escalated to stronger and stronger antibiotics. Levy recovered, but his relief was short-lived. By September, the *C. difficile* had roared back. He went on antibiotics again. He recovered again. But by November, the infection had returned like a bad dream. "All hell broke loose on Thanksgiving," says Ilan, who didn't need a doctor to know what they were dealing with. "By then, I knew the smell and texture," he says. "It was horrendous."

Levy had no choice but to go back on antibiotics, even though the medication was destroying him. "Every time my dad was on antibiotics, he got weaker and weaker," his son says. "I felt like we were torturing him."

Fortunately, there was promising alternative. Ilan's nephew, a nurse at NYU Langone, told him about a treatment offered at the Medical Center for severe recurring cases like his dad's. Called fecal microbiota transplant, or FMT, the procedure involves transferring healthy human feces into the colon of people infected with *C. difficile*. The idea, he learned, was to reestablish the beneficial strains of bacteria that normally keep *C. difficile* in check.

Poop to cure diarrhea? Ilan thought the idea sounded a little bizarre, but after everything he and his father had been through, he wasn't fazed. Forget about the ick factor. He was simply grateful to learn of an alternative to the grueling cycle of antibiotics. "I knew that another outbreak would kill him," Ilan says. He immediately scheduled an appointment with Lea Ann Chen, MD, a clinician-researcher and instructor in the Division of Gastroenterology at the Medical Center, to see if his father was a candidate.

Ilan Levy had an open mind about FMT, but not everyone has been as receptive. The procedure is controversial, and understandably so. Human stool is generally filthy stuff. Poop harbors parasites, viruses, and pathogenic bacteria, including groups like coliforms and streptococci, which are used as indicators of sewage contamination. Salmonella and certain strains of *E. coli* can land you in the hospital.

Gastroenterologist Dr. Mark Pochapin had to convince himself that fecal microbiota transplants would work. The concept of human stool as a therapeutic medication, he says, "was just beyond anything I would have considered in my field."

PHOTO BY JOHN ABBOTT

Researchers are only just beginning to understand all the living matter within human feces. An average sample of it contains between 400 to 1,000 different bacterial species, says Dr. Cho, and the lower gastrointestinal tract harbors one of the densest bacterial ecosystems known in nature. Many groups of bacteria found there are believed to be benign or beneficial, helping the body break down food, boost immunity, and kill pathogens. But relatively little is understood about how individual strains cause or prevent disease. Consequently, the Food and Drug Administration has taken a cautious stance, restricting FMT to only those patients with *C. difficile* who have failed antibiotics.

The results among such patients have been encouraging, however. Small trials conducted worldwide over the past few years consistently show a 90 percent cure rate. One study, performed in the Netherlands and published last year in *The New England Journal of Medicine*, found that fecal transplants cured 15 of 16 *C. difficile* patients, while antibiotics alone cured only 3 of 13 patients. Indeed, FMT was so successful that the trial was halted to allow all volunteers access to the better treatment.

Mark Pochapin, MD, the Sholtz/Leeds Professor of Gastroenterology and director of the Division of Gastroenterology at NYU Langone, has witnessed similar results in his own practice. He first began using FMT two years ago. While Dr. Pochapin supports the concept of probiotics to help restore healthy bacteria in the gut, he was initially leery of treating his patients

WHILE IT MAY BE HARD TO CURB ENTHUSIASM FOR A MEDICAL THERAPY WITH A 90 PERCENT CURE RATE, EXPERTS ARE QUICK TO ACKNOWLEDGE THAT FMT IS STILL IN ITS INFANCY.

with human feces. "It's one thing to try a new treatment, but to think of stool as a therapeutic medication was just beyond anything I would have considered in my field," he says. "I really had to convince myself that it would work."

His first patient was an elderly woman who had struggled with *C. difficile* for a year. "We couldn't get rid of it," he says. "She was miserable." Dr. Pochapin took a stool sample from the patient's husband; screened it for parasites, viruses, and pathogenic bacteria; screened the husband for communicable diseases like HIV, hepatitis, and syphilis; and then transplanted the processed stool sample into the patient's colon during a colonoscopy. Dr. Pochapin was amazed by his patient's response. "She started to feel better almost the next day." The infection never came back.

Dr. Pochapin went on to successfully treat five more *C. difficile* patients with FMT. Only one required a second transplant, which Dr. Pochapin attributed to complications from irritable bowel syndrome, a complex gastrointestinal disorder. He would have treated more patients had it not been for an FDA decision in May 2013 to begin regulating human feces as an investigational new drug, a move that saddled clinicians with time-consuming paperwork. (The FDA has since announced that it would not enforce this new regulation for *C. difficile* treatments while it reconsiders its stance on the therapy.) Today, Dr. Pochapin refers FMT candidates to Dr. Chen, who has worked with him and others at the Medical Center to establish a formal protocol for FMT based on standards set by the American Gastroenterological Association.

It was Dr. Chen who delivered the good news to Ilan last fall: his father qualified for the transplant. The only question was where to find the feces.

When the Scottish microbiologist Alexander Fleming discovered penicillin, the first antibiotic, in 1928, the notion that bacteria could cause disease was only just beginning to gain widespread acceptance among the American medical community. As late as the mid–nineteenth century, sepsis infection, often spread through unsterile surgical equipment and bare hands, accounted for more than 50 percent of postoperative deaths. President James A. Garfield's physicians, who dismissed antiseptic practices as quackery, repeatedly wedged unwashed fingers into his back to try to find the bullet that lodged near his spine after an assassination attempt in 1881. The president might have survived had he not developed a massive blood infection.

Of course, a lot has changed in the intervening 133 years. Today, antibiotics are among the most commonly prescribed medications. The drugs have saved countless lives. Yet we often receive them whether we need them or not. The Centers for Disease Control and Prevention estimates that up to 50 percent of antibiotic prescriptions are unnecessary or ineffective as prescribed. As a result, an estimated 2 million people in the U.S. become infected with bacteria that are resistant to antibiotics every year; about 23,000 of them die.

Over the past two decades, Martin Blaser, MD, the Muriel G. and George W. Singer Professor of Translational Medicine, director of the NYU Human Microbiome Program, and professor of microbiology at NYU School of Medicine, has led a growing chorus of researchers who contend that antibiotic overuse isn't just robbing us of a lifesaving medical tool, but it's also wreaking havoc on the invisible ecosystem of microbes that populate every inch of our body, known collectively as the microbiome. The rise of antibiotics, which kill off good and bad bacteria alike, may be linked to the dramatic rise in diseases such as obesity, type 1 diabetes, inflammatory bowel disease, allergies, and asthma. "Everyone thinks that antibiotics are biologically free, meaning you get over a bacterial infection and you're fine," says Dr. Blaser, who recently published a book on the subject called *Missing Microbes: How the Overuse of Antibiotics Is Fueling Our Modern Plague*s. "But *C. difficile* is a clear indication that there is a biological cost."

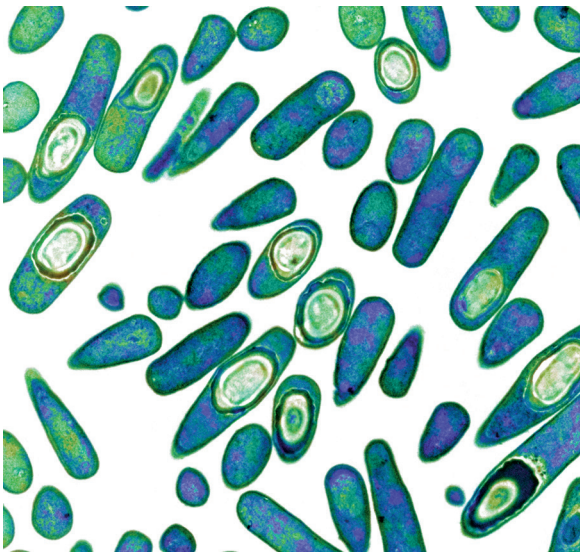
Dr. Blaser's team was among the first to recognize that the long-vilified *Helicobacter pylori*, a gut microbe implicated in peptic ulcers and gastric cancer, might not be so evil after all. In what has become known as Blaser's Hypothesis, he and his colleagues have found evidence that wiping out *H. pylori* with antibiotics disrupts the production of stomach hormones ghrelin

and leptin, which may, in turn, increase susceptibility to acid reflux and esophageal cancer. Moreover, they've discovered that children without the bacterium in their stomachs are more likely to develop asthma, hay fever, or skin allergies. "As a biologist, I began to wonder how an organism that's been around for so long could be all bad," recalls Dr. Blaser. "We began to make linkages with diseases of the esophagus that have been rising dramatically as *H. pylori* has been falling."

The research spurred others to start exploring how gut bacteria influence health. Dr. Cho, a protégé of Dr. Blaser who now has his own laboratory, found that gut microbes play a significant role in metabolism. In one study, published in *Nature*, he showed that mice treated with antibiotics absorbed more calories from food than untreated mice, and quickly became obese. Most recently, Laurie M. Cox, PhD, also a Blaser mentee, who currently works in his laboratory, published a paper in August in *Cell* extending Dr. Cho's work and offering strong biological evidence that antibiotics taken in early life can reprogram metabolism and immunity (see sidebar). "We're changing early life development," says Dr. Blaser.

As science reveals more and more about the inner workings of the gut microbiome, researchers have come to think of it as an organ, and a very big one at that: microbial cells outnumber human cells 10 to 1, and there are at least 330 times as many bacterial genes on our body as human genes. Theoretically, bacteria could exert more influence over our health than the DNA we inherit from our parents. Dan R. Littman, MD, PhD, the Helen L. and Martin S. Kimmel Professor of Molecular Immunology and professor of pathology and microbiology, has spent years investigating the intimate relationship between gut bacteria and human immunity. In a recent paper published in *Nature*, he and his colleagues showed how the gut microbe *Candidatus savagella*, also known as segmented filamentous bacterium, helps immature immune cells become T helper 17 cells, which produce a potent signaling protein called interleukin 17 that's largely responsible for the inflammation seen in autoimmune diseases like multiple sclerosis and rheumatoid arthritis. "We've found that most of these immune cells have surface receptors that recognize antigens made by gut bacteria," says Dr. Littman. "They're generally beneficial or harmless microbes that can shape the specificity and function of the cells of the immune system."

This new thinking about microbes and health has inspired heated clinical interest in the concept of "dysbiosis," an imbalance of bacteria within or on the body. "That's what *C. difficile* is," says Dr. Pochapin. "It's a disease of the disruption of the normal microbiota within the colon." Like an increasing number of physicians, he believes FMT may one day replace antibiotics as a first-line therapy for *C. difficile*. "I think right now FMT may be more effective than antibiotics in the treatment of *C. diff*," says Dr. Pochapin. "Rather than just killing off bacteria, it makes much more sense to give back the healthy microbiota. But we have to work within the realm of the FDA."



Clostridium difficile, a normal member of the intestine, can turn deadly. This colored transmission electron micrograph shows spores (green ovals) that are resistant to heat and many chemicals.

BIOMEDICAL IMAGING UNIT, SOUTHAMPTON GENERAL HOSPITAL / SCIENCE SOURCE

For Shalom Levy, qualifying for FMT was the easy part. Finding a donor proved to be much more challenging. After filling out a donor questionnaire similar to one used by blood banks, and offering stool samples for screening, Ilan and his sister learned that their samples both tested positive for *Blastocystis hominis*, a common protozoan parasite that can cause diarrhea in people with weakened immune systems. Shalom's other relatives who offered to help had all used antibiotics within the past 90 days—another disqualifier. "It's actually quite difficult to find donors," says Dr. Chen.

As an alternative solution, Dr. Chen coordinated a stool sample from the MIT start-up OpenBiome, the world's first stool bank, opened in 2013 to make FMT more accessible

for both patients and doctors. A nonprofit, OpenBiome provides physicians with screened, frozen, ready-to-use stool samples at a nominal cost of $250 per sample—just enough to cover the expense of donor screening, lab management, and material preparation. (It's also conducting research—some of it in collaboration with Dr. Blaser—to advance the computational analysis of microbial communities and explore additional indications for FMT, such as for irritable bowel syndrome and even autism.)

Only the healthy few meet OpenBiome's strict donor criteria. Currently the organization's intensive two-phase screening process has winnowed its donor pool to only three people. Remarkably, a total of four donors, making contributions about four times a week, have managed to supply the raw material for 442 treatments delivered to 42 hospitals nationwide since the organization began. "Frankly, the screening is pretty invasive," says OpenBiome cofounder James Burgess. The rigorous process is intended to identify risk factors for communicable diseases and autoimmune disorders, rule out comorbidities and past antibiotic use, and test for a host of transmittable diseases, parasites, and pathogenic bacteria, including *H. pylori*. "Right now, our donors are all scientists who are passionate about the microbiome," adds Burgess. "We try to have them incorporate the donation into their daily routine. They come in, get a cup a coffee, make a contribution, and then get on with their day."

OpenBiome has certainly made Levy's life easier. His

ALTERED GUT BACTERIA AND OBESE MICE

Two years ago, landmark research from Dr. Blaser's lab showed that lifelong exposure to low doses of antibiotics altered the intestinal microbiota of mice and caused the rodents to pack on 10 to 15 percent more fat than untreated mice. The findings were the first to prove a causal link between altered intestinal microbes and obesity, but one big question remained: Did it matter when the antibiotics were delivered?

Now, a follow-up study from Dr. Blaser's lab published in August in *Cell* offers a clear answer: Timing indeed matters. Their latest experiments show that mice exposed to the same low doses of antibiotics in the womb and during nursing pack on even more fat in adulthood than mice exposed later in life. Antibiotics in early life, the scientists conclude, can disrupt a critical window of development for gut bacteria and set off permanent, lifelong metabolic changes.

In one experiment, the researchers administered penicillin-treated water to two groups of mice. One group received antibiotics in the womb during the last week of pregnancy and continued the medication throughout life. Another received antibiotics after weaning and, like the first group, continued the medication throughout life. A third group served as the control and received no antibiotics. "While we saw increased fat mass in both penicillin groups, mice treated in the womb were the fattest," says lead author Laura Cox, PhD, a postdoctoral fellow in Dr. Blaser's lab.

In other experiments, the treated mice also grew fatter than the untreated mice when both were fed high-fat chow. Treated mice also suffered elevated levels of fasting insulin, and alterations in genes related to liver regeneration and detoxification—effects consistent with metabolic disorders in obese patients. "Antibiotics potentiate a high-fat diet," says Dr. Blaser.

But could the medication also be driving the metabolic changes? To address this question, the researchers transferred bacteria from treated mice to infant mice specially bred to be germ-free. After three weeks, the researchers discovered that mice inoculated with bacteria from donor mice treated with antibiotics were indeed fatter than the germ-free mice inoculated with bacteria from donors not exposed to penicillin. "This shows us that the altered microbes alone are driving the obesity, not the antibiotics," says Dr. Cox.

Intriguingly, the metabolic changes persisted even when the antibiotics were stopped. "The effects on the microbes are transient," explains Dr. Blaser, "but the effects on host metabolism are permanent. This supports the idea of a developmental window in which microbes participate. It's a novel concept, and we're providing direct evidence for it." —*NICOLE DYER*

DR. BLASER'S TEAM WAS AMONG THE FIRST TO RECOGNIZE THAT THE LONG-VILIFIED *HELICOBACTER PYLORI,* A GUT MICROBE IMPLICATED IN PEPTIC ULCERS AND GASTRIC CANCER, MIGHT NOT BE SO EVIL AFTER ALL.

transplant took place last February during a 30-minute colonoscopy. Dr. Chen maneuvered an endoscope to the end of Levy's colon, near his small intestines, and then released the OpenBiome sample. That was it. A week later, Levy experienced his first solid stool in 10 months. He's still free of *C. difficile* today. "Whatever the fecal matter did, it was amazing," says his son. "My dad is more energetic because he's absorbing more nutrients from his food. He's also calmer and more focused." Ilan attributes the mental clarity to the lack of antibiotics in his father's system. "The less medication I need to give my dad, the better."

While it may be hard to curb enthusiasm for a medical therapy with a 90 percent cure rate, experts are quick to acknowledge that FMT is still in its infancy. "As a treatment, it's an inelegant sledgehammer, a blunt instrument," says Dr. Cho. "It's like using a bulldozer to get rid of a couple of dandelions in your yard." Yet the media frenzy over FMT has inspired people desperate for relief from a whole host of gastrointestinal conditions beyond *C. difficile*—for which the data are much murkier—to take matters into their own hands, quite literally.

Frustrated by the FDA restrictions and the lack of physicians trained and willing to perform FMT (one popular patient-resource website lists fewer than 200 physicians in the U.S. that offer fecal transplants), patients are turning to the Internet for instructions on how to perform the procedure at home. The do-it-yourself protocols typically involve a blender, rubber gloves, an enema bag, and a lot of courage. Not to mention patience, as anecdotal reports suggests that at-home protocols must be repeated weekly.

"We know that enemas don't work as well as colonoscopies," says Dr. Chen, citing research at Massachusetts General Hospital. Dr. Chen says this may simply be because the sample isn't delivered far enough into the colon or that it doesn't stay put for as long as it should. Either way, most *C. difficile* patients who receive fecal transplants by colonoscopy never have to do it again.

The hope is that fecal transplants of the future won't involve feces at all, but rather the medicinal bacterial strains within it. "Feces is the nuclear approach, where you give everything," says Dr. Pochapin. "Eventually we will isolate the strains that make the most difference."

Healthy stool is usually dominated by just two bacterial phyla, Bacteroidetes and Firmicutes, which contain hundreds of species. In her own research, Dr. Chen has found that stool samples from patients with recurrent *C. difficile* often show diminished bacterial diversity within these two groups, while samples taken after a successful FMT reveal microbial populations remarkably similar to the donor's.

But what's the optimal mix of bacteria? Could the bile acids, proteins, and bacteriophages (viruses that infect bacteria) found in stool also play a role in its medicinal magic? Until scientists find the answer to these and other questions, the prospect of isolating specific strains in a petri dish, controlling them in an artificial environment, and then delivering them as a more palatable pharmaceutical remains a very expensive challenge. Elaine Petrof, a microbiologist at Queen's University in Ontario, Canada, spent two years creating a kind of synthetic poop, painstakingly cultivating a mix of 33 beneficial bacterial strains in an artificial colon. In a proof-of-principle study, the lab mixture, called RePOOPulate, fought off *C. difficile* in two patients. But it's hard to justify the time and expense when conventional FMT works just as well, and Dr. Petrof has since gone back to offering patients FMT.

Despite the practical hurdles, Dr. Blaser still finds the Canadian results encouraging. "It's not as good as using feces, but it still works," he says. "It's the principle that matters. It's not the last time we'll hear of this kind of approach. Several biotech companies have *C. difficile* in their sights. People are working on it. That's the great thing about American science and entrepreneurship. I don't think we'll be doing FMT five years from now."

In the meantime, Ilan hopes we can get over the gross-out factor and expand access to FMT. "We donate blood and organs. Why not stool?" he asks. "You shouldn't be squeamish about a procedure that's going to save someone's life. The alternative is more money, more medication, and more suffering."●

Ketamine

A RAPID ANTIDOTE TO MAJOR DEPRESSION?

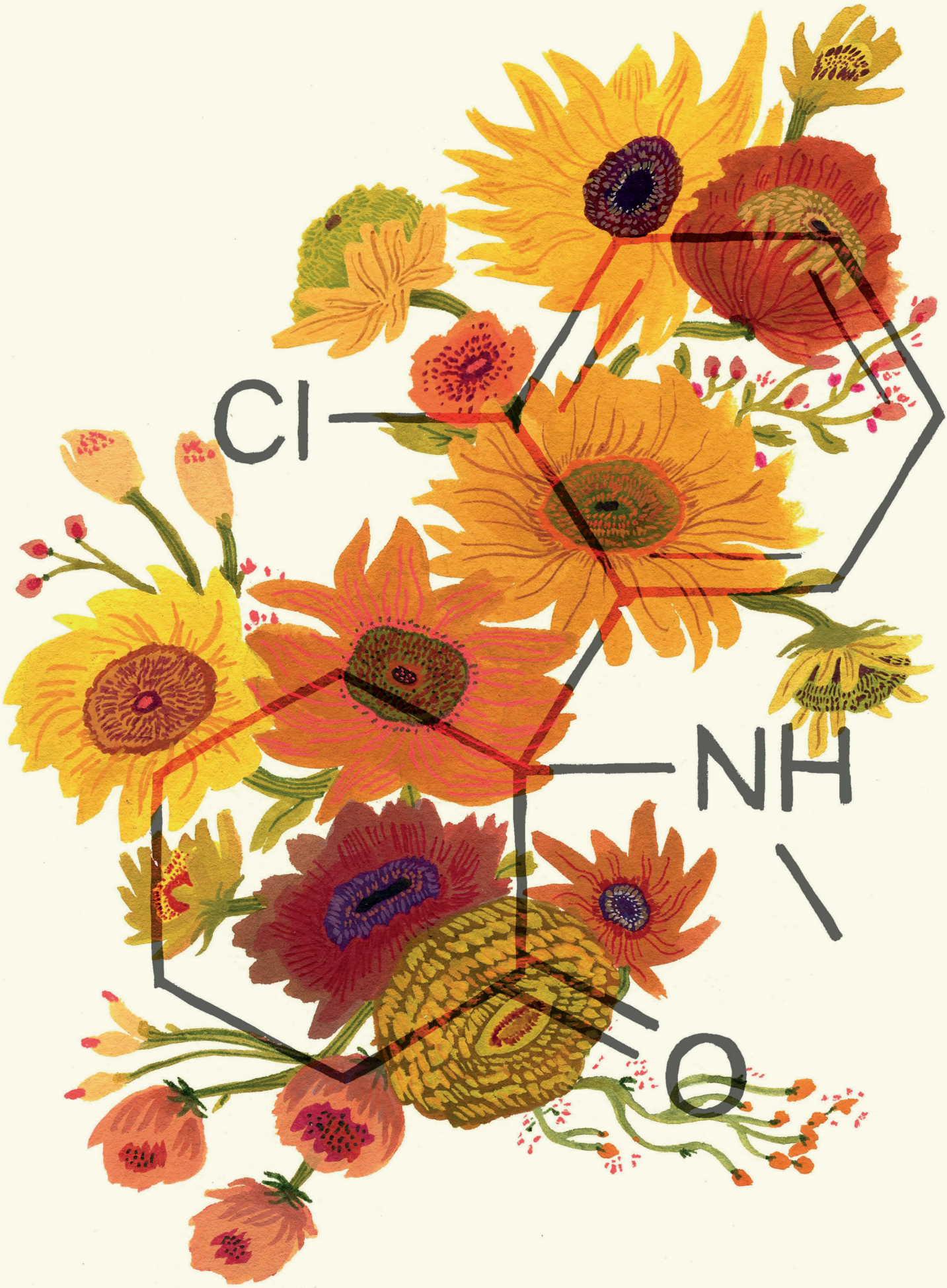
BY GARY GOLDENBERG • ILLUSTRATION BY BECCA STADTLANDER

A clinical trial is asking whether a drug widely used as an anesthetic, and widely abused in clubs, can revolutionize the treatment of major depressive disorder.

IN JUNE OF THIS YEAR, five people in New York City were arrested for luring wealthy men into strip clubs, drugging them with ketamine and other substances, and then running up thousands of dollars on their credit cards. This incident is just the latest adding to the notoriety that surrounds the short-acting general anesthetic known on the street as Special K or Vitamin K. Approved by the FDA in 1970, ketamine—a derivative of phencyclidine (PCP), another anesthetic—was first adopted by American military surgeons in Vietnam because of its ability to quickly tranquilize injured soldiers without compromising heart or lung function. Before long, ketamine became a staple in emergency rooms around the U.S., where it has proven to be especially helpful in calming young children who need stitches or other anxiety-provoking procedures.

Illicit use started almost immediately among self-styled philosophers and spiritualists of the West Coast counterculture. Moderate to high doses of ketamine brought on hallucinations, out-of-body experiences, and feelings of euphoria. Word spread in underground comics such as the *Fabulous Furry Freak Brothers* and books such as Howard Alltounian's *Journeys into the Bright World*, spurring wider recreational use. By the mid-1980s, ketamine became popular with young adults at dance clubs and raves, where users undertook hour-long trips to "K-land" (if the journey was particularly mellow) or down the "K-hole" (if it triggered a near-death or catatonic experience). Soon reports emerged of ketamine being used as a "date rape" drug, although the extent of these crimes is hard to measure. Colleges and universities now routinely warn students to be aware of how ketamine, alongside other drugs such as Rohypnol and GHB, can be surreptitiously slipped into a person's food or drink, rendering them defenseless.

Despite its notoriety, the drug has been quietly stirring interest in psychiatric circles since 2000, when the first of a series of studies suggested that low doses of intravenous ketamine can have a dramatic antidepressant effect in a remarkably short amount of time—as little as 40 minutes—with minimal adverse effects, and the improvement in symptoms from a single dose can persist for a week or more. Psychiatrists especially took notice after a study at Yale–New Haven Hospital in 2011 showed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for the first time that the drug, delivered in a quick IV push of only two to three minutes, helped emergency room patients with severe depression.

These findings were welcome news to those who work on medicine's front lines. "When patients with severe depression come into the emergency room, there's very little we can do," says Casey A. Paleos, MD, clinical instructor of psychiatry at NYU School of Medicine and attending staff psychiatrist at Bellevue Hospital Center and in the Ronald O. Perelman Center for Emergency Services at Tisch Hospital. Tisch and Bellevue are among a handful of facilities around the country with full-time emergency room psychiatrists. "Antidepressants usually take weeks to have an effect, and psychotherapy even longer," he says. "When patients are acutely depressed, suicidal, and a danger to themselves, which is often the case, the best we can do is admit them to a psychiatric unit for round-the-clock observation until first-line therapies begin to take hold." The only other option, electroconvulsive therapy, can work relatively fast. However, because of potential side effects, it's typically reserved as a treatment of last resort.

Almost everyone experiences a case or two of the "blues," the mild feelings of sadness that typically resolve on their own in hours or days, but severe depression—or major depressive disorder (MDD), as psychiatrists call it—is far more serious. In simple terms, MDD is characterized by intense and persistent feelings of sadness, hopelessness, worthlessness, and helplessness that interfere with one's ability to work, sleep, eat, and experience pleasure. It's often accompanied by thoughts of suicide. The precise number of suicides due to MDD is hard to determine. However, it is known that depression is the main reason for suicide, which in 2009 surpassed motor vehicle accidents as the leading cause of injury-related death for adults in the U.S., according to the National Center for Health Statistics.

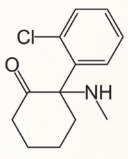
"Major depression is one of the most disabling and costly diseases," says Stephen Ross, MD, associate professor of psychiatry, and child and adolescent psychiatry, and director of Addiction Psychiatry at Tisch Hospital. "It causes weeks and weeks of pure misery. If we had a tool that could quickly lift people out of their depression, it would be a huge clinical advancement."

The economic ramifications would be huge, too. Each year, about 395,000 people are hospitalized with MDD, with an average length of stay of 6.5 days, reports the Centers for Disease Control and Prevention. All told, the condition costs the nation $80 billion annually in lost productivity and health expenditures, according to National Alliance on Mental Illness figures.

A new clinical trial will help psychiatrists assess ketamine's potential new role in reducing depression's toll. Earlier this year, Drs. Ross and Paleos launched the first randomized, double-blind study of ketamine for patients with MDD in an emergency room. The primary aim of the study is to determine whether ketamine can rapidly improve symptoms of depression and lessen the risk of suicide. The researchers intend to enroll 60 patients with MDD who come to the emergency room at Tisch Hospital or Bellevue Hospital Center. Patients will receive either a single low-dose intravenous infusion of ketamine or a placebo (administered, as in the Yale study, by a quick IV push) and then will be admitted to an inpatient psychiatric unit.

KETAMINE TIMELINE

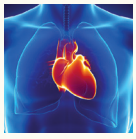
1960



1962

Ketamine is developed as a **fast-acting general anesthetic** and is used in veterinary medicine as a **horse tranquilizer.**

1970



1970

The Food and Drug Administration approves ketamine **for human use** as a general anesthetic. The drug is quickly **adopted by battlefield surgeons** in Vietnam due to its **unique cardiovascular properties** and becomes a **staple in emergency rooms across the U.S.**

1970–1980

The counterculture discovers that the drug in moderate to high doses **produces hallucinations, feelings of euphoria, and out-of-body experiences**. New forms are introduced into the illegal drug markets as **capsules, powder, crystals, tablets,** and **solutions,** in addition to **other injectable forms.**

1980

1980s

Ketamine, known on the street as **Special K** or **Vitamin K,** among other names, becomes **popular with young adults at dance clubs and raves.**

Each patient will be followed for four months, even though the direct effects of the drug are expected to wane in a couple of weeks. "The hope is that we can quickly alleviate their suffering and provide a bridge to standard therapy," says Dr. Paleos, who came up with the idea for the study. "And it may be that if we quickly lift their depression, we can set them on a more favorable trajectory."

The researchers will also assess whether the drug can reduce repeat emergency room hospital admissions and the amount of time patients are hospitalized. "This would be particularly important in public hospitals like Bellevue, where inpatient psychiatric beds are constantly in short supply," says Dr. Ross, the study's principal investigator.

The study, a collaborative effort of the Departments of Psychiatry, Emergency Medicine, and Anesthesiology, is funded by the Clinical and Translational Science Institute, which is a partnership of NYU, NYU Langone Medical Center, and the New York City Health and Hospitals Corporation, and by a gift from Medical Center Trustee Daniel Rosenbloom, Esq.

Meanwhile, a small but growing number of private practices are already promoting ketamine for MDD—a trend that deeply concerns Dr. Ross. "It's legal, but it's reckless," he says. "Ketamine can be addictive, and it can induce psychotic symptoms. Also, the effects of the drug degrade after 10 to 14 days, so it would have to be redosed or used in conjunction with other therapies. We need to learn more about how to use this drug and whether it even works in this context. Ultimately, ketamine should be used in a psychiatric setting with careful screening and monitoring."

Exactly how ketamine might affect depression is not clear. What is known is that the drug blocks the N-methyl-D-aspartate (NMDA) receptor, a major receptor for glutamate, the primary excitatory neurotransmitter in the central nervous system. (All of the other antidepressants affect one or more of the monoamine neurotransmitters: serotonin, norepinephrine, and dopamine.) Studies have found that depressed patients have elevated levels of glutamate in their blood and cerebrospinal fluid, as compared to healthy controls, and that these levels can be lowered by long-term administration of conventional antidepressants. Further, postmortem studies have found significant abnormalities in glutamate signaling in NMDA receptors in the frontal cortex of patients with MDD and in the prefrontal cortex of people who have committed suicide. "So, despite ketamine's checkered past," says Dr. Ross, "the use of this drug for depression does make sense."

Dr. Ross is less concerned about how ketamine works than if it works at all. "Infectious disease specialists have the luxury of choosing from many classes of antibiotics, each with its own unique mechanism of action and its own special niche in the arsenal," he says. "We psychiatrists, in contrast, have essentially only one option when it comes to drugs for depression, and that is to intervene with the monoamine neurotransmitters, all of which have delayed effects of up to several weeks. Before ketamine, there were no pharmacotherapies for MDD that worked acutely, something we desperately need especially to deal with the danger of suicide associated with MDD. In this context, ketamine could be the biggest advance in pharmacotherapy for depression since the first antidepressant was discovered in the late 1950s by Nathan Kline." ●

1997
New York State passes a law **criminalizing the sale or possession of ketamine.**

1999
Following reports of the sale, theft, and abuse of ketamine, the federal government classifies it as a **Schedule III controlled substance,** making it **illegal to possess the drug** for recreational or nonmedical purposes.

2011
A Yale–New Haven Hospital study shows for the first time that lower doses of the drug, delivered in a quick IV push, can **alleviate major depression in emergency room patients.**

1990 **2000** **2010**

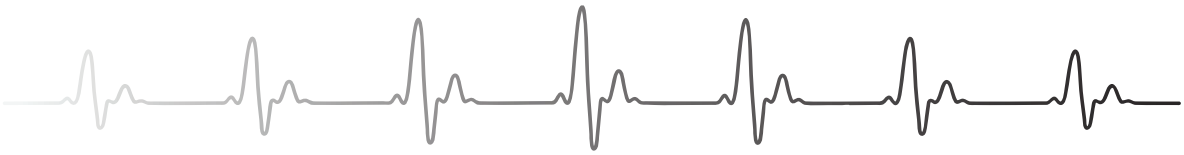
1990s
Recreational use of ketamine, **especially sniffing,** becomes more widespread.

2000
The first report of ketamine's **remarkable antidepressant effects** when delivered at **low doses in an IV infusion** appears in medical literature. In the following years, other studies **confirm the results** of the initial report.

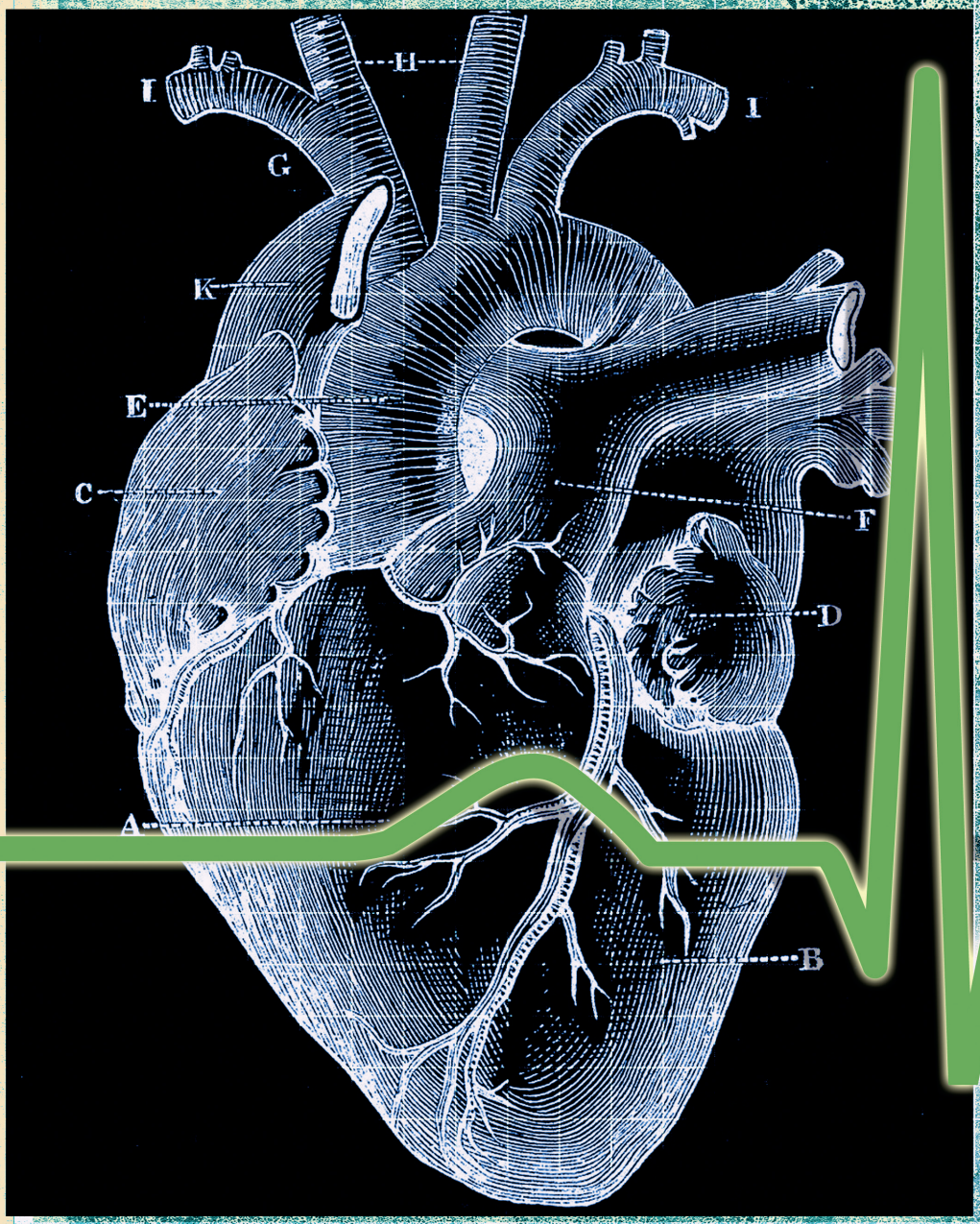
2014
The first **randomized, double-blind study** of ketamine for patients with MDD in an emergency room setting is launched at **Tisch Hospital** and **Bellevue Hospital Center.**

NANOMETERS FROM DEATH

A cardiology researcher and a geneticist collaborate to understand why the heart can suddenly stop beating in young people in the prime of their lives.



BY NICOLE DYER • PHOTOGRAPH BY JAKE CHESSUM



ON AUGUST 25, 2007, Antonio Puerta, a professional soccer player in Spain, was jogging down the field, only 35 minutes into the opening game of the season, when he grabbed his chest and collapsed. He recovered, walked to the locker room, and then collapsed again. His heart stopped beating. Paramedics and doctors performed cardiac resuscitation several times, but the soccer star died a few days later in the hospital. He was only 22 years old.

How could the heart of a young athlete in peak condition just suddenly stop ticking? It's a mystery central to the research of Mario Delmar, MD, PhD, professor of medicine in the Leon H. Charney Division of Cardiology, and Marina Cerrone, MD, research assistant professor at the NYU Langone Cardiovascular Genetics Program, which offers genetic screening, counseling, and treatment to patients with inherited cardiac diseases.

The husband-wife duo specializes in an incurable heart condition called arrhythmogenic right ventricular cardiomyopathy (ARVC).* This is a heritable disease that affects 1 in 5,000 people in the U.S. In advanced stages, it causes fatty, fibrous tissue to build up in the ventricles of the heart (most commonly on the right side, which pumps blood to the lungs). But even in the earlier "concealed" stages of the disease, when the heart shows no outward signs of distress, hidden damage can disrupt the heart's electrical rhythms, causing dangerous palpitations, or arrhythmias. In extreme cases, the heart can pound wildly, up to 300 times a minute, leading to sudden cardiac death.

Puerta, who was posthumously diagnosed with ARVC, never even knew he had a heart problem. "ARVC can be a silent killer," says Dr. Delmar. "Many cases of sudden cardiac death occur in young patients before damage to the heart becomes apparent."

Working down the hall from one another at the Joan and Joel Smilow Research Center, Drs. Delmar and Cerrone hope to develop new ways to identify people with ARVC and other inherited cardiac diseases before it's too late. Dr. Delmar, a native of Mexico, performs basic science, investigating the molecular underpinnings of inherited cardiac diseases. Dr. Cerrone, a native of Italy, works on the clinical end, studying the genetic profiles of patients enrolled in the Cardiovascular Genetics Program. "We come from different backgrounds, but we're both very passionate about what we do," says Dr. Cerrone. "We always have something to talk about over dinner."

Dr. Cerrone recalls a recent discussion about a particularly tough case. A mother had come to the Cardiovascular Genetics Program not long after she had collapsed from cardiac arrest during a routine run. Fortunately, she was resuscitated by EMS. At the clinic, she was diagnosed with ARVC and tested positive for a mutated gene called plakophilin-2, or PKP2, which is associated with 50 to 70 percent of familial ARVC cases. Sadly, both her sons—two healthy and athletic teenagers—had also tested positive for the same mutation. Now she feared that they, too, would suffer from sudden cardiac arrest.

The PKP2 gene is crucial for proper heart function because it codes for a protein that helps form desmosomes, molecular complexes that act as a kind of cellular glue to bind together heart cells. When defective, desmosomes can cause cardiac cells to "unstick" and pull apart over time, but the boys' hearts show no outward signs of damage. "Genes alone do not determine whether one will develop the disease," says Dr. Cerrone. "We don't know all risk factors."

With such an uncertain prognosis, the boys' doctors are faced with a difficult decision: whether or not to recommend that the young, spritely boys receive an implantable defibrillator. Doing so would hedge against the risk of sudden cardiac death, but it would also subject them to a different lifestyle and, perhaps, to a lifetime of surgical interventions required to maintain and replace the device. Did

HOW COULD THE HEART OF A YOUNG ATHLETE IN PEAK CONDITION JUST SUDDENLY STOP TICKING?

** ARVC was originally named arrhythmogenic right ventricular dysplasia, or ARVD, and was also dubbed arrhythmogenic cardiomyopathy, since the left ventricle is also often involved.*

Marina Cerrone, MD,
and Mario Delmar, MD

THE DISTANCE BETWEEN CARDIAC PROTEINS MIGHT GIVE CLINICIANS A POWERFUL NEW TOOL TO PREDICT THE LIKELIHOOD OF SUDDEN CARDIAC ARREST.

both boys even share the same risk factors? Should they both be treated the same way?

Drs. Delmar and Cerrone's research into the molecular behavior of heart cells could help solve this and other clinical dilemmas. Essentially a living battery, a heart is made of billions of muscle cells, each one fused to others by an intercellular junction, or intercalated disc, made of structures such as desmosomes, sodium channels, and gap junctions. Heart cells, when healthy, propagate electrical signals by opening sodium-ion channels and passing charged ions through the intercalated disc. The electrical current allows the cells to twitch simultaneously so the heart can pump blood throughout the body. The cells stick together, via the desmosomes, so that the force of the individual twitching multiplies to generate one mighty heartbeat. Dr. Delmar refers to these two functions as the "glue" and the "jolt," respectively.

Historically, the glue and the jolt have been conceived as two separate mechanisms. But Drs. Delmar and Cerrone began to wonder whether desmosomes and sodium channels, which neighbor each other within the intercalated disc, actually work together. Perhaps, Dr. Delmar thought, PKP2 multitasks, making not just desmosomes, but also affecting sodium current. So in 2009, he and his colleagues conducted a simple experiment, published in the journal *Circulation Research*, in which they blocked the expression of PKP2 in isolated heart cells. If PKP2 only makes desmosomes, they reasoned, nothing should happen since a single cell doesn't have desmosomes. But something did happen: sodium current decreased by 50 percent.

The researchers then expanded the idea to the clinic and began investigating another inherited arrhythmia disease called Brugada syndrome, thought to stem from a genetic mutation that codes for faulty sodium channels. Unlike ARVC patients, those with Brugada syndrome typically manifest arrhythmias but display no structural damage to the heart. "We proposed that maybe some of these cases could be consequent to PKP2 mutations that largely affect sodium channels," Dr. Delmar explains.

Screening the DNA of 200 patients with Brugada syndrome from the Registry of the Molecular Cardiology Laboratory in Pavia, Italy, all with structurally healthy hearts, they found that 2.5 percent of the patients indeed had PKP2 mutations. Further research in mice confirmed that the mutated PKP2 gene not only interferes with cell-to-cell adhesion, but also alters the function of molecules that regulate the electrical rhythm. "We found that the glue and the jolt are not independent and controlled by separate molecules as previously believed," says Dr. Delmar. In fact, they are both controlled by a common molecular network within the intercalated disc, which the researchers coined the "connexome." Clinically, this meant that ARVC and Brugada syndrome weren't separate diseases at all but rather bookends of a spectrum of clinical manifestations, a finding that helps explain why among a family of patients who all test positive for mutated ARVC genes, for example, one might die, one might have severe arrhythmias, and one might be asymptomatic.

The next big step was to figure out precisely how these molecules interact. Evidence suggested that PKP2 mutations could cause molecules within the connexome to pull apart, which in turn could prevent other molecules from delivering the appropriate electrical jolt to a neighboring cell. By measuring the distance between proteins that connect cardiac cells, Dr. Delmar reasoned, he could calculate the distance at which the cells began to malfunction and cause arrhythmias. The only problem was that he lacked the tools to visualize the tiny gaps between molecules, a space about 40 million times as small as the head of a pin.

Fortuitously, a chance encounter in 2010 would solve that problem. In a moment of what he calls "facilitated serendipity," Dr. Delmar met Eli Rothenberg, PhD, assistant professor of biochemistry and molecular pharmacology, at a lunch for new recruits, which Dr. Delmar attended. When Dr. Rothenberg explained that he worked with single-molecule fluorescence microscopy, a tool capable of nanometer resolution, a light went off in Dr. Delmar's head. "I thought, 'Well, that sounds very cool. I don't work in that field, but I have this problem.' " Thus began a long and fruitful collaboration.

Over the next year and a half, the researchers worked together to begin mapping the molecular interactions and architecture of proteins within the connexome. Bolstered by super vision, the researchers were able to document that cardiac proteins positioned more than 40 nanometers apart lost their ability to effectively propagate electrical impulses, just as two people seated on opposite ends of a banquet table would be unable to shake hands. The result is arrhythmia. Says Dr. Delmar, "We all live nanometers away from sudden death."

The discovery raised a tantalizing possibility: the distance between cardiac proteins might give clinicians a powerful new tool to predict the likelihood of sudden

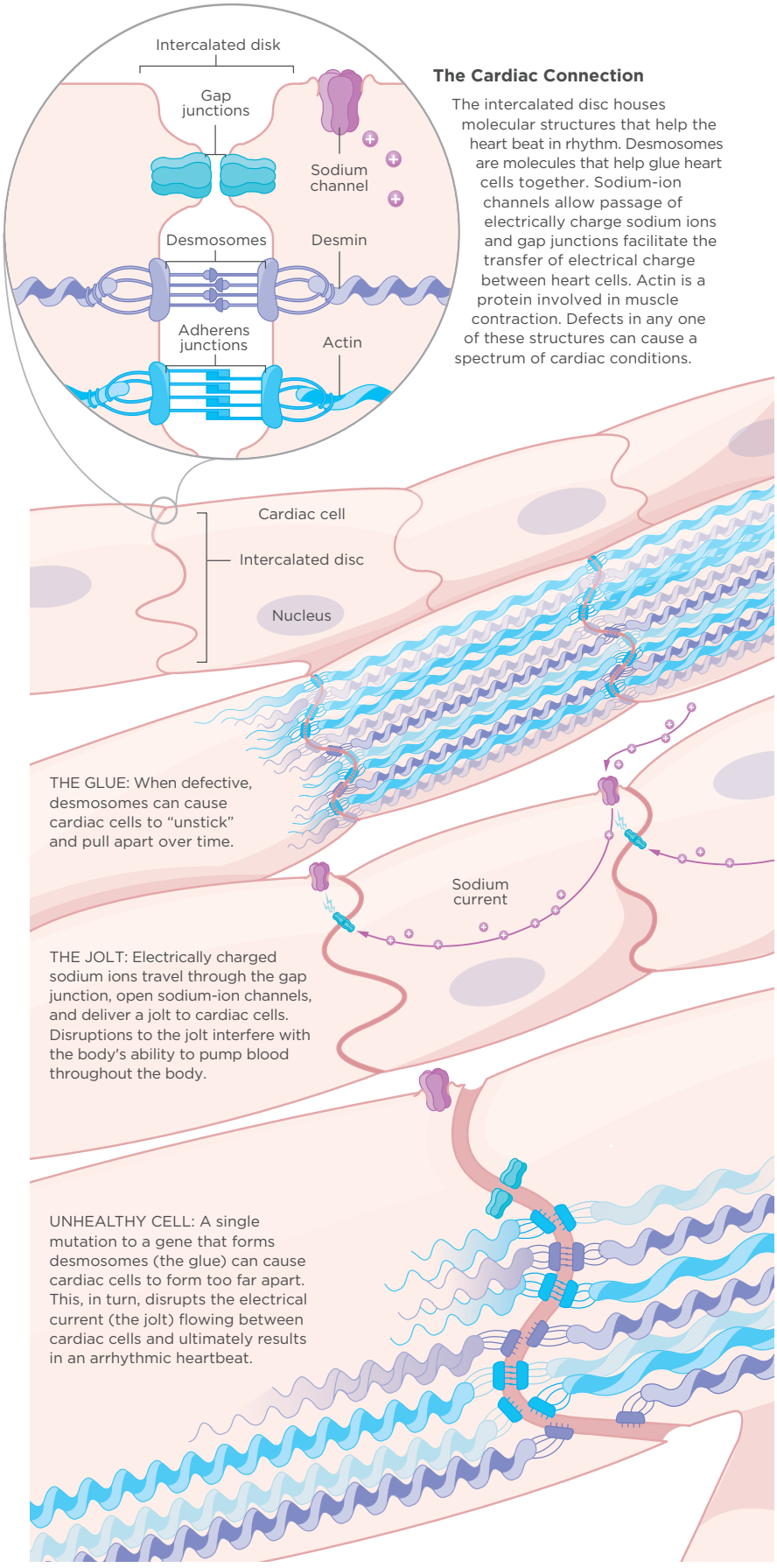
Each of the heart's billions of cells connect to each another through a junction called the intercalated disc.

cardiac arrest. For example, a patient with a mutated ARVC gene but perfectly positioned cardiac proteins might be less at risk for sudden cardiac arrest than a patient with the same ARVC mutation, whose proteins were too far apart. "This could help us eliminate the gray line," says Dr. Cerrone. "You do genetic testing, you find the genes, but the disease may or may not develop."

Dr. Delmar likens the protein placement within the connexome to a watch. You can assemble a thousand pieces of a watch, but it won't run unless each piece fits together perfectly. "By visualizing the proteins, we see that there is something wrong in the cells. The location of a protein is crucial," he explains. "So even if we can't find the gene signature, we hope to be able to find the protein signature. It's a step ahead of the genomic information."

Drs. Delmar and Cerrone are now collaborating with Lei Bu, PhD, assistant professor of medicine and cell biology, to turn this information into a clinical diagnostic. Using an experimental yet promising new technique that avoids painful heart biopsies, Dr. Bu can extract cells from a patient's blood and revert them to their original state as stem cells, which possess the ability to give rise to any of the body's 200 tissue types. From there, the cells are reprogrammed to become cardiac cells, at which point Dr. Rothenberg's superresolution microscopy can reveal the distance between the proteins. "We can physically see if something is wrong," says Dr. Delmar. "If the molecules are too far apart, if they cannot cooperate with each other, the risk of sudden death increases tremendously."

It's an insight that extends to scientific partnerships, as well. Collaboration, after all, is what makes them tick. ●



The Cardiac Connection

The intercalated disc houses molecular structures that help the heart beat in rhythm. Desmosomes are molecules that help glue heart cells together. Sodium-ion channels allow passage of electrically charge sodium ions and gap junctions facilitate the transfer of electrical charge between heart cells. Actin is a protein involved in muscle contraction. Defects in any one of these structures can cause a spectrum of cardiac conditions.

ILLUSTRATION BY LUCY READING

Neuroscientist Nicholas Stavropoulos, PhD, studies sleep in the fruit fly using a technique called forward genetics.

An Ancient MYSTERY

SOME SAY IT'S NEEDED TO CONSOLIDATE MEMORIES OR TO CLEAR OUT METABOLIC WASTE FROM THE BRAIN. BUT NOBODY REALLY KNOWS WHY WE SLEEP. NOW, NEUROSCIENTISTS ARE PROBING THAT MYSTERY IN AN UNLIKELY CREATURE, THE FRUIT FLY.

BY JIM SCHNABEL • PHOTOGRAPHS BY BEATRICE DE GEA

BIRDS DO IT, BEES DO IT, even humble fruit flies do it—sleep.

Flies can't close their eyes, because they don't have eyelids, and their tiny brains almost certainly cannot dream. They don't snore or drool on the pillow or murmur the names of old flames in the dead of night. Yet, like pretty much every other animal with a central nervous system, they spend a large part of their lives catching Zs.

"If you deprive a fruit fly of sleep, it will sleep longer the next day, just like a human," says Nicholas Stavropoulos, PhD, assistant professor of neuroscience and physiology, and a member of the NYU Neuroscience Institute. "You can even give a fly a drug such as caffeine or methamphetamine that alters sleep in humans," he says, "and it will have more or less the same effects."

That's good news for scientists, who are always on the lookout for useful animal models of human behaviors and disorders. Of course, lab mice sleep, too, but they are comparatively slow growers, requiring a few months to develop from embryo to adult. Fruit flies—particularly the *Drosophila melanogaster* species favored by laboratory biologists—can become breeders in 10 days, making them especially well suited for genetics experiments. Individual flies measure only about an eighth of an inch long, and thus take up much less space than mice. They can live at room temperature on a simple soup of sugars and other nutrients. Dr. Stavropoulos keeps thousands of vials of *Drosophila*, each containing a line, or family, with a certain set of mutations, on racks of shelves in refrigerator-like incubators. "It's almost like a library," he says.

Of course, *Drosophila* are evolutionarily far removed from us. Yet among their four pairs of chromosomes are genes that have been largely preserved over the hundreds of millions of years since our common ancestors slithered through the Paleozoic muck. Some of these conserved genes help regulate sleep. In fact, experiments on *Drosophila* in recent decades have illuminated genes and signaling networks that maintain the daily pacemaker, the so-called circadian clock. The various parts of this key enforcer of nighttime sleep work together in surprisingly similar ways in flies and humans.

Yet much remains unknown about sleep, and experiments on flies and other animals have failed to answer the biggest question of all: Why must animals with brains—even those with simpler nervous systems such as crayfish and honeybees—revert to this inactive, almost deathlike state for at least a few hours each day?

A TWIST ON GENETIC SCREENING

A technique called forward genetics is helping biologists approach such questions. Instead of mutating one known gene to see how its loss affects a fruit fly, a DNA-altering chemical is employed to create random, unknown gene mutations in a population of flies. From this population, single flies are bred to create lines, each of which may carry a unique gene mutation. Each line can then be scrutinized for an abnormal trait of interest, such as a reduced level of sleep. If this trait is found, the genomes of these flies are screened to identify the mutation that caused it, and that gene would now be implicated in the regulation of sleep. The technique, with its potential to probe entire genomes and find genes with previously unknown functions in thousands of fly lines, is considered particularly powerful for biological discovery. "You cast a wide net. You make no assumptions," says Dr. Stavropoulos. "You embrace the unknown."

You also embrace hard work and tedium. The process of isolating and examining tiny flies for sometimes subtle abnormalities is time and labor intensive. It is also quite risky in terms of careers. Despite all that effort, the thousands of mutant fruit fly lines that one creates may not yield any of scientific interest.

Even so, Dr. Stavropoulos has been pursuing his forward genetics experiments since he earned his PhD in genetics from Harvard in 2003, hoping that he'd end up with something dramatic to show for his work. Upbeat about the possibilities of sleep research using *Drosophila,* he began a postdoctoral fellowship at The Rockefeller University and spent most of his time mutating fruit flies, breeding them into lines, and watching for abnormalities in their sleep patterns. Week after week in the prime of his life, he was *watching flies sleep*. In a typical week, he'd screen 500 to 800 flies, representing more than a hundred different mutant lines.

How do you know a *Drosophila* is asleep? Its behavior changes subtly. It stops moving and becomes slower to move when startled. Experience has taught biologists that a fly may safely be considered asleep when it has failed to cross an infrared beam in a specially designed tubelike chamber, about two and a half inches long, for five minutes. (Other work has shown that sleep does alter brain activity in flies.)

In the Rockefeller lab, Dr. Stavropoulos kept track of automated recorders that marked the intervals of fruit fly slumber. Weeks and then months went by. Some flies displayed interestingly odd patterns of sleep, but most behaviors turned out to be random quirks of individual flies that were not seen in others of their line. In two lines, the flies displayed genuine, reproducible reductions in sleep, but these flies turned out to have mutations in a sleep-related gene that others had already discovered and published in the scientific literature. He wanted to discover something novel.

By the time seven months had passed, Dr. Stavropoulos had bred and screened an eye-popping 21,000 flies, representing more than 3,500 distinct mutant lines. At this point, he was tired, but he wasn't entirely empty-handed: several lines displayed odd sleep behaviors caused by mutations in genes that hadn't been previously linked to sleep.

"YOU CAN EVEN GIVE A FLY A DRUG SUCH AS CAFFEINE OR METHAMPHETAMINE THAT ALTERS SLEEP IN HUMANS," HE SAYS, "AND IT WILL HAVE MORE OR LESS THE SAME EFFECTS."

One of these lines really stuck out. The flies in this otherwise ordinary family slept only about a third as many hours as usual—the equivalent of about two and a half hours per night for a human. It can take a scientist a long time to pull a true discovery out of the usual experimental tangle of bias, error, and random variation. "But this was so far outside the norm of *Drosophila* sleep behavior that I knew I had something," Dr. Stavropoulos recalls.

Nevertheless, it took him two more years to identify the fruit fly gene whose mutation had caused this weird, stay-up-all-night phenotype, and then to confirm the discovery by restoring the regular version of that gene to the mutant flies, who thereafter slept normally. In keeping with the practice of fly geneticists, he named the gene for what the fly is without it: *insomniac*.

THE MYSTERY OF SLEEP HOMEOSTASIS

The discovery led to other big questions. First, does *insomniac* have relevance to human biology or merely to fly biology? In subsequent experiments, Dr. Stavropoulos found that the fly gene does have close cousins in the genomes of humans, mice, and other vertebrates, suggesting that its function is fundamental enough to have been preserved over the eons.

Another question was how *insomniac* affects sleep. Dr. Stavropoulos found that it doesn't work through the circadian clock; it doesn't switch on at night and off in the morning as a circadian enforcer of sleep would. To a scientist seeking new and deep insights, this was good news. The basic network of genes that regulate the circadian clock

had already been largely illuminated, thanks to pioneering experiments on *Drosophila* by a number of investigators, including Michael Young, PhD, Dr. Stavropoulos's adviser at Rockefeller. Moreover, there was evidence that the circadian clock, while a fundamentally important phenomenon in its own right, isn't necessarily the best mechanism to study in searching for the ultimate purpose of sleep. "The circadian clock seems to be more ancient than sleep—there are bacteria and plants, for example, that have circadian rhythms," says Dr. Stavropoulos.

The other major regulator of sleep, which some researchers believe may offer better clues to sleep's deep evolutionary meaning, is a broad mechanism called sleep homeostasis, or sleep drive. This homeostatic mechanism constantly adjusts how much sleep an animal needs, independent of the circadian clock, which synchronizes our sleep to the earth's day and night cycles. The sleep homeostasis process seems to involve the dialing down of arousal circuits in the brain—circuits that can be pepped up by caffeine, for example—but just how it works is still unclear. Perhaps *insomniac* is one of the keys to solving that mystery.

A third big question about sleep is how (and why) its loss affects the health of an animal. Virtually all studies addressing this issue have linked sleeplessness to ill health and often to early death. Rats totally deprived of sleep die within weeks, for instance. Intriguingly, Dr. Stavropoulos found evidence that *insomniac*'s sleep-inducing function might be distinct from its health effects. Flies without the gene died young on average, but when Dr. Stavropoulos suppressed the gene *only in the flies' neurons*, not elsewhere, the insects lived an ordinary life span while sleeping only about half as much as normal. It was only a preliminary finding, but it pointed to the tantalizing possibility that sleep—some sleep anyway—isn't as strictly necessary as has long been assumed. "I think there's a lot of room for exploring that issue," he says.

The *insomniac* experiments were published in a paper in *Neuron* in 2011, earning Dr. Stavropoulos a Blavatnik Award for Young Scientists in 2012, a Leon Levy Neuroscience Fellowship in 2013, as well as a Sloan Foundation Fellowship grant in early 2014, shortly after he had established his own lab at NYU Langone Medical Center. "Nick's risky project was a success," says Dr. Young, his mentor at Rockefeller, who notes that *insomniac* now "appears to have a substantial role in the control of sleep duration."

Today in his lab at the NYU Neuroscience Institute, Dr. Stavropoulos and his growing team of scientists are continuing to study the gene. It is largely connect-the-dots work—tying the *insomniac* protein to other factors that operate together to make flies sleep. Several of these have been identified, and the data so far suggest that *insomniac* and its partners enforce sleep by enhancing the normal breakdown of proteins related to arousal.

How this sleep-enforcing network gets switched on and off in the brain isn't known, but Dr. Stavropoulos hopes that the answer will help solve the deep mystery of why brains need sleep at all. Is it to remodel synapses? To clear out neurons' accumulated metabolic wastes? To conserve energy? "We just keep pulling on the proverbial ball of yarn, hoping that in the fullness of time, we'll unravel it all and get the answers to those big questions," he says. "We know that sleep is there for a reason." ●

Using their forward genetics strategy, Dr. Stavropoulos's laboratory recently found fruit flies that wake near twilight, remain active into the early night, and return to sleep well before dawn. His team named the gene mutation in these flies *Dracula*. They are trying to clone the gene to understand how it might play a role in controlling when animals fall asleep.

Public Enemy Number One: Cardiovascular Disease

Three cardiologists offer their expertise on the prevention and treatment of heart attacks

BY ROYCE FLIPPIN

Despite significant advances in the prevention and treatment of cardiovascular disease, it remains the nation's leading killer, claiming 600,000 lives annually. Almost two-thirds of these are largely preventable deaths from coronary artery disease, in which the arteries develop plaque deposits that can eventually rupture and cause an artery-blocking blood clot—commonly known as a heart attack. Three cardiologists at NYU School of Medicine discuss why coronary artery disease is still so widespread and how to change that state of affairs. They are Eugenia Gianos, MD, assistant professor of medicine, who specializes in cardiovascular preventive treatment and research; Harmony Reynolds, MD, assistant professor of medicine, a general cardiologist and clinical researcher whose focus is women's heart health; and Binita Shah, MD, instructor of medicine, an interventional cardiologist who is studying how to modify poor prognostic factors around the time of a heart attack and treatment of coronary artery blockages.

With all of our knowledge about preventing coronary artery disease, why is it still so prevalent?

DR. GIANOS: Overall, heart disease has actually been declining over the last 10 years. What's *not* declining are things like obesity, metabolic syndrome, and diabetes, all of which increase heart disease risk. We still need to do better at targeting people's lifestyle and behavioral risk factors. Many patients don't visit their physicians regularly, and when they do have blood work done, risks may be noted but not fully addressed. In a recent study at the Center for the Prevention and Treatment of Cardiovascular Disease at NYU Langone, we found many patients undergoing cardiac catheterization were prediabetic and didn't know it. Even when patients are aware of their risk factors, they have to be motivated enough to lose weight, increase exercise, and take medication consistently.


Harmony Reynolds, MD

DR. REYNOLDS: A lot of people just aren't following what the American Heart Association calls Life's Simple Seven: Maintain a healthy weight; exercise; eat healthy food; have a normal blood sugar, blood pressure, and blood cholesterol; and don't smoke. If everyone followed these guidelines, there would be an enormous further reduction in cardiovascular mortality.

Most people have their cholesterol checked by their primary care physician. When is it a good idea to see a cardiologist?

DR. GIANOS: If your internist is aggressive about preventive care, that's wonderful. But when a patient is at intermediate risk and it's unclear whether they would benefit from preventive medications, it may be beneficial to consult a cardiologist or a cardiovascular prevention specialist. Cardiologists use a number of diagnostic tools to help figure this out. Calcium scoring, for example, uses a low-radiation CT scan to detect calcium in the coronary arteries, indicating plaque deposits. Someone's LDL cholesterol level might be normal, but if they have a high calcium score, that changes things. Our assessment tools also include stress tests, stress echocardiograms, ultrasound to measure arterial wall thickness, and of course, coronary angiograms.

DR. REYNOLDS: Getting your blood pressure and cholesterol checked by your primary care physician is very important. I think the primary care doctors at NYU Langone are especially attentive to this sort of thing. So part of our message is to get primary care doctors to focus even more carefully on these kinds of issues.

PHOTOGRAPHS BY JOHN ABBOTT

". . . the arterial walls are often lined with mild plaques that don't cause significant blockage, and these are usually the ones that rupture and cause heart attacks. All of the interventions we're asking people to do are really about making these small plaques less vulnerable to rupture."

DR. SHAH: Whichever type of doctor you see, it's important that a team-based approach be available. NYU Langone's prevention center will soon have a new office space where its physicians will collaborate with registered dietitians, exercise physiologists, diabetes educators, and smoking cessation experts. Our cardiac catheterization laboratory also collaborates with the prevention center both clinically and in research to address secondary preventive measures in patients treated with angioplasty and stenting.

Are statins effective on a preventive basis?
DR. GIANOS: Absolutely, for the right group. Multiple trials have shown that the lower your LDL cholesterol is, the better your outcomes are. For that intermediate group where the risk isn't clear, many do benefit from being on a statin. The newest prevention guidelines advocate using statins in even more patients, because of the multiple beneficial effects they have beyond lowering cholesterol.


Eugenia Gianos, MD

Statins also reduce inflammation, correct?
DR. REYNOLDS: Yes, which is very important. We still don't fully understand which plaques are vulnerable to rupture, and inflammation appears to play a role in this. The prevailing wisdom used to be that the rusty pipe was the problem—that if we just cleared out the plaque and got enough blood flow to the heart, everything would be fine. But the arterial walls are often lined with mild plaques that don't cause significant blockage, and these are usually the ones that rupture and cause heart attacks. All of the interventions we're asking people to do are really about making these small plaques less vulnerable to rupture.

DR. SHAH: If, despite all the medications, patients are still having chest pain, then we'll consider opening up a chronic blockage. Sometimes, however, we'll do an angiogram and not see any severe blockages, meaning that there's nothing to open up surgically. That doesn't mean the patient is in the clear, though. As we said, it's the mild plaques that tend to rupture. But the concept that these mild plaques can't be fixed with a stent or bypass is sometimes hard for patients to grasp. Medical therapy, including statins, is most likely to prevent these mild plaques from rupturing.


Binita Shah, MD

Are people getting emergency treatment in time to save their lives?
DR. REYNOLDS: Another reason people are dying from heart attacks is that they aren't getting to the hospital quickly enough when they have a coronary event. This is a particular problem for women, who are less likely than men to experience chest pain during heart attacks. The American Heart Association and the National Heart, Lung and Blood Institute have a campaign under way to improve recognition of heart disease risk and warning signs among women. We also need to educate older people, who are even less likely to have chest pain during a heart attack.

DR. SHAH: If someone is having a heart attack, the quicker we can open their arterial blockage—which is what I do—the more heart muscle we can salvage, and the better their long-term outcome.

(continued on page 31)

Theresa Morrogh at her home in New Jersey.

Back to Her Former Self

After a long road to recovery, a breast cancer survivor feels as good as she looks

HER FIRST CANCER DIAGNOSIS came the same week her grandmother died. With a high-necked blouse to hide her bandaged neck, 26-year-old Theresa Morrogh and her new husband, Bill, kept the news of her Hodgkin's lymphoma to themselves at the funeral. Afterward, Morrogh's strength and courage were severely tested. She would endure a life-threatening reaction to chemotherapy, the loss of her fertility, and a bone marrow transplant that cured her lymphoma but increased her lifelong risk for developing other types of cancer. "The doctors didn't think I'd live to 50," she says.

Despite Morrogh's poor prognosis, years passed in good health. Then, at age 44, a mammogram revealed a small lump in her right breast. The long-dreaded secondary cancer had become reality. Morrogh underwent a double mastectomy in 2006. As in 75 percent of the 90,000 breast reconstructions performed each year in the U.S., she had implants tucked under her pectoral muscles to fill out her chest. While the saline implants looked good, they felt tight and constricting, like a bra three sizes too small. "They pinched, they pulled, they itched," Morrogh says. "They hurt 24 hours a day."

Using the tricks of distraction she had learned during her first cancer treatments, Morrogh tried not to focus on the discomfort, hoping it would improve with time, as her surgeon suggested. "The fourth year with the implants, I finally said to myself, 'I can't take it anymore. Just open me up and take them out,' " she recalls. "I was miserable."

Morrogh consulted several plastic surgeons about removing the implants and forgoing reconstruction. All tried

PHOTO BY JOSHUA BRIGHT

to dissuade her. Two believed it was not the implants but the mastectomy that caused discomfort. One suggested that her symptoms were purely psychological. Her nerves frayed, Morrogh took the advice of members of an online cancer forum and visited Christina Ahn, MD, associate professor of plastic surgery at NYU Langone Medical Center, who specializes in breast reconstruction and implant problems. "Dr. Ahn asked: 'Do you have trouble raising your arms? Do you have itching and tingling?' " Morrogh recalls. "I started crying before I could answer. Finally, somebody understood."

Morrogh's reaction to the implants, it turned out, was not unusual. Up to 12 percent of those with breast implants (and up to 40 percent of those, like Morrogh, with prior radiation treatments) develop a dense, fibrous, sometimes deforming scar around the prosthesis known as capsular contracture, a biological response to foreign material within the body. Morrogh's case was among the worst Dr. Ahn had ever seen.

Offering to remove the implants and scar tissue, Dr. Ahn counseled Morrogh against leaving herself flat chested. "Living without breast mounds can be a liberating choice for some women," explains Dr. Ahn, "but I told Theresa that without any fat padding she might still feel some irritation and pain." Dr. Ahn offered two types of breast reconstruction, both utilizing the body's own transplanted fat tissue. The first involves extracting a large section of fat and skin tissue from the thighs, buttocks, or abdomen, which is formed into a breast during a lengthy, complex surgery.

The second, which Morrogh chose, is autologous fat grafting, a less invasive technique. In the first of several surgeries spaced out over the course of a year, Dr. Ahn removed Morrogh's implants and scar tissue, extracted "microdroplets" of fat from her thighs and her flank above the hip, and then slowly injected fat into the mastectomy area, carefully layering the droplets. "The fat cells need to be placed carefully into an optimal vascularized tissue bed so that they can stick to the surface and start to grow new blood vessels to supply oxygen and nutrients," explains Dr. Ahn. "It is both art and science," she adds, noting that fat cut off from an adequate blood supply could turn into scar tissue or get reabsorbed into the body.

Even in the recovery room, Morrogh's chest no longer felt tight and irritated. "If we'd stopped right there," she says, "I would have been thrilled." After surgery, she avoided sleeping on her stomach and wore compression pants to minimize swelling in her thighs. Three more surgeries followed. "Each time," she says, "my breasts were a little bigger and looked a little better."

Just before Morrogh turned 50, a birthday she never thought she'd live to celebrate, Dr. Ahn declared the reconstruction a success. Morrogh's new breasts looked and felt natural. Best of all, they felt natural *to her*. "Now I don't think about my breasts or worry about them," she says. "Dr. Ahn gave me back who I was before the mastectomy, before the discomfort took over my life." ●

—AMY ENGELER

Faculty Conversation

(continued from page 29)

At NYU Langone, we have excellent "door-to-balloon times"—the time from when the patient reaches the hospital to when we open the blockage with a balloon angioplasty and stent. When someone is brought here with a heart attack, they'll fax us the EKG from the ambulance. When the patient arrives, our team is waiting to take them straight to the catheterization lab to open the blockage. It's one reason we have one of the lowest mortality rates for cardiovascular procedures in New York State.

DR. GIANOS: Secondary prevention is an area where we've made significant progress. For most people, suffering a heart attack, undergoing angioplasty or stenting, or having coronary bypass can be a real wake-up call. We feel that during this crucial time, patients may be more likely to make needed changes in terms of lifestyle and medication adherence.

What are some of the newer approaches being used at NYU Langone?

DR. REYNOLDS: One is intravascular ultrasound. Angiograms show where blood is flowing, but don't give much detail about the arterial wall. Intravascular ultrasound uses a tiny catheter to view the arterial wall from the inside. If we don't know the exact site of the heart attack, ultrasound can show where the plaque breakdown occurred. If Dr. Shah is inserting a stent, intravascular ultrasound can tell her exactly where to place it.

DR. SHAH: We're also employing innovative techniques for catheterization. Catheters are typically inserted through the femoral artery in the groin. An alternative is to go through the radial artery in the wrist. It carries less bleeding risk and fewer vascular complications, and the patient can get up and walk right away. This approach is a little more challenging technically, and nationally only 10 percent of catheterizations are done this way. At NYU Langone, we now perform one-third of our procedures radially, and that percentage is sure to increase because patients seem to prefer this method. ●

A CONSUMMATE DRAFTSMAN

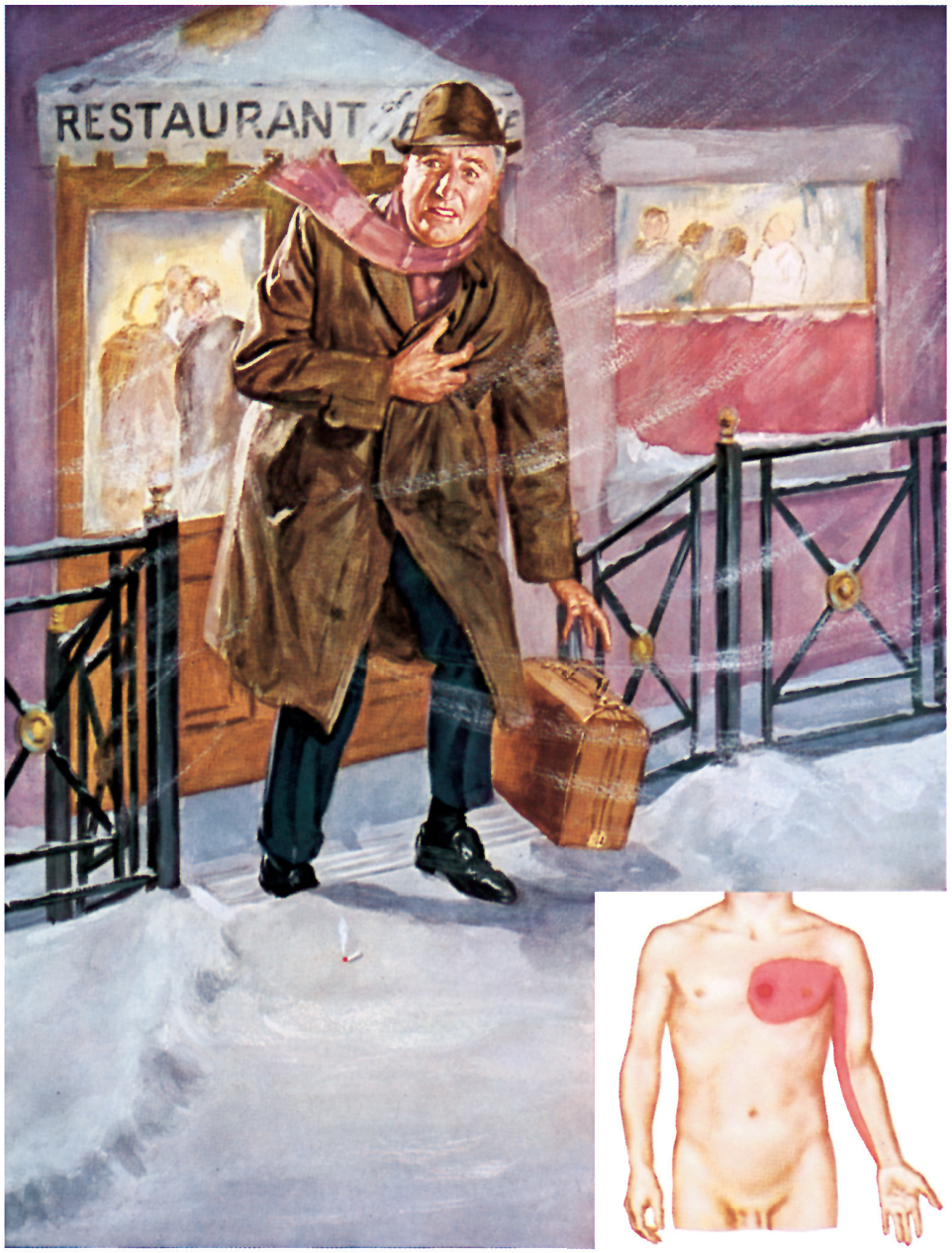
Countless doctors have used Frank Netter's illustrations as diagnostic aids. A graduate of the School of Medicine, his contribution to medicine is legendary.

BY KENNETH MILLER

AMONG THE MANY ALUMNI of NYU School of Medicine who've achieved renown in their respective fields, just one is remembered primarily for his accomplishments as an artist. Generations of medical students have learned anatomy by studying the drawings and paintings of Frank H. Netter, MD (1906–1991), and countless doctors have used his illustrations as diagnostic aids. "Dr. Netter's contribution to the study of human anatomy is epochal," the pioneering heart surgeon Michael DeBakey, MD, once declared. "He has advanced our understanding . . . more than any other medical illustrator since the 16th century, when Vesalius introduced drawings based on cadaveric dissections."

To Francine Mary Netter, however, the great man was simply Dad. "When I was little," she recalls, "and my teacher asked what my father did for a living, I said, 'He paints pictures of people's insides.' The teacher looked confused, so I went to my father and asked how I should answer that question. He said, 'You can say I'm a physician.' The next time someone asked, that's how I responded. But when they wanted to know where he practiced, I said, 'He doesn't practice. He paints pictures.' Then they looked confused again."

It was Dr. Netter's perspective as a physician combined with his genius as a draftsman that



Netter captured what *The New York Times* once called a "kind of multimedia presentation on the page." His classic depiction of a heavyset man clutching his chest, a cigarette smoldering at his feet, shows the triggers for angina pectoris: overeating, physical exertion, cold, or smoking. His illustration of a shoulder on page 35 reveals how he combined artistry with scientific accuracy.

gave his art its unique power. As his daughter reveals in her new biography, *Medicine's Michelangelo: The Art and Life of Frank H. Netter, MD,* he might never have chosen a medical career if his mother hadn't been a bit of a nag.

The son of immigrant shopkeepers from Lithuania, Netter grew up in a Hell's Kitchen tenement. His initial ambition was to become a magazine illustrator; he haunted the Metropolitan Museum of Art and took night classes at the National Academy School of Fine Arts. To his mother, however, being an artist meant "starving in a garret and carousing with nude models." (At the time, Netter later recalled, "this did not sound like such a bad life to me.") When he was 17, she made him promise to pursue a respectable profession, like engineering or medicine.

IT WAS DR. NETTER'S PERSPECTIVE AS A PHYSICIAN COMBINED WITH HIS GENIUS AS A DRAFTSMAN THAT GAVE HIS ART ITS UNIQUE POWER.

Soon afterward, she died of septicemia after a routine hysterectomy. Although Netter continued to study art as an undergrad at City College, he never forgot his vow. By senior year, he'd decided to become a doctor.

Still, he never relinquished his brush. In medical school, while training as a surgeon at Bellevue Hospital, Netter earned extra cash by illustrating textbooks and classroom materials for his professors, and when he went into private practice, in 1933, he discovered that his artistic talents were a far more reliable source of income than his medical skills. At the nadir of the Great Depression, few patients could afford a physician's care. To make ends meet, Dr. Netter began moonlighting for pharmaceutical companies, painting pictures to explain the function of their new products. After a few months, he felt guilty about neglecting his "real" work. So the next time an advertising manager called, he decided to ask for an exorbitant fee to scare him off: Instead of his usual $50 per picture, he demanded $1,500 for five. When the manager agreed to pay $1,500 for each painting, Dr. Netter was too shocked to correct him. In 1934, he quit seeing patients and devoted himself full-time to making art.

During his six decades as a medical illustrator, Dr. Netter wound up helping far more people than he could have as a surgeon, and he achieved a level of financial success and professional acclaim that surely would have made his mother proud. He was fond of big cars, flashy suits, and good Scotch, yet his manner remained humble and unpretentious. "People expected him to walk in with an ego that couldn't fit through the door," says Francine Netter, on the phone from her home in Charlottesville, North Carolina. "But he saw himself as a man with a job to do. He just sat down and got it done."

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THE TITLE OF MS. NETTER'S absorbing book is adapted from a phrase the *Saturday Evening Post* used in 1976 to describe her father: "The Michelangelo of Medicine." Like the original Michelangelo, whose genius was nurtured and promoted by the Medicis, Dr. Netter made history with the help of a powerful patron: the Ciba Pharmaceutical Company.

The Swiss-based firm (later known as Ciba-Geigy, and now as Novartis) approached him in 1937 to create a promotional flyer for a new heart medication. Dr. Netter designed a folder cut in the shape of a heart, with the organ's anatomy rendered in lifelike detail. Physicians loved it, and many asked for a version without advertising copy obscuring the illustration, which could be used to explain heart function to patients. Ciba then commissioned similar flyers for other organs. When those proved equally popular, Dr. Netter proposed producing a series of pathology illustrations, to be presented as cards in a folder (again, with ad copy printed separately). Over the next decade, Ciba released 14 of those portfolios; in 1947, they were published in book form as *The Ciba Collection of Medical Illustrations.* The collection, which eventually grew to eight volumes (with "Netter" replacing "Ciba" in the title) remains in print today.

In 1948, Ciba began producing another decades-long series of Netter-illustrated educational materials, the *Clinical Symposia*—magazine-style monographs on medical conditions and their treatment. Then, in 1989, the company published the first edition of the *Atlas of Human Anatomy,* a massive tome (still the top-selling reference book of its kind) illustrated entirely by the artist-physician. By then, he was 83 years old. He kept working, cigar in hand, until his death of heart disease two years later. All told, he produced more than 4,000 illustrations.

Dr. Netter's oeuvre was revolutionary in several ways. When he started out, the reigning illustrated guide for physicians was *Gray's Anatomy*—little changed stylistically since its debut in 1858, with intricate (and mostly monochrome) engravings of the body's inner workings.

Dr. Netter brought modern graphic techniques to medical illustration, along with a commercial artist's eye for visual emphasis; as a surgeon, he knew just what details needed to "pop" for maximum pedagogic value. His goal, he wrote, was to achieve "a happy medium between complexity and simplification . . . a middle course of realism without the clutter of confusing minutiae." Miraculously, he achieved that objective without sacrificing scientific accuracy.

Dr. Netter was a voracious observer, chronicling a tremendously fertile half-century of medical progress. He brought his sketchbook to the first implantation of a permanent artificial heart and to some of the earliest organ transplants and joint-replacement procedures. He recorded the advent of dialysis and pacemakers, and traveled the globe to document the effects of exotic diseases on human tissues.

Perhaps most important, he had a gift for creating what *The New York Times* once called "a kind of multimedia presentation on the page." A classic example is his depiction of angina pectoris, whose symptoms can be triggered by overeating, physical exertion, cold, or smoking. Dr. Netter painted a heavyset man clutching his chest as he climbs the steps outside a restaurant on a winter evening; a cigarette smolders in the snow at his feet. An inset diagram shows how angina pain typically centers in a patient's left chest and radiates down the inside of the arm.

"These are not machines we are treating," Dr. Netter often said. "They are real live human beings." His illustrations convey that truth with a vividness seldom matched before or since.

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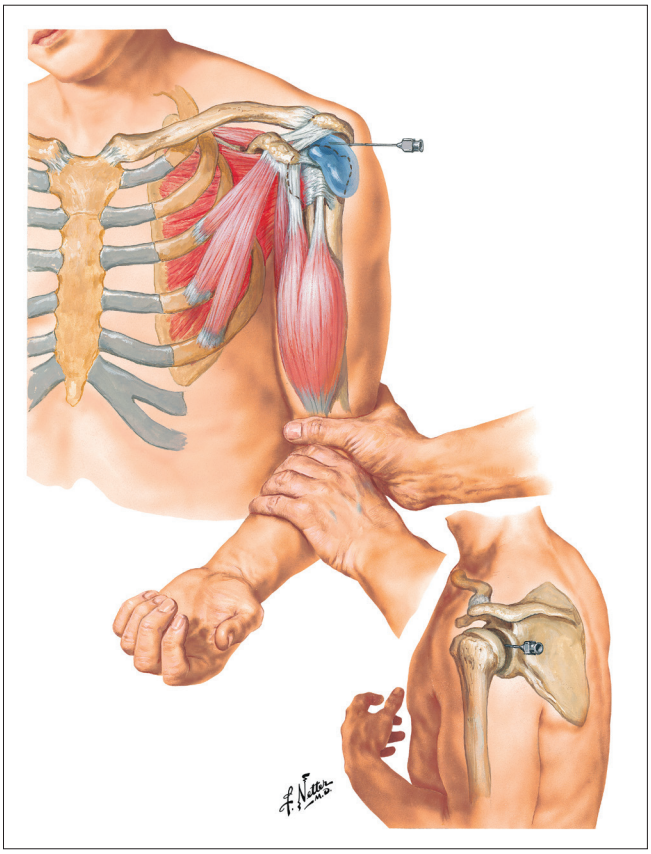
AT THE SCHOOL OF MEDICINE, where Dr. Netter's portrait hangs in the lobby, he is remembered with affection as well as pride. "We view him as one of our own," says Dean Robert I. Grossman, MD. "He ranks with our most notable graduates, including Salk and Sabin and a number of Nobel Prize winners." Dean Grossman's connection with the illustrator goes beyond the institutional: as a young neurosurgeon, he memorized one of Dr. Netter's *Clinical Symposia* for the first operation he ever performed—the removal of a subdural hematoma. To honor the master, the dean keeps four Netter drawings on display in his office.

Joseph Zuckerman, MD, the Walter A. L. Thompson Professor of Orthopaedic Surgery and chair of the Department of Orthopaedic Surgery at NYU Langone Medical Center, has an equally intimate connection with Dr. Netter's work. As a teenager, he loved to leaf through the *Clinical Symposia* that his older brother used as a study aid in medical school. When Zuckerman went to med school himself, he inherited his brother's monographs; his father also bought him the multivolume *Netter Collection*. When his own son began studying medicine, Dr. Zuckerman presented him with a later edition of that magnum opus.

DR. NETTER WAS A VORACIOUS OBSERVER, CHRONICLING A TREMENDOUSLY FERTILE HALF-CENTURY OF MEDICAL PROGRESS.

The enduring appeal of Netter's art, Dr. Zuckerman believes, is the way it marries medical precision to artistic punch. "You can read a passage in a textbook, and you may get it or you may not," he explains. "What drives it home—what makes it both comprehensible and memorable—is a good picture. And no one could make pictures like Frank Netter." ●



Sylvia K. Hassenfeld

SYLVIA K. HASSENFELD, 93, a longtime trustee of NYU Langone Medical Center, philanthropist, human rights activist, and children's advocate, died August 15, 2014.

A resident of Palm Beach, FL, Mrs. Hassenfeld was the matriarch of the family that built Hasbro, Inc., the $4 billion toy company, from a rag business started by two Jewish immigrants from Poland—her father-in-law and his brother.

A trustee of the Medical Center since 1984, she was also president of the Hassenfeld Foundation and spearheaded the family's gift of $50 million to create the Hassenfeld Children's Hospital. Scheduled to open in late 2017, the hospital is NYU Langone Medical Center's first comprehensive inpatient facility devoted to the treatment of children.

"The well-being of children is one of our great passions," she said in a 2011 interview with *NYU Physician*. "The first toys Hasbro made were doctor and nurse kits. I like to think that they inspired some youngsters who are now practicing pediatric medicine at NYU Langone. This gift is special to me and to my family."

Mrs. Hassenfeld gave generously to the medical center's Stephen D. Hassenfeld Children's Center for Cancer and Blood Disorders, named for her eldest son, who died in 1989. She also supported many institutional needs beyond children's services.

"Sylvia's desire to help children in need will thrive in the legacy she created with the Hassenfeld Children's Hospital, allowing us to begin a new era of pediatric healthcare in New York and help ensure bright, healthy futures for generations of children," said Robert I. Grossman, MD, the Saul J. Farber Dean and CEO of NYU Langone Medical Center.

Outside the NYU community, Mrs. Hassenfeld was known for her leadership and generosity in Jewish causes. She served as national chair of the Women's Division of the United Jewish Appeal; vice-chair of the Jerusalem Foundation; president of the American Jewish Joint Distribution Committee, where she oversaw the rescue of Jews and Muslims from Sarajevo; and president of Operation Solomon, which airlifted more than 14,000 Ethiopian Jews to safety in just 36 hours. She served on the boards of Brandeis University, the Hasbro Children's Foundation, United Israel Appeal, Hospice of Palm Beach, the Israel Museum, and other organizations. She was also director of The Society of the Four Arts, a Palm Beach cultural organization.

Born September 19, 1920, in Philadelphia, PA, the only child of Sophie and Joseph Kay, she married Merrill L. Hassenfeld in 1940. The couple settled in Providence, RI, where he went to work for the textile remnant firm Hassenfeld Brothers, started in 1923 by his father, Henry, and his uncle, Hillel. The company began making toys during World War II. By the early 1950s, the name was shortened to Hasbro Industries, which took off with the introduction of Mr. Potato Head and, later, G.I. Joe.

After her husband's 1979 death from a heart attack, Mrs. Hassenfeld's son Stephen served as chair and CEO for a decade until his death. In 1989, his brother Alan succeeded him in those posts.

"Giving back was something that my parents imbued in our family from a very early age," Alan Hassenfeld said in a 2013 interview with the online magazine *Leaders*. "Over dinner, they would discuss with us some of the different causes they were supporting and why they were doing it."

Sylvia Hassenfeld, with her great-grandson Kinsey Casdin, announcing the family's $50 million gift to NYU Langone Medical Center in fall 2011. The gift is being used to create the Hassenfeld Children's Hospital.

In 1944, Mrs. Hassenfeld earned a BA from Cedar Crest College in Allentown, PA, and in 1998, an honorary doctorate in humane letters from Brandeis University. For her humanitarian work, she has received honors and awards from the United States Holocaust Memorial Council, the American Jewish Historical Society, the National Conference of Christians and Jews, and other organizations.

Funeral services were held August 19 in Providence. She is survived by her two children, Alan Hassenfeld (and his wife, Vivien) and Ellen Hassenfeld Block; three grandchildren, Laurie Block, Michael Block, and Susan Block Casdin (and her husband, Alexander); and two great-grandchildren, Kinsey and Blaisdell Casdin. ●

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