NYU PHYSICIAN
THE MAGAZINE OF NEW YORK UNIVERSITY SCHOOL OF MEDICINE
FALL 2015

Unlocking the Potential of Cannabidiol

A new extract offers controversial hope for uncontrolled seizures

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NYU PHYSICIAN

ON THE COVER:
ILLUSTRATION BY
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ROBERT NOONAN / SCIENCE SOURCE

"They are hedonic flies," says Dr. Suh. "They only care about the sweet stuff."

COVER STORIES

DEPARTMENTS

NYU School of Medicine
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Nature is a master pharmacist.

Its unrivaled genius is the inspiration for more than 120 medications on the market today. We are all familiar with salicylic acid, better known as aspirin, which was once harvested from the bark and leaves of the willow tree. Penicillin was first discovered in a moldy petri dish. Then there's sweet wormwood, a fern-like plant native to Asia whose prized ingredient, artemisinin, is a potent treatment for malaria.

It's not surprising that medicine should seek to harness the therapeutic properties of marijuana. For the cover story of this issue of *NYU Physician,* we visited with Orrin Devinsky, MD, professor of neurology, neurosurgery, and psychiatry at NYU Langone Medical Center, and one of the country's leading epilepsy specialists. Dr. Devinsky has launched the first large-scale trial of cannabidiol, marijuana's main non-psychoactive chemical, for the treatment of the most severe forms of pediatric epilepsy. Early data are encouraging. The compound, delivered as a purified liquid extract, has already improved the lives of many children for whom conventional seizure medications have failed. It has also given parents a safer alternative to untested medical marijuana.

Whether we are researching new ways to treat intractable epilepsy, cure a devastating form of pediatric cancer, or elucidate the molecular drivers of obesity—you will read about all of these efforts on the following pages—uncompromising science is at the heart of everything we do. At NYU Langone, it's the foundation of our world-class patient care, and our commitment to it has never been stronger.

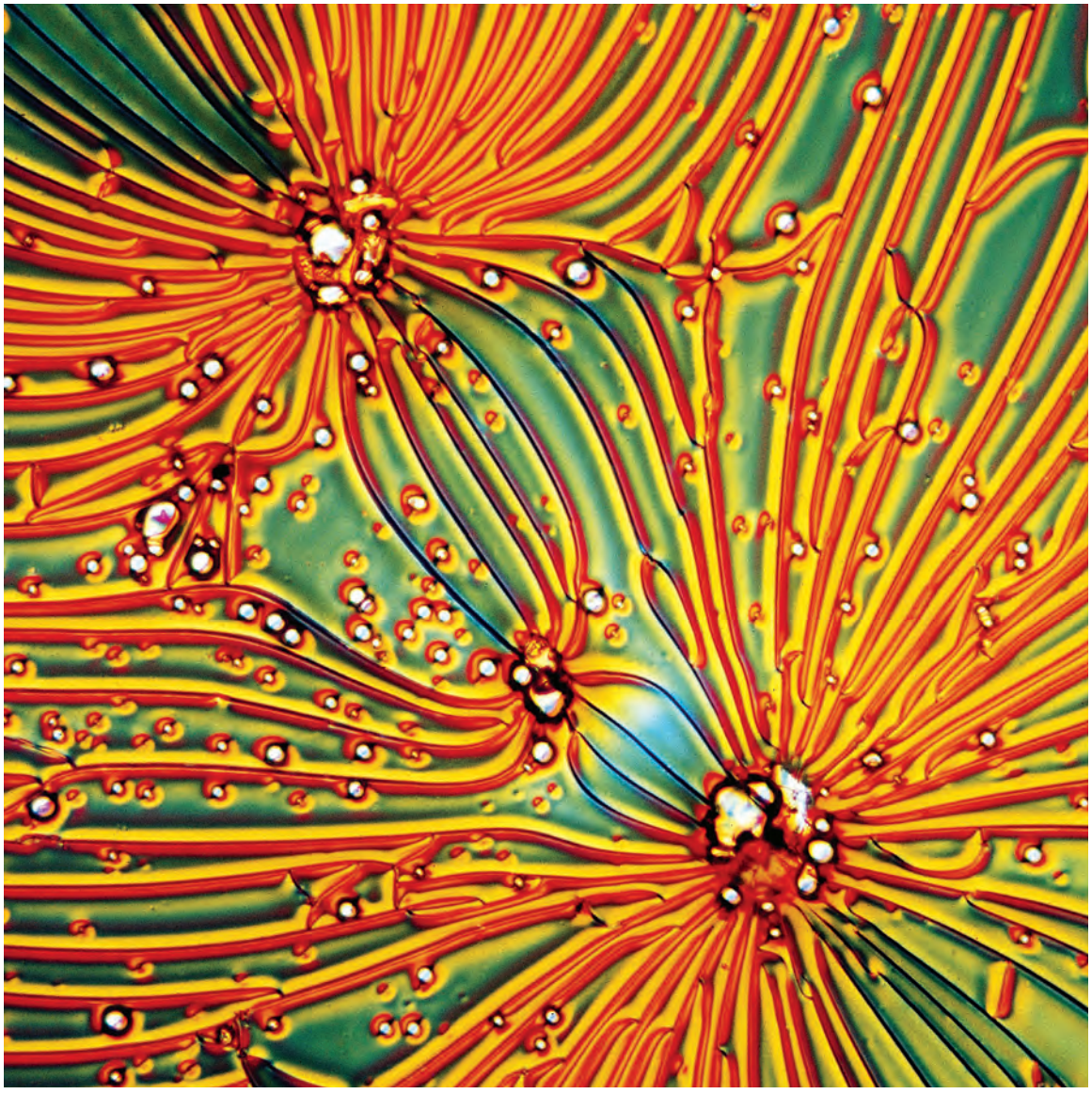
DEAN & CEO ROBERT I. GROSSMAN, MD

PHOTOGRAPH BY
JOHN CARNETT

NEWS FROM MEDICINE

FALL 2015

ADVANCES IN PEDIATRIC CANCER, THE MICROBIOME, HEART DISEASE, AND MORE



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Antibiotics magnified beneath a microscope.

"We have been using antibiotics as if there was no biological cost." MARTIN BLASER, MD PAGE 5 →

SUSAN SCHWAB, PHD

FRESH HOPE FOR TREATING A DEVASTATING PEDIATRIC CANCER

Researchers discover a way to reverse T-ALL in mice.

DESPITE GREAT strides in treating pediatric cancers, doctors have long known that one in four children diagnosed with a devastating form of cancer known as T-cell acute lymphoblastic leukemia, or T-ALL, will relapse within five years and face a grim prognosis. Even those who do respond to treatment often suffer serious long-term side effects from the drug and radiation therapies, underscoring the need for more effective and less toxic treatments.

Now, there is fresh hope. Researchers from NYU Langone Medical Center found that a protein on the surface of infection-fighting T-cells, named CXCR4, is essential for T-ALL survival. Blocking its activity, they discovered, can halt and even reverse the leukemia's growth and progression in mice. The unexpected finding, if verified in human clinical trials, could point toward a powerful new approach for treating the childhood cancer.

The research, published in the journal *Cancer Cell*, yielded dramatic results in mice that were afflicted with the equivalent of T-ALL and stripped of the CXCR4 protein. "When 100 percent of the mice with the wild-type leukemia had died, every single mouse in which we had deleted CXCR4 in the leukemia cells was alive and running around the cage," says Susan Schwab, PhD, assistant professor of pathology and an investigator in the Skirball Institute of Biomolecular Medicine, who co-led the study.

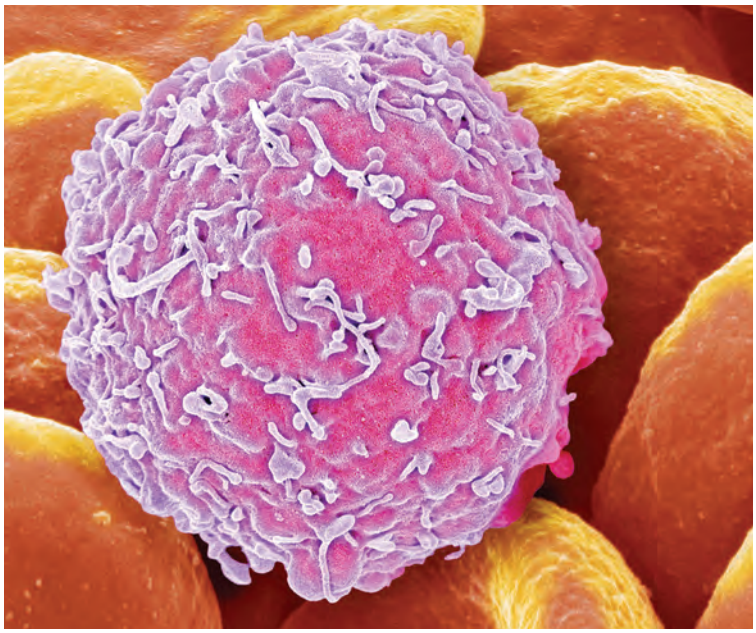
A second set of experiments, in which the collaborators transplanted leukemia cells from humans into immune-deficient mice, led to similarly surprising effects. Two weeks after some of the mice received a drug designed to block CXCR4, the therapy effectively halted leukemia progression.

"Every single mouse in which we had deleted CXCR4 was alive and running around the cage," says Susan Schwab, PhD.

Meanwhile, the leukemia continued unabated in the untreated mice.

Coauthor Iannis Aifantis, PhD, professor of pathology and chair of the Department of Pathology at the Laura and Isaac Perlmutter Cancer Center and an Early Career Scientist at the Howard Hughes Medical Institute, says researchers have only begun to explore the microenvironment, or physical niche, of cancer cells.

"It is actually the first study



A leukemia cell at 8,000x magnification.

STEVE GSCHMEISSNER / SCIENCE SOURCE. PORTRAITS: THEA BRINE.

that shows there are specialized microenvironments where leukemia cells reside," Dr. Aifantis says. "We are now able to visualize these microenvironments even in a living organism, using microscopy." By better understanding these physical niches within the bone marrow, he adds, researchers may be able to target them with antileukemia interventions.

How do cancerous cells co-opt CXCR4? The protein normally acts like a homing beacon to recruit blood cells to the bone marrow and help T-cells mature. Among its partners, the protein binds to a signaling molecule named CXCL12, which is secreted by blood vessels and attracts other cells to create T cell–supportive niches in the marrow. The researchers suspect that T-ALL exploits this same signaling pathway to attract blood cells and nutrients to places where it can thrive instead.

Without the guidance of CXCR4, "the leukemia just essentially melts away," Dr. Schwab says. The study showed that depleting CXCL12 itself also stalls T-ALL progression. CXCR4 may play a key role in human development but seems to be less important later in life. In adults, drugs that block the protein's activity in targeting other diseases have been well tolerated, though researchers caution that the medication's safety must be evaluated in children, as well.

The NYU Langone researchers plan to study next-generation inhibitors of CXCR4 that may be even more effective. Some of these drugs are already in clinical trials for other conditions, meaning that tests of their application for T-ALL could proceed quickly. The exciting potential, Dr. Aifantis says, owes much to the multidisciplinary exploration of leukemia's unexplored niches. "We've just approached it from different angles," he says. ●

—BRYN NELSON

MARTIN BLASER, MD

ANTIBIOTICS: TOO MUCH, TOO EARLY?

New mouse study links overexposure to antibiotics in infancy to lifelong metabolic disorders.

EVERY YEAR, up to 10 million U.S. children receive antibiotic prescriptions that are unlikely to do them any good, according to the American Academy of Pediatrics. A new study of antibiotic use in mice by NYU Langone Medical Center researchers suggests why the dangers of repeated and potentially unnecessary antibiotic use, especially early in life, may extend well beyond immediate side effects and eventual bacterial resistance.

"We have been using antibiotics as if there was no biological cost," says senior author Martin Blaser, MD, the Muriel G. and George W. Singer Professor of Translational Medicine and director of the NYU Human Microbiome Program. "Our latest experiments are yet another piece of evidence suggesting that overexposure to antibiotics indeed has long-lasting effects."

The study, published in *Nature Communications*, found that mice treated with two classes of antibiotics in doses proportional to those commonly used in children gained more weight, developed bigger bones, and had more disruptions in the microbial communities in their guts than untreated mice.

Although the implications for humans are still unclear, multiple studies in rodents and children by Dr. Blaser and other researchers have suggested that early-life antibiotic exposure can indeed alter the bacterial landscape of the gut and increase the risk of obesity and other metabolic disorders. Dr. Blaser, who was recently appointed chair of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, says the data could help improve guidelines for pediatric antibiotic prescriptions to minimize the potential harm.

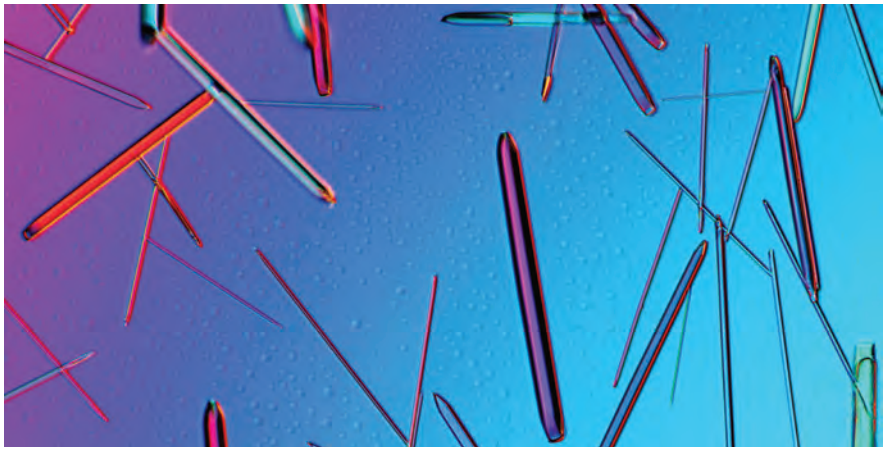
For the study, female mouse pups received three short courses of tylosin, an antibiotic used in veterinary medicine that represents an increasingly popular class of pediatric antibiotics called the macrolides; amoxicillin, a commonly used broad-spectrum antibiotic in the beta-lactam class; a mixture of both drugs; or no drugs at all. To mimic the effects of standard pediatric prescriptions in the U.S., the researchers gave mice the same proportional dose that the average child

receives. The mice received their first dose when they were just 10 days old.

While tylosin had the most pronounced effect on weight gain once the mice were three to six weeks old, the study found that amoxicillin had the biggest impact on bone growth. Based on extensive DNA sequencing, the research also showed that both antibiotics disrupted the development of the gut microbiome, or the trillions of microorganisms inhabiting the intestinal tract, by markedly reducing both the overall microbial diversity and specific markers linked to normal maturation. The results, Dr. Blaser says, suggest that the drugs are "stunting the maturity of the microbiome."

The study, supported in part by the Diane Belfer Program for Human Microbial Ecology, also suggested that antibiotic-exposed microbiomes may be less adaptable to environmental changes, such as a new diet. When the researchers moved six-week-old mice to a high-fat diet, the microbiomes of the untreated mice all adapted within a day by increasing the proportion of microbes linked to fat metabolism. Among the mice on amoxicillin, some microbiomes shifted in one day, while others took two weeks. "In the tylosin-treated mice, some of the microbiomes didn't adapt to high-fat diets until months later," says lead coauthor Laura M. Cox, PhD, an adjunct instructor in NYU Langone's Department of Medicine.

Antibiotics are vitally important for treating serious bacterial infections. With the average child receiving three courses of the drugs by the age of two, however, Dr. Cox and Dr. Blaser say the new study highlights the need for more targeted therapies, antibiotic stewardship, and scrutiny of the potential downsides of overuse early in life. ● *—BRYN NELSON*



Crystals of amoxicillin, an antibiotic widely used in children.

GLENN FISHMAN, MD

THE PURKINJE PUZZLE

Researchers create a new method of generating cardiac-conduction cells.

REPRESENTING less than 1% of heart cells, Purkinje fibers are nonetheless vital to a healthy, beating heart. These specialized cells form a critical but delicate network within the heart's muscular walls, transmitting life-sustaining electrical impulses. "Purkinje fibers branch out like a tree root, interfacing with millions of cardiac muscle cells to synchronize contractions," explains Glenn I. Fishman, MD, the William Goldring Professor of Medicine in the Department of Medicine and director of the Leon H. Charney Division of Cardiology at NYU Langone Medical Center.

In a study recently published in *Stem Cell Reports*, Dr. Fishman and a team of researchers at NYU Langone, in collaboration with the Weill Cornell Medical College, announced a new technique for growing large numbers of these specialized cells. Their exciting discovery opens the door to new therapies for cardiac arrhythmias and other heart conditions.

As part of the study, supported by the Weisfeld Family Program in Cardiovascular Regenerative Medicine and the Korein Foundation, the researchers scoured a library of nearly 5,000 chemicals, hunting for a substance that would help transform mouse stem cells into Purkinje cells. The team ultimately zeroed in on a chemical known as sodium nitroprusside, finding that it elevated levels of cyclic AMP, a

ANTONIO ROMERO / SCIENCE SOURCE.

multi-functional signaling molecule that appears to promote the differentiation of Purkinje cells. By exposing mouse stem cells to sodium nitroprusside, researchers found it was possible to generate populations of cardiac cells that include nearly 40 percent Purkinje cells.

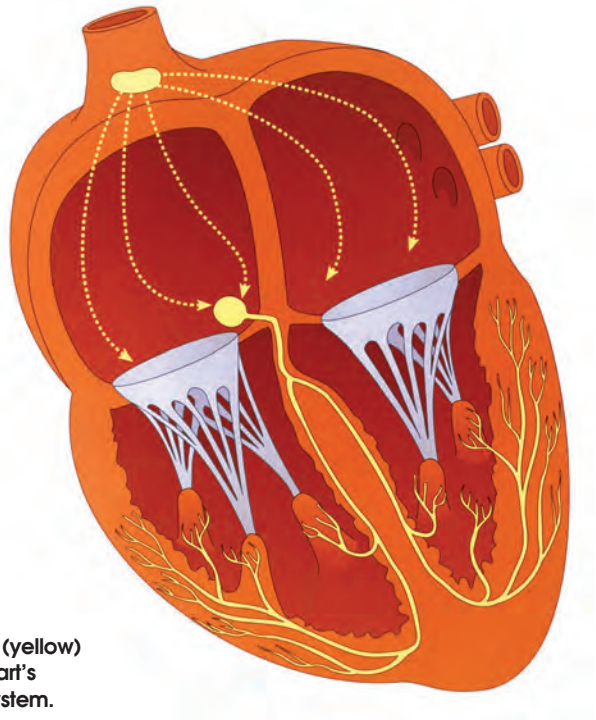
The finding holds important clinical implications. Damage to Purkinje cells due to cardiovascular disease or congenital disorders can disrupt the electrical signals that regulate heart beats. By inducing stem cells to become Purkinje cells, it may be possible to reconstruct the Purkinje network anew rather than implanting a pacemaker, the standard solution. "The ultimate goal is to create artificial Purkinje fibers and reconstruct part of the heart's original conduction system," says Dr. Fishman.

In addition to acting as a patch for a damaged conduction network, artificial Purkinje cells could also be used to develop new drugs to treat abnormal heart rhythms. Current antiarrhythmic drugs are fraught with side effects because they target the entire heart. "Now that we have a way to isolate Purkinje cells, we can screen them with candidate antiarrhythmic drugs and perhaps identify those that specifically target the biology of the Purkinje cell," says Dr. Fishman.

Next up, the researchers hope to apply the same methods to coax Purkinje cells from human cardiac stem cells. ●

—JOSHUA FEBLOWITZ

The researchers scoured nearly 5,000 chemicals for one that would transform mouse stem cells into Purkinje cells.



The branched extensions of Purkinje fibers (yellow) sustain the heart's conduction system.

PETER GARDINER / SCIENCE SOURCE. PORTRAITS THEA BRINE

ROBERT FROEMKE, PHD

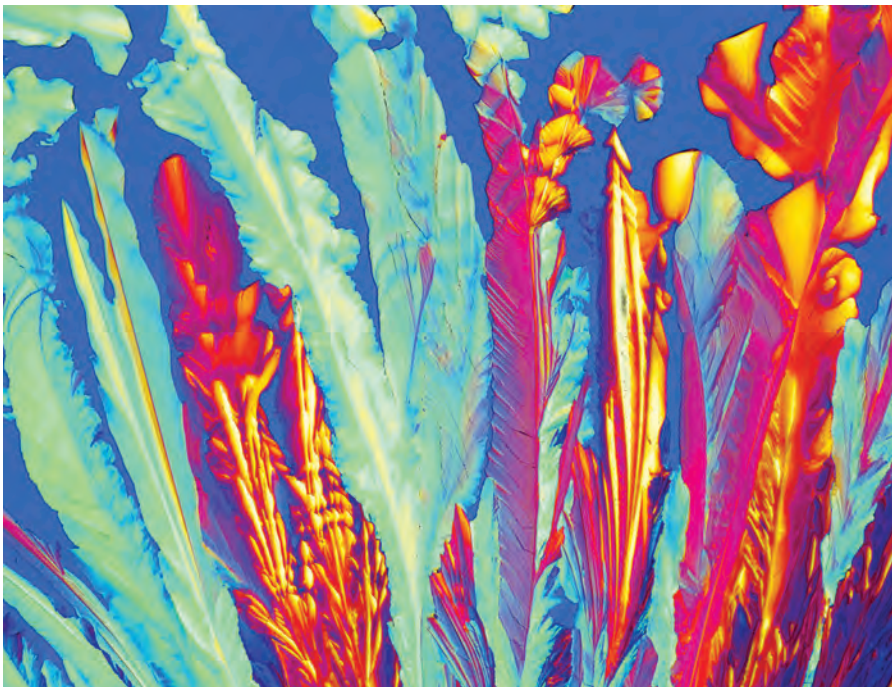
MOTHER LOVE AND OXYTOCIN

A new study reveals the brain region where oxytocin exerts its remarkable effects.

THOUGHT TO be the hormonal glue that binds mother and infant, oxytocin is often referred to as the "love hormone." In mice, this chemical messenger, synthesized deep in the hypothalamus, attunes mothers to the ultrasonic distress calls of lost pups, enabling them to find and return their helpless newborns to the safety of the nest.

Where and how does oxytocin work in the brain to facilitate this lifesaving social behavior? Robert Froemke, PhD, assistant professor of otolaryngology and of neuroscience and physiology at NYU School of Medicine, and his team at the Skirball Institute of Biomolecular Medicine tackled this question in a recently published study in *Nature*. "We know a lot about how oxytocin works in the body, but not in the brain," Dr. Froemke says.

Ordinarily among mice, only veteran mothers respond to the squeaky, high-pitched cries of a lost pup. Males and females without offspring simply tune out the pleas. But nonmoms cohoused



Crystals of oxytocin at 50x magnification.

"In the past 10 years, there's been a lot of buzz around oxytocin as a trust drug, a love hormone," says Dr. Froemke. "But I don't think it's either of those things."

with veteran moms can learn the maternal behavior, and Dr. Froemke's new research shows that injections of oxytocin can help them learn it faster. "With oxytocin, the female without offspring begins to act like a foster mom," says Dr. Froemke. "She isn't lactating, she can't feed the pups, but she can pick them up and return them to the nest."

To study how oxytocin facilitates this remarkable transformation, the researchers set up an experiment in which three groups of female mice without offspring were cohoused with veteran mothers and observed for pup-retrieval behavior. One group received systemic injections of oxytocin prior to each testing session, while a second group received saline injections. A third group was genetically engineered to express light-sensitive proteins in the brain, courtesy of an emerging technology known as optogenetics. Implanted fiber optics allowed the researchers to flash blue light onto the engineered cells and stimulate the release of oxytocin. "It's one thing to inject a drug," says Dr. Froemke, "but with optogenetics, we can stimulate the release of oxytocin internally to really understand how the native circuitry behaves in living animals."

Within 12 hours of sharing the same habitat with the veteran mothers, more of the nonmoms that received oxytocin, either by injection or via optical stimulation, began retrieving distressed pups than the mice that received saline injections. Not only did the oxytocin groups begin retrieving pups earlier than the saline group, but they also retrieved more pups. Remarkably, after three days, the oxytocin-enhanced non-moms were rescuing pups at the same rate and speed as the veteran mothers. In a separate experiment, the researchers showed that even nonmoms housed alone can acquire the ability to rescue lost pups faster and more efficiently with an oxytocin boost than without it.

But which brain regions were responding to the oxytocin and how? To answer this question, the researchers developed a novel antibody that binds to and illuminates oxytocin receptors in the auditory cortex, a brain structure in the temporal lobe that facilitates hearing. Their findings revealed that oxytocin receptors concentrate in the left side of the auditory cortex in female mice with and without offspring, suggesting that this brain region, which plays an important role in speech recognition, may also underlie our ability to process social information.

"In the past 10 years, there's been a lot of buzz around oxytocin as a trust drug, a love hormone," says Dr. Froemke. "But I don't think it's either of those things." Instead, he believes oxytocin is more like a sort of chemical volume control: turning it up allows us to pay more attention to relevant social cues. For people with autism, schizophrenia, PTSD, and other disorders in which the ability to "hear" social cues has been muffled, oxytocin-based therapies could prove therapeutic.

As for why oxytocin appears most active in the left side of the auditory cortex than the right, Froemke says, "That's the next big question." ●

—NICOLE DYER

PASIEKA / SCIENCE SOURCE

JORGE GHISO, PHD

CHOP SHOP

In a boost for Alzheimer's research, scientists reveal how two enzymes chop up toxic plaques in the brain for easier removal.

ROUGHLY 700,000 people in the U.S. will die from Alzheimer's disease in 2015, making it the sixth leading cause of death. A hallmark of the degenerative brain disorder is the buildup of a small protein called beta-amyloid, which forms the main constituent of clumplike plaques. Based on recent research, many scientists believe that these potentially toxic aggregations throughout the brain may be caused by errors in the brain's disposal process rather than by excess protein production.

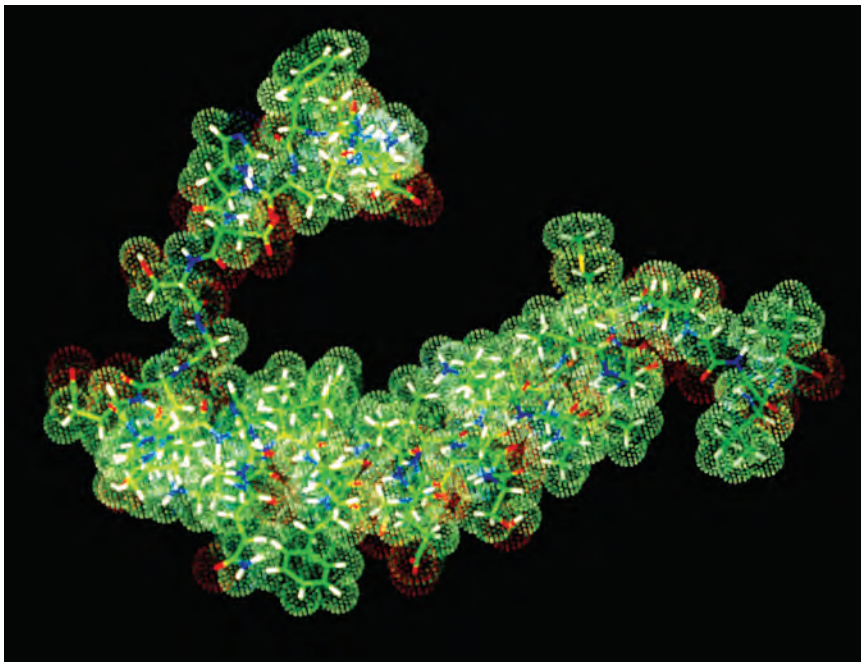
A new study led by Jorge Ghiso, PhD, professor of pathology and psychiatry at NYU Langone Medical Center, suggests that two enzymes in the brain may play a vital role in chopping up the dangerous beta-amyloid protein into smaller, nontoxic pieces that can be safely removed. The apparently beneficial actions of these two enzymes, known as MMP-2 and MMP-9, may point to new targets for therapeutic interventions that help disrupt the disease process.

"Researchers are trying to develop therapies for this disorder without understanding the molecular mechanisms of the disease," Dr. Ghiso says. Until recently, for example, many investigators overlooked the potential ability of protein-digesting enzymes, or proteases, to prevent the accumulation of disease-linked molecules. "By making the molecules smaller, perhaps it is easier to get rid of them," he says.

The new study, published in *The Journal of Biological Chemistry*, found that the MMP-2 and MMP-9 proteases begin chopping from the tail end of the main beta-amyloid proteins, which are either 40 or 42 amino acids in length. The proteases initially pare the proteins down to exactly 34 amino acids. That shorter version, in turn, is trimmed to 30 amino acids, and finally to only 16 amino acids.

This last remnant, the study found, is nontoxic and relatively stable, suggesting that it may be an important part of the removal process instead of a building block for beta-amyloid construction. Given the shortage of good biomarkers for Alzheimer's disease, Dr. Ghiso says, his lab is exploring the potential of the 16-amino acid piece as a better indicator of disease progression.

Dr. Ghiso cautions that the "promiscuous" proteases have many functions and can be harmful in high amounts. "So, simply increasing their concentration in the brain may have damaging consequences since these molecules will degrade other things," he says. The proteases can target the brain's network of blood vessels, for instance, and cause hemorrhaging. Nevertheless, he says, the new data may better illuminate the beta-amyloid disposal process and lead to experiments on whether carefully calibrated enzyme levels can improve clearance of the toxic protein without triggering unwanted side effects. ● *—BRYN NELSON*



Beta-amyloid molecules, shown here as a computer animation, form clumplike plaques in the brain associated with Alzheimer's disease.

LEONARD LESSIN / SCIENCE SOURCE. PORTRAITS: THEA BRINE.

UNLOCKING

The Potential of Cannabidiol

A nonpsychoactive ingredient of marijuana called cannabidiol has been hailed as miracle cure for intractable pediatric epilepsy. Now Dr. Orrin Devinsky of NYU Langone Medical Center's Comprehensive Epilepsy Center and colleagues are putting the contentious claim to the test in the first large-scale study of the compound.

BY KENNETH MILLER

UNTIL HE WAS TWO YEARS OLD, Liam O'Brien was a typical toddler—happy, active, and curious about the world. He would trot around his family's home on Staten Island, leaving a trail of toys and exercising his growing vocabulary.

THEN, ONE DAY in June 2011, Liam did something strange: He walked into the kitchen, dropped his chin to his chest, and thrust one of his arms in the air. He stood motionless for several seconds before continuing on his way.

In the weeks that followed, such episodes became more frequent. Liam also began losing his language skills. His worried parents, Karyn and Kevin, took him to a pediatric neurologist, who diagnosed him with autism. An electroencephalogram showed that he also had epilepsy, a condition in which abnormal bursts of electrical activity interfere with normal brain function. The resulting seizures can take many forms, from a brief dimming of consciousness to body-racking convulsions. Liam was experiencing a type known as myoclonic seizures, which sometimes cause involuntary movements in just one area of the body.

The neurologist started him on an anticonvulsant medication, but it had little effect. A second drug was added, but the seizures multiplied. They came in clusters, totaling 50 or 60 a day.

Seeking a team of specialists who could handle Liam's complex case, his parents brought him to NYU Langone Medical Center's Comprehensive Epilepsy Center to meet with its director, Orrin Devinsky, MD, professor of neurology, neurosurgery, and psychiatry. One of the country's leading epilepsy specialists, Dr. Devinsky has led many major studies of novel treatments. He ordered a thorough workup and prescribed a regimen of targeted medications. Although they reduced the frequency of the seizures, new problems arose. Liam began having atonic seizures, suddenly losing all muscle tone and crashing to the floor. He also developed tonic seizures, in which his entire body stiffened; often, he stopped breathing for 30 seconds or longer. "It was so scary," Karyn recalls. "I never knew if he was going to start breathing again."

As the months wore on, Liam was given more than half a dozen medications, but none eased his symptoms. Moreover, the drugs brought troubles of their own, making him floppy limbed and sleepy. The combined effects of the drugs and the seizures, which disrupt learning and may cause brain damage, added to the developmental delays associated with his autism. By age four, Liam could speak fewer than 10 words and was unable to use a toilet. To avoid injury, he was forbidden to climb stairs unassisted or sit in a chair without arms. He had to wear a helmet at all times to prevent concussions when he fell.

Liam's condition took a toll on his parents as well. His nighttime seizures left them perpetually sleep deprived. Any family outing could turn into an ordeal. Letting him play unsupervised was unthinkable. Kevin worked as a computer programmer, but Karyn's full-time job was making sure their son survived each day.

In July 2013, a TV documentary gave her a sliver of hope. Its subject was a little girl in Colorado who suffered from severe epilepsy and had received little benefit from conventional treatments. But the girl's seizures seemed to have been all but banished by a highly unconventional remedy: an extract of cannabis. Along with a handful of other children with similar conditions, she used a strain that was high in cannabidiol (CBD), the plant's main nonpsychoactive chemical component, and low in intoxicating tetrahydrocannabinol (THC).

Karyn knew there were reasons to be wary. Possession of marijuana was a felony under federal law, and though Colorado had legalized medical marijuana, New York had not yet done so. But she was willing to try anything. "We can't live like this anymore," she told Dr. Devinsky's nurse practitioner, Erin Conway, RN. "I'm ready to move to Colorado."

Conway suggested a less radical move. Dr. Devinsky, she said, was about to launch the first large-scale study of CBD as a treatment for severe, treatment-resistant epilepsy, and Liam might be eligible.

• • •

DR. DEVINSKY had begun looking into CBD after another patient's father asked him about reports in the national media of supposed miracle cures wrought by extracts containing the substance. While there was very little in the literature about marijuana's anticonvulsant effects in humans, the neurologist was encouraged by the research in animals. Data showed that two of the most plentiful of the plant's 80-plus unique compounds, known as cannabinoids, could quell seizures—THC in 61 percent of animal studies, and CBD in 81 percent. THC interacts primarily with the endocannabinoid system, a neurological network that helps regulate physiological processes including sleep, memory, mood, appetite, inflammation,

PHOTO BY KARSTEN MORAN

By studying the potential of cannabinoids for treating epilepsy, researchers hope to separate truth from rumor.

Liam O'Brien with Dr. Orrin Devinsky, one of the country's leading epilepsy specialists.

immune function, and bone growth. (The body makes chemicals, known as endocannabinoids, which transmit messages through the system by binding to two types of receptors—CB1, found largely in the brain, and CB2, found mainly in other organs. THC fits into those receptors like a key into a lock.) CBD, meanwhile, works mainly with other signaling systems. Its anticonvulsant effects seem to involve receptors that help regulate the excitability of brain cells by altering the balance of calcium ions, and unlike THC, it doesn't deliver a high.

Dr. Devinsky was intrigued enough by CBD to begin exploring his own study. But there was one big catch: the compound was available only in the form of homemade oils and tinctures, with little control over consistency or purity. Then Dr. Devinsky heard about GW Pharmaceuticals, a British company that manufactured a cannabis-based medication, Sativex, which was approved in 22 European countries for relief of multiple-sclerosis spasticity. The firm's manufacturing processes were cutting-edge, and its product—an extract standardized to 50 percent THC and 50 percent CBD—met strict pharmaceutical standards. Dr. Devinsky called the company's CEO in London to explain what he had in mind.

Soon afterward, GW representatives sat down with researchers from NYU Langone and several other institutions in a conference room at the Medical Center's Comprehensive Epilepsy Center. Together, they hatched a plan for a multicenter trial of a purified CBD extract.

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EPILEPSY IS NOT a single disorder, but rather a group of disorders characterized by recurrent seizures that have no immediate cause. The condition, which afflicts about 1 percent of the population, occurs when the brain's electrochemical balance is disrupted, allowing neurons to fire excessively and for too long. In a seizure, a group of overexcited brain cells begin firing in an abnormally synchronized way. This sets off a storm that can involve just part of the brain (a partial seizure) or both hemispheres (a generalized seizure). Some rare types of epilepsy result from a defect in one gene. Other varieties can be triggered by brain injury, stroke, tumors, or substance abuse. Population studies indicate that heredity is a factor, but in most cases, the underlying cause is unknown. In about half of those affected, the disease can be controlled by a single medication. (More than two dozen types of anticonvulsants are available.) Around 30 percent of patients continue to have seizures, however, even when taking two or more drugs at once. Up to 25 percent experience adverse effects that limit treatment options. For some patients with severe epilepsy who don't respond to any treatments, removal of malfunctioning brain areas, though a last resort, is a viable option. Another is implanting a pacemaker to stimulate the thalamus (a structure deep within the brain) or vagus nerve. Such surgical procedures, however, can also lead to serious complications.

Liam O'Brien, with his parents, Kevin and Karyn, at NYU Langone Medical Center.

Caring for a child with a severe, chronic disease is always difficult, but because intractable pediatric epilepsy is usually associated with cognitive and behavioral problems, the challenges can be particularly daunting. Kids with epilepsy also have a four fold higher risk of death, according to the Centers for Disease Control and Prevention. Yet parents desperate for alternatives to conventional treatments will sometimes expose their children to other kinds of dangers. "They may try remedies they've seen on the news or on the Internet but that haven't been objectively proven to be helpful," observes Judith Bluvstein, MD, assistant professor of neurology and codirector of Pediatric Special Procedures at NYU Langone. "In some cases, such treatments may actually do more harm than good."

By studying the potential of cannabinoids for treating epilepsy, researchers hope to separate truth from rumor and to develop new treatments that are safer and more reliable than any do-it-yourself nostrum. Yet the hurdles facing scientists who wish to study cannabis and its active ingredients remain discouragingly high. The U.S. Controlled Substances Act, first enacted in 1970, stipulates five "schedules," or levels of restriction, based on a drug's degree of danger and medical value. Cannabis is classified as Schedule I—a category for drugs such as heroin and LSD, with a high potential for abuse, no accepted medical use, and no standard for safe use. Possession of the plant or its byproducts, except by specially licensed individuals, is punishable by prison and heavy fines.

Since 1996, when California became the first state to legalize medical marijuana, 22 others have followed. (New York's statute, passed in July 2014, is more restrictive than many but includes epilepsy among conditions legally treatable with cannabis.) Meanwhile, the drug's outlaw status on the federal level has increasingly been called into question. "Schedule I is crazy," Dr. Devinsky says bluntly. In recent years, the American Medical Association and more than 30 other mainstream medical groups have asked the government to consider reclassification. They cite cannabis's relatively low addictive power (9 percent of users get hooked, versus 32 percent of cigarette smokers) and demonstrated ability to ease symptoms stemming from chemotherapy, HIV, and other serious conditions, as well as growing evidence that cannabinoids could help control—or even cure—many ailments. (See box.) As the AMA's position paper puts it, the fact that marijuana is also used for getting high "does not obviate its potential for medical product development."

Nonetheless, researchers continue to navigate a grueling legal obstacle course. In addition to FDA approval, researchers must get permission from the Drug Enforcement Administration and state drug-control agencies. Marijuana must be obtained through the National Institute on Drug Abuse, which grows a small crop at the University of Mississippi. As mandated by law, the plant and its derivatives—even nonpsychoactive CBD—must be

PHOTO BY KARSTEN MORAN

FROM 40 SEIZURES A DAY TO 3 A MONTH: NICOLE CANO'S STORY

When Nicole Cano had her first seizure in 1998, at 10 weeks old, few would have imagined that her best hope for relief would come from the cannabis plant. Nicole was born with Aicardi syndrome, a rare genetic disorder in which the corpus callosum—the bundle of fibers that connects the brain's hemispheres—fails to develop. Along with developmental delays, patients suffer from seizures called infantile spasms, which often progress to severe epilepsy.

Nicole's spasms initially resembled stomach crunches; soon she was having hundreds a day. A neurologist prescribed phenobarbital, a powerful sedative. When that stopped working, she was given another medication, and then another—up to three at a time. None helped for long. Over the years, surgeons implanted several pacemaker-like devices to stimulate nerves associated with seizures, but they had a limited effect. By her teens, her whole body would go rigid for 20 minutes or more, sometimes leaving her unable to breathe. She often required rescue medications which made her sleep all day. Occasionally, she had to be rushed to the ER. "Her seizures took control of our lives as well," says her mother, Laura. "It was horrible watching her suffer."

Then, at 16, Nicole entered NYU Langone Medical Center's clinical trial of cannabidiol—a nonintoxicating component of marijuana—for patients with intractable epilepsy. Over the next year, she went from 40 major seizures a day to a mild one every three months. Although Nicole remains too intellectually disabled to speak, her mother sees significant improvement in her alertness and mood. "She's happier, and so is the rest of the family," says Laura, who also has two younger children. "It's changed our world."

stored in an extra-heavy safe with an elaborate alarm system. "Federal oversight essentially handcuffs cannabis researchers in the U.S.," explains Dr. Devinsky. "Other countries are far ahead of us."

Despite all this, Dr. Devinsky and colleagues managed to launch the 10-center study in January 2014, using a new GW Pharmaceuticals product called Epidiolex, an orally administered extract containing 99 percent CBD. The initial report, released in March of this year, provided data for 123 patients who had been treated for at least 12 weeks. The results were promising: Total seizures showed a median reduction of 46 percent. For patients with Dravet syndrome—a devastating and often treatment-resistant form of epilepsy—the reduction was 52 percent. Overall, 10 percent of patients—and 22 percent of Dravet's patients—were seizure-free. Adverse effects compared favorably with many conventional epilepsy medications: 21 percent of patients experienced sleepiness, 17 percent diarrhea, 17 percent fatigue, and 16 percent loss of appetite.

Does that confirm CBD's growing reputation as a miracle drug? Hardly. The study was mostly intended to establish parameters for further research. It was "open label," meaning that everyone involved knew what patients were getting, and there was no control group receiving a placebo. Nor does CBD appear to be strikingly superior to other anticonvulsants, aside from its relatively benign side-effect profile. "There are some patients who benefited, some who didn't, and some who actually worsened," notes epileptologist Daniel Friedman, MD, who helped lead the study. Because so little is known about CBD's effects, all patients in the study continued taking their existing medications, leading, in some cases, to problematic drug interactions.

Still, the prospect of having another weapon in the antiepileptic arsenal is encouraging to many. Dr. Devinsky's team recently began a double-blind, placebo-controlled study of Epidiolex for children with Dravet's and another genetic form of severe epilepsy, Lennox-Gastaut syndrome. He hopes that CBD will eventually improve the lives of large numbers of epilepsy sufferers—adults as well as children. Meanwhile, he's pleased that that the drug has helped at least a few of his patients. "Nothing makes me happier than seeing people get better," he says. "It's very gratifying."

Liam O'Brien was among the lucky 10 percent, though it took a week for the results to become clear. He got his first dose of Epidiolex on February 7, 2014, and remained at NYU Langone's Comprehensive Epilepsy Center for three hours afterward to be monitored for adverse effects. None appeared, but he had a seizure later that day. On February 8, he had three seizures, the following day, none. There were several seizures on February 10 and 11, none on February 12, and one each day on February 13 and 14. He hasn't had a seizure since.

Liam is six years old now, a round-cheeked boy with a blond crew cut and lively blue eyes. Those terrifying episodes of falling to the floor, unable to breathe, are gone. His autism hasn't vanished, but he's far more engaged with his surroundings. He finally mastered the potty. He can say more than 100 words, including his name, and form short sentences ("I want iPad" is a favorite). He no longer needs a helmet for most activities. He even learned to ride a bike. "I can relax a little bit," says Karyn O'Brien. "I can actually sit down and just let him be a kid."●

CANNABINOIDS: A VERSATILE NEW SOURCE OF MEDICINE

Research into the medical potential of cannabinoids, marijuana's unique chemical constituents, is still in its infancy. But some of these 80-plus compounds show signs of promise as disease-fighters. As a recent clinical study led by NYU Langone researchers suggests cannabidiol (CBD), the plant's main nonpsychoactive component, may help control epileptic seizures. In other laboratory studies, CBD has also been shown to kill tumor cells from cancers of the breast, brain, and skin, and protect mice from diabetic retinopathy, a leading cause of blindness.

Meanwhile, tetrahydrocannabinol (THC), the ingredient responsible for marijuana's "high," has been shown to slow the growth of lung tumors in mice by 50 percent; mixture of THC and CBD delays the onset of Huntington's disease in rats; a cocktail of five cannabinoids kills MRSA bacteria in vitro.

Cannabinoids are highly versatile: They can act as chemical triggers, forcing cancer cells to self-destruct, or as antioxidants, shielding healthy cells from harm. They also interact with the body's endocannabinoid system and other signaling networks, which regulate a wide range of physiological functions. Much more research will be needed before these complex molecules can be turned into lifesaving medications, but several pharmaceutical companies are already investing in the field known as "cannabis biotech."

TIME LINE

CANNABIS IN MEDICINE

2737 BCE

First recorded reference to medical use of cannabis, in treatise by Chinese Emperor Shen-Nung.

7TH CENTURY BCE

First documented use of cannabis for epilepsy, by ancient Assyrians.

1621 CE

Cannabis mentioned in *The Anatomy of Melancholy,* by English clergyman Robert Burton, as treatment for depression.

1839

Irish physician William O'Shaughnessy publishes first modern medical paper on cannabis, citing its use in India for conditions including pain, nausea, spasticity, and convulsions.

1840s

Medicinal cannabis extracts gain widespread acceptance in the West, becoming part of standard pharmacopoeia in Britain and the U.S.

1937

U.S. Marijuana Tax Act passed, effectively outlawing possession and sale of cannabis.

1970

U.S. Controlled Substances Act classifies marijuana (along with heroin and LSD) as a Schedule I drug, the highest level of restriction.

1986

The Food and Drug Administration approves Marinol, a synthetic version of THC (the active ingredient in cannabis), for treating anorexia in AIDS patients.

1996

California voters pass Proposition 215, making their state the first to legalize medical cannabis.

2009

U.S. Department of Justice declares that "it will not be a priority" to prosecute medical marijuana patients or caregivers.

2015

Obama administration streamlines approval process for cannabis research, eliminating requirement that proposals undergo review by Public Health Service.

The Sweet Life of a Fruit Fly

Why do we crave sugar? Why do we overeat? In the laboratory of Dr. Greg Suh, banana-loving fruit flies are yielding intriguing clues.

BY JOSIE GLAUSIUSZ

ROBERT NOONAN / SCIENCE SOURCE

Drosophila melanogaster, **a common fruit fly, snacks on a wedge of rotted fruit.**

FOR GREG SUH, PhD, it was a humble yet hungry little fruit fly that first convinced him of the universal allure of sugar.

In one simple experiment, conducted in 2010, Dr. Suh offered fruit flies a choice presented in a multiwell teriyaki plate: a dropper full of caloric sugar solution and a near-identical sugar with zero calories. The flies had no preference when they were sated but preferred the caloric sugar when they were starved. Later, he and his collaborators tethered flies in place with wax and offered the same choice. It took just 30 seconds for the flies to decide. Starved flies lapped up the caloric sugar, but when offered the empty-calorie alternative, they drank for a mere 20 seconds and then stopped. "That was really surprising," says Dr. Suh, associate professor in the Department of Cell Biology at NYU Langone Medical Center. "It is an innate behavioral response, because these flies were not previously exposed to pure sugars: They know right away that this is good stuff."

An award-winning neurobiologist, Dr. Suh studies the biochemical mysteries of feeding and appetite by probing the genes and nervous systems of *Drosophila* fruit flies. He and his research team at NYU Langone's Skirball Institute of Biomolecular Medicine have identified sensors in the fruit-fly brain that trigger sugar cravings. Complex interactions between genes, neurons, and hormones, Dr. Suh believes, can explain how these insect brains respond to hunger or satiation—and what happens when the balance goes awry. "We can learn a lot by studying fruit flies," Dr. Suh says, "and we can learn a lot about us, about our feeding preferences, by studying these small organisms."

By scrutinizing fruit flies, which carry some of the same disease genes as humans and can even get fat, Dr. Suh hopes to determine the role sugar plays in our propensity to overeat. The question has never been more relevant. While sugar consumption has actually declined since 1999, primarily due to reduced soda consumption, the average American still consumes more than 75 pounds of the sweet stuff each year, and that consumption is thought to contribute to an escalating obesity epidemic. According to the latest figures, almost 75 percent of men and 67 percent of women in the United States are now overweight or obese.

That's one reason why the National Institute of Diabetes and Digestive and Kidney Diseases recently awarded Dr. Suh a $1.9 million grant to investigate the causes of obesity. He is also funded by the National Institutes of Health and has received accolades from a wide range of sources. At the spring 2015 meeting of the Association for Chemoreception Sciences, Dr. Suh was honored with the Ajinomoto Award for Young Investigators in Gustation. He was, to his surprise, the first "fly person" to win the $3,000 prize.

• • •

Born in the city of Busan in South Korea, Dr. Suh personifies playful scientific curiosity. In conversation, he cites a wide range of influences, from Steve Jobs to his mentor, the late, legendary Dr. Seymour Benzer, "the father of neurogenetics," who pioneered the study of how genes control the development of the nervous system and hence behavior.

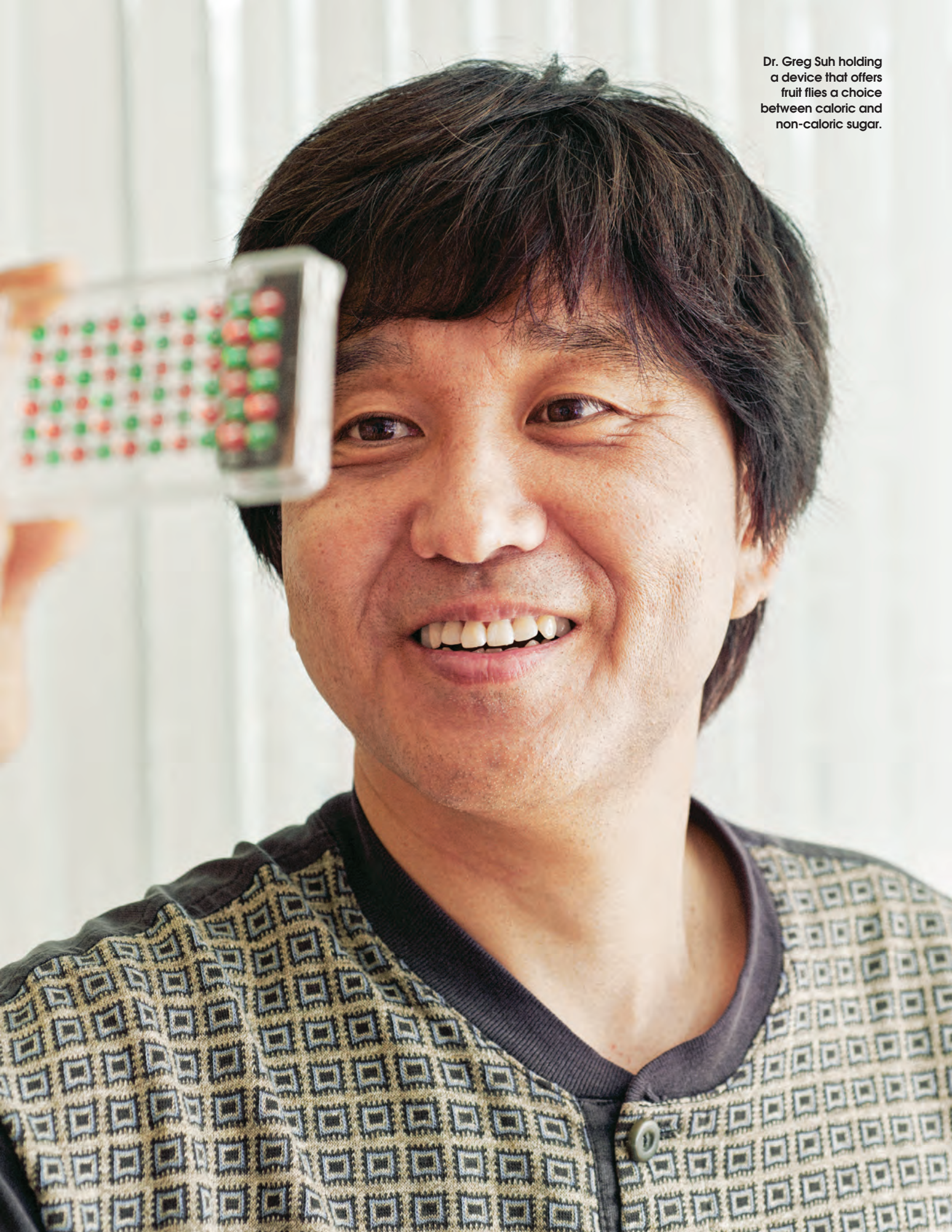
Dr. Suh first became interested in the feeding habits of fruit flies in 2003, while he was a joint postdoctoral student in the labs of Dr. Benzer and David Anderson at Caltech. On a whim, he decided to see what would happen if he fed fruit flies bananas. He quickly discovered that fruit flies willingly eat banana paste when starved but avoid it if they are sated—a typical response among mammals, as well.

That set Dr. Suh off on a quest to understand how hunger and satiation are encoded in the brain—one that he's continued ever since setting up a laboratory at the Skirball Institute in 2008. "It's not easy to study feeding behavior," he says. "There are many factors that influence feeding. You eat because you are hungry. You eat because the food tastes good. I thought perhaps there is a way to uncouple these two pathways." Though the average adult fruit fly is only about three millimeters long (about a tenth of an inch) with a brain only 100 microns wide (the diameter of a human hair), they are good model organisms for studying human appetite, because they are "cheap, easy to grow, and are genetically malleable," Dr. Suh says, sharing about 77 percent of their disease genes with humans (see "A Brief History of the Fruit Fly in Science," page 23).

In 2011 Dr. Suh and a postdoctoral student in his laboratory, Monica Dus, genetically engineered a fly in an attempt to uncouple pathways to hunger and taste. Their model insect carried mutant genes for sugar-detecting receptors located on its mouthparts. Publishing their work in the *Proceedings of the National Academy of Sciences*, the researchers found that the fly was unable to taste sugar, yet if starved for 15 hours, it would still choose to consume sugar over tasteless agar gel.

The implication of the finding was clear: Flies and other animals must possess a fail safe mechanism—one that is fundamental to their survival—for detecting energy-laden but bland foods. "In ancient times, we lived in a world that was very scarce of food," explains Dr. Dus, who left NYU Langone in late 2014 to head her own lab at the University of Michigan, Ann Arbor. "It was important for our ancestors, and animals in general, to be able to quickly get a handle on whether the

PHOTO BY SASHA NIALLA



Dr. Greg Suh holding a device that offers fruit flies a choice between caloric and non-caloric sugar.

food was good or not. Flies, if you think about how they feed, they just land in a patch of food that might have trash next to it, or there might be a really great food source. It's important for them to be able to recognize whether the food is edible, as well as the quality."

In their research, which was generously supported in part by the Irma T. Hirschl/Weill Caulier Trust, Drs. Suh and Dus had also found that starved flies without taste receptors prefer a form of sugar that can be digested and metabolized, called D-glucose, over a calorie-free artificial sweetener (sucralose) or a nonmetabolizable form of sugar, called L-glucose. A mystery neural pathway was enabling the taste-blind flies to identify caloric foods when they were hungry—possibly by detecting a rise in sugar levels in the insects' blood after the sugars get absorbed by the gut. But what form did it take?

In 2013, the team published new results in the journal *Nature Neuroscience* identifying a gene that they dubbed *Cupcake*, both for its action—it is a "hunger sensor" that enables the flies to gorge nutritionally valuable sugars—and an homage to Dr. Dus's dog, of the same name. (It's a tradition for fruit-fly researchers to choose offbeat names for the genes that they identify.) Starved flies with the *Cupcake* mutation could no longer distinguish between nutritional and nonnutritional sugars; they simply preferred the sugars with the most concentrated sweetness, even if they were calorie free.

The human analog of *Cupcake* is called, with slightly less pizzazz, SLC5A11. It encodes a transporter protein that enables cells in the small intestine to absorb glucose. But the *Cupcake* gene in flies is expressed only in a specific set of nerves, called R4 neurons, in a structure called the ellipsoid body within the insect brain. The researchers speculate that the neurons within the ellipsoid body monitor the insects' internal energy status, triggering feeding behavior if they are starved. But how?

Last July, Dr. Suh and his team announced that they had discovered a crucial piece of the puzzle. In findings published in the journal *Neuron*, they identified six neurons within the *Drosophila* brain that release a hormone that, in turn, is activated by nutritive sugars within the insects' blood. The hormone, a nutrient sensor called Dh44, or Diuretic hormone 44, is a homolog of a mammalian hormone named CRH, or corticotropin-releasing hormone. Starved Dh44-deficient flies in which the activity of these six neurons was disrupted could not sense caloric sugar. Instead, these pleasure-seeking insects lapped up only the sweetest sugar—artificial or genuine. "They are hedonic flies," Dr. Suh says. "They only care about the sweet."

In wild-type, nonmutant flies, the rise in caloric sugar levels within the insects' blood activates Dh44, which, in turn, stimulates the neurons in the brain to trigger feeding: the flies extend their mouthparts, or proboscis, to suck in more food. They also excrete more often, which indicates that their gut is moving. This positive feedback loop increases the flies' consumption of energy-rich sugars—the sort found in the fermenting fruits. "When they nibble, they know that this is caloric sugar and go, 'Oh, wow, this is the good stuff. I better start feeding,'" Dr. Suh says. Mutant flies with silenced Dh44 neurons, by contrast, can't tell the difference between caloric and noncaloric sugars.

"I always say that flies are little people. By studying flies, you can understand human nature a little better," says Dr. Suh.

In humans, the homologous hormone CRH is released by the brain's hypothalamus in response to stress and has a role in a range of stress responses, from food intake to the timing of birth. The researchers are now investigating the possibility that CRH neurons in mammals can sense glucose, allowing them to respond to the stress of starvation.

Understanding how CRH helps detect the caloric value of sugar is crucial, because animals with an inactive nutrient sensor will keep on eating; they are not satiated, leading to obesity. Overactivation of the gene could have the opposite effect, inhibiting feeding. Sequencing the human genes and unraveling their role could therefore help researchers determine the causes of both over-and-under eating.

"He really has been the pioneer on this range of *Drosophila* studies," says Yale neurobiologist Ivan de Araujo DPhil, whose own research focuses on nutrient-sensing and feeding behavior in mice. "Usage of flies is an extremely powerful tool from a genetic point of view," he says. "You can play with their brains." Screening fly genes for nutrient detection and selection that have homologs in the mammalian genome, "can help us understand how exactly we choose foods and whether we can intervene in some way to reduce effective intake."

Delving into the roots of human motivation is Dr. Suh's goal, ultimately. It's a habit that dates back to his early childhood years. On train trips with his family, he recalls, "my parents didn't have to babysit me. I would go to other passengers, and I would ask all kinds of questions, about him or her, about the universe, about the fourth dimension, UFOs." That thirst for knowledge still extends far beyond fruit flies. "I am a curious person in general," Dr. Suh says. "I'm mostly curious about human behavior. I always say that flies are little people. By studying flies, you can understand human nature a little better." ●

DAVID M. PHILLIPS / SCIENCE SOURCE

A BRIEF HISTORY OF THE FRUIT FLY IN SCIENCE

In 2008, as Dr. Greg Suh, PhD, was establishing his laboratory at the Skirball Institute of Biomolecular Medicine, Republican vice-presidential candidate Sarah Palin made a speech in which she cited research on fruit flies as having "little or nothing to do with the public good." The scientific community begged to differ. In fact, the contribution of the humble fruit fly to medical and genetic research is hard to overstate. "The fruit fly has led to an astounding number of discoveries in our understanding of human health and disease," says Dr. Suh, assistant professor of molecular neurobiology at NYU Langone Medical Center. Dr. Suh's own research on fruit flies, for instance, is casting much-needed light on the biochemical riddle of obesity.

The fruit fly, known more formally as *Drosophila melanogaster*, emerged as a champion model organism in 1910, when embryologist Thomas Hunt Morgan of Columbia University found sex-linked genes in mutant white-eyed male flies. His discovery confirmed the chromosomal theory of inheritance and, by extension, launched the field of classical genetics. Morgan's "Fly Room" at Columbia spawned not just thousands upon thousands of flies (one mating can yield hundreds of offspring) but generations of *Drosophila* scientists who discovered everything

from how to map genes on a chromosome to mutant Methuselah flies with an extended lifespan.

Perhaps the most pivotal moment in fruit-fly research came in 2000 when a team of scientists decoded the insect's entire genome, a monumental accomplishment that gave scientists the technical knowledge needed to sequence the human genome. We now know that *Drosophila*'s four chromosomes encode more than 14,000 genes, three-quarters of which have functional analogs in humans. With the aid of mutant forms of *Drosophila* (some of which sprouted legs from their head in place of antennae, or two pairs of wings) researchers have discovered so-called homeotic genes, which direct the process of embryonic development.

The fruit-fly brain offers an equally valuable window into human biology. Its constellation of more than 100,000 neurons direct complex behaviors such as learning and memory, sleep, and courtship. By analyzing fruit flies that undergo nerve degeneration in larval or adult stages, researchers have modeled neurodegenerative brain diseases impossible to study in humans, including Alzheimer's disease, Parkinson's, and fragile X mental retardation. Fruit-fly mutants also serve as model organisms for studying cancer, diabetes, and heart disease.

Among the many benefits of studying fruit flies, beyond the enormous potential to improve human health, is the long-standing, playful tradition of assigning odd names to the genes that one discovers. This practice has led to such quirky labels as the *Ken and Barbie* gene, mutations that lead to lack of external genitalia (as in the dolls); *hunchback*, which aids in the development of the fly's thorax; *swiss cheese*, which causes hole-pocked brain degeneration; the creepy Halloween family of genes (*disembodied, shade, shadow, shroud, phantom*), which trigger embryonic death before the exoskeleton has formed, giving these mutant embryos a spooky look; and then there's Dr. Suh's personal contribution, the *cupcake* gene, which lets fruit flies do what they do best: sense sugar. ●

A Focus on Prevention

Cheryl Pegus, MD, the new associate director for clinical innovation in the Department of Medicine at NYU Langone Medical Center, is devoted to breaking down barriers to wellness. BY RICH MALOOF

CHERYL PEGUS, MD, has enjoyed an unusually wide-ranging career in healthcare. She has served as medical director of the Cardiovascular Risk Factor Group at Pfizer, Inc.; national medical director and clinical product head for Aetna, Inc.; and chief medical officer of Walgreen Co. In October 2014, she was appointed director of the Division of General Internal Medicine and Clinical Innovation and named associate director for clinical innovation in the Department of Medicine at NYU Langone Medical Center. In her new position, Dr. Pegus is focusing her skills on preventing chronic conditions and dismantling barriers to wellness, pursuing a vision forged in childhood. She recently shared her thoughts with *NYU Physician*.

What made you become a crusader for preventive medicine?
Growing up in Trinidad, I was raised by a family that encouraged me to try new things. My grandparents let me climb coconut trees, and that was something most girls didn't do. Then, my grandfather passed away when I was 12. He could not afford healthcare and didn't really know enough to trust that you should go to the doctor before you got really, really sick. We cared for him at home. That stuck with me, and I decided back then I was going to be a doctor when I grew up.

Despite all the information and care available today, Americans are still dying of preventable conditions like most heart disease. Why?
Cardiac disease is the number one cause of death not just in the U.S. but globally. It kills more people annually than all cancers combined. Why is it still such a problem? Partly because we've spent a lot of time focusing on the later stages of the disease, treating a group that already has it. We've made great progress with treatment and decreasing deaths from heart disease, but we haven't focused enough on the earlier years when risk factors like diabetes and obesity begin to develop.

How do we integrate wellness earlier in patients' lives?
Managing wellness is a team sport. The physician is the captain when it comes to managing patients throughout the disease process, from the earliest phases and beyond, but there are many important players. Parents teach the first important lessons about diet and exercise, and they need their communities to help support lifelong healthy habits in children. Grocery stores need to provide healthy food options, and schools should be instituting lessons about nutrition and the importance of physical activity. Employers are great partners for wellness and prevention of chronic diseases. Programs that can engage and incentivize employees are also helpful. Healthy workplaces have been shown in studies to have positive results. Some of this is policy driven, but the bottom line is that many partners must be at the table to improve the health of populations.

"It's critical to have a buy-in from the patient and mutuality in achieving health goals. That's a shift from the past."

Who else should be involved?
I've found it very humbling to work with and learn from experts outside of the health sector who engage patients in their own self-management. Look at a tech company like Fitbit. They are not a traditional healthcare company, but they know how to engage people with digital health tools and programs, and the personalization is excellent. Partnerships with areas with different competencies are necessary to prevent people from developing chronic diseases.

When you look at demographic factors such as ethnicity, gender, and age, which has the greatest impact on health?
There is a lot of data on this, and income plays a very large role. Health systems in our poorest areas are the most pressed to improve quality, regardless of the population's race. In areas where you are concerned about life's basic necessities, your health takes a backseat. The income level of a community defines its resources, prioritization, and health.

PHOTO BY SASHA NIALLA

That seems like an especially intractable problem.
People go abroad and succeed in improving health dramatically in places where there is sometimes a great deal of poverty. The solutions are targeted to the community and its health resources, and are personalized to improve selected areas. This is where the policy piece comes in. Recently I was elected as an advisory panel member in the Addressing Disparities program at the PCORI [Patient-Centered Outcomes Research Institute], where the focus is on evidence-based research to improve the accessibility and effectiveness of care in communities. Multiple stakeholders will be looking at cost-effective solutions.

Is the relationship between patients and primary care physicians changing?
Patients now have to understand co-pays, deductibles, formularies, whether a prescription is generic or not—issues that are new. They also have mobile health tools and lots of information and data at their fingertips. In response, we physicians are modeling shared decision making. It's critical to have a buy-in from the patient and mutuality in achieving health goals. That's a shift from the past. NYU Langone is leading in this area, with changes to the medical curriculum, focusing on value, utilizing electronic medical records, and undertaking many new avenues of research.

How does your position at NYU Langone fulfill your broader ambition to improve wellness and prevention?
I'm fortunate to be working with great people right in my own sweet spot, where changing healthcare markets and data analytics meet great clinical care. There aren't many institutions that are ready to address all the big questions about changing a medical curriculum, integrating cost, quality, and access, and doing innovative research. NYU Langone is. In my role, we are developing care management programs across populations, utilizing data information systems, and integrating e-health. We are participating in collaborative research across population health, basic science, and innovation, and we are also educating the next generation of doctors. ●

Renowned Orthopaedic Surgeon Joins NYU Langone to Lead Research Efforts

THOMAS A. EINHORN, MD, an internationally renowned expert in adult hip and knee reconstructive surgery, whose award-winning research has included the study of novel biologic techniques to treat joint ailments, has been appointed director of clinical and translational research development for the Department of Orthopaedic Surgery at NYU Langone Medical Center. In this role, Dr. Einhorn will oversee the department's translational and clinical research efforts, which contribute to the understanding, treatment, cure, and prevention of musculoskeletal diseases. Dr. Einhorn, professor of orthopaedic surgery at NYU School of Medicine, is currently the principal investigator of a multicenter research project sponsored and supported by the National Institutes of Health. His research has been featured in more than 230 peer-reviewed journals. He has also authored six textbooks, more than 70 book chapters, and dozens of monographs. He previously served as chair of the Department of Orthopaedic Surgery at Boston University Medical Center, a position he held since 1997, and professor of orthopaedic surgery, biochemistry, and biomedical engineering at the Boston University School of Medicine.

An alumnus of Rutgers University, Dr. Einhorn earned his MD from Cornell University Medical College. He completed his residency at St. Luke's–Roosevelt Hospital Center, and his fellowship at The Hospital for Special Surgery. ●

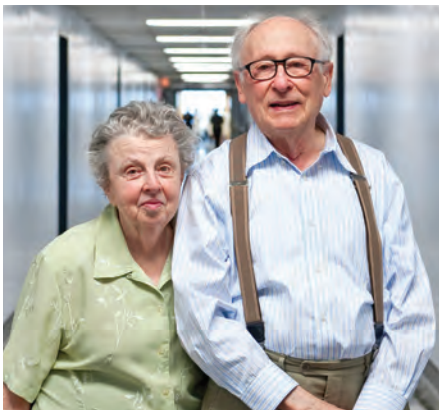
PHOTO BY ANDREW NEARY

Ruth and Victor Nussenzweig Receive Prestigious Alpert Foundation Award

SINCE JOINING NYU SCHOOL OF MEDICINE more than 50 years ago, Ruth S. Nussenzweig, MD, PhD, and Victor Nussenzweig, MD, PhD, have emerged as two of the most prominent researchers in the field of tropical medicine. Adding to their long and illustrious list of accolades, the husband-wife duo have received the prestigious Warren Alpert Foundation Prize in recognition of their groundbreaking research on malaria, a disease that kills nearly 600,000 people every year, mostly children in Africa.

Dr. Ruth Nussenzweig, research professor of pathology and professor emerita of microbiology and pathology, made her first big contribution to malaria research in 1967 when she immunized mice against malaria by inoculating them with irradiated sporozoites, the parasites that cause malaria. In doing so, she overturned the widely held belief that malaria was too complicated to vaccinate against, and launched a decades-long effort to create a malaria vaccine. In 1980, Dr. Victor Nussenzweig, research professor of pathology and professor emeritus of pathology, collaborated with his wife on the discovery of a sporozoite protein called the CS protein, showing that antibodies against it conferred partial immunity to malaria. This important insight laid the groundwork for the RTS,S vaccine, the most promising malaria vaccine in clinical trials today.

During her tenure at NYU Langone Medical Center, Ruth Nussenzweig has served as head of the Division of Parasitology in the Department of Microbiology and the first chair of the Department of Medical and Molecular Parasitology. She holds the distinction of becoming the first woman to chair a department at NYU School of Medicine. Victor Nussenzweig, meanwhile, has led the Michael Heidelberger Division of the Department of Pathology at the Medical Center since 1987. Both researchers are members of the American Academy of Arts and Sciences. Together, they have authored over 500 scientific papers.



The Warren Alpert Foundation honors innovative biomedical researchers dedicated to understanding and curing disease through groundbreaking research, scholarship, and service. Since 1987, the foundation, in partnership with Harvard Medical School, has awarded the Warren Alpert Foundation Prize to many of the world's foremost physician-scientists and researchers. Each fall, Harvard Medical School hosts a scientific symposium in October in honor of the recipients. ●

PHOTO BY MIKE WEYMOUTH

Building Stronger Bridges to Fight Parkinson's Disease

$25 million grant establishes international institute based at NYU Langone

THE PAOLO AND MARLENE FRESCO FOUNDATION has donated $25 million to NYU Langone Medical Center to establish the international Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders (the Fresco Institute) to advance the understanding and treatment of Parkinson's disease and movement disorders.

In honor of the gift, NYU Langone's Parkinson's and Movement Disorders Center will be renamed the Fresco Institute. The center has been a designated a National Parkinson Foundation Center of Excellence since 2009, and it will retain this designation. The gift will help establish a fully integrated Parkinson's center in Italy that coordinates efforts to care for patients. It will also create opportunities for early-career scientists and researchers in Italy through a fellowship program. Some of those fellows will train at NYU Langone for two to three years.

Jointly led by a clinician and a neuroscientist—Executive Director Alessandro Di Rocco, MD, and Scientific Director Richard Tsien, DPhil, respectively—the institute, in this respect, is believed to be the first of its kind devoted to Parkinson's disease. Afflicting an estimated 4 to 6 million people worldwide, including some 1 million Americans, Parkinson's is an incurable, progressive neurological disorder that destroys the brain cells that produce dopamine, an essential neurotransmitter. Early symptoms of the disease are movement related (shaking, rigidity, slowness of movement, and gait problems), while cognitive and behavioral problems may arise in advanced stages. According to the Centers for Disease Control and Prevention, complications from Parkinson's disease are the 14th leading cause of death in the United States.

From left: Dean Grossman, Kenneth G. Langone, and Paolo Fresco

"Treatment for Parkinson's is not one size fits all," explains Dr. Di Rocco, the Founders Professor of Neurology and director of the Division of Movement Disorders in the Department of Neurology. "People associate Parkinson's with tremors and slow movement, but it goes far beyond that. There are literally dozens of potential symptoms. The longer someone has it, the more intricate and individualized their symptoms become. Its progression also varies—slowly in some people and quite rapidly in others."

"The Fresco Institute will establish stronger bridges between clinical science and basic science of movement disorders, particularly Parkinson's disease," notes Dr. Tsien, the Druckenmiller Professor of Neuroscience, chair of the Department of Neuroscience and Physiology, and director of NYU Langone's Neuroscience Institute. "It will also build vibrant connections between scientists in the United States and in Italy working on disorders of the brain. The vision, leadership, and generosity of Paolo and Marlene Fresco have made this possible."

"Dr. Di Rocco and his team have cared for some of my dearest loved ones, for which I am profoundly grateful," says Paolo Fresco. A trustee at NYU Langone since 2013, he operates the Fresco Foundation and is involved in various charitable initiatives in Italy. He was previously chairman of Fiat and executive vice chairman at General Electric, where he worked for more than 35 years. Mr. Fresco received a law degree from the University of Genoa. ●

PHOTO BY KARSTEN MORAN

Martin S. Nachbar, MD

MARTIN S. NACHBAR, MD ('62), a passionate and dedicated teacher and mentor who early on grasped the enormous potential of computers in medical education, died on May 16. He was 78.

In the 1980s, Dr. Nachbar brought to NYU School of Medicine an entirely new field—educational informatics—by creating the Hippocrates Project, the School's first computer-based learning program.

"He handed us each a Phillips head screwdriver and told us to take apart what was in this box. We looked inside, and it was one of the very first personal computers," recalls Adina Kalet, MD, professor of medicine and surgery. Dr. Nachbar, she notes, taught them to program the computer and create tools to care for their patients—for example, to graph blood pressure and list medications—that are all part of chronic disease management and clinical informatics today.

Over the next decade, the Hippocrates Project pioneered innovations in computer simulation, 3D modeling and animation, and online learning, creating essential resources for the School's curriculum.

Dr. Nachbar was attracted to medicine for its "admixture of humanism and science," he said. In 1993, he and his wife, Felice Aull, PhD, who taught physiology at NYU School of Medicine, founded the Literature, Arts and Medicine Database, an online public resource for annotated works of literature, fine art, music, and the performing arts related to the science of healing. It has become the largest medical humanities website in the world.

In 2001, Dr. Nachbar became director of the newly created Department of Advanced Educational Systems, a forerunner of the current Division of Educational Informatics, established in 2007. The division, now under the umbrella of the Institute for Innovations in Medical Education, created e-learning tools like the Virtual Microscope and the WISE-MD surgical modules used by medical schools and health professions schools nationwide. In 2012, in partnership with a biomedical computer graphics company, the division introduced an online virtual cadaver with 3D images of the human body. Dr. Nachbar also cofounded the Consortium on Medical Education and Technology, a partnership of medical schools that share computer learning technology.

"He was unfailingly supportive, curious, and inquisitive—an incredibly powerful presence."

"He really was one of the fathers of an entirely new field," says Marc Triola, MD, associate dean for educational informatics, and director of the Institute for Innovations in Medical Education. "He was unfailingly supportive, curious, and inquisitive—an incredibly powerful presence."

Dr. Nachbar was born 1937 in the Bronx, the son of first-generation Americans of Russian and Hungarian ancestry. He attended Bronx High School of Science. He entered NYU School of Medicine in 1958, at a time he described as "electric" with the presence of giants like Severo Ochoa, MD, whose groundbreaking work on the synthesis of RNA won him a Nobel Prize; father of nephrology Homer Smith, MD; and award-winning author Lewis Thomas, MD, who served as dean of NYU School of Medicine.

Martin S. Nachbar, MD

Dr. Nachbar completed a residency in internal medicine at Bellevue in 1966. He subsequently joined the Department of Microbiology as an NIH Basic Science Training Fellow. In 1970, he accepted a joint appointment in the Departments of Medicine and Microbiology.

Dr. Nachbar received numerous educational honors and awards. He was named a Sackler Distinguished Lecturer, Tel Aviv University (1996). He won the Distinguished Teacher Award, NYU School of Medicine (1997); New York University's Distinguished Teaching Award (2005); and the Master Teacher Award, NYU School of Medicine (2007). In 2009, he became director emeritus of the Division of Educational Informatics. Dr. Nachbar is survived by his wife, Felice Aull; a daughter, Nancy; and a grandchild, Simone. ●

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One patient at a time. When you include a bequest in your will to NYU Langone Medical Center you help us deliver outstanding health care to the many patients and families who rely upon us to improve their lives. Superb physicians, an award-winning nursing staff and internationally ranked scientists make the difference. **Join our community, and create your legacy today.**

To learn more about making your planned gift to NYU Langone, please contact Marilyn Van Houten at 212.404.3653 or marilyn.vanhouten@nyumc.org.

Sasha Nialla

Moses V. Chao, PhD, professor of cell biology, neuroscience and physiology, and psychiatry, is a distinguished researcher at NYU Langone, and former president of The Society for Neuroscience.

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