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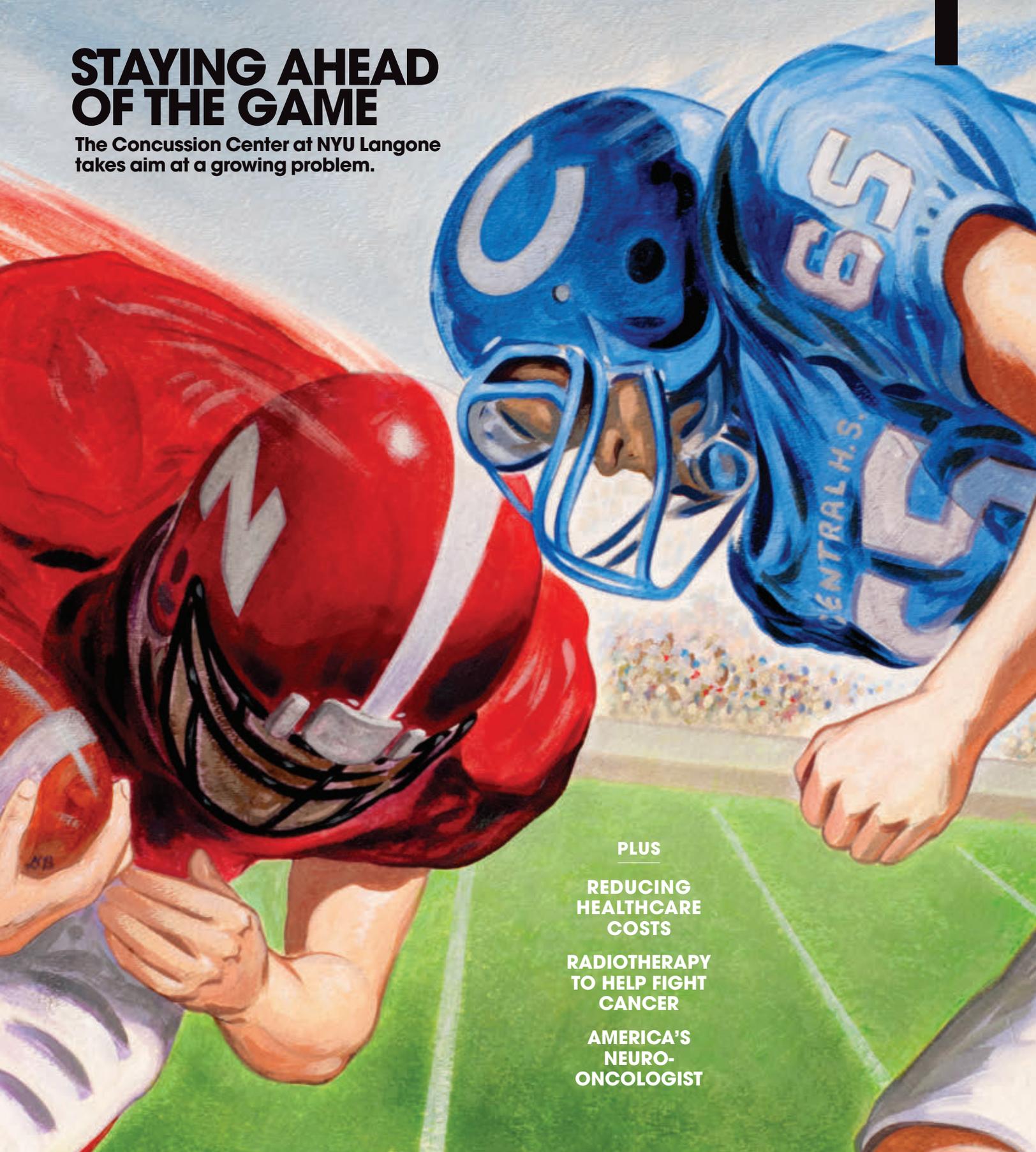
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1

STAYING AHEAD OF THE GAME

The Concussion Center at NYU Langone takes aim at a growing problem.



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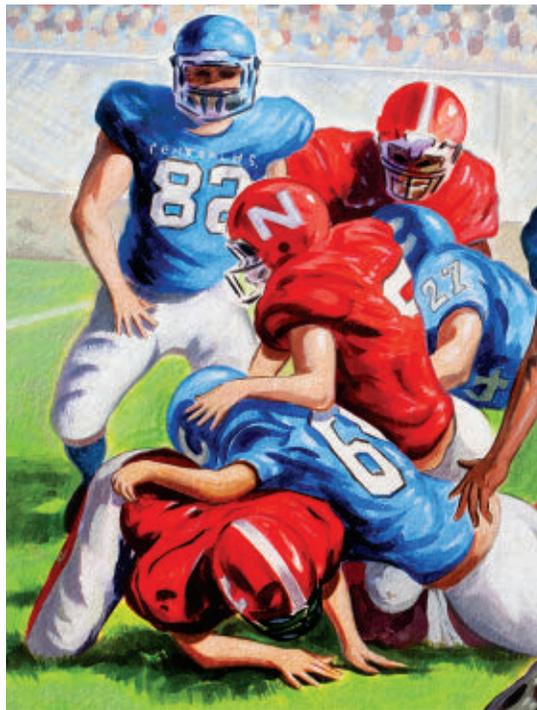
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One year after Hurricane Sandy,
a researcher looks back.

Last year, athletes in the United States suffered an estimated 4 million concussions, and many more go undiagnosed.

Bold Initiatives

THE CONTINUOUS DETERMINATION TO PUSH BOUNDARIES—building on existing strengths to take on new challenges—is a hallmark of an organization’s vitality. You will find in this issue two very different but equally telling examples that our Medical Center is brimming with life.



The first is our new Concussion Center, which opened in March, marshaling the expertise of more than a dozen specialties. Tackling a problem that sends skyrocketing numbers of children and young adults to ERs across the country—in part due to the growing awareness that such injuries can be far more serious than they seem—the Concussion Center has shouldered a broad mandate that encompasses comprehensive evaluation and treatment; research to deepen the understanding of specific effects on the brain and to devise evidence-based therapeutic guidelines; and educational outreach to the community, schools, and families.

The second is the Centers for Medicare & Medicaid Services (CMS) pilot program for which we have volunteered. With the objective of lowering costs, CMS is moving in the direction of having medical providers assume responsibility for an entire episode or “bundle” of treatment, including all follow-up care for postsurgical infections and hospital readmissions. This approach entails tremendous rigor on our part, and I salute the specialists doing the procedures (total joint replacements, cardiac valve replacements, and spinal fusions) that are leading the way. Doing all we can to avoid possible complications is an enduring commitment to our patients. At the end of the day, the concept of bundled payment is where our commitment to the highest-quality, patient-centered care meets the bottom line.

That we have continued to break new ground with initiatives like these, even while overcoming the devastation our Medical Center suffered from Superstorm Sandy last fall, is a sign of tremendous resolve and resilience. I am deeply proud of that, and grateful to everyone who has worked so hard to keep bringing our dreams to fruition.

A handwritten signature in black ink that reads "Bob". The signature is written in a cursive, slightly slanted style.

DEAN & CEO ROBERT I. GROSSMAN, MD

Hunger Games

Some cancer cells use giant protein harvesters to collect the fuel they need to grow.

SCIENTISTS HAVE puzzled over how cancer cells consume more sugar and amino acids than their environment seems to provide in order to grow, divide, and pile up into tumors. Where do they find the extra fuel to sustain their relentless growth? A new study by researchers at NYU Langone Medical Center proposes an explanation for this paradox, setting the stage for new and highly targeted cancer therapies.

The answer, reported earlier this year in *Nature*, lies in macropinocytosis, a sort of giant protein harvester that allows cells to engulf and ingest great volumes of liquid from their surroundings. After a cell engulfs the liquid, its membrane then pinches off, trapping the fluid in a bubble known as a macropinosome, which moves to the cell's interior.

The new study shows for the first time that certain cancer cells can use macropinocytosis to take up nutrients within the fluid. "This work offers up a completely different way to target cancer metabolism," says Dafna Bar-Sagi, PhD, senior vice president and vice dean for science, chief scientific officer, professor of biochemistry and molecular pharmacology, and the study's principal investigator.

Nearly all pancreatic cancers, and a high percentage of lung and colon cancers, carry mutations in a gene called Ras. Some 20 years ago, Dr. Bar-Sagi

discovered that mutated Ras stimulates macropinocytosis. While normal cells utilize it perhaps once an hour, she found that Ras-mutated cancer cells go into overdrive and can form one or two macropinosomes every minute. No one knew why, and it remained a mystery.

Five years ago, Cosimo Commisso, PhD, now a postdoctoral fellow in the Department of Biochemistry and Molecular Pharmacology at NYU School of Medicine, joined Dr. Bar-Sagi's lab. At the time it was known that some immune system cells use macropinocytosis to patrol for infectious organisms or other antigens. Conversely, bacteria and viruses can use the process to slip into, and infect, cells. Beyond that there was only one other clue: An amoeba that lives in soil was known to ingest soluble nutrients by the same means.

So Dr. Commisso, whose work was funded in part by the Pancreatic Cancer Action Network and the Canadian Institutes of Health Research, decided first to find out what

the tumor cells could be trawling for in the surrounding fluid. Body fluids are made up mostly of the protein albumin, which is made of many amino acids, including glutamine, a critical nutrient for cancer cells. Wondering if the cancer cells were harvesting glutamine from albumin, Dr. Commisso cultured Ras-transformed pancreatic cancer cells in a medium depleted of glutamine, mimicking the nutrient-starved environment of a tumor. The cancer cells multiplied slowly. When he added albumin, however, cell growth took off.

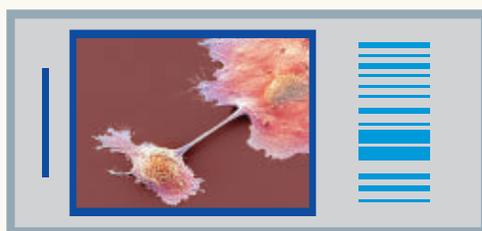
To test how cells were consuming glutamine, he used a chemical to block the uptake of albumin by macropinocytosis in mice with pancreatic tumors. The tumors stopped growing and in some cases even shrank.

"Nobody knew that macropinocytosis was a way to get nutrients into cancer cells,"

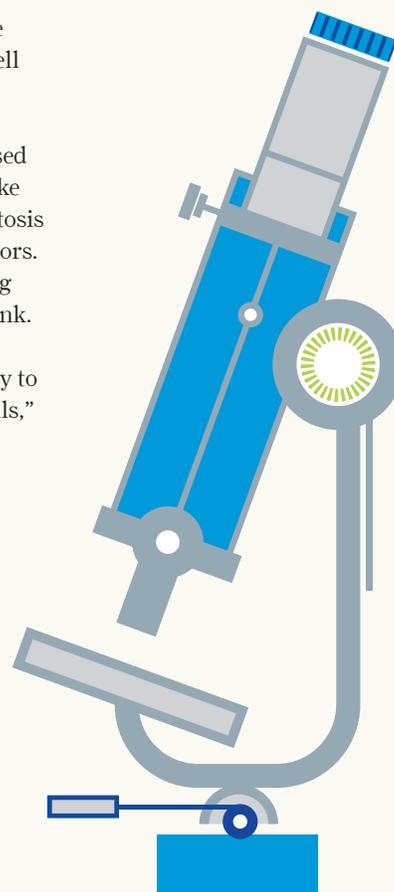
says Dr. Commisso.

The results suggest new approaches to treating pancreatic cancer, a notoriously aggressive disease with few treatment options that kills nearly 38,000 Americans annually. "It's exciting to think that we can cause the demise of some cancer cells simply by blocking this nutrient delivery process," says Dr. Bar-Sagi. "Macropinocytosis really is an Achilles' heel of cancer." ●

—ELIZABETH HANSON



▼ A cytoplasmic bridge joins pancreatic cancer cells in this scanning electron micrograph.





The Mysteries of PTSD

A brain chemical with an uncanny resemblance to the active ingredient in marijuana may hold some answers.

WHILE RESEARCHERS have long known that trauma can inflict lasting psychological scars—what physicians during the Civil War called soldier’s heart—surprisingly little is known about how those scars manifest in the brain. What are the neurobiological hallmarks of trauma, why are some people affected by it more than others, and how can we design medications to mitigate its damage and alleviate symptoms?

These are the questions that Alexander Neumeister, MD, professor of psychiatry and radiology, seeks to answer about post-traumatic stress disorder, or PTSD. A debilitating chronic condition that affects nearly 8 million Americans, PTSD develops in the wake of a traumatic event and can burden victims with frightening flashbacks, emotional instability, and memory gaps, among other problems.

Dr. Neumeister studies the underpinnings of PTSD in veterans, using imaging techniques such as positron emission tomography (PET). With the ability to see into the brain, he and his colleagues are discovering biological clues to the mystery of why nearly one in three veterans with PTSD also seeks treatment for addiction and why women are more prone to PTSD than men.

The answers have much to do with a potent brain chemical called anandamide, a molecule produced by the body that bears an uncanny

▼ The THC molecule relieves stress when it binds CB1 receptors in the brain.

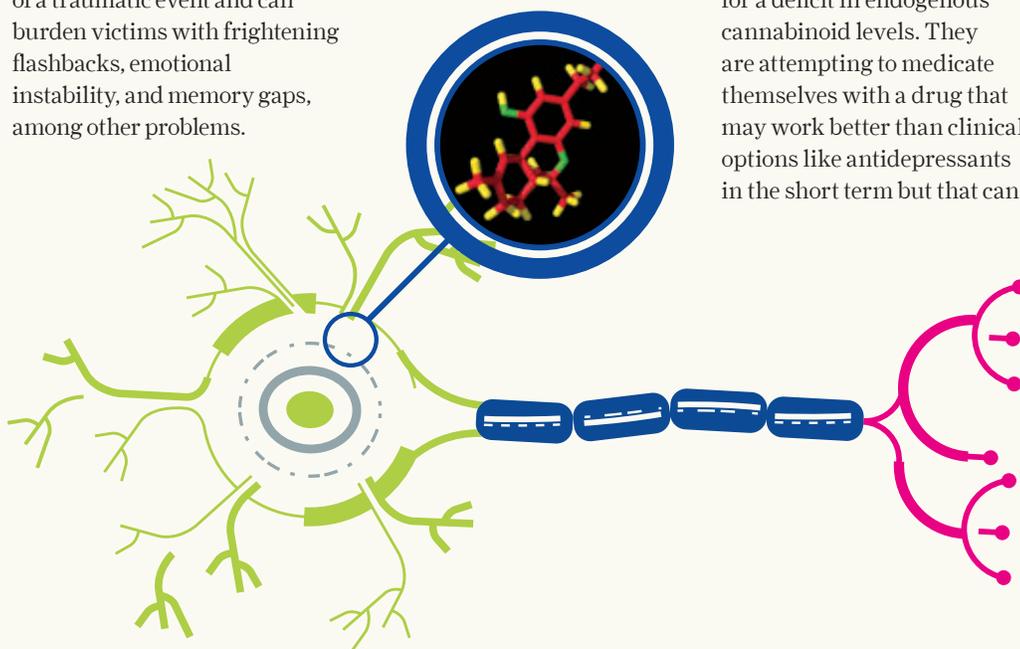
resemblance to THC, the active ingredient in marijuana. Like THC and other so-called cannabinoids, anandamide can alleviate pain and anxiety, increase appetite, and impair memory by binding to receptors in the brain known as CB1, short for cannabinoid 1. When anandamide runs low, the body responds by casting a wider net for the chemical and sprouting more CB1 receptors. If left empty, those same “feel good” receptors can leave people depressed, anxious, and craving relief.

In a recent paper in *Molecular Psychiatry*, Dr. Neumeister’s team showed for the first time that veterans with PTSD had markedly lower levels of anandamide than people without the disorder. “We know very well that people with PTSD use marijuana to help control anxiety and mood,” Dr. Neumeister says. “Our research supports the hypothesis that they smoke pot to compensate for a deficit in endogenous cannabinoid levels. They are attempting to medicate themselves with a drug that may work better than clinical options like antidepressants in the short term but that can

worsen problems over time.”

Their latest experiment divided 60 participants into those with PTSD; those with a history of trauma but no PTSD; and those with no history of trauma or PTSD. Participants in all three groups received a harmless radioactive tracer that, when exposed to PET scans, illuminates CB1 receptors. Participants with PTSD had more CB1 receptors in brain regions associated with fear and anxiety than volunteers without the disorder, indicating that the body may overcompensate for an anandamide deficiency by generating more CB1 receptors. The discrepancy was pronounced in women, corroborating earlier data that women have more CB1 receptors in the brain than men. “We know women are more vulnerable to psychiatric disorders such as depression, anxiety, and PTSD,” Dr. Neumeister says. “Naturally higher levels of CB1 receptors could be one of the reasons.”

In July, Dr. Neumeister and his team received \$4.9 million from the Department of Defense to help them develop a new drug to boost anandamide and bind it to CB1 receptors. “There’s not a single treatment out there that has been developed based on the specific molecular pharmacology of PTSD,” Dr. Neumeister says. “Clearly, there is a very urgent need to develop novel evidence-based treatments for the disorder.” ● —NICOLE DYER



PROF. KENNETH SEDDON & DR. TIMOTHY EVANS; QUEEN'S UNIV BELFAST/SCIENCE SOURCE

Fascinating Rhythms

Learning and memory depend on the daily oscillation of stress hormone levels in the brain.

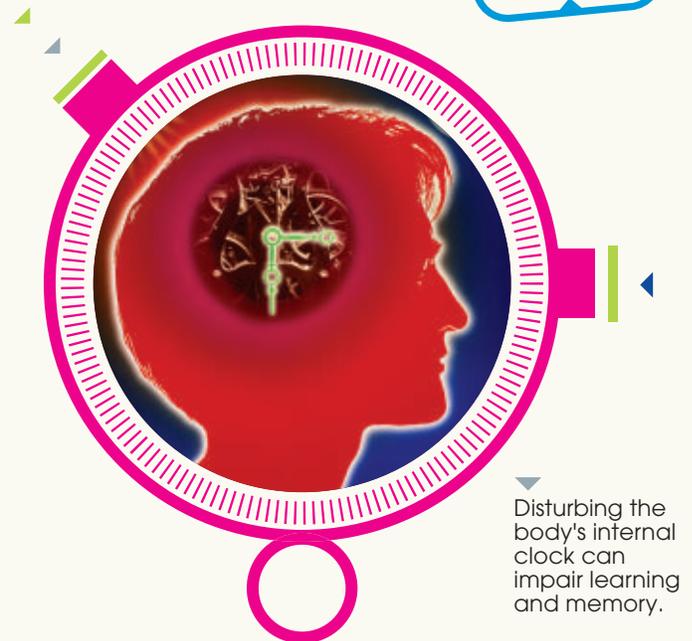
CHRONIC STRESS creates a flood tide of cortisol and other glucocorticoid stress hormones that wash over the brain, overwhelming the natural variation in the daily levels of these hormones, which, among other activities, have been associated with the ability to learn. But brief bouts of stress, it has been found, can actually improve learning. Why is this so?

Now Wen-Biao Gan, PhD, professor of physiology and neuroscience and molecular neurobiology, and a member of the Skirball Institute of Biomolecular Medicine, has an explanation. His team recently reported in *Nature Neuroscience* that the natural oscillation of glucocorticoid stress hormones in the brain affects the formation and maintenance of new synapses, the minute junctions where nerve cells communicate. A growing body of research suggests that our ability to retain lifelong memories and learn new information appears to lie in these tiny junctions.

Conor Liston, PhD, a postdoctoral researcher, trained mice on a standard motor-coordination learning device—the rotarod—which challenges them to stay on an elevated, slowly rotating cylinder. Using a powerful optical imaging technique pioneered in Dr. Gan's laboratory, Dr. Liston periodically peered through

a thinned area of the animal's skull and captured images of spiny protrusions called dendritic spines along the branching ends of neurons in the motor cortex. Previous work by Dr. Gan's lab has revealed that the learning of a new task such as mastering the rotarod causes new spines to sprout, forming new synapses, and old ones to wither—and the behavioral memory of that task corresponds to the persistence of those newly created spines. Mice trained at the peak of the daily oscillation in stress hormones, Dr. Liston found, formed many more new spines and stayed on the rotarod longer than mice trained at the lowest hormone levels. But the trough wasn't just a learning dead zone: It proved crucial for the survival of newly formed spines and the appropriate elimination of old ones. To simulate chronic stress, mice were given corticosterone, the principal glucocorticoid in mice, for 10 consecutive days. The injections smothered the natural daily rhythm of the hormone and suppressed both new spine formation and old spine pruning. Further experiments revealed distinct biological mechanisms through which glucocorticoids exert these effects.

"You can see how the natural daily peak and trough, which occurs in the morning and early evening, respectively, for humans, corresponds to our



usual rhythms of activity and learning," Dr. Gan says. "It hints too that you shouldn't try to keep learning all day—you should take a break to let your brain maintain its new connections."

The study helps explain the observation that jet lag and other disturbances of circadian rhythms impair learning and memory. For example, notes Dr. Gan, a study of international, time-zone-crossing flight attendants in 2000 found that they had disrupted glucocorticoid rhythms and reduced short-term learning ability compared to their deskbound colleagues.

Additionally, the new findings may shed light on

some of the adverse cognitive effects of prednisone and other medicinal glucocorticoids, which include not only memory impairment but also a striking, schizophrenia-like psychosis.

Neuroscientists Mitra Heshmati, PhD, and Scott J. Russo, PhD, of the Icahn School of Medicine, noted in a commentary in *Nature Neuroscience* that Dr. Gan's findings suggest a different approach to treating chronic stress disorders. Therapies for these conditions, they wrote, could be "aimed at not just reducing overall stress, but also at restoring the normal, diurnal oscillation in glucocorticoid secretion." ● —JIM SCHNABEL



Dan Littman

The Good, the Bad, and the Evasive

How healthy intestinal bacteria evade the immune system.

WHILE THE TRILLIONS of resident bacteria flourishing within the human gut rarely provoke immune reactions in healthy people, these same microorganisms can incite a violent response in those with inflammatory bowel disease. A recent study in *Nature* by NYU School of Medicine researchers may help explain this enigma. In a healthy intestinal tract, the research suggests, beneficial, or commensal, bacteria may send signals that prevent sentrylike cells called phagocytes from dragging the bacteria to the lymph nodes for eventual destruction.

When the signals fail, due to mutations, disease, or a breach of the intestinal wall, the immune system attacks the bacteria as it would any other foreign microbe. This onslaught can result in chronic inflammation of the intestinal tract that leads to Crohn's disease, ulcerative colitis, and other forms of inflammatory bowel disease that affect as many as 1.4 million Americans.

"We have identified one of several possible strategies that prevent the immune system from responding inappropriately to beneficial bacteria," says study co-author

Dan Littman, MD, PhD, the Helen L. and Martin S. Kimmel Professor of Molecular Immunology and a Howard Hughes Medical Institute Investigator. "We have found that, in the absence of damage to the wall of the bowel, the commensal microbes signal the immune system to keep its cells from migrating to sites where immune responses against those microbes can be set off."

In the study, the researchers found that phagocytes recognized harmless bacteria within the intestines of healthy mice and left the microbes alone. But when the scientists gave the mice antibiotics, the phagocytes could no longer distinguish friend from foe, triggering an immune reaction within the gut. The antibiotics, the scientists believe, may kill off enough commensal bacteria to weaken the signal that keeps away phagocytes and prevents autoimmune reactions. Similarly, when researchers deleted a gene in mice (also found in humans) called *Myd88*, the immune system again responded strongly against a nonthreatening microbe. The gene, they believe, may help bacteria

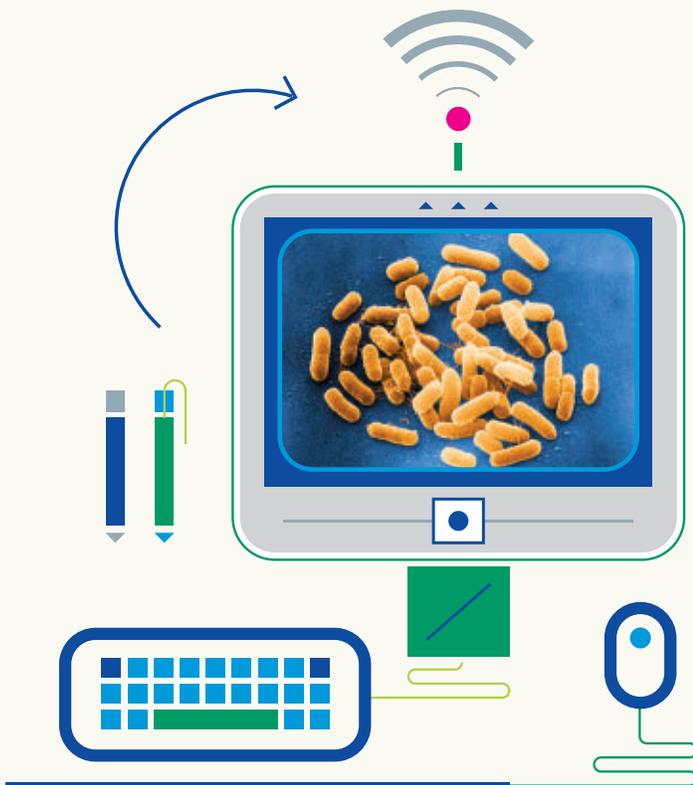
communicate with phagocytes.

"We hypothesize that people with inflammatory bowel disease have problems sending immune recognition signals or turning down this inflammatory response, which would make them react against the microorganisms within their intestines," says Gretchen Diehl, PhD, a postdoctoral research fellow in Dr. Littman's lab and the study's lead author.

Researchers have identified many beneficial roles for commensal bacteria, such as synthesizing essential vitamins and helping us digest food. In 2009 the Littman lab identified a bizarre-looking bacterium in the small intestine that warns against dangerous pathogens, advancing the idea that our resident microbes may also play a vital role in regulating the immune system and preventing disease.

Drs. Littman and Diehl are now working to identify the exact mechanism by which commensal gut microbes signal the immune system and gain a sharper understanding of which types of microbes are at play. Such insights could lead to treatments that address underlying causes of inflammatory bowel disease, and not simply its symptoms. Says Dr. Littman: "The hope is that someday it will be possible to quell destructive inflammatory processes." ● —BRYN NELSON

▼ Rod-shaped *E. coli* bacteria are natural denizens of the intestine.



DAVID M. PHILLIPS/SCIENCE SOURCE

Sticky Cells and Autoimmune Disease

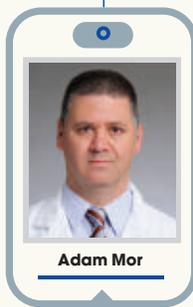
Researchers take aim at the biological process of adhesion.

ALTHOUGH HE HAD already completed his residency at Tel Aviv University and two fellowship years in rheumatology at NYU School of Medicine, Adam Mor, MD, was eager to learn more about the inflammatory diseases he was treating. So in 2004 he joined the NYU lab of Mark Philips, MD, professor of medicine, cell biology, and biochemistry and molecular pharmacology, to investigate molecular signaling pathways—the complex communication networks inside cells that ultimately turn genes on or off and thereby play crucial roles in a host of diseases.

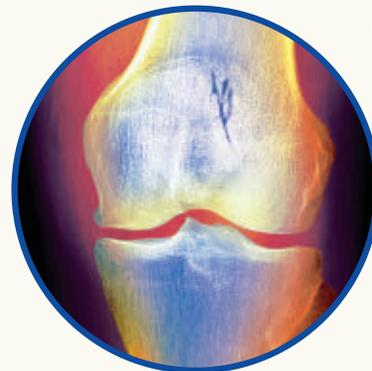
Inspired by translational science, Dr. Mor decided to pursue a PhD in immunology with Yoel Kloog, PhD, of Tel Aviv University. He then returned to NYU as an assistant professor of medicine and pathology and started his own lab to study the promising signaling pathways in cellular adhesion—the process that binds T cells, the white blood cells that drive autoimmune-related inflammation, to the endothelium (blood vessel walls) of inflamed organs. This process occurs when an inflammatory trigger releases T cells into the bloodstream. Specialized adhesion molecules on the endothelial cells of the affected organ—the joint membranes in rheumatoid

arthritis, the skin in psoriasis—then emit signals that draw the T cells to the blood vessel wall. Molecules on the T cell recognize the endothelial adhesion molecules, like keys fitting into locks, enabling the T cells to migrate into the organ. Monoclonal antibodies that bind to adhesion molecules stop adhesion completely, but several years ago the FDA withdrew two such medications (for psoriasis and multiple sclerosis [MS]) after patients developed a fatal brain infection. (The MS drug was later reintroduced.)

“We hope to find better treatments that block organ inflammation without impairing overall immunity,” says Dr. Mor. To that end, his lab is surveying multiple signaling pathways activated inside T cells after they adhere to endothelial cells. Blocking just one, he suspects, might disrupt adhesion and cause fewer side effects than currently available medications for autoimmune diseases. Pathways are identified using a flow chamber containing a tube lined with endothelial cells similar to those found in rheumatoid arthritis patients. Researchers stain certain molecules in T cells taken from patients, then pump those same cells through the tube and photograph them by means



▶ A knee deformed by arthritis. Adhesion molecules play a role in the autoimmune condition.



of a confocal microscope; lab members can thus observe the split-second adhesion process.

Two years ago this process revealed a new signaling pathway in T cells that utilized a kinase enzyme, a promising drug target. “However, there are 2,000 kinases,” Dr. Mor says. “You can test for any single one using a genetic technique called siRNA to knock out that molecule, but testing for 2,000 enzymes would take years.”

A six-month literature search narrowed the list to 32—few enough to make siRNA testing feasible. After another six months of tests, they got a hit: Without a kinase called Hck, T cells no longer adhered to the chamber’s endothelial cells. Just as important, the

T cells appeared viable in all other respects after the Hck enzyme was removed.

Dr. Mor, who collaborates with Dr. Philips, Dr. Kloog, and Michael Dustin, PhD, research professor of pathology at NYU School of Medicine, will now test his finding in animals and check patients’ tissues for elevated Hck levels. If these experiments succeed, they will look for one drug that can block Hck and potentially become the next-generation rheumatoid arthritis treatment.

“Identifying a target doesn’t mean that much—you have to link the target to the disease,” says Dr. Mor. “Still, Hck is a very interesting find. We’re extremely excited about it.” ● —ROYCE FLIPPIN





STAYING AHEAD OF THE GAME

The Concussion Center at NYU Langone Medical Center takes aim at a silent epidemic of head injuries that has left millions of Americans dazed, confused, and undiagnosed.

BY ADAM PIORE • ILLUSTRATION BY DAVID BRINLEY

LAST MARCH, Oliver Kennedy Andrews, 13, was zipping down a black-diamond trail at the Mohawk Mountain Ski Area in Cornwall, Connecticut, when he slammed into one of the chairlift towers in the middle of the slope. He awoke in the hospital, vomiting continuously, and so dizzy he could stand only with assistance. After three days in the hospital, Oliver returned home to Westchester, where a neurologist at the local emergency room instructed his parents to keep him out of school for four to six weeks and make sure that he got plenty of rest. Their pediatrician suggested they purchase homeopathic herbs and return in two weeks.

But Oliver's walking continued to deteriorate, and his headaches were close to 10 on the pain scale. Finally, his mother, Andrea, decided to consult an old college friend who had medical expertise. The friend suggested she call NYU Langone Medical Center immediately; within just a couple of hours, Oliver was at the Medical Center's Concussion Center, and the tide finally began to turn.

"The first thing they did was tell us, no television, computers—even board games," Andrea recalls. Research suggests that activities that require extended mental effort and concentration—including homework—can exacerbate concussion symptoms. "It was hard," Andrea says, "but within five days he started to improve a little bit." Since then, his walking and balance have normalized, and his headaches have gone from 9s to 3s. "In my opinion, if we had not come to NYU Langone, he would be in much worse shape," Andrea adds. "Nobody really understood concussions where we live."



Longtime collaborators Dr. Steven Galetta and Dr. Laura Balcer have pushed the boundaries of concussion testing.

Such confusion over concussion care coincides with an American epidemic of traumatic brain injuries—the technical term for concussions. Last year, athletes in the United States alone suffered an estimated 4 million concussions, and many more go undiagnosed. The statistics are particularly alarming among children and young adults. The number of Americans aged 11 to 22 admitted to the ER for sports-related concussions has shot up 60 percent in the past decade. Adding to the alarm, new research suggests that kids who suffer repeated blows to the head often require longer recovery times than those who experience just one concussion. A recent study published in the journal *Pediatrics*, for example, found that children and young adults who had more than one concussion in a year took up to 28 days to recover, about two weeks longer than those who had suffered a single incident. (About 60 percent of the study participants were injured while playing sports.)

Yet despite this growing awareness, surprisingly little is understood about

concussions. How do they manifest in the brain? Why do some people suffer more severe symptoms than others? What's the best way to diagnose and treat them? This lack of understanding has led to disparate clinical practices throughout the country and anxiety among parents like Andrea who often receive conflicting medical advice about how to help their children heal. The Concussion Center, opened in March, hopes to cut through the confusion. Its multidisciplinary team of nearly 50 clinicians and physicians combines the latest evidence-based treatment, research, and education to treat all aspects of concussions.

“It’s about bringing the disciplines together, both for treating individuals with concussion and advancing the research,” says Dennis Cardone, DO, associate professor of orthopaedic surgery and chief of primary care sports medicine in the Department of Orthopaedic Surgery, and one of the new center’s three co-directors. “There are very few models like that out there.”

At the center, Oliver’s care was coordinated by Mara Sproul, RN, an experienced nurse based at NYU Langone Medical Center’s Rusk Rehabilitation, who carefully tracks patients from the moment they call the center’s toll-free concussion hotline to the completion of treatment, helping them shuttle seamlessly across departments and access a wide range of specialties, including neurology and neurosurgery, physical medicine and rehabilitation, orthopaedic sports medicine, emergency medicine, nursing, neuropsychology, neuroradiology, and occupational and physical therapy. “Everybody has the same goal in mind,” Andrea says, “to see Ollie get better.”

SUCH COMPREHENSIVE CARE AND expertise is a rare commodity. As recently as five years ago, many athletes—and parents, in fact—were unaware of the danger of concussions and often chafed at precautionary limitations imposed after such incidents. Indeed, the standard treatment for “getting your bell rung”

“TODAY, IF ANY STUDENT ATHLETE HAS A SUSPECTED CONCUSSION—SUSPECTED—THEY ARE REMOVED FROM PLAY, AND THEY CANNOT RETURN UNTIL THEY HAVE BEEN EVALUATED BY A PHYSICIAN.”

during a game was even more poorly defined than it is today. Team physicians and coaches were instructed to observe a player on the sidelines, and if, after 20 minutes, hallmark symptoms like dizziness and confusion seemed to have abated, the players could resume play. Under standard protocols, players knocked unconscious or experiencing memory loss were allowed to return to the field in three weeks, regardless of their condition, Dr. Cardone says.

“Today, if any student athlete has a suspected concussion—*suspected*—they are removed from play, and they cannot return until they have been evaluated by a physician,” says Dr. Cardone, who is the lead team physician for all NYU undergraduate sports and also serves as medical director for the New York City Public School Athletic League, overseeing 36,000-plus high school athletes. “Today I have athletes who are still symptomatic and unable to return to play after five months.”

This new caution is a reaction to a growing body of evidence linking repeated head trauma to permanent damage that can result in emotional instability, cognitive decline, and even suicide. The human costs have been driven home in stark terms by the high-profile suicides of several former football and hockey stars, including Hall-of-Famer Junior Seau, who shot himself in the chest last year. In January the National Institutes of Health confirmed that the brain of the popular former San Diego Chargers

linebacker—which his family had donated for study—showed abnormalities associated with chronic traumatic encephalopathy (CTE), also known as dementia pugilistica, a degenerative brain disease recently discovered in the brain tissue of deceased athletes who had suffered years of repetitive head trauma.

The telltale mark of CTE is clusters of weedlike tangles of a protein known as tau that accumulate in the brain and cause it to atrophy over time. As the brain deteriorates, dementia sets in. Scientists estimate that CTE affects about 20 percent of people diagnosed with concussions, but the real number is impossible to pin down, as the webs of protein are best identified through autopsy. In fact, much of the subtle molecular damage caused by head trauma is simply invisible to standard brain scanning technologies. As a result, most caregivers are put in the uncomfortable position of relying on their own subjective judgment when determining if a concussed patient has recovered enough to resume team sports even as the evidence grows that returning prior to complete recovery can badly compound the damage and create lasting repercussions.

“There is a great saying in medicine, ‘you see what you look for and you look for what you know,’ says co-director of the center, Steven R. Flanagan, MD, the Howard A. Rusk Professor of Rehabilitation Medicine and chair of the Department of

Rehabilitation Medicine at NYU Langone. “But with concussions, it’s almost an invisible injury. There are often no physical signs. CT scans are negative. MRIs are oftentimes negative. But folks come with complaints and symptoms and you have to know what to ask for.”

NYU’s research team is already hard at work developing tools to help diagnosticians do just that. The center’s research efforts are coordinated by a subcommittee led by Laura Balcer, MD, MSCE, professor and vice chair of the Department of Neurology, Yvonne Lui, MD, assistant professor of radiology, and William Barr, PhD, associate professor of neurology and psychiatry. The committee submitted its first grant proposal to the NIH in May.

All three have already made names for themselves in the field. Dr. Barr was among the pioneers to identify some of the key physical symptoms to look for when administering the popular sideline test known as the Sports Concussion Assessment Tool (SCAT 3). The test consists of a detailed questionnaire given to athletes aged 10 and older, both at the beginning of the season—to get a baseline score—and on the sideline or in a doctor’s office after an incident. The questions probe symptoms (“Do you feel dizzy?”) and cognitive function (“What month is it?”). It also includes memory tests, such as repeating back strings of numbers.

Dr. Balcer arrived at NYU Langone from the University of Pennsylvania last fall, along with Steven Galetta, MD, the Philip K. Moskowitz Professor and chair of the Department of Neurology. She, too, brings extensive experience pushing the boundaries of concussion testing. Several years ago, Drs. Balcer and Galetta showed that a one-minute reading test widely used to diagnose learning disabilities could also be used as a fast and accurate sideline screening tool to identify boxers and mixed martial artists with head trauma. The test, known as the King-Devick, requires users to read increasingly complex sequences of numbers aloud as quickly as possible from



Optical coherence tomography is one of the tools used to gauge the impact of concussions.

left to right on three test cards, capturing impaired eye movements, concentration deficiencies, and problems processing language—all signs of head trauma.

Since Dr. Balcer and her team demonstrated that fighters who suffer overt head trauma during sparring matches consistently performed poorly on the test compared to a pre-fight baseline, researchers from around the world have begun studying the King-Devick test in

a range of sports from youth soccer to professional rugby. If the results can be replicated in larger studies and among different types of athletes, the test could provide a valuable window into concussions that would complement the currently used SCAT3 diagnostic.

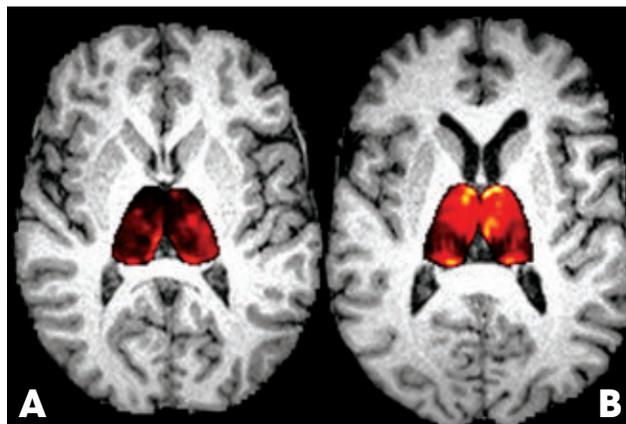
Elucidating the neurological correlates of poor performance on tests like the King-Devick and SCAT will be high on the research agenda of the new center.

Drs. Balcer and Galetta plan to collaborate with NYU Langone physicians who can recruit athletes from local schools, leagues, and universities for further studies of sideline testing, while Dr. Lui, an expert in MRI brain imaging technologies, can help examine them to search for detectable physical and functional changes.

Drs. Galetta and Balcer believe the King-Devick test works because at least 50 percent of the brain's circuits are involved in vision. Thus the test can pick up deficiencies occurring across a wide range of neurological geography. Some have speculated that concussions are the result of the shearing of the brain's axons, the main transmission lines of the nervous system, caused by violent turning of the head; others suggest it may result from direct trauma and cell death at areas of impact.

VISION IS A CONVENIENT WINDOW into the brain to test both these ideas because the eyes are the only areas that allow an unobstructed view directly into the brain. To access that view, researchers rely on a technique called optical coherence

Magnetic resonance images of the thalamus, which controls sensory perception and movement. Compared to a healthy brain (A), the concussed brain (B) shows more non-uniformity (yellow) in the magnetic field, believed to be caused by cellular iron. Dr. Yvonne Lui is measuring iron deposition after concussions.



TOP PHOTOGRAPH: SASHA NIALLA; SCIENCE IMAGE COURTESY OF DR. YVONNE LUI

VISION IS A CONVENIENT WINDOW INTO THE BRAIN TO TEST BOTH THESE IDEAS BECAUSE THE EYES ARE THE ONLY AREAS THAT ALLOW AN UNOBSTRUCTED VIEW DIRECTLY INTO THE BRAIN.

tomography (OCT), which uses light to image the back of the eye and can measure different retinal layers. At the back of the eye, bundles of axons merge together in the optic nerve, which is a superhighway of sorts through which electric signals carry information to the brain. By using OCT, Drs. Balcer and Galetta, and their collaborators at Johns Hopkins, the University of Texas Southwestern in Dallas, and the University of California, San Francisco, have already been able to detect the loss of axons and nerve cells in the back of the eye that correlate with poor performance on a visual test designed to gauge contrast acuity, or the ability to discern light from dark. Diminished contrast acuity can make it difficult to drive at night or see stairs, for example. Poor test scores can be symptomatic of disease, such as multiple sclerosis or glaucoma, but they can also indicate brain trauma. Dr. Balcer hopes the OCT technique might yield insights about the neurological impact of concussions—and provide another tool clinicians can use to examine patients and determine if new therapies that protect nerve cells are effective. “It could be that what we see in the eye, even though that’s only a part of the visual system, might reflect in part what the overall brain is going through,” she says.

Drs. Balcer and Galetta hope to correlate visual tests with brain scans such as those

conducted by Dr. Lui and her colleagues. By observing healthy research subjects lying in an MRI machine with eyes closed, in a relaxed state, researchers can track the level of oxygen in blood flowing through the brain and indirectly measure neural activity. The idea is to compare blood-oxygen levels in the brains of healthy patients at rest with those from a cohort of patients with concussions, using specially designed algorithms. In the future Dr. Lui might search for activity patterns present in the brains of patients who perform poorly on Dr. Balcer’s concussion tests.

That would build upon a growing body of research that shows concussion can significantly impact brain function. Dr. Lui’s early results, for example, indicate that those who have suffered concussions seem to have less activity in posterior areas of the brain, which are normally activated at rest, and increased activity in frontal regions. Imaging has also revealed that people with concussions tend to have measurable atrophy in the brain a year after the injury, beyond what you would expect in healthy individuals. Although the diminishment is global, one of the specific regions affected is the anterior cingulate, an area that has long been implicated in depression and other affective disorders.

“That’s interesting,” notes Dr. Lui, “because a big psychiatric problem after injury is depression. It’s a little too early to

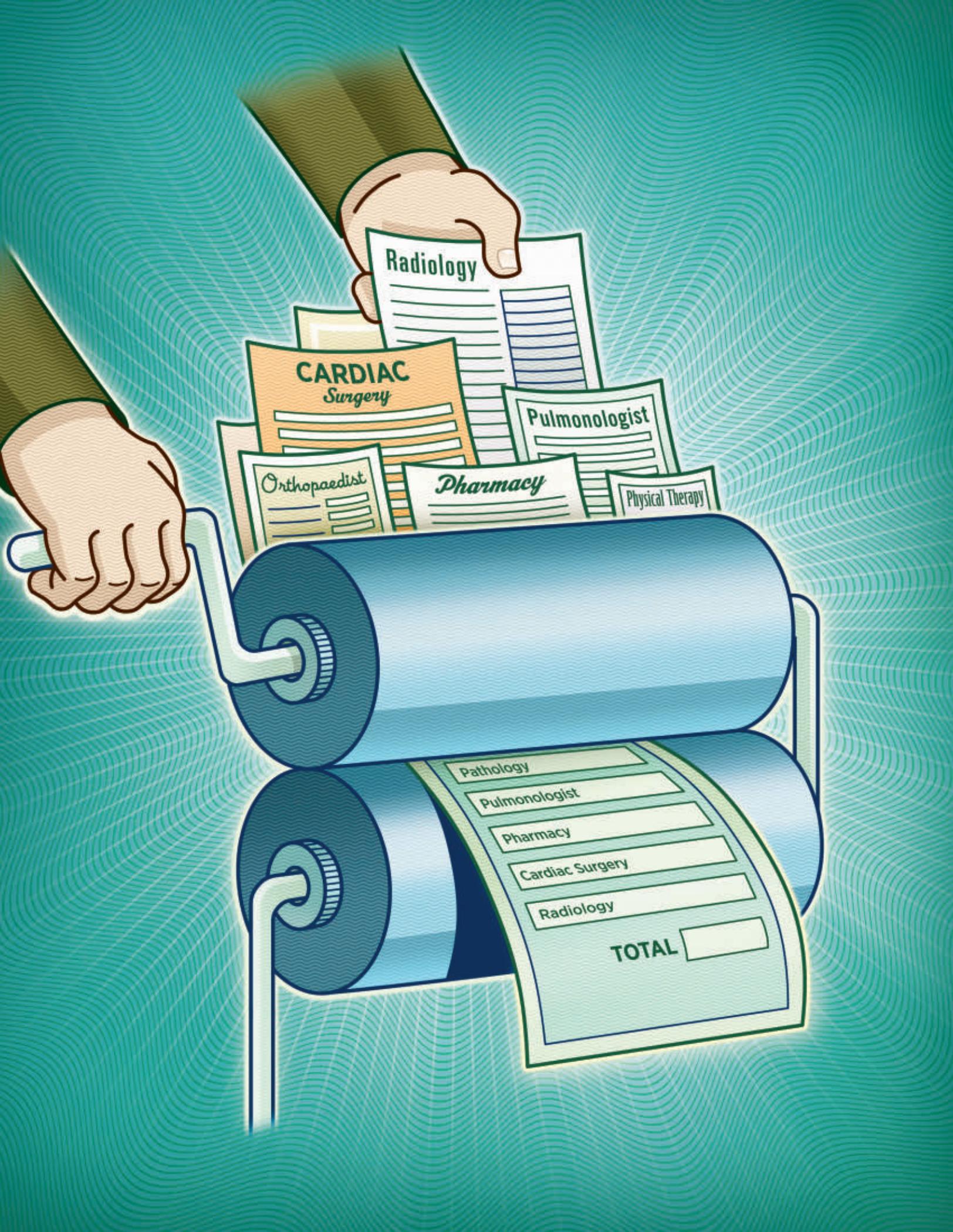
say that this is the cause of depression. But it’s provocative.”

THAT QUESTION AND OTHERS LIKE it will continue to be of immediate concern to physicians who bear responsibility for determining whether an athlete is healthy enough to return to play. One of them is Gerard Varlotta, MD, a member of the Concussion Center and clinical associate professor of rehabilitation medicine and orthopaedic surgery at NYU Langone. Dr. Varlotta, who often serves as ringside physician at professional boxing fights, is keenly aware of the shortcomings of current diagnostic tools.

He recalls one boxer who aced his baseline concussion test, reading off four sets of numbers and repeating them back in reverse order with ease. His scores were “pristine.” Then, a few months after a big fight, he could get through only the first two sets, even though he claimed he was fine. Technically his scores qualified him for the next fight—but clearly, the fighter’s memory had dropped from his baseline. Dr. Varlotta was left to ponder a crucial question: Was the fighter just having a bad day? Or was he still suffering from memory loss associated with the concussion he suffered during his last bout?

The truth is, there is no way to know for sure, and without knowing for sure, it’s hard to kill a dream. “We could really have used a scan at that point, or some other means of testing to peer inside the brain,” Dr. Varlotta says. “Unfortunately it doesn’t exist.”

Dr. Varlotta cleared the young man to box in Madison Square Garden since he passed the tests currently in use. But throughout that match, he watched closely and never did have to call the fight. The young boxer was simply too quick for his opponent, ducking the most devastating head blows and winning the match. Still, Dr. Varlotta can’t help but wonder what would have happened had things gone differently. Someday soon, he may not have to. ●



Radiology

CARDIAC
Surgery

Pulmonologist

Orthopaedist

Pharmacy

Physical Therapy

Pathology

Pulmonologist

Pharmacy

Cardiac Surgery

Radiology

TOTAL

THE NEW DEAL

NYU Langone Medical Center joins an historic experiment in Medicare reimbursements with the bundling initiative.

BY ROYCE FLIPPIN • ILLUSTRATIONS BY PETER AND MARIA HOEY

AGE AND OBESITY ARE TAKING A TOLL ON THE JOINTS OF MILLIONS OF MIDDLE-AGED AMERICANS. ARTHRITIS MEDICATION AND PHYSICAL THERAPY MAY PROVIDE SOME RELIEF, BUT MANY BABY BOOMERS WILL BE SHOPPING FOR NEW HIPS AND KNEES AT SOME POINT IN THEIR LIVES. HOSPITALS REPLACE MORE THAN A MILLION HIPS AND KNEES ANNUALLY.

Medicare shoulders the bulk of the cost, since most of these patients are 65 or older, but even if patients had to pay out of pocket, shopping prices would be a struggle. One study published last March in the *Journal of the American Medical Association* found that more than 55 percent of top-ranked hospitals could not provide an estimated cost for an elective hip replacement. And of the hospitals that could, estimates varied wildly, from \$11,000 to nearly \$126,000.

This baffling variation and lack of transparency in hospital costs is set to change under the Affordable Care Act, better known as Obamacare. As part of the legislation, the Centers for Medicare & Medicaid Services (CMS) has selected 500 hospitals nationwide, including NYU Langone Medical Center, to pilot a new billing model known as bundled payments. The three-year initiative, started in January 2013, will assess if it can improve cost transparency and significantly lower the cost of Medicare, an insurance program that covers an estimated 44 million elderly and disabled Americans.

With the bundled-care initiative, hospitals and physicians guarantee to deliver all services for an episode or bundle of care, which is typically the hospital stay plus a recovery period of 90 days, explains Gary Kalkut, MD, MPH, senior vice president of network integration and associate chief clinical officer, who is directing implementation of the Medical Center's bundled payments initiative. Medical providers still bill per service as usual, he notes, but under the new arrangement they assume responsibility for any complications over the entire episode of care, including post-surgical infections and hospital readmissions. At the end of the year, Medicare tallies up the total cost of the "bundles" at a medical center—and then compares that number with a baseline cost, which it calculates by analyzing the historical costs at the medical center. If the total cost for the year is lower than the baseline cost, the hospital and physicians share in the savings.

The idea, says Dr. Kalkut, is to motivate care providers to

collaborate more effectively across the continuum of care, from intake to home rehabilitation. If the episode of care goes as planned, everyone stands to win: Medical providers receive bonuses, the government saves money, and patients go home healthier.

The bundling initiative provides a strong incentive for caregivers to work together to prevent posttreatment complications, including wound infections and exacerbation of chronic conditions like asthma or congestive heart failure, that can lead to costly hospital readmissions—the biggest budget buster. A widely cited paper published in the *New England Journal of Medicine* in 2009 estimated that Medicare patients who experienced unplanned readmissions to the hospital within 30 days after surgical procedures cost the federal insurance system \$17.4 billion in 2004. If bundled payments result in greater vigilance during the recovery period, thereby keeping patients out of the hospital, the model will have fulfilled its mission.

"The bundled-payment model is clearly the future of healthcare," says Andrew Brotman, MD, senior vice president and vice dean for clinical affairs and strategy. Hospitals and insurance agencies have been experimenting successfully with the model since the early 1980s. Today, private insurance agencies such as Aetna and UnitedHealthcare are already making bundled payments to some doctors and hospitals, but the scale of the Medicare pilot is unprecedented. Jonathan Blum, a deputy administrator at CMS, calls the pilot "huge" and "historic."

But if this grand experiment in medical reimbursement is to work, hospitals must get a better handle on total costs across the continuum of care. "It's taken us five or six years of investigation to figure out exactly our costs and risks so that we can enter into these agreements with confidence," says Joseph Bosco, MD, vice chair for clinical affairs of NYU Hospital for Joint Diseases, in the Department of Orthopedic Surgery, and associate professor of orthopaedic surgery. That exacting preparation is one of the reasons NYU Langone

Medical Center applied to participate in the pilot initiative for total joint replacements, along with cardiac valve replacement, and spinal fusions. “We asked to pilot these three types of procedures because they are areas where we think we have a good opportunity to streamline care,” Dr. Brotman says.

NYU Langone Medical Center ranks number 5 in the nation for orthopaedics, according to the *U.S. News & World Report’s* 2013–14 Best Hospitals rankings, and the NYU Hospital for Joint Diseases performs more than 1,200 hip replacements alone each year. For CMS, which pays an estimated \$6 billion yearly for major joint replacements—more than for any other procedure—the Medical Center makes a promising partner in cost efficiency. “Our surgeons know exactly how long it will take them to perform a hip replacement, right down to the minute,” Dr. Bosco says. “Standardization and repetition improves quality and decreases mistakes.”

NYU Langone Medical Center also benefits from Epic, an electronic health-records system that puts medical and billing data at administrators’ fingertips. With Epic, the Medical Center can analyze historical data on patient care and costs in real time. In turn, this will make it easier to negotiate reimbursement amounts for bundled billing—a process that is still being worked out.

Like other participants in the pilot program, NYU Langone receives a report from Medicare every three months, tallying total charges for all patients who have undergone a bundled payment procedure that quarter. If the average per-patient cost is below the preset reimbursement amount—\$37,000 for a hip replacement, for example—NYU Langone and any other caregivers involved in the episodes of care will receive bonus payments, representing a portion of the savings. If the per-patient charge is over the reimbursement limit, care providers must shoulder the extra cost. “Each medical center’s reimbursement levels are based on its own past performance,” notes Dr. Brotman. “So we’ll be compared against ourselves.”

The pilot is currently in a risk-free phase, while the Medicare administration gathers cost data that will be used to refine baseline reimbursement levels. During the pilot program’s second phase, slated to begin in October, participants actually start sharing in savings and paying for cost overruns.

Dr. Bosco, for one, believes NYU Langone is ready. “We realized a long time ago, before most other institutions, that bundled payment was the model of the future. You won’t get paid for volume. You will get paid for quality, and you’ll need to share risks with the payer,” he says. “If you possess

data about complications and cost, then you’re in a position to understand the risks and share those risks with the payers and still come out OK. The medical institutions I feel sorry for are the ones that have no idea of the cost, no idea of the complications or the risks.”

“Our surgeons know exactly how long it will take them to perform a hip replacement, right down to the minute.”

BUT HOW DO HOSPITALS manage risk once the patient goes home? For the Medical Center’s physicians, nurses, and administrators, the biggest challenge of bundled care is reaching beyond the institution’s walls to keep Medicare patients on a steady path of recovery after they have been discharged, while avoiding complications or setbacks that might land them back in the hospital—and send their medical bills spiraling upward.

One interesting aspect of the bundled payments pilot program is that Medicare is now sharing longitudinal patient data that was previously unavailable. Richard Donoghue, senior vice president for strategy, planning, and business development at NYU Langone Medical Center, was surprised to learn that readmission rates for the Medical Center’s joint replacement and cardiac valve patients have actually been significantly higher than previously believed. Data from CMS revealed that 8 percent of patients who had joint replacements at the Medical Center were readmitted to a hospital within 90 days of the procedure, up from the rate of 3.8 percent that return to NYU Hospitals Center. Many patients were getting readmitted to their local hospitals, Donoghue explains, without the Medical Center realizing it. Now, it will share responsibility for preventing these additional readmissions.

Under the new model, arrangements for home care begin before rather than after a procedure. This includes reviewing the patient’s home environment and educating family members on the rehabilitation process. Following surgery, inpatient recovery is tracked against a new set of guidelines that measure wound healing, pain, mobility, and other health markers. Progress is noted in a patient’s electronic medical record. If a patient falls behind in a given area, his or her

care will immediately be ramped up to ensure a timely discharge, including calling in necessary resources such as a pain-management physician, an occupational therapist, or an infection-control specialist.

Medicare patients retain the same right as ever to choose where they go for post-acute care rehabilitation, but in the pilot program, patients are strongly encouraged to return home under the care of a preferred home healthcare provider. “The dogma used to be that sending patients home would result in higher readmission rates than sending them to a nursing home or rehabilitation center,” Dr. Bosco explains. Leaving patients to manage their own recovery—change dressings, juggle medications, monitor for signs of infection—would lead them right back to the hospital, it was thought. “But when we looked at three years’ worth of data from more than 10,000 patients, we found just the opposite—patients who go home tend to stay home. We now know that home is the safest place to be.” Several independent studies corroborate this finding, citing faster, less invasive surgical procedures and better follow-up care, including clearer discharge instructions. In 1980, 84 percent of surgeries required an overnight hospital stay. Today, it’s only 35 percent.

Home is also the most economical. Caring for a patient at home for three weeks costs about \$3,000, says Dr. Bosco, versus about \$14,000 for similar care in a nursing home or rehab facility. However, if a physician decides that a patient does need recovery time in a skilled nursing facility, the patient will be encouraged to go to one of NYU Langone Medical Center’s preferred providers, such as Gouverneur Healthcare Services’ facility in lower Manhattan, which now has an orthopaedic rehab unit staffed by Medical Center physical therapists and overseen by a Medical Center physiatrist. If the patient ultimately chooses a facility outside the preferred provider network, his or her care will be closely followed by an NYU Langone clinical care coordinator, a position newly created for the pilot study and staffed by registered nurses who monitor the progress of patients, both in the hospital and for 90 days afterward. “Having registered nurses follow our patients once they leave the hospital is a major change,” notes Dr. Kalkut, who directs implementation of the Medical Center’s bundled payments initiative. “In the past, physicians and their offices were on their own when it came to following up with patients.”

“Patients can call us whenever they need help or have questions,” says Michelle Palazzo, RN, a clinical care coordinator overseeing joint replacement patients. “We ask patients to let us know right away if something’s wrong,” she says.

Since the bundled payment pilot began, these coordinators have helped guide the recovery of several hundred hip and knee replacement patients. They have steered patients with swollen wounds to NYU Hospital for Joint Disease’s urgent care facility, avoiding more costly trips to local emergency rooms; arranged prescriptions for patients who ran out of pain medication; and intervened when a skilled nursing facility insisted a patient use a wheelchair, stalling their recovery. They may also facilitate transportation to doctor’s appointments, double-check that medications are being taken appropriately, and push for additional therapy services as needed.

“Every step of the way, we’re part of the conversation,” says clinical care coordinator Kim McIntyre, RN.

Progress is noted in a patient’s electronic medical record. If a patient falls behind in a given area, his or her care will immediately be ramped up to ensure a timely discharge.

NEARLY A YEAR INTO THE PILOT, there are no hard numbers yet on how bundled payments are affecting cost or patient outcomes. Anecdotally, however, clinicians are seeing a positive impact. “It’s definitely improved our continuity of care for cardiac valve repair and replacement procedures,” says Aubrey Galloway, MD, Seymour Cohn Professor of Cardiothoracic Surgery and chair of the Department of Cardiothoracic Surgery. Dr. Galloway estimates about 120 such operations have been done so far under the pilot program. “Patients are doing physical therapy sooner and more consistently,” he says. “We’re using more of a team approach to optimize discharge planning, and our patients are getting better home-care services.”

“In our joint replacement procedures, we’ve reduced patients’ average length of stay in the hospital by over half a day since bundled payments were implemented,” adds Richard Iorio, MD, the William and Susan Jaffe Professor of Orthopaedic Surgery and chief of adult reconstructive surgery, who directs NYU Langone’s joint replacement program. “We’ve also increased the proportion of our



Providers pull together to prevent posttreatment complications.

patients undergoing rehab at home from less than a third to almost half.”

At present, however, the Medical Center is cutting its teeth mostly on elective procedures with clearly defined recovery paths. Implementing bundled payments for all of its Medicare inpatients, if the program is expanded to include the entire Medicare system—an eventuality “we assume will happen,” according to Dr. Brotman—is another prospect altogether. NYU Langone Medical Center’s Medicare population, which accounts for 12,000 patients, or one-third of its annual patient flow, includes 6,000 chronically ill patients, prone to repeated hospitalizations for conditions like congestive heart failure, diabetes, and respiratory ailments. Managing their healthcare outside the hospital will be substantially harder than overseeing recovery from a knee replacement or cardiac valve repair.

“Moving from a decentralized fee-for-service system to a coordinated process is going to be a big challenge for us and our patients,” acknowledges Dr. Brotman. “We’re trying to create a system where patients can get care in a

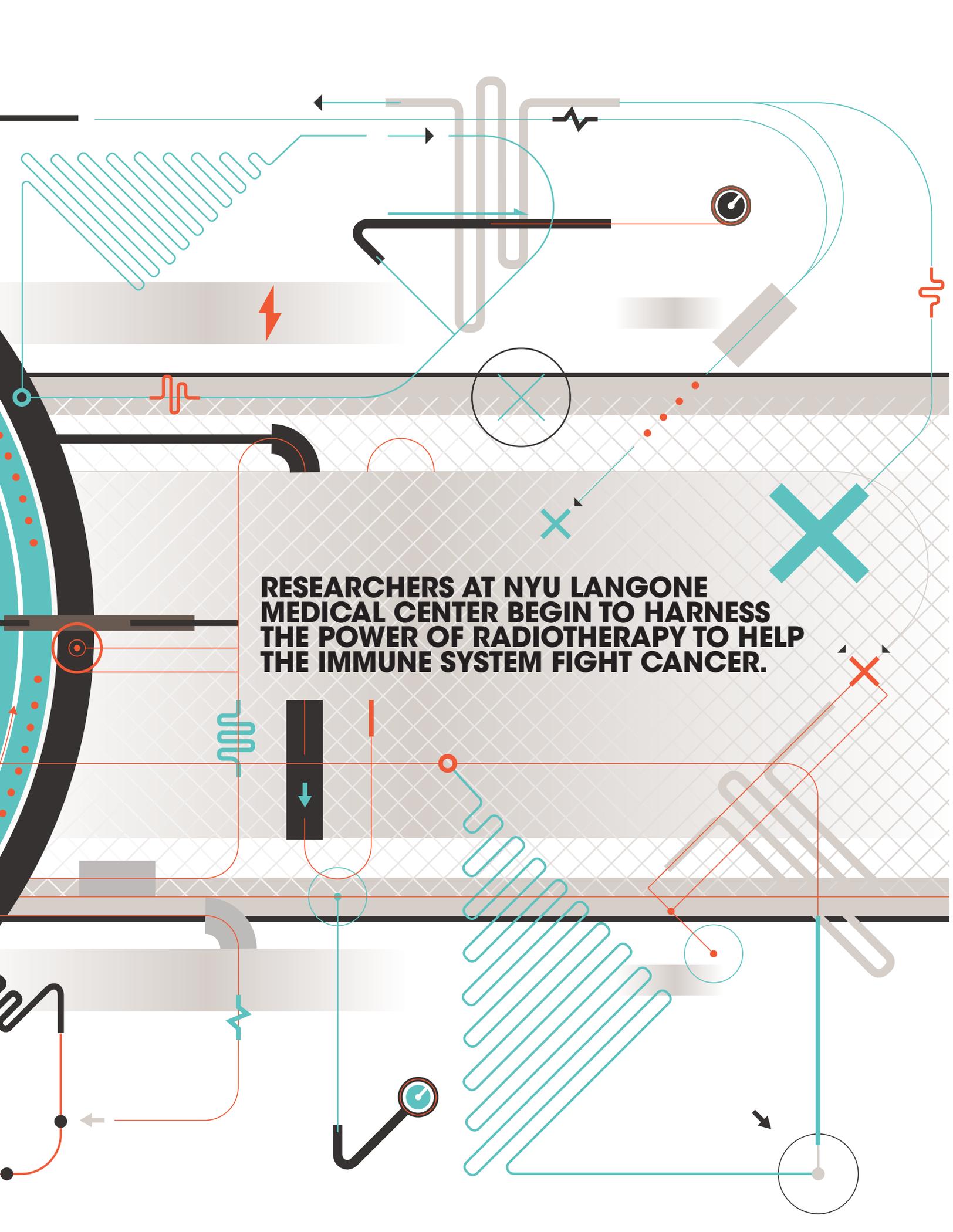
“We’re using more of a team approach to optimize discharge planning, and our patients are getting better home-care services.”

predictable fashion within a preferred provider network. Since patients have no obligation to stay within this system, we’ll need to convince them that their care will have better outcomes and be more efficient if they do. This is particularly difficult in New York, where patients have so many options to choose from. It remains to be seen if it can happen, but we’re committed to giving it a shot.” •



REINVENTING RADIOTHERAPY

BY AMY ENGELER • ILLUSTRATION BY LEANDRO CASTELAO



**RESEARCHERS AT NYU LANGONE
MEDICAL CENTER BEGIN TO HARNESS
THE POWER OF RADIOTHERAPY TO HELP
THE IMMUNE SYSTEM FIGHT CANCER.**

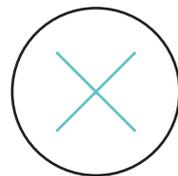


VARIAN
medical systems

RapidArc

IN USE

Shirley Finkel, M.D.



THE IDEA THAT RADIOTHERAPY could help the immune system fight cancer sounded like a pipe dream when Silvia Formenti, MD, chair of radiation oncology and the Sandra and Edward H. Meyer Professor of Radiation Oncology at NYU Langone Medical Center, first proposed it more than a decade ago. Actively dividing cells such as cancer are more sensitive to ionizing radiation, which destroys them by tearing apart their DNA. At the same time, radiation has immunosuppressive effects. Cell death and the tamping down of the immune response hardly seemed likely to enable the immune system to fight tumors.

Yet a few dramatic but isolated cases reported in the medical literature suggested that radiotherapy might help some rare patients overcome their tolerance to cancer—their tumors shrank *outside* the radiation zone, and they sometimes had complete remissions. In the 1950s, British radiologist R.J. Mole coined the term *abscopal*—derived from Latin and Greek words meaning “away from” and “target”—to denote the effect.

As an unexplained and rarely observed phenomenon, the abscopal effect was largely forgotten by the late 1990s, when Dr. Formenti herself noticed that adding radiotherapy to chemotherapy often appeared to improve the overall health of her metastatic breast cancer patients. “It gave me the impression,” she says, “that the radiation was doing more than enhancing local tumor control.”

How could this occur? The immune system is constantly searching for aberrant cells within the body, and cancers are known to be masters at disarming or evading it. Each type of cancer, and there are estimated to be hundreds, uses a slightly different mechanism. Some evade the system by foiling the sentinels that identify invaders. Dr. Formenti wondered if radiation, by causing the death of cancer cells and thereby releasing proteins and other material into the bloodstream, could allow the immune system to see anew, at least in some patients, the dangerous cells it should be destroying.

From left: Dr. Sylvia Adams, Dr. Sandra Demaria, and Dr. Silvia Formenti next to a linear accelerator at NYU Clinical Cancer Center. The three researchers share a passion to cure cancer.

DR. FORMENTI HOPED SHE MIGHT CREATE A VACCINE WITHIN THE BODY, IN SITU, USING RADIOTHERAPY.



A Shared Passion

Harnessing the immune system against cancer has been a goal of medical researchers for more than a hundred years. The earliest crude attempts to draw an immune response to cancer came in the late 1800s, when doctors injected tumors with powerful toxins, such as killed streptococcus cultures, to create inflammation. (The technique continues to be used today with rare bladder-lining cancers.) After a century with little progress, immunotherapy is again on the cutting edge of cancer research, with dozens of new immune-boosting drugs and vaccines. While most of the latest therapeutic vaccines are crafted in vitro, sometimes from a patient’s own lymphocytes (like adoptive cell therapy and the FDA-approved dendritic-cell vaccine for advanced prostate cancer), Dr. Formenti hoped she might create a vaccine within the body, in situ, using radiotherapy.

To test the idea in the laboratory, Dr. Formenti found a kindred spirit in Sandra Demaria, MD, associate professor of pathology and radiation oncology, who had pursued a related line of inquiry with chemotherapy and the immune system. While studying antitumor lymphocytes called CD8+ cells in breast cancer tumors during her residency in pathology at NYU School of Medicine in the late 1990s, Dr. Demaria noted a correlation between the number of lymphocytes inside tumors and the course of disease in patients. Her observations suggested that a boosted immune response played a role even with standard chemotherapy. The two women share not only a passion to end cancer; they are both Italian (Dr. Formenti attended medical school at the University of Milan and Dr. Demaria at the nearby University of Torino), and they met at NYU Langone.

In 2001 they designed their first study, with funding from a National Institutes of Health Career Development Award to Dr. Demaria. “We decided in the mouse model to combine radiation not with chemotherapy but immunotherapy,”

Dr. Formenti says. “If radiation has a positive effect on the immune system, why not help it?”

They chose a promising new immunotherapy drug, ipilimumab, being tested at the time for its activity against cancer. The drug binds to a receptor on certain T lymphocytes (called CTLA-4) that is often involved in making these immune cells tolerant to cancer. Ipilimumab blocks the receptor, helping reactivate these T lymphocytes against malignant cells. Neither the drug nor the radiotherapy alone worked in the mice, but in combination the response became powerful. Tumors shrank or disappeared entirely and the mice lived longer. Moreover, the animals maintained a remarkable resistance to cancer, as if they had been vaccinated.

This striking observation led to a lot of hard work to explain what had happened. What allowed the radiotherapy to synergize with the drug? Why did it help most mice, but not all? Over the following years, Drs. Formenti and Demaria published their findings on the combined treatment, supported in part by Susan G. Komen for the Cure, in 24 articles (in *Lancet Oncology*, the *Journal of the National Cancer Institute*, and *The Journal of Clinical Investigation*, among others), and they continued experimenting.

On a cellular level, the researchers discovered that radiation altered even the cancer cells that survived to make them more visible to roving lymphocytes. “As always, things are more complex than they appear,” says Dr. Demaria, who completed much of the initial experimental work herself. “We found a few mechanisms to explain why this combination worked—the irradiated tumor cells release antigens that prime the immune response and produce soluble factors that attract the immune cells to the tumor and induce their activation. Some of these factors might be helpful in predicting which patients might benefit, because there is big variability in how patients respond to immunotherapy.”

Last year an intriguing report published in the medical literature confirmed their theory that radiotherapy could boost the immune response in some patients. A woman with late-stage melanoma at Memorial Sloan-Kettering Cancer Center had received a regimen of radiotherapy for the palliative relief of a lesion pressing on her spine, along with ipilimumab, which on its own had not been working for her. She shocked her doctors by going into complete remission. Her numerous tumors simply disappeared, her oncologists reported in the *New England Journal of Medicine*

“THIS WAS ENCOURAGING TO US BECAUSE IT SUGGESTED THAT THE TUMORS THAT DON’T RESPOND TO THE IMMUNOTHERAPY ALONE WILL RESPOND WHEN COMBINED WITH RADIOTHERAPY.”

in March 2012, citing the work of Drs. Formenti and Demaria to explain the “miracle.”

“This was encouraging to us because it suggested that the tumors that don’t respond to the immunotherapy alone will respond when combined with radiotherapy,” says Dr. Demaria. “That said, it is not proven until it succeeds in a clinical trial.”

Clinical Trials

Indeed, the combination therapy is being tested in six clinical trials at NYU Langone’s Cancer Institute, in addition to research at eight other medical centers. Radiotherapy is being paired with fresolimumab, an “exciting new monoclonal antibody,” Dr. Demaria says, in a Phase I metastatic breast cancer trial with 28 participants. The antibody neutralizes a devastating cytokine (a substance released from tumors and some immune cells) called TGF-beta that not only suppresses the immune response but also helps repair tumor cells after radiation. A Phase II trial will test ipilimumab alone against combined treatment in melanoma patients; another will evaluate radiation in conjunction with a topical immunotherapy drug, imiquimod, to be applied to exposed skin tumors. Finally, a Phase I trial for lung cancer patients is expected to open next year.

Part of the promise of the combined therapy is its utter simplicity. “Radiotherapy is an established cancer therapy and is available everywhere,” says Dr. Demaria. “The drugs are simple to administer. This combination of therapies could quickly become widespread.” ●



CAN A CREAM TREAT SKIN LESIONS CAUSED BY METASTATIC BREAST CANCER?

A NEW CLINICAL TRIAL HOPES TO ANSWER THIS QUESTION AND HELP THOUSANDS OF WOMEN.

THE RASHES on the woman's upper chest looked at first like insect bites and felt like small grains of rice beneath the skin. But the itchy bumps did not heal and only became more inflamed. Eventually, they turned into painful open sores that oozed and scabbed over. The cause was not poison ivy or an allergic reaction: It was breast cancer.

Surprisingly, the most common type of tumor to spread to the skin is breast cancer and, based on autopsy studies reported in the medical literature, as many as 25 percent of women with metastatic breast cancer are affected. The skin lesions aren't as immediately life threatening as disease that has spread to the lungs, liver, and bones, the more common sites of breast cancer metastases, but they can cause excruciating pain and become infected. Unfortunately, the lesions are associated with or inevitably herald metastasis to other organs.

Extensive lesions may be especially hard to treat, says Sylvia Adams, MD, associate professor of medicine at NYU Langone Medical Center. In

some women, she explains, skin lesions may appear as raised nodules in the scar area after a mastectomy or lumpectomy, and even extend along the chest and arm and onto the back.

Radiotherapy is the standard treatment for chest wall recurrences of breast cancer. At NYU Langone previously irradiated patients often receive a combination of superficial hyperthermia and low-dose radiotherapy. Dr. Formenti, chair of radiation oncology and the Sandra and Edward H. Meyer Professor of Radiation Oncology, collaborated with Dr. Adams to test a novel approach to chest wall recurrences and other skin metastases of breast cancer that combines radiotherapy with immunotherapy.

Unlike other metastases, skin can be treated with topical medications. Dr. Adams tested a topical medicine for skin metastases in a small prospective trial at NYU Langone. The cream contains a drug called imiquimod that appears to stimulate the immune system to produce the protein interferon, as well as other substances that fight infection

and attack abnormal cells such as cancer. It is currently used to treat conditions ranging from genital warts to basal-cell carcinoma.

Two of 10 women with skin metastases from breast cancer had a partial response to the imiquimod therapy, according to a recent article in *Clinical Cancer Research*. "These were women who had undergone multiple prior treatments with little response," Dr. Adams says.

For more than a decade Dr. Formenti and another colleague, Dr. Demaria, have been pursuing the theory that local radiation treatment can act synergistically with immune-based treatments like imiquimod to produce a larger, systemic antitumor effect.

Most tumors are adept at concealing themselves from the immune system. Research indicates that radiation therapy produces significant changes in a tumor's microenvironment that render the cancer more susceptible to destruction by the body's own immune defense. Preclinical work by Dr. Demaria supports that theory, including a recent

study of imiquimod published in *Clinical Cancer Research*.

The team used the drug to treat breast cancer-related skin metastases in mice, some of which also received radiation. Imiquimod slowed the growth of metastases, but it was even more effective when combined with radiation. Intriguingly, mice that received the combined treatment along with low doses of cyclophosphamide appeared to develop a sort of long-term immune system memory of the cancer cells; they beat back a subsequent infusion of new cancer-producing cells without receiving a new round of treatment.

"We believe that when you combine radiotherapy with an immune system modifier like imiquimod, you can improve the immune system's response to the cancer not just in the immediate area, but throughout the body," says Dr. Demaria. A \$1 million grant from the National Cancer Institute is now enabling Drs. Formenti and Adams to test in a clinical trial the combination of topical imiquimod with local radiotherapy for breast cancer skin metastases.

-Gina Shaw

America's Neuro-Oncologist

BY JESSICA WAPNER



Dr. Howard Fine

WHEN SENATOR Edward M. Kennedy was diagnosed with a malignant brain tumor in 2008, he and his family consulted Howard Fine, MD, then chief of the neuro-oncology branch of the Center for Cancer Research at the National Cancer Institute (NCI). Dr. Fine is world-renowned as a pioneering neuro-oncologist and cancer researcher, and Senator Kennedy, like so many other patients facing the specter of brain cancer, was eager to tap his expertise.

Called America's neuro-oncologist by the National Brain Tumor Society, Dr. Fine has built his reputation on decades of innovative

research and clinical care. His laboratory at the National Institutes of Health was the first to identify the presence of tumor stem cells, which drive tumor growth, in glioblastoma, a subtype of brain cancer. At both the Dana-Farber Cancer Institute/Harvard Cancer Center and the NCI, Dr. Fine pioneered translational research centers to bring science out of the lab and into the clinic, a strategy that he intends to continue in his new role as deputy director of the NYU Cancer Institute, an appointment announced last August. He will also direct the Brain Tumor Center;

supported in part by the Making Headway Foundation and the Sohn Conference Foundation.

This summer we spoke with Dr. Fine, who is the Anne Murnick Cogan and David H. Cogan Professor of Oncology and chief of the Division of Hematology and Medical Oncology, about his new position and the state of brain cancer research.

What drew you to NYU Langone?

With its renowned clinicians, patient care, and laboratory researchers, it offers an outstanding foundation for

creating translational research centers. By *translational*, I mean bringing research out of the laboratory into meaningful advances for patients and also bringing patients closer to the experimental research.

What's your vision for your role here?

As a researcher and clinical oncologist, my area of specialty is brain cancer. Having seen the importance of keeping laboratory research connected to patient care and vice versa, I established brain tumor programs, first at Harvard University and then at the National Institutes of Health, focused on translational research. At NYU Langone, I will continue this work. We started by establishing a Brain Tumor Center and plan to use that program as a model for the creation of translational research centers for other tumor types.

Will you also continue researching brain cancer and treating patients with this disease?

My own research will remain focused on brain cancer, and I will still treat patients in the clinic and in the critical care setting. But my impetus for coming to NYU was not to advance my own research. Rather, I want to take the skills I have developed over the years and apply them to other tumor types. The Brain Tumor Center will likely be fully established within a year or two. After that, I will assist other oncology experts and newly recruited faculty to build such programs for other cancer types, such as breast, lung, and prostate.

What is the benefit of a translational research center to cancer patients?

First and foremost, a translational research center is a place where patients can obtain the best possible standard of care with leading clinicians. Patients will also have the opportunity to avail themselves of advanced treatments and diagnostics. Clinicians can obtain tumor tissue and clinical data from patients that then feed the research engine. That integration is how biomedical research will advance our understanding of intractable diseases like brain cancer and so many other

“What makes glioblastomas such harrowing tumors is that they grow in an indispensable organ. With many other cancers, tissue or an entire organ can be removed and the patient’s life can be saved. While such procedures are not trivial, neither are they usually fatal. We don’t have the option of removing someone’s brain.”

malignancies: world-class clinical care and access to pioneering research.

You have devoted your career to devising new approaches to treating glioblastoma. Why is this type of brain cancer so deadly?

There are several reasons why glioblastoma is such a harrowing disease. First, these tumors are growing in an indispensable organ. With many other cancers—breast and prostate, for example—tissue or an entire organ can be removed and the patient’s life can be saved. While such procedures are not trivial, neither are they usually fatal. We don’t have the option of removing someone’s brain.

Other challenges inherent in treating brain cancer include the risk of exposing healthy brain tissue to radiation; the presence of the blood-brain barrier, which, in keeping the brain safe from toxic drugs, prevents the entry of chemotherapy medications; and the fact that brain tumor cells are highly resistant to cancer medications, for reasons that are not well understood.

Recently your research has focused on glioblastoma stem cells and their role in creating better models for cancer research. How does this work change our understanding of brain cancer?

The traditional model of cancer cells is that they grow like bacteria: One makes two, two make four, four make eight, and on and on. With this model, all the cells have the same potential to generate new tumor cells, and so each cell contributes to tumor growth.

Several decades ago, a new hypothesis arose suggesting that perhaps not all tumor cells have the same capability to reproduce. Rather, just a small population of cells initiate tumor growth. These cells were dubbed tumor stem cells, because they are analogous to embryonic stem cells. In an embryo, a simple stem cell leads to the formation of all our various tissues, but most adult cells lack this capacity. Similarly, according to this hypothesis, only tumor stem cells have the capacity to divide and are thus responsible for cancer progression.

The stem cell hypothesis did not catch on when it was first posited. But about 15 to 20 years ago, researchers identified tumor stem cells in some blood cancers. More recently, working with surgical specimens from patients with glioblastoma, our group at the NCI was among the first to identify tumor stem cells in a solid tumor. The current outlook for cancer research is that the tumor stem cell model will hold true for most, if not all, solid tumors.

What is the implication of this finding for the treatment of glioblastoma and other cancers?

Among the many implications is what it means for the study of new drugs. Tumor stem cells are chemically different from other cancer cells. If we want to find drugs that will stop tumor growth, then we need to target the cells responsible for that growth. Screening experimental compounds against tumor stem cells in the laboratory is far more likely to lead to the discovery of effective drugs than screening compounds against

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Face Value

Philosophers since Aristotle have argued that symmetry is one of the foundations of beauty. But everyone who knows Maggie Porcelli would say that true beauty comes from something other than ideal balance or proportion.

BY GARY GOLDENBERG



DUE TO A SPONTANEOUS BIRTH defect called craniofacial microsomia, Maggie came into the world with no left ear, an underdeveloped left cheekbone, and an undersized and misaligned lower left jaw that gave the impression that one side of her face had collapsed on itself. Although she endured physical pain, the emotional hurt was often greater. Her unconventional looks drew teases and taunts from other children and rude stares from the occasional adult.

Now 23, Maggie still draws attention, but only because of her sharp wit and vivacious personality. Her face bears few traces of craniofacial microsomia. How she got from there to here is a story of remarkable personal resilience and advanced reconstructive surgery and orthodontics.

Maggie's parents, Carl and Patti Porcelli of Sea Cliff, New York, had never heard of craniofacial microsomia before their daughter's birth in 1989. However, as they soon learned, the syndrome is relatively common, occurring in about one in every 5,000 live births, second only to cleft lip and palate among facial birth defects. It's not clear what causes it, only that something during early fetal development compromises blood flow to the first and second pharyngeal arches, the part of

Maggie Porcelli at this year's Races for Faces event in Central Park, sponsored by the National Foundation for Facial Reconstruction.

the embryo that gives rise to the lower facial structures. The syndrome ranges in severity, from minor facial asymmetries (which, some speculate, could explain Abraham Lincoln's distinctively craggy visage) to major deformities that affect appearance as well as vision, hearing, breathing, and swallowing. Maggie's case fell somewhere in between.

At first, the Porcellis struggled to find appropriate help. One medical center offered a few surgical remedies, far short of a coordinated approach that would make her whole. A year later, the Porcellis learned of a special program for microsomia patients at the Institute of Reconstructive Plastic Surgery (IRPS) at NYU Langone Medical Center. The IRPS team, led by Joseph McCarthy, MD, the Helen L. Kimmel Professor of Reconstructive Plastic Surgery and former chair of Plastic Surgery, assured the couple that Maggie's appearance could be dramatically improved—with the caveat that it would require multiple surgeries over many years. "We were scared," says Patti. "But we did everything they recommended."

Dr. McCarthy and his colleagues began by crafting a staged, multidisciplinary treatment plan that would take two decades to play out. "We try to get these children to look as good as possible at a young age, but certain procedures have to wait until the facial structures stop growing, some as late as age 17 or 18," says Dr. McCarthy, whose team is currently following about 1,000 microsomia patients, from toddlers to twenty-somethings.

At age two, Maggie underwent her first major operation, a mandibular distraction. In this procedure, pioneered by Dr. McCarthy in 1989, the lower jaw on the affected side is cut in two and then gradually pulled apart (distracted) with an external fixator. This scaffoldlike device consists of pins inserted through the skin and anchored into the bone on either side of the break in the jaw. Every day for about one month, a family member turns the rods fixed between the

How to Make an Ear

One of the most common manifestations of craniofacial microsomia is a microtia, a condition in which the patient is missing the internal and external structures of the ear. While nothing can be done to restore the patient's hearing, it's possible to rebuild the external part of an ear, using the patient's own tissues.

"It's best to wait until the patient is 9 or 10, when the ear is 95 percent developed," says Charles Thorne, MD, associate professor of plastic surgery and surgery.

Making an ear from scratch requires several surgeries. The first step, says Dr. Thorne, is to harvest cartilage from the patient's ribs, which is then stitched together to form the ear's underlying structure. To complete this round of surgery, the cartilage patchwork is placed into a newly dissected pouch on the side of the head and covered with skin. Nothing further is done for about six months, allowing the cartilage time to heal and establish its own blood supply. In subsequent surgeries, the surgeon molds the skin around the cartilage and fashions an earlobe.

"The idea is not to create an ear that is going to stand up to intimate scrutiny—to be frank, your lover is always going to know," Dr. Thorne says. "The goal is to make an ear that, at conversational distance, doesn't draw attention."

Maggie's ear more than passes this test. "It looks great," says her mother. "Dr. Thorne's an artist."



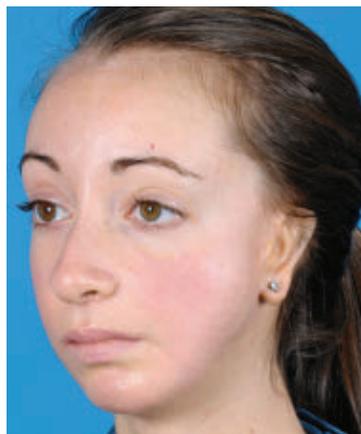
pins to push them in opposite directions. The device remains in place for another two months, during which time the body naturally fills in the gap with bone cells, resulting in a longer jawbone. The procedure was challenging but Maggie still manages to find the humor in it. "The device makes you look like Edward Scissorhands," she jokes. Over the next 20 years, she would endure another 20 procedures to straighten her teeth, construct a new ear (see sidebar), build up the soft tissue over her cheekbone, and repair her nasal passages, plus several years of speech therapy. In late 2011 Maggie underwent one last major operation, to further reposition her jaw. This time, both sides of the mandible were broken, so the jaw could be aligned symmetrically, and the side that was previously distracted was elongated with

bone harvested from her ribs.

From the start, Maggie found ways to cope. "I can remember kids in kindergarten asking what happened to me," she recalls. "I really didn't know, so I made up stories, like that I was in a car accident or a dog fight. I don't know what went through my head," she says, laughing. In later grades, children would make fun of her. "Kids can be very cruel. It hurts, but I blocked out the negativity," she says. Through it all, Maggie earned high grades and made friends. She even danced competitively for years, never shying from public view.

Other children with microsomia have a tougher time. "With our beauty-obsessed culture, it's especially hard for preteen girls," says Patricia Chibbaro, RN, CPNP, IRPS's nurse practitioner. "Many feel they won't ever have a normal life. Our psychosocial support services are

PATIENT STORY



Born with craniofacial microsomia, Maggie Porcelli has undergone more than 20 procedures since she was two years old. The color photo was taken last year, nine weeks after her last operation.

geared toward building their self-esteem and helping them come to terms with their appearance. You can do a hundred operations, but if they aren't going to leave the house, we really haven't helped them."

To make matters worse, children with facial deformities are sometimes mistakenly perceived as mentally challenged. "We often advise parents to have their kids psychologically tested just to show their schools that they don't need to be placed in special ed," Chibbaro says.

Maggie encountered this misperception too, but she wouldn't stand for it. "If people

looked at me in a certain way, I'd go right up to them and say, this is what's wrong with me, and if you have questions you can ask me. But please don't stare at me and make judgments when you don't know who I am and what I've been through," she says.

Today, Maggie is a college senior with a double major in childhood education and speech pathology. Nursing school is next on her agenda. She also volunteers for the National Foundation for Facial Reconstruction (an organization that underwrites many IRPS activities), where she counsels young microsomia patients

and participates in fundraising activities.

"I was so happy when she decided to become a nurse," says Chibbaro, who has worked with Maggie since she was a toddler and has become part of the Porcelli family. "It's strange, after all these years I don't have anything else to offer her—except my job when I retire."

Freshly healed from her last operation, Maggie is thrilled with her looks—even though, in her view, her jaw is still a little off kilter. No one else would notice. As Chibbaro notes, "She's a glowing, beautiful young woman." Inside and out. ●

FACULTY CONVERSATION

CONTINUED FROM PAGE 27

traditional cancer cell line models in which all tumor cells are the same.

In fact, our NCI group showed that a laboratory model of glioblastoma based on tumor stem cells mirrored glioblastoma in humans far more accurately than our older laboratory model.

What are some of the challenges with using a tumor stem cell model to study cancer and potential treatments?

One challenge is that tumor stem cells are very heterogeneous, meaning that they show a very high degree of genetic variation. That feature is helpful because it mirrors glioblastoma in people, which is very heterogeneous. But the challenge is that a drug or other treatment might

work against one stem cell but not another. Studying tumor stem cell models in animals therefore requires a larger population, to account for that variation.

Also, these models grow very slowly. Again, that mirrors human glioblastoma but makes research more arduous. Growing tumor stem cells in the laboratory is also very difficult. They have to be obtained from human tumors and need to be put into a highly specialized growing medium within minutes of removal.

What are the next steps for your research?

One focus of our research is on the tumor microenvironment; that is, the ecosystem in which cancer grows. Cancer research is increasingly realizing the

importance of a tumor's surroundings: the immune system, the pH, blood flow, and other biological mechanisms. We want to better understand the complexity of tumor growth by incorporating the microenvironment into our research, rather than looking at cancer cells in the artificial setting of an isolated Petri dish.

Are you optimistic about the future of cancer treatments?

When I first began treating brain cancer, the median survival time was 9 or 10 months. Today, it is 16 months. That gain is not enough. We need new approaches for treating all cancers. That is the goal of my research. That is why I am here at NYU Langone. ●

Berson Award Winners Alumni Achievement Awards for 2013

The Solomon A. Berson awards are named in honor of the brilliant researcher and 1945 graduate of NYU School of Medicine, whose work contributed to the development of the radioimmunoassay. The awards recognize distinguished alumni each year on Medical Alumni Day. Outstanding achievement by a young alumna was also recognized this year in April.

★ **AWARD IN BASIC SCIENCE**

ROBERT I. LEHRER, MD ('62), a member of Alpha Omega Alpha, discovered and named the antimicrobial peptides called defensins in immune and epithelial cells, which act like innate antibiotics to defend the body against bacterial, fungal, and viral infections. His laboratory is now investigating how alpha-defensins inactivate bacterial exotoxins, among other projects. He holds 24 U.S. patents and is the author of nearly 250 peer-reviewed scientific publications and more than 75 review articles and book chapters. Dr. Lehrer is Emeritus Distinguished Professor of Medicine at UCLA, which he joined in 1974. He completed his residency in internal medicine at Massachusetts General Hospital, a fellowship in biochemistry at Harvard University, and he also served on the faculty at University of California, San Francisco.

★ **AWARD IN HEALTH SCIENCE**

RONALD KLEIN, MD ('69), AND BARBARA KLEIN, MD ('69), have pursued groundbreaking research in ophthalmic epidemiology, enabling clinicians to help countless patients suffering from eye diseases and to counsel patients to prevent those same disorders. This dynamic husband-and-wife team is especially interested in the epidemiology of diabetic retinopathy and

other diabetic complications, age-related macular degeneration, hypertensive retinopathy, and chronic kidney disease, among other conditions. Both physician scientists are professors in the Department of Ophthalmology and Visual Sciences at the University of Wisconsin School of Medicine and Public Health. Their work has earned many honors and awards, including the National Eye Health Education Outstanding Achievement Award, the Eva Kohner Award from the European Association for the Study of Diabetes, the Hilldale Award in Biological Sciences, and the American Academy of Ophthalmology Achievement Award.

★ **AWARD IN CLINICAL SCIENCE**

BENJAMIN TYCKO, MD, PHD ('84), a member of Alpha Omega Alpha, is widely recognized for his studies of the epigenetics of human diseases, particularly Wilms' tumor, acute myeloid leukemia, and other cancers. During his wide-ranging career, he has identified the physiological functions of imprinted genes and the genetic and epigenetic basis for the phenotypes seen in Down syndrome, and he has also explored the population genetics of Alzheimer's disease. Dr. Tycko is the author of more than 100 peer-reviewed publications, many of them landmark papers, as well as 25 reviews, chapters, and editorials,

and he has served as director of the autopsy service at New York-Presbyterian Hospital. After completing his residency in pathology and a postdoctoral fellowship at Stanford University, he joined the faculty at Harvard University. In 1990 he moved to Columbia University, where he is now professor of pathology and cell biology.

★ **JULIA ZELMANOVICH YOUNG ALUMNI AWARD**

ALYSSA R. TERK, MD ('01), a member of Alpha Omega Alpha, completed her residency in otolaryngology at Yale University School of Medicine and a fellowship in pediatric otolaryngology at the Nemours/Alfred I. duPont Hospital for Children in Wilmington, Delaware. She subsequently joined the faculty at Yale, and then moved to Philadelphia, where she is attending otolaryngologist at St. Christopher's Hospital for Children and assistant professor of pediatrics at Drexel University College of Medicine. Dr. Terk's life story embodies NYU School of Medicine's motto, "to persevere and to excel." She overcame the adversity of hereditary progressive sensorineural hearing loss, which ultimately required cochlear implants, to become an otolaryngologist. A large part of her practice is devoted to identifying and treating children with hearing loss. Dr. Terk serves on the Board of Trustees of the Hearing Loss Association of America. ●

One Year After Hurricane Sandy, a Researcher Looks Back



The East River hours before Hurricane Sandy hit.

FRIDAY, OCTOBER 26, 2012, was perfectly ordinary for our group of 28 scientists and graduate students on the 18th floor of the Manhattan Veterans Affairs (VA) New York Harbor Healthcare System, affiliated with NYU School of Medicine, where we work on developing HIV vaccines and a serodiagnostic test for tuberculosis. As Hurricane Sandy approached New York City, the only storm-related discussion we had was about two freezers that we knew weren't on hospital backup emergency power. But by Sunday, the news was increasingly ominous.

Though the VA is in Evacuation Zone A—that at greatest risk—I wasn't concerned because the hospital's backup generators were tested regularly, and I was confident that the lab would be safe. The hurricane struck Monday night as predicted, abetted by a full moon and an unusually high tide. As feared, it cut electricity below 39th Street. We awoke on Tuesday to the news that NYU Langone Medical Center's Tisch Hospital, only eight blocks north of the VA, had lost both electricity and backup power, but I assumed our labs were fine.

Fortunately, I live close by, so I went to check the two freezers that were not on backup. I soon learned that the VA had not been spared: The basement and ground floor had been flooded by a 14-foot tidal surge, destroying everything below ground level. Much of the hospital's

infrastructure had been damaged, and there was no power in the building—or in our labs, where our freezers and incubators held specimens and cell lines collected over the course of 25 years.

I needed to get up to the lab, but no one was allowed in the building. As I sat in the cold lobby, Dr. Catarina Hioe, associate professor of pathology, and Constance Williams, my lab manager for more than 20 years, arrived. Together, we explained to the hospital administrator that we had to secure our HIV and TB cultures and frozen specimens so that they posed no threat. Given the gravity of the situation, we were allowed in.

First, we filled the 15 liquid nitrogen storage tanks containing patient specimens and cell lines with whatever liquid nitrogen was available. Our 19 freezers were still holding temperature, but we were painfully aware that the next critical step was to stabilize them with dry ice, none of which was available at NYU Langone. In the evening, we contacted a party supply dealer who could deliver only 350 pounds of dry ice because existing orders for Halloween parties took priority. The following morning, several lab members met us to haul seven 50-pound blocks of dry ice up 18 flights of stairs. We were able to order another 1,000 pounds, and on Wednesday we hauled 20 blocks of dry ice up the stairs and packed the remaining freezers. Then we had to figure

out how to evacuate the specimens, since it had become clear that the building would be closed for weeks, if not months.

A colleague put me in contact with BioStorage Technologies in Indianapolis, and miraculously, they assured me that on Saturday morning the company would deliver 15 people and two 18-wheeler rigs filled with -80° freezers and dry ice. We mobilized the entire lab, and one of our graduate students, Colleen Courtney, organized more than a dozen of NYU Langone's medical and graduate students to help reverse the process of the last few days—lugging specimens and liquid nitrogen tanks down 18 floors. Meanwhile, our ranks of "specimen Sherpas" had mushroomed to include spouses, two visiting fellows from India who had arrived that week for training in our labs, and even a complete stranger who offered to help as he was walking by. By midday on Sunday, November 4, our specimens were safely stored in facilities in New Jersey and Indiana.

The first anniversary of the storm should see us back in our labs. In the interim, our group has been dispersed but functional, working at nine sites in Manhattan, Brooklyn, and Newark. We are gradually retrieving our specimens as our research gets back up to speed, and we can finally say that we weathered the storm. ●

—SUSAN ZOLLA-PAZNER, PHD
Professor of Pathology

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the world...



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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.

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