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THE COURAGE TO CUT

A Journey Into the Hearts and Minds of NYU Langone's Neurosurgeons

PLUS

Dr. Glenn Saxe on Sandy Hook and Childhood Trauma

Earning an MD in Three Years

How Molecular Autopsies Can Help Solve Mysterious Deaths

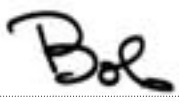
Because It Is Brain Surgery

LONG BEFORE I BECAME DEAN & CEO OF NYU LANGONE MEDICAL CENTER, I began a residency in neurosurgery. Though I eventually changed course, deciding on the field of radiology, I never lost my fascination, my respect, my awe, for the mysteries and marvels of the human brain. Indeed, that passion for neuroscience steered me toward neuroradiology as a subspecialty. So while I try not to play favorites, I must admit that neurosurgery and neurosurgeons, whom I've consulted with closely for many years, hold a special place in my heart.

I'm immensely proud of our Department of Neurosurgery, which has a long and distinguished history, and I'm delighted to see it featured in this issue. It's a well deserved tribute to a remarkable team of surgeons. Fifty years ago, the late Joseph Ransohoff, MD, chair of our Department of Neurosurgery from 1962 to 1992, served as medical consultant to the pioneering TV series Ben Casey, whose title character was loosely modeled after the brash, brooding surgeon. For several consecutive years, U.S. News & World Report's Best Hospital Rankings has placed our program in neurosurgery among the top 10 in America.

In the last two years, the Department has become even stronger, recruiting several outstanding neurosurgeons, some of them world-renowned for their expertise in certain subspecialties. What heartens me most about these master surgeons is their compassion and can-do attitude. As one of them puts it: "Many patients are told that their tumor is 'inoperable,' but then they come here and they survive."

I think you'll enjoy this inspirational journey into their hearts and minds. •



DEAN & CEO ROBERT I. GROSSMAN, MD

JOHN ABBOTT


Julia Meyer

EVERY YEAR in the United States, roughly 6,000 patients are diagnosed with acute lymphoblastic leukemia (ALL), a disease in which the body's bone marrow produces a glut of lymphocytes, or white blood cells. Improved chemotherapy and other treatments have dramatically boosted the cure rate of ALL, the most common type of childhood cancer, to about 80 percent. For the unfortunate 20 percent of children who relapse after a bout with the aggressive blood-borne disease, however, the prognosis remains dire.

"There has been no progress in curing children who relapse, in spite of giving them very high doses of chemotherapy and bone marrow transplantation," says William L. Carroll, MD, director of NYU Langone Medical Center's Cancer Institute and the Julie and Edward J. Minskoff Professor of Pediatrics.

Dr. Carroll's team may now be closer to changing that grim reality with the discovery of 20 genetic mutations linked to relapse, including one that may allow ALL to reemerge months or years after the initial diagnosis. "For the first time, we have pinpointed genetic mutations that lead to chemotherapy resistance and relapse," he says.

In the new study, led by Dr. Carroll and graduate student Julia Meyer and published in the March issue of Nature Genetics, researchers analyzed bone marrow samples from 10 pediatric ALL patients for telltale clues to the disease's progression. After receiving samples from the Children's Oncology Group, the medical researchers painstakingly pieced together a complete sequence of ribonucleic acid, or RNA, extracted from each patient's bone marrow—or about 100 billion letters of RNA in all. "It took years of effort analyzing samples from the same patient at diagnosis and relapse," Dr. Carroll says.

RNA is an essential intermediary in the cellular process that uses DNA blueprints to assemble proteins, meaning that a complete RNA sequence can give researchers a view of all active genes within a patient's leukemia cells. By comparing the sequences at the moment of diagnosis and upon relapse, the team found that most patients had acquired multiple mutations that changed the genetic code over the course of the disease.

Intriguingly, two patients harbored a mutation in the same gene, NT5C2, which encodes an enzyme that regulates some DNA building blocks but can also degrade an important class of drugs used in ALL therapy. When the researchers fully sequenced the NT5C2 gene in 61 other cases in which pediatric ALL patients had relapsed, they found five more mutations that had altered the gene. Experiments suggested that these seven NT5C2 mutations all made the cancer cells more resistant to chemotherapy.

By identifying a specific disease mechanism, the finding may help doctors detect the early emergence of chemotherapy-resistant leukemia cells and adjust their strategy before the disease can fully reassert itself. Andrew Place, MD, PhD, an instructor in pediatrics at Harvard Medical School and associate director of developmental therapeutics at the Dana-Farber/Children's Hospital Cancer Center in Boston, says the discovery may help clinicians create personalized treatment strategies.

A micrograph of a white blood cell. In acute lymphoblastic leukemia, white blood cells turn malignant and flood the bone marrow.

"This paper identifies an abnormal enzyme that could be specifically targeted and exploited in some patients with relapsed leukemia," Dr. Place says. Inhibiting the enzyme may also prove useful in initial ALL therapies, he says, helping doctors prevent those relapses in their pediatric leukemia patients. ● —BRYN NELSON

AS a D L a

O A P T
D a D a

SEVENTEEN YEARS experimented with immune cells that Dr. Unutmaz had developed during his previous HIV research, including a genetically engineered T cell that has excess copies of the CCR5 receptor decorating its surface. When the scientists exposed these cells to a purified Staph toxin called LukED, all the cells died. Cells that had been completely stripped of the receptor, however, resisted the toxin's effects and survived.

Other studies have revealed a remarkably similar phenomenon in HIV infection: Due to a genetic mutation, about 1% of Northern Europeans completely lack the CCR5 receptor on their T cells and are thereby protected against infection. The NYU Langone collaborators' research suggested that the LukED toxin does indeed share a common target with HIV, in this case using the CCR5 receptor as a landing pad from which the toxin can lethally puncture the immune cells.

If removing CCR5 from T cells warded off Staph infections, the researchers wondered, could simply blocking access to the receptor have the same beneficial effect? To find out, they treated T cells with maraviroc—an anti-HIV medication that clings to CCR5 and makes it inaccessible to the virus—and then exposed the cells to the Staph toxin. The result, says Dr. Unutmaz, was remarkable. "Maraviroc completely blocked the toxic effects of LukED at doses similar to those used to inhibit HIV infection."

Dr. Torres was equally surprised. "While maraviroc does not protect other immune cells from the other leukotoxins, it might give the immune system the upper hand in controlling a Staph infection," he says, "and that would be a real clinical advance."

Given the results, the CCR5 receptor could become a focal point for new anti-HIV strategies as well. Dr. Unutmaz, for example, wonders whether clinicians could protect the body's vulnerable mucosal areas by ridding them of CCR5-bearing cells that would otherwise be targeted by the virus. His lab is also exploring the possibility of using the LukED toxin to target and kill CCR5-containing T cells that harbor hidden reservoirs of HIV. "These are highly speculative approaches, of course, but it's exciting," he says. "One breakthrough 17 years ago may beget another." ● —RENEE TWOMBLY

E B a Y Ta

Scientists discover a way to trace the motor neurons central to healthy breathing.

Neuroscience that they have discovered a genetic fngerprint of PMC neurons as well as the two key genes that control their

AC aC A

SCIENTISTS HAVE long puzzled over the fact that some bacteria can dramatically boost the health and life spans of their hosts—the organisms in which they dwell. Evgeny Nudler, PhD, the Julie Wilson Anderson Professor of Biochemistry and newly appointed Howard Hughes Medical Institute investigator, recalls being particularly struck by research suggesting that a roundworm can survive roughly 50% longer than its average two-week life expectancy simply due to the type of bacteria it hosts.

In a study published in February in Cell, a team led by Dr. Nudler and Ivan Gusarov, PhD, research assistant professor, traces part of that difference in roundworm longevity to the ability of host bacteria to make nitric oxide, a chemical messenger implicated in everything from nerve signaling to blood flow. The new study, funded in part by Timur Artemyev, concludes that nitric oxide sends a signal to activate multiple genes in the worm that may protect it from stress and extend its life.

The worm, Caenorhabditis elegans, is a common stand-in for humans in studies of the aging process, and the discovery suggests how the microbiome, the trillions of bacterial colonists on and within our bodies, might similarly influence human health.

"In worms, we now know that bacteria can use nitric oxide not only to their own advantage but also to provide their host with a beneficial response, and the same thing could be true in a human gut," Dr. Nudler says. "It may well be the case that our commensal bacteria control some of our genes, at least in the gut, to protect those cells against stress and aging."

Dr. Nudler's lab used fluorescent labels and other techniques to document how the worm hijacks nitric oxide from a soil-dwelling bacterium called Bacillus subtilis that is both a favored food and a common colonist within its gut. Once nitric oxide penetrates the worm's tissue, the researchers discovered, it helps activate a set of 65 genes, including some previously implicated in stress resistance, immune response, and increased life span. Crucially, the chemical's control over these genes requires the presence of two regulatory proteins that are evolutionarily conserved from worms to humans and act like master switches to turn on or off the vast majority of the genes.

When the researchers corrected a defect that prevented mutant B. subtilis from producing nitric oxide—thereby restoring the worm's supply of the chemical—they increased the average life span of the worm by about 15%. Dr. Nudler believes this finding holds several important medical implications. Unlike worms, we make our own nitric oxide. However, levels gradually decrease over time, a decline he speculates could contribute to aging and could be at least partially reversed by supplemental bacteria supplying some of the missing compound.

"It's striking that a small molecule produced by one organism can dramatically affect the physiology and even life span of another organism through direct cell signaling," Dr. Nudler says. Given the potential for nitric oxide–generating microbes to likewise pay big dividends in the human gut, he adds, "I think it's a very interesting direction to explore." ● —BRYN NELSON

Dr. John Golfinos, chair of the Department of Neurosurgery, at home with his daughter Phoebe.

pleasures, joys, laughter, and jests, as well as our sorrows, pains, grief, and fears." Chandranath Sen, MD, professor of neurosurgery and director of the Division of Skull Base Surgery, speaks of "the sacred privilege" of being a neurosurgeon. "When I first meet a patient, that person has never seen me before, yet he or she is willing to put their life in my hands. This is the weakest moment in that person's life—they are lost, helpless, scared to death. I have to treat this person very gently. I never take the risk. It's the patient who takes the risk. He or she must have courage. I must have conviction. Before a big case, I meditate. It gets my mind in the zone."

That gentleness, says Dr. Sen, must carry over into the OR. "The brain has the consistency of Jell-O. A tumor feels like a piece of meat. The nerves are like small wet noodles," he explains. "You must peel away the meat without disrupting the Jell-O. Along the way, you must be careful not to damage any blood vessels, which could cause a stroke, or nerves, which could cause blindness, deafness, paralysis, or other problems. To succeed, you must have the touch of a woman—and the heart of a lion. Once you are done.333the operation, the brain

Is it any wonder that neurosurgeons speak so reverentially of this three-pound mass of pinkish-gray tissue about the size of a cantaloupe? “The brain is the most complex organ in the

Neurosurgery. “Before we had aneurysms and vascular malformations, spine ailments, epileptic seizures, deep brain stimulation for Parkinson’s disease, and a range of other conditions. “Some of our new colleagues are iconic,” says Anthony Frempong-Boadu, MD, associate professor of neurosurgery and director of the Division of Spinal Surgery. “We observe each other in the OR like it’s our first time there. The intellectual exchange has upped everyone’s game.” Dr. Jafar is so proud of his newly expanded department that he says, “I’ve visited many departments of neurosurgery around the world, and few of them rival ours. Many patients are told that their tumor is inoperable, but then they come here and they survive.”

“Our goal,” Dr. Golfnos says, “is to be the place that other neurosurgery centers refer their really difficult cases to because we can get the job done.” For neurosurgeons, that often requires what Dr. Frempong-Boadu describes as “walking the tightrope” between confidence and hubris. “Neurosurgeons are comfortable going into the unknown,” he says. “A lot of what we do is shrouded in mystery. What makes a great neurosurgeon is his thinking. It’s not about technical skills. It’s about knowing what you can and can’t touch, what you can and can’t move. A great neurosurgeon can almost see through things.”

For all the information and insights that sophisticated imaging can provide, the map is not the same as the territory itself, and danger, if not disaster, is sometimes only a millimeter away. “You’re often working in a surgical field the size of a quarter or half dollar,” Dr. Wisoff explains.

> “If you don’t have fear,” adds Dr. Jafar, “you’re dangerous. You can work for hours, and in the last 10 seconds you can ruin everything. The most dangerous part of the operation is the last 5 minutes

because you think you're finished. You can't afford to let your guard down, even for a moment. I don't listen to music while I'm operating. The night before, I listen to Mozart. In the OR, I'm listening to the patient's heart rate, one of many things that guide me."

The importance of total concentration is just one of the lessons Dr. Jafar tries to instill in his residents, mostly by example. Unlike many programs in neurosurgery, NYU Langone has a training period of seven years instead of six. During the last year (the second of two as chief resident), the newly minted neurosurgeon functions as the operating surgeon for more than 300 varied neurological procedures. Yet there's one thing, says Dr. Jafar, that you can't teach: judgment. "For a neurosurgeon," he explains, "common sense is knowing what your limits are. Knowing how to stay out of trouble—or get yourself out of trouble. Knowing when to stop the surgery if you have to."

Dr. Wisoff feels that the key to mastering the art of critical thinking inside the OR is to anticipate as many pitfalls as possible and carefully consider the options outside the OR. "When you're removing a malignant tumor," he says, "you have to be appropriately aggressive. If you go in with a timid attitude, you'll perform a timid operation—what we call peek and shriek. If that's not right for the patient, you've done him or her a tremendous disservice." In the still fairly uncharted landscape of the brain, doing what's

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Throughout his career, Dr. Saxe has dedicated himself to understanding the impact of traumatic events on children and adolescents and improving their care. He pioneered a unique community-based program, Trauma Systems Therapy (TST), and also helped develop the National Child Traumatic Stress Network, a nationwide program that partners academic research centers with community practice sites. In February 2013, the Child Study Center, in collaboration with the New York City Administration for Children’s Services and Bellevue Hospital, received grants totaling more than $7 million to enhance trauma services for young people. The grants built on seed funding provided by generous gifts from Michele and Timothy Barakett and the Bloomgarden-Willner Family.

How do you define childhood trauma?

Trauma is when a child experiences something that threatens life and limb. Community violence, violence within families, abuse, rape, disasters, war, terrorism, significant medical illnesses—all of these fit the category of trauma. Violence in the family and a school shooting are very different events, but there’s a core similarity that defines most reactions to trauma, involving ancient, powerful survival systems in the body. When a threat occurs, a structure deep in the brain called the amygdala fires. It’s a very important structure because it prepares us to survive in the face of threat. It makes your heart pound and your muscles tense, preparing you to fight or flee. Following a trauma, it’s hard for the amygdala to settle and so it’s normal to be intensely distressed and concerned about safety over days, and even weeks after trauma. In most people, this emotional state diminishes dramatically with time, but in some people it persists: Their amygdala keeps firing, even in situations where there’s no real threat.

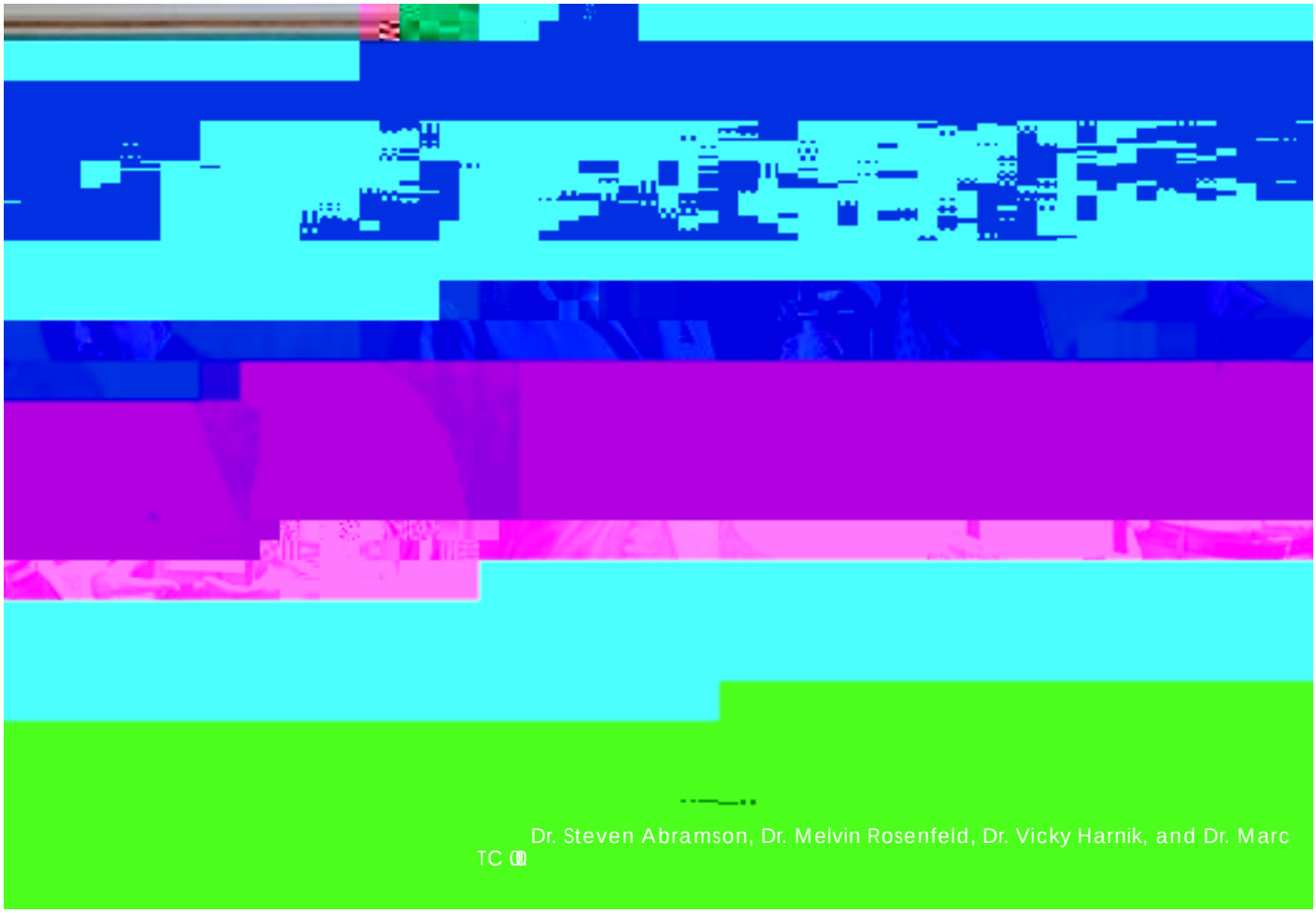
A GLORIA BAKER

What happens when those fearful emotions persist?
Ordinarily, other areas of the brain such as the hippocampus and prefrontal cortex help inhibit the amygdala from mis f ring after a trauma by bringing context and memory to the situation. The hippocampus is responsible for helping people understand context. After an injury, for example, the hippocampus will recognize that once you're in the hospital you're safe. But in some children this mechanism gets disordered and they can no longer recognize that they're in a safe place. Something will remind them of what happened and trigger those survival systems. It might be someone using a tone of voice similar to the one used by your stepfather just before he raped you. You get f ooded with painful memories and may experience yourself back in the place and time of the trauma. You're not under immediate threat, but you're living as if you are. That's the central problem of post-traumatic stress disorder, or PTSD.

Does trauma leave any permanent effects on the brain?
There is research that indicates kids who endure chronic stress and PTSD early in life may develop smaller brains and have lower IQs. If this is true it indicates an unspeakable tragedy: They're starting life with a strike against them that can in f uence a great many things and have cumulative impact. It can affect learning and school performance. It can affect how they experience themselves, their effectiveness in the world, and how others view them.

How big is the problem of childhood trauma and how will your new grant help?
Obviously, what happened at Sandy Hook is a terrible tragedy, and our hearts break for the families who lost these young children. But there are also many hidden cases of childhood trauma. Do you know how many American children last year lost their lives at the hands of their parents or other caregivers? About 1,500. And that's just the tip of the iceberg: The child welfare system gets 6 million calls about possible child abuse annually. Any one call may end up as one of the 1500 children who die. How do they get it right? What if they get it wrong? Our grant involves partnering with the child welfare system and building their capacity to get it right. We're helping child welfare workers better understand trauma, training them to screen children for trauma and working with them to implement interventions, particularly TST, for kids at risk. The burnout rate for child welfare workers is very high, so we're also working with the child welfare system to support their workforce.0(t can a)15(ffect learning)-20( )]TJ T*[and -20(a(nt(ers is))15(s)10(bu -0.0 irreTt35vT Ty t

TWELVE-YEAR-OLD STEVEN RHODES (not his real name) has no shortage of interests. He can hold forth on Albert Einstein, the atomic bomb, Marvel Comics, and any number of other subjects that fascinate him. The trouble is, he doesn't know when to stop sharing. "He can talk about Einstein for a half hour straight," says his mother.



Dr. Steven Abramson, Dr. Melvin Rosenfeld, Dr. Vicky Harnik, and Dr. Marc

TC

A Matter of Degrees

Starting this year, a select group of students have the option of earning an MD in three years.

ON AN AVERAGE of once every minute, a new scholarly article is added to the medical literature—a statistic that would seem to suggest that medical schools should lengthen their curricula to better prepare physicians for 21st century clinical practice. Yet NYU School of Medicine is doing just the opposite. Starting this year, a select group of students have the option of earning an MD in three years, slicing a full year off the traditional education.

This radical rethinking of how doctors are made has prompted some to fear that NYU School of Medicine is on the road to becoming a "trade school" where training is pared down to the bare minimum. But NYU Langone Medical Center's educators believe that accelerated study, if done properly and offered to selected highly qualified applicants, can be an effective counterbalance to ever more extensive training periods, which now average 10 years for subspecialties, without sacrificing quality.

"Our new plan is based on the premise that medical students should be offered the ability to differentiate and accelerate their careers if they were qualified to do so. We must keep in mind that you become a doctor over the entire course of your training, not just during medical school," says Steven Abramson, MD, the Frederick H. King Professor of Internal Medicine and chairman of the Department of Medicine, senior vice president and vice dean for education, faculty, and academic affairs,

JOHN ABBOTT

the heart OF THE MATTER

When seemingly healthy individuals suddenly die, medical examiners often turn to molecular autopsies for clues. Thanks to a multiagency collaborative effort, the results are not only solving mysterious deaths but also saving lives.

BY BRYN NELSON
PHOTOGRAPHS BY JOHN ABBOTT

THE SUDDEN DEATH of a 26-year-old mother of two initially seemed like an open-and-shut case: a tragic cocaine and alcohol overdose. Beyond the toxicology results, the Office of Chief Medical Examiner of the City of New York's woman's family raised the possibility of an inherited heart condition.

An ensuing collaboration between the OCME's molecular genetics lab and the Montefiore Einstein Center for CardioGenetics (MECC) in the Bronx uncovered a mutation in one of her genes linked to a rare but dangerous heart arrhythmia called long QT syndrome (LQTS) that affects an estimated 1 in 7,000 people in the United States. On its own, cocaine was unlikely to cause the woman to collapse and die, the joint investigation suggested. But in combination with a genetic defect that altered her heart's electric current, the drug proved deadly.

This case and others like it highlight the power of a so-called molecular autopsy, a method of genetic sleuthing that can determine the cause of a mysterious death, identify potentially lethal mutations that might run in families, and even help solve crimes. Now, owing to the OCME's collaborative efforts, the technique is also spurring new insights into how stress and drugs can compound preexisting heart conditions.

Although it functions as a governmental agency, the OCME has long-standing ties to NYU Langone Medical Center's Departments of Forensic Medicine and Pathology, and many of its medical and research staff are on the faculty of NYU School of Medicine. The agency performs about 5,000 autopsies each year, a good number of them after the sudden, unexpected death of a seemingly healthy New Yorker. In

blockage by cocaine.

That knowledge can save lives. Dr. Tang and Dr. Sampson point to their blossoming relationship with the Montefore-Einstein Center for CardioGenetics as one example of how genetic sleuthing can open the door to lifesaving testing services and support. Thomas McDonald, MD, the center's co-director, says the "collegial and collaborative exchange" between the groups allowed them to publish two recent case studies in the journal Pacing and Clinical Electrophysiology. Solving the cocaine-LQTS case also helped his team provide preventive care to the victim's two children after genetic tests revealed that both had inherited the same mutation. "It's very important because we can do things that will hopefully decrease their risk for having a heart rhythm disturbance and sudden death like their mother had," he says.

A second collaboration between Dr. Tang and Dr. McDonald underscores the diffculty of predicting how genetic mutations might affect individual patients. When a young woman suddenly collapsed and died at home several months after undergoing a gastric banding operation to help control her obesity, investigators focused on the frequent vomiting episodes reported by her family.

Her symptoms heightened suspicions that she was dehydrated and running low on potassium. Meanwhile, E rhear htr( )]TJ T*[e a)-18(n)-1((8 t)-22(h42(t)-21(r)-249Gd)b)h j-1(d d9)-18(l h)18(lp)-10(a)15(t11(t)-6(o)5(n t)t b)-166(o)9(e)-6(r u)-6(v)-23(iu f)14(o)-118(f)-27a 3(g a)-13(g a h)4(ec)-1513- (e)-14(c(e)-6((m)216g)-4(h)16(t a)-18(f)-25(f)13(e)-144b)h whe[illegible]

molecular testing," she says, "we will whittle at this and gradually give more and more parents an answer."

Dr. Tang credits Dr. Sampson and Dr. Hirsch for recognizing the importance of establishing her lab a decade ago. The publicly fnanced detective work, she says, is still unique among cities in the United States and would have been prohibitively expensive without the extensive infrastructure already laid within the OCME's Department of Forensic Biology.

Despite the tragedies she encounters on a regular basis, Dr. Tang revels in her lab's ability to help other doctors provide happier endings. In one heartbreaking case, a seven-year-old boy collapsed and died at school. After the OCME's standard autopsy tests were inconclusive, the molecular autopsy revealed yet another mutation in a gene linked to LQTS. Two of the boy's relatives had previously died of heart problems and his half-sister was already under the care of Montefore-Einstein cardiologists.

Unbeknownst to her doctors, the half-sister harbored the same rare mutation, and her existing heart medication was particularly ill suited for the syndrome subtype. "We did very fast in-house molecular testing for this case," Dr. Tang says, recalling that the lab's post-mortem testing spurred the half-sister's cardiologist to switch her medication immediately to a more appropriate therapy. "They were very happy with that change," Dr. Tang says, "because that could actually be lifesaving." ●

NEAR THE END of President Barack Obama's State of the Union address last February 12, he turned everyone's attention to the balcony, where First Lady Michelle Obama was joined by 23 special guests. Seated between the First Lady and the vice

STEVEN ABRAMSON, MD, senior vice president and vice dean for education, faculty and academic affairs, professor of medicine and pathology, has been appointed chair of the Department of Medicine. The largest academic department of NYU School of Medicine, the department has a long and distinguishe9(is)1(is61(b)1(S7(d)-)10(35(7)11(9(ii9611(9(636 0 2.57 -1.333 Td [(o)10(f M)8(e)-1522 [B0(22 [(4)-14(i)-ti)1 Td [(o)10(f M)8(e)-14(
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rose to number 7 in U.S. News & World Report's annual "Best Hospitals" issue. Dr. Abramson will continue to serve as vice dean, a role in which he guided the major medical education reform that created our Curriculum for the 21st Century (C21). ●

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