MISSING A CRUCIAL TARGET

BIOPSIES FOR PROSTATE CANCER OFTEN OVERLOOK DANGEROUS LESIONS

PLUS

The Truth About Low Testosterone

The Male Biological Clock

Neuroscience and the Love Song of Finches
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“We’ve made progress. But if anyone thinks that we’ve optimized screening by using a nonspecific marker and randomly placing 12 needles and taking 12 specimens, then he’s naive.”

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Men’s Health

Although men are living longer and enjoying healthier lives, there is much room for improvement. This issue of NYU Physician highlights some of the health challenges men encounter as they age. Prostate cancer is the second leading cause of cancer death, but today in the United States doctors are still unable to distinguish reliably between aggressive and nonaggressive tumors. You will read about how our urologists and radiologists are working to solve this urgent problem, proving once again that collaborative teamwork can yield meaningful results in the clinic. Our story on hypogonadism, or low testosterone, explores whether testosterone replacement therapy works and who should receive it, an important and relatively recent issue in men’s health. Another story describes the emerging evidence for a male biological clock, a phrase almost unheard of a mere decade ago.

You will also find a remarkable story about a neuroscientist who is learning about the neuronal basis of behavior through the love song of finches, a thoughtful Q&A with Dr. Richard Novick, one of our pioneering microbiologists, and the latest research from our laboratories.

I cannot end this letter without mentioning Hurricane Sandy. The accompanying story provides many details about the heroism of our healthcare providers during the night the hurricane slammed into our Medical Center. The following weeks brought many losses and many lessons, but it also highlighted what I will always remain thankful for, the dedication of the entire NYU Langone community and our determination to prevail.

Eugene Braunwald (’52), the Distinguished Hersey Professor of Medicine at Harvard and one of our most illustrious alumni, wrote a letter to the class of 2016 that bears repeating here. “I admire enormously the courage of the entire NYU Medical School family to deal with this extraordinary event. I know from personal experience that from adversity comes strength and that my beloved alma mater will be even better and stronger after the recovery from this devastating event.” I wholeheartedly concur.

DEAN & CEO ROBERT I. GROSSMAN, MD
The Balm After the Storm
NYU Langone confronts the worst crisis in its history.

ON MONDAY, OCTOBER 29, 2012—one year after Hurricane Irene forced NYU Langone Medical Center to evacuate its patients and close its doors—Hurricane Sandy did one better, plunging the Medical Center into the worst crisis of its history. Extensive damage to the main campus forced the closure of Tisch Hospital, the Rusk Institute of Rehabilitation Medicine, and our three research buildings—the Skirball Institute of Biomolecular Medicine, the Joan and Joel Smilow Research Center, and the Medical Sciences Building—for more than two months. The storm also shuttered Bellevue Hospital Center and the Manhattan VA Medical Center, both home to many of NYU Langone’s researchers and clinicians and our primary teaching affiliates. All told, the unprecedented disaster disrupted operations at the heart of our three core missions: education, research, and patient care.

On the night of the disaster, 322 patients were safely transferred to 14 other hospitals within 13 hours—a physical and logistical challenge of epic proportions. Some 1,000 medical and professional personnel—including nurses, physicians, fellows, residents, medical students, and therapists—along with firefighters and countless volunteers from our administrative and support staff rose to the challenge, evacuating every single patient.

Another population was also at risk. Tens of thousands of genetically altered mice used to study myriad diseases were housed in the basements of two of the research facilities. The power outage damaged sensitive, sophisticated equipment, compromised ongoing experiments, and destroyed specimens and reagents. Tragically, many of the animals in the Smilow building were lost when water filled its basement. For some researchers, this represented the loss of years of work. In the aftermath of the hurricane, every effort was made to salvage as much as possible in research laboratories. “I have been inspired by the entire NYU Langone community,” said Dafna Bar-Sagi, PhD, senior vice president and vice dean for science, “not the least of which are our postdocs and grad students. Armed with positive attitudes, determination, and apparently quite strong biceps, they carried more than 3,500 pounds of dry ice up hundreds of stairs and then repeated this and many other tasks. Their efforts saved countless specimens and samples, bolstering the future success of our research programs.”

Days before the storm’s arrival, the Medical Center began implementing a wide range of measures designed to mitigate its impact. Led by Bernard Birnbaum, MD, senior vice president, vice dean, and chief of hospital operations, the Incident Command Team (ICT)—administrators charged with hospital-wide crisis management—began meeting and conferring frequently. The ICT and executive leadership faced an impossibly complex calculation. Would more than 575 inpatients, particularly those who were most frail, be less at risk if they were sheltered in place during the storm? “There are significant risks to transferring patients,” Dr. Birnbaum notes. “It’s the least desirable option.”

On the previous Friday, NYU Langone began to discharge all medically stable patients, reducing its census to 325. At the same time, Real Estate Development + Facilities also began implementing a wide range of measures to secure the physical plant and mitigate the storm’s impact. As an additional precaution, the Medical Center announced on Sunday, October 28, the cancellation of all scheduled surgeries and procedures—with the exception of emergent procedures—through Tuesday, October 30, and the closure of all off-campus ambulatory care centers and on-campus physician offices. To ensure that the patient census be kept at a minimum throughout the storm, Tisch Hospital’s Emergency Department was also closed. “Based on all the preparations we had made, and knowing that we had emergency power in place if needed, we were confident that we could weather the
storm," Dr. Birnbaum explains.

Hurricane Irene, which forced the evacuation of NYU Langone in August 2011, had been dubbed “the storm of the century.” But Hurricane Sandy created a storm surge at Battery Park that was 2.68 feet higher than the record level set in 1821, qualifying Sandy—in those terms, at least—as the worst storm to hit New York City in two centuries. Along Flood Zone A, which includes our campus, the surge rose to 14½ feet, more than a half foot higher than at Battery Park. When the team learned on Monday night that water had reached buildings on campus, that the entire phone system was down, and that the emergency backup power system was at risk, the writing was on the wall. “The storm surge that crippled the city and overwhelmed our defenses occurred over only 30 minutes,” Dr Birnbaum notes. “When it became clear that our emergency power could be compromised, there was no doubt by the ICT, Dean Grossman, and executive leadership that the decision to evacuate patients was the best course of action.”

At that point, the rapid discharge of remaining patients began. Members of the ICT immediately notified the appropriate agencies, including the New York City Fire Department and Office of Emergency Management, that an evacuation was imminent; called area hospitals to coordinate transfers; and visited clinical units throughout the Medical Center to personally inform physicians and nurses of the situation. For the most part, the evacuation was performed by hand—many hands, in fact. Working in teams of six or more and assisted by members of the NYC Fire Department, caregivers used “med sleds” designed for high-rise evacuations to maneuver patients down the dark, humid, twisting stairwells of Tisch Hospital and the Schwartz Health Care Center with carefully choreographed synchronization and tender loving care.

NYU Langone’s medical staff was concerned about the safety and well-being of all its patients, of course, but there was particular concern for our pediatric patients because of their inherently vulnerable condition. Seven patients were evacuated from the Laurence D. and Lori Weider Fink pediatric intensive care unit, six from the congenital cardiovascular care unit (CCCU), and 20 from the KiDS of NYU Langone Neonatal ICU (NICU). The daunting logistics were orchestrated, in part, by Bret Rudy, MD, associate professor of pediatrics and vice chair of the Department of Pediatrics. “The evacuation could not have been so successful without many helping hands,” Dr. Rudy concedes. “Calling other hospitals to assess who could take patients, handwriting summaries of medical charts and histories by flashlight, notifying and reassuring anxious parents of the situation—none of this could have been done in record time without the superb teamwork of attending physicians, fellows, residents, medical students, nurses, and so many others.”

Numerous administrative departments also played key support roles in ensuring that the operation went smoothly. Among them were Emergency Management; Real Estate Development + Facilities; the Office of Science and Research; Information Technology; Security; Human Resources; Environmental Health and Safety; Building Services; Supply Chain; the Division of Animal Laboratory Resources; Facilities Operations; Patient Experience; Food Services; and Therapeutic Recreation, Child Life, and Creative Arts Therapies.

In the ninth-floor NICU, as the day nurses were briefing the night nurses during a shift change, the unit went dark, and the vitally important mechanical respirators and electronic monitors fell silent. “Everybody ran to the babies to make sure they were fine,” recalls one nurse. “If you had a flashlight in your phone, you held it right over the baby.” The four most critically ill infants, who couldn’t breathe on their own, relied on oxygen from battery-powered respirators, but the emergency batteries wouldn’t last long. Menchu Sanchez, RN, senior nurse clinician, who was caring for the sickest baby in the unit, was quick to realize—and propose—that the safest way to evacuate the infants would be to carry them down the stairs without their incubators. She was the first to do so.

One by one, the infants were covered with blankets and heating pads. Nurses and physicians held them snugly against the skin of their chests. All the while, they carefully squeezed bags of oxygen into the babies’ lungs. Throughout the journey down nine flights of stairs—in some cases, with the baby’s mother accompanying the team—the nurses would not take their eyes off the infants. “We were making sure that the breathing tube was in place and that the baby was pink,” explains Margot Condon, RN, senior nurse clinician. If the baby’s heart rate indicated that it was in distress, the team would pause until it stabilized. Once they reached the lobby, the nurses and their tiny patients were transferred to gurneys and whisked into waiting volunteer ambulances. They escorted the babies to their respective receiving hospitals, along with their handwritten medical summaries, to ensure continuity of care.

About two hours later, power was also lost in the 15th-floor CCCU. Achiau Ludomirsky, MD, the Andrall E. Pearson Professor of Pediatric Cardiology and chief
of the Division of Pediatric Cardiology, a veteran of three wars, went from being battle ready to being triage oriented. “We brought the patient on a ventilator down first,” he explained, “and the other five quickly followed. Within about 15 minutes, all six patients were brought safely down 15 flights of stairs to the main lobby.” One of the biggest challenges, he recalls, was simply to keep opening the stairway door. “Because we were on a high floor,” he explains, “the wind in the stairwell was whipping so ferociously that it would take three of us just to push the door open.”

Throughout the crisis, there were countless episodes of courage, compassion, and cleverness. With the subway system shut down, one attending physician hitched a ride on a Con Ed truck to get to the Medical Center, while another flagged down an NYPD patrol car. After many trips to and from higher floors of Tisch Hospital, one medical student was so visibly exhausted and dehydrated that a nurse insisted he drink a liter of sterile water. Even those most at risk showed grace under pressure. At one landing, a firefighter who was sweating profusely asked the patient he was helping carry how he was doing. “Me? I’m okay,” said the man with a Russian accent. “But you, I worry about.”

By 11:00 a.m. on Tuesday, October 30, the last patient had been evacuated from NYU Langone Medical Center, and another kind of displacement—the removal of more than 15 million gallons of water—had already begun. About 24 hours later, amid the aftermath of the storm on Wednesday morning, Robert I. Grossman, MD, NYU Langone’s dean and CEO, and Kimberly Glassman, PhD, RN, vice president for patient care services and chief nursing officer, gathered in a conference room to receive a scheduled call from the White House (see photo). President Barack Obama, hearing of NYU Langone’s ordeal, wanted personally to extend his praise and support. “I want to thank you for the extraordinary work you and the whole Medical Center team did to safely evacuate patients,” President Obama told them. “I hope you know how much the whole country appreciates what you’re doing.”

Kimberly Glassman, PhD, RN, and Dean and CEO Robert I. Grossman, MD, used an iPhone to receive a call from the White House.

“Damage to the Medical Center was costly and extensive, but there was a silver lining. During the period when Tisch Hospital, the Emergency Department, and other facilities on campus have been closed and without patients, NYU Langone has been able to advance planned improvements and new construction projects, including the installation of new telephone and fire alarm systems, and the construction of the Tisch elevator tower and the new Emergency Department.”

“This crisis has brought many losses and many lessons,” Dean Grossman noted, “but it has also highlighted what I will always remain thankful for, the dedication of the entire NYU Langone community and our determination to prevail. I predict that we’ll look back on these difficult times with much-deserved pride, seeing Hurricane Sandy as a turning point that ultimately propelled us to heights we might never have reached otherwise.”
Regional Differences Found in Imaging

Use of advanced scans in prostate cancer is often inappropriate.

A little more than a year ago Danil Makarov, MD, MHS, assistant professor of urology and director of urological health services research, published a study showing that nationwide about 34 percent of men with high-risk prostate cancer do not receive the imaging scans they require, potentially delaying their diagnosis and treatment for more advanced disease. The study, published in the *Journal of Urology*, prompted Dr. Makarov to look more closely at the problem on a regional level, using the giant Surveillance, Epidemiology and End Results (SEER)-Medicare database from the National Cancer Institute.

“We thought we would find that certain regions adhered better to the guidelines published by the National Comprehensive Cancer Network—that in some areas, they would do a great job of imaging high-risk patients and not imaging low-risk patients,” Dr. Makarov says.

If the tumor is entirely within the prostate and a man’s prostate-specific antigen (PSA) level and Gleason score (a rating of how mutated cells look under a microscope) are below certain ranges, then he’s considered low risk and doesn’t need testing beyond an annual biopsy. High-risk men should get a bone scan and pelvic imaging, such as CT or MRI, to see if the disease has spread beyond the prostate gland.

Dr. Makarov’s most recent findings appeared in the journal *Health Affairs* last April. To his surprise, he found that decisions about when and whether to perform advanced imaging in prostate cancer patients fall prey to what he calls a regional thermostat effect. In New Jersey, for example, a large majority of men—nearly 80 percent—who need imaging get it. But about 65 percent of low-risk patients receive imaging that they don’t need, exposing them to unnecessary radiation and burdening the system with excess cost. In Utah, on the other hand, little more than 20 percent of low-risk men get unneeded CTs and MRIs. But nearly half of high-risk Utah men who *should* have these scans do not.

“No region really nailed it,” Dr. Makarov reports. “It doesn’t appear that there’s a great deal of discrimination going on to ensure that the right person is getting the right test at the right time. Some regions just like to use imaging, and some don’t.”

In the wake of these findings, he has received a $1.6 million, five-year career development award from the Department of Veterans Affairs to study the factors that cause these thermostat variations in imaging use and to develop and test decision-making tools that can optimize such use in prostate cancer.

“We’re trying to understand what drives these behaviors,” Dr. Makarov says. As the government develops policies to ensure more appropriate use of costly medical technologies such as imaging, this is vital information. “A bluntly designed policy effort to decrease inappropriate use of imaging could also dial back appropriate imaging,” he says. “What’s needed is a policy to discourage inappropriate imaging and reward appropriate imaging at the same time.”

—GINA SHAW
Paying the Toll in Pancreatic Cancer

Studies show that toll-like receptors help fuel the cancer.

When pathologists examine a pancreatic tumor, they find relatively few cancer cells. Instead, fibroblasts and infiltrating immune cells fill the mass. Equipped with special receptors, they engage in a lethal cross talk with pancreatic cells containing a mutation in the KRAS oncogene. Chemotherapy can do little to stop the cancer, which usually betrays few symptoms until it’s relatively advanced, making it one of the most deadly.

“Pancreatic cancer is the quintessential example of an inflammatory cancer,” says George Miller, MD, assistant professor of surgery and cell biology. “But inflammation itself is a double-edged sword. It can fight cancer or promote it, depending on the circumstances.”

Dr. Miller, who received a generous grant from the Irma T. Hirschl Trust, focuses his attention on toll-like receptors (TLR), proteins that act as a sort of surveillance system on the outside of immune cells such as macrophages and dendritic cells. TLRs ordinarily recognize foreign proteins from bacteria and other invaders, and trigger the body’s innate immune defenses. But in the presence of the pancreatic cancer cells, the receptors actually promote the cancer by sending inflammation into overdrive.

Interestingly, Dr. Miller’s studies have shown that TLRs are scarce in normal pancreatic cells, but human pancreatic cancer cells actively produce them, as do pancreatic cancer cells and the surrounding inflamed tissue in mouse models. In his latest research, he and his colleagues Atsuo Ochi, MD, assistant professor of surgery, and Dafna Bar-Sagi, PhD, vice dean for science, systematically worked out the roles of TLR4 and TLR7, which both contribute to the signaling cascade leading to pancreatic cancer growth.

Using a mouse model, they showed that induced TLR7 activation potently accelerated the development of pancreatic cancer, while uninduced animals had none of the molecular markers of cancer. Most important, adding a TLR7 antagonist prevented this malignant progression and diminished inflammation. These results, published in October in *Journal of Clinical Investigation*, led the researchers to conclude that TLR7 is required for progression of pancreatic cancer, and that TLR7 antagonists could prove to be effective treatments for pancreatic cancer and chronic pancreatitis, for which there is currently no effective treatment.

But Dr. Miller urges moving toward the clinic cautiously, because a similar set of experiments in his lab, published last August in *Journal of Experimental Medicine*, provided a shocking result: Blocking TLR signaling through a helper molecule called MyD88 actually accelerated tumor growth. Further study implicated dendritic cells that reside in the inflamed pancreas.

“Toll-like receptors are central to driving the inflammatory component of the tumor microenvironment,” says Dr. Miller. “But because of its complexity if you block one aspect of the signaling pathway, you can generate alternate proinflammatory mechanisms that drive the cancer.”

Fortuitously, TLR inhibitors are being tested in human clinical trials for the treatment of lupus, an autoimmune disease characterized by inflammation. Those trials may help prove Dr. Miller’s hypothesis that blocking TLRs could help dampen the inflammatory response in pancreatitis and pancreatic cancer, providing a glimmer of hope for patients who now have few options.

—KARYN HEDE
New Hope for Diagnosing Mesothelioma

Researchers find a promising candidate molecule for a blood-screening test.

For more than a decade, Harvey Pass, MD, the Stephen E. Banner Professor of Thoracic Oncology, has been searching for a biomarker for mesothelioma, a particularly virulent form of cancer that attacks the lining of the chest and lungs. Mesothelioma patients have usually worked in industries like construction or mining that expose them to high levels of asbestos.

Often taking decades to develop, the disease is hard to diagnose. Nearly 95 percent of patients are diagnosed with late-stage disease and typically survive less than a year; each year mesothelioma kills about 3,000 people in the United States. Dr. Pass, who is vice chair of research for the Department of Cardiothoracic Surgery and division chief of general thoracic surgery, wants to improve this grim outlook by finding a biomarker that signals early-stage mesothelioma, when surgery, radiation therapy, chemotherapy, and new targeted therapies may help extend patients’ lives.

His research, supported in part by Belluck & Fox, LLP, Levy Phillips & Koningsberg, LLP, and the Simmons Mesothelioma Foundation, has uncovered a number of promising biomarkers, but all have fallen short of being useful in a screening test because they aren’t specific to mesothelioma.

Even the protein osteopontin, discovered several years ago by his team, was subsequently found in other kinds of cancer.

In October a team led by Dr. Pass reported on another biomarker that appears to rise only in mesothelioma patients. The finding, published in the New England Journal of Medicine, measured the expression of a protein called fibulin-3 in the blood of three different groups: 92 patients with pleural mesothelioma; 136 individuals who had been exposed to asbestos but did not have cancer; and 136 patients who had not been diagnosed with mesothelioma but who had fluid in their lungs, an early symptom of mesothelioma and several other conditions.

The results were significant. Although fibulin-3 levels did not vary with age or sex, they consistently increased in patients who had pleural mesothelioma but remained stable in individuals in the other two groups. “It is present in levels four to five times higher in the plasma of patients with mesothelioma compared with levels in asbestos-exposed patients or patients with several other conditions that cause tumors in the chest,” Dr. Pass says.

“It’s an exceptional molecule,” adds Chandra Goparaju, PhD, research scientist in the Department of Cardiothoracic Surgery and one of the study’s authors. If these initial studies are validated, Dr. Pass thinks a diagnostic blood test could be developed in three years. Those with elevated levels of fibulin-3 would undergo follow-up tests, including a CT scan of the chest.

Another promising biomarker was revealed in a study published last October in PLOS. Dr. Pass and researchers from SomaLogic, Inc., based in Boulder, Colorado, identified a set of 64 unique molecules that together form a profile of protein activity in the blood of mesothelioma patients versus those who did not have the disease. Follow-up studies will refine the findings, Dr. Pass says.

Even if fibulin-3 and the SomaLogic profile fall short of being a screen for mesothelioma, Dr. Pass will continue his research. “We have many options for discovering biomarkers,” he says, “and we’ll keep looking.”

—JANE BOSWELL

A colored scanning electron micrograph of asbestos, a fibrous mineral once used widely in insulation and fireproofing. Prolonged exposure to high levels causes deadly mesothelioma.
The Synapse You Can’t Live Without

Decades of basic research yields insights into delaying paralyzing disease.

Entranced with the junction between muscle and nerve, Steven J. Burden began studying the neuromuscular synapse in the 1970s, when he was earning his PhD. This synapse allows a neuron to pass a chemical signal, acetylcholine, to muscle and stimulate movement, and it is the only synaptic connection required for survival. Neurons in the brain help us perceive the world, but aren’t essential for survival, he says. “Neuromuscular synapses, however, are crucial for breathing.”

Today Dr. Burden, professor of biochemistry and molecular pharmacology and cell biology and a member of the Skirball Institute of Biomolecular Medicine, is an internationally recognized expert in the workings of this fundamental synapse. Over the years he has been methodically decoding the interplay among three key molecules that are critical to its health. Lately, his discoveries offer potential strategies to delay the devastating muscle wasting seen in amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig’s disease. It has taken Dr. Burden decades to reach a stage where his basic research offers clinical implications.

In 1993 Dr. Burden identified a molecule, MuSK, which he describes as a master molecule “for everything that happens at the neuromuscular synapse.” Without MuSK, there is no transmission between neurons and muscle cells. As a postdoctoral fellow, he began studies that led to the discovery of Agrin, which is released from neurons to stimulate MuSK, and in 2008 he identified Lrp4 as another master protein. Most recently, in 2012, Dr. Burden found that Lrp4 also plays a crucial feedback role in signaling from muscle to nerve.

Simply stated, the trifecta of molecules works this way: On one side of the synapse, muscle cells express both MuSK and Lrp4. On the other side, nerve cells express and release Agrin. The binding of Agrin to Lrp4 allows Lrp4 to turn on MuSK, which prepares the muscle to respond to acetylcholine. Then Lrp4 does a neat trick—it signals back to the nerve to ensure that neurotransmitter release is efficient.

“You need all three of these molecules working in concert for nerve stimulation of muscle,” Dr. Burden says. He also discovered a central fact: If this dance is interrupted, nerves disconnect from muscle—which is exactly what happens in ALS. The withdrawal of motor nerve terminals from muscle, making the brain no longer able to control muscle movement, is the first sign of ALS. The nerves soon die, and no one has been able to find a way of keeping them alive, Dr. Burden says. Given no effective therapies, only two to three years commonly separate ALS diagnosis and death.

Dr. Burden, however, believes it is possible to rev up the activity of MuSK to keep the nerve-muscle attachment viable longer. In fact, a mouse study published last August in Cell Reports provides proof of that concept. He and his team are now working to test potential human therapies to boost MuSK to improve muscle function and the quality of life of ALS patients.

“It’s a great delight to spend a career making basic discoveries, but there is also wonderful enjoyment applying this knowledge to treat diseases,” Dr. Burden says. “That is very, very gratifying.”

A light micrograph depicts neuromuscular synapses, the connections between a motor neuron axon and skeletal muscle fiber that it controls.
HITTING THE BULL’S-EYE IN PROSTATE CANCER

NEW IMAGING TECHNIQUES PIONEERED AT NYU LANGONE DISTINGUISH DEADLY LESIONS.

BY BRYN NELSON • ILLUSTRATIONS BY STUART BRIERS

Imagine a blindfolded archer taking aim at a bull’s-eye hung randomly in a room. A direct hit would be rare, even with 12 arrows in his quiver. For years, doctors have faced a similar challenge when using biopsy needles to probe the prostate gland in search of potentially lethal tumors.

The walnut-size gland surrounding a man’s urethra is a hot spot for cancer, but notoriously difficult to access with existing imaging technology. As a result, the mostly blind biopsy technique that is still the standard of care often misses dangerous tumors while highlighting clinically insignificant ones.

New MRI–based imaging methods pioneered by NYU Langone Medical Center researchers could offer clinicians some much-needed insight, potentially transforming how tumors are detected, diagnosed, and treated. “I’m very excited and believe we can correct all the woes of screening by integrating imaging,” says Samir Taneja, MD, the James M. and Janet Riha Neissa Professor of Urologic Oncology and professor of radiology.

Prostate cancer, the second leading cause of cancer-related death among men in the United States, behind only lung cancer, struck nearly 242,000 men and killed more than 28,000 in 2012, the American Cancer Society estimates. Autopsies on men over the age of 50 who died from other causes have added a startling twist, however: nearly one-third showed early signs of prostate cancer. Scientists believe that most of these slow-growing tumors never become problematic during a man’s lifetime. But which ones might remain small and contained, and which ones could eventually become aggressive killers?
Tissue biopsies have long been imperfect tools for spotting signs of trouble within the prostate. The prevailing technique of inserting a dozen needles in a largely random pattern throughout the gland may reveal microscopic, nonlethal cancers that would never have harmed the patient, contributing to over-detection. At the other extreme, the biopsies may completely miss a potentially lethal cancer, contributing to under-detection through false-negative results. “So even if the patient walks out with a negative biopsy, you’re never able to comfortably tell him, ‘You don’t have cancer,’” Dr. Taneja says.

A biopsy can also underestimate the size and aggressiveness of a prostate tumor if the needle grazes the outside edge, leading clinicians to erroneously recommend deferring treatment in favor of regular monitoring, a strategy known as active surveillance. Herbert Lepor, MD, the Martin Spatz Chair of Urology, says a recent analysis of his extensive patient database—one of the largest in the world—suggests the problem may be widespread. Since his arrival at NYU Langone in 1993, Dr. Lepor has performed thousands of surgical prostatectomies to remove a malignant prostate gland after digital rectal exams, PSA tests, and standard biopsies suggested a slow-growing cancer. Among his prostatectomy patients who might have been candidates for active surveillance because of their biopsy results, more than half actually had clinically significant disease, according to pathology exams of their removed prostates.

A more general assessment of cancer risk based on a prostate protein called prostate-specific antigen, or PSA, has also proved less than ideal. Unusually high PSA levels or a sudden spike in its production can sound the alarm and suggest that a follow-up biopsy is warranted. Although the blood-based PSA screening test is simple and inexpensive, allowing it to be widely used, the protein marker is not specific for cancer. Several major clinical studies, in fact, have reached conflicting conclusions about whether the test provides a significant survival advantage.

The uncertainty led the U.S. Preventive Services Task Force to issue a controversial recommendation last May against performing the PSA screen for men in the general population. False-positive test results, the task force reasoned, often trigger an equally unreliable biopsy, leading to over-diagnosis and overtreatment of cancers that may never become symptomatic. Bleeding and infection can occur after a biopsy, and incontinence and sexual impotency may result after a surgical or medical treatment, even with the care of highly experienced and skilled doctors.

Despite the risks, Dr. Taneja and Dr. Lepor, whose research has been supported in part by the Joseph S. and Diane H. Steinberg Charitable Trust and NYU Langone Medical Center Trustee Joel Smilow, are convinced that the PSA test has saved many lives; they say they are “extremely disappointed” with the task force’s recommendation. “I am a firm believer in prostate cancer screening,” says Dr. Lepor. “Turning the clock back to prescreening would be absurd, based on what we know.” Before doctors began embracing screening in the late ’80s and early ’90s, he says, “the diagnosis of prostate cancer was pretty much a death sentence.” Since then, the mortality rate of prostate cancer has dropped by more than 40 percent, a dramatic decline that he and Dr. Taneja contend is almost certainly due in part to the widespread availability of early screening.

“We’ve made progress. But if anyone thinks that we’ve optimized screening by using a nonspecific marker and randomly placing 12 needles and taking 12 specimens, then he’s naive,” Dr. Lepor says. “There’s no doubt in my mind that we have to keep screening, but we have to screen smarter.” Improved imaging, the researchers say, is the best way forward because it will likely identify many of the aggressive tumors often missed by random biopsies in the past. “It will reduce over-detection, do away with false-negatives, and potentially give us a more accurate depiction of that cancer,” Dr. Taneja notes.

At NYU Langone, this ardently sought goal could spring from a technology called multiparametric MRI, developed by a collaborative team of urologists, radiologists, and other researchers. “In one exam, the patient is imaged with a variety of different MRI techniques that collectively let us better see tumors and their location in the prostate, and assess their biological potential to cause harm,” says Andrew Rosenkrantz, MD, assistant professor of radiology.
One method, called a T2-weighted image, produces an anatomical view of the prostate. Another, known as diffusion-weighted imaging, assesses the motion of water molecules within cells: the more restricted the movement of the molecules, the denser the cells, and therefore the more likely that cancer is present.

A third MRI-based measure, called dynamic contrast enhancement, can indicate the likelihood of cancer by assessing how blood is flowing in the prostate. Together, the data signals are helping researchers distinguish between harmful and harmless tumors.

“We’re learning that the MRI is rather selective in that it typically identifies cancers that are higher grade and larger in size,” Dr. Taneja says. “So therefore, those are cancers that would theoretically be lethal for the patient.” In contrast, the researchers have detected clinically significant cancer in only about 5 percent of patients with negative MRI results, suggesting that the technique is missing relatively few cases. Based on the advanced imaging, Dr. Rosenkrantz is helping to validate a five-point prostate cancer suspicion score, similar to what oncologists have used for other cancers. A score of five indicates that an abnormality is almost certainly cancer, while a score of one strongly suggests that it is benign.

Within the next few years, the researchers hope to improve upon their initial results and confirm preliminary data from other centers suggesting that a patient with a negative MRI result is highly unlikely to have clinically significant disease. If a multicenter trial demonstrates that the results are reproducible, men with negative MRIs may eventually be able to forgo biopsies altogether. Such patients might remain on a form of active surveillance, with doctors monitoring their levels of PSA or other markers such as the prostate cancer antigen 3 gene, a cancer-specific probe that has shown early potential.

For men with positive MRI test results highlighting an area of concern, subsequent biopsies can become smarter too. NYU Langone is among the few medical centers in the nation with access to a powerful navigational aid called Artemis, a robotic system that fuses MRI imaging results with ultrasound technology. The resulting guidance system allows clinicians to aim biopsy needles with unprecedented precision at areas of concern. The computer software displays a three-dimensional view of abnormalities on MRI and marks those same sites on an ultrasound image of the prostate. Robotic technology then directs the biopsy needles to those spots for the tissue sampling.

“Now with imaging, we can target not only the areas most likely to have a tumor but also the areas most likely to have aggressive tumors,” Dr. Rosenkrantz says. And because ultrasound is much faster and more comfortable for the patient, targeted biopsies based on the MRI–ultrasound fusion can be performed in an office setting.

The collaborators say initial results look promising, and several team members are building their own software program to further refine the process, while others are examining the technique’s cost effectiveness. Despite the added expense of multiparametric MRI imaging, Dr. Lepor and Dr. Taneja say the technology could actually save cost over time by decreasing unnecessary biopsies, surgeries, and other interventions, “I would venture to say that within two to three years, if all goes well, we’ll prove it, and it will change the way we screen men,” Dr. Taneja says.

In many ways, prostate cancer patients at NYU Langone are already benefiting from the loosening blindfold. Anyone with an abnormal PSA test result is now examined with the advanced MRI technique to provide a clearer view of the prostate. For now, all patients still undergo a biopsy regardless of their MRI results, but the arrival of the MRI–ultrasound fusion method in 2012 has allowed the doctors to zero in on regions of interest. In some cases, 4 guided needles have provided a better indication of the threat than the typical 12 randomly placed ones, an encouraging sign that the archers are zeroing in on the bull’s-eye. “I think we’re headed in the right direction,” Dr. Rosenkrantz says. “This isn’t just something with future potential—we’re using it day in and day out now to help patients.”
The Truth About Low T

As testosterone replacement therapy grows more popular, debate rages over its safety and efficacy. How can patients and physicians sort out the science from the hype?

BY KENNETH MILLER • ILLUSTRATION BY LONNIE BUSCH
Robbie Donato, 54, woke up one morning with testicular pain so severe that it sent him to the emergency room. It didn’t occur to Donato that the event could be related to the bouts of fatigue and impotence that had plagued him since his teens. But his doctor, Joseph Alukal, MD, assistant professor of urology and director of male reproductive health at NYU Langone Medical Center, discovered a condition that might have caused the patient’s earlier problems as well as his more recent one: a varicose vein in Donato’s testicles that kept his testosterone levels unusually low.

Rather than undergo surgery, which was not guaranteed to be effective in his case, Donato opted for testosterone replacement therapy, or TRT, an increasingly popular treatment option for men with waning testosterone levels. Patients on TRT take regularly scheduled doses of artificial testosterone delivered through a variety of ways—injectons, gels, patches, subcutaneous pellets, or buccal tablets attached to the gums. Donato opted for the gel, which quickly relieved his pain and restored his vigor. When its effect wore off after a couple of days, he tried injections but found that he disliked giving himself shots. Finally, he turned to testosterone pellets embedded beneath the skin of the buttocks. The insertion—performed in-office under local anesthesia—was surprisingly easy, and the drug kept working for months.

For the first time in recent memory, Donato was no longer dependent on Viagra or Cialis. A creative director in a busy ad agency, he found he could work long days without feeling utterly exhausted. Other men have not been as fortunate. Although nearly half of men over age 50 who have low testosterone notice nothing amiss, according to a 2007 study by the New England Research Institutes, a nonprofit public health research group, others may experience a vague constellation of ills including erectile dysfunction, loss of libido, fatigue, insomnia, anxiety, depression, anemia, and impaired concentration. Yet they may ignore it, not realizing the symptoms indicate a condition often referred to as andropause.

TESTOSTERONE PRODUCTION naturally dips with age. A man can expect his testosterone levels to decrease by about 1 percent a year starting in his 30s. Some men continue to churn out enough of the hormone to father a child well into old age. But by the time they turn 70, according to the Baltimore Longitudinal Study of Aging, up to 50 percent of men have levels below the normal range for any age. Studies suggest that hypogonadism—the clinical term for testosterone deficiency—affects between 2 million and 4 million men in the United States, most of them middle-aged or older. And a recent report by the market research firm Global Industry Analysts, Inc., estimates that fewer than 12 percent of hypogonadal men receive treatment for it.

That troubles Dr. Alukal. Research over the past decade has linked hypogonadism to decreased muscle mass and strength, decreased bone density, increased body fat, and a greater risk of type 2 diabetes and cardiovascular disease. “The medical implications of this condition are real,” he says. “It’s not a negligible entity.”

The question is what to do about it. Annual prescriptions for TRT have more than doubled since 2006, to 5.6 million, according to Bloomberg L.P., driven by both the lengthening lifespans of American men and their desire to remain active (sexually and otherwise) in their 50s, 60s, and beyond. A barrage of pharmaceutical commercials on TV urge men with a diminished appetite for romance—or pickup basketball—to ask their doctors, “Is it low T?” Meanwhile, ads for testosterone-replacement clinics sprout up on the Internet like garden weeds.

But does testosterone therapy really work? More important, is it safe? An increasingly loud chorus of critics says the answer to both questions is no. “You’re talking about worrisome potential toxicities with trivial benefit,” says Nortin Hadler, MD, a professor of medicine at the University of North Carolina, Chapel Hill, and the author of Rethinking Aging: Growing Old and Living Well in an Overtreated Society. A review of 19 clinical trials in 2006,
he notes, found a higher rate of prostate cancer in men receiving TRT. A 2008 study in the Netherlands found no improvement in strength, body fat, bone density, or quality of life among 230 TRT recipients. A 2010 Boston University study was halted when elderly men receiving testosterone replacement developed heart problems at five times the rate of those taking placebos. Some physicians worry that TRT could eventually prove to be as dangerous as HRT—the hormone therapy given to millions of menopausal women before 2002, when it was found to raise the risk of heart disease, breast cancer, and stroke.

Dr. Joseph Alukal explains some of the medical implications of low testosterone to a patient.
IN REALITY, DIAGNOSING HYPOGONADISM CAN BE TRICKY EVEN FOR A CONSCIENTIOUS PHYSICIAN, AND EFFECTIVE TREATMENT MAY REQUIRE FAR MORE THAN HORMONE THERAPY. TO BEGIN WITH, THERE'S LITTLE CONSENSUS ON WHAT ACTUALLY CONSTITUTES LOW TESTOSTERONE.

NOT EVERYONE is convinced of TRT’s dangers, however. Defenders counter that the negative studies were small, short-lived, poorly designed, and, in some cases, statistically flawed. “I think it’s a relatively safe drug,” says John Morley, MD, director of the division of geriatric medicine at Saint Louis University School of Medicine. “I don’t think it should be given to every man who walks in saying, ‘I’m feeling bad.’ But if you can show they’re hypogonadal, it’s a very reasonable thing to do.” He points to a 2009 research review that he coauthored in the journal Therapeutics and Risk Management, which concluded that TRT may improve “libido, sexual function, bone density, muscle mass, body composition, mood, erythropoiesis [red blood cell production], cognition, quality of life, and cardiovascular disease.”

Yet even physicians who routinely prescribe testosterone therapy concede that the supporting data are inconclusive; so far, no one has completed a large, long-term study that could settle the debate. And while they may discount reports of cardiac complications, they acknowledge that TRT can have unwelcome side effects. Because the brain signals the testicles to stop producing testosterone in response to TRT, prolonged use may lead to permanent infertility. Other potential problems include polycythemia, or overproduction of red blood cells (which can lead to stroke), and sleep apnea (which can lead to insulin resistance and high blood pressure). Although there’s no evidence that testosterone replacement causes prostate cancer, it may accelerate a previously undetected one. A responsible doctor will warn patients of the possible dangers, check their prostates and their PSA counts before beginning treatment, advise them to bank a sperm sample if they hope to conceive children, and then monitor them regularly for signs of trouble.

GIVEN ALL THE UNCERTAINTIES, Dr. Alukal (an andrologist as well as a urologist) is reluctant to endorse TRT carte blanche for his hypogonadal patients. “All I can do,” he says, “is educate people about the risks and benefits and let them make a decision they’re comfortable with.” What worries him far more than the treatment itself, however, is the knowledge that men who don’t really need testosterone supplements may be getting them from unscrupulous practitioners—or dosing themselves. All those ads, he believes, can stoke deep-seated male insecurities about virility, sexual potency, and physical strength, prompting many men to wonder: Do I have enough testosterone? If those men go online to research the symptoms of low testosterone, they’re likely to run across the standard 10-point ADAM questionnaire (the acronym stands for Androgen Deficiency in Aging Males). This quiz, designed to help doctors make an initial screening, inquires not only about the strength of the subject’s erections and libido, but also his overall mood and energy level: “Are you sad or grumpy? Have you noticed a recent deterioration in your ability to play sports?” If the answer is yes to at least one of the sex-related questions or three of the others, a physician may advise a testosterone test; in most cases, the results will be normal. But a middle-aged Web surfer might mistake his answers for a diagnosis and then go off in search of a cure. “A lot of men out there are convinced that they have low testosterone,” says Dr. Alukal, “and a massive industry has sprung up to take advantage of them.” Some testosterone clinics, he observes, are willing to treat virtually any paying customer. Men who would rather bypass the doctor entirely (and the black-market) can legally purchase nutritional supplements, such as DHEA, which is converted to testosterone in the body. Although often labeled as “natural,” such products can have side effects similar to those of testosterone-replacement drugs—potentially disastrous without proper medical supervision.

IN REALITY, DIAGNOSING hypogonadism can be tricky even for a conscientious physician, and effective treatment may require far more than hormone therapy.
To begin with, there’s little consensus on what actually constitutes low testosterone. The most common test assays the total amount of testosterone in a patient’s blood. But while the Endocrine Society defines the normal level as a measurement between 300 and 1,000 nanograms per deciliter (measured in the morning, when levels are highest), reputable labs may set the limit as low as 240 ng/dl, depending on their own calibrations. “If it’s a lab that knows what it’s doing,” Dr. Alukal says, “I’ll generally go with their number.”

But testosterone levels tell only part of the story. As men age, increasing amounts of testosterone are bound to a protein known as sex hormone binding globulin (SHBG) and can no longer be absorbed by the body’s tissues. For that reason, Dr. Alukal also orders assays for “free testosterone,” the portion not bound to SHBG. An older patient may have a low free-testosterone count, even if his total testosterone registers as normal.

Hypogonadism is especially easy to miss in men under the age of 40. “Most of them have no primary physician,” Dr. Alukal says. “There’s no demographic that utilizes healthcare resources less than guys between 18 and 35.” Men in this age group typically show up in his office because they’re suffering from erectile dysfunction or find themselves unable to conceive a child. A small number prove to have abnormally low testosterone levels. (Because TRT itself can cause infertility, Dr. Alukal prescribes a different treatment for patients who are trying to conceive—perhaps clomiphene, which boosts the body’s own testosterone production, or anastrozole, which prevents the breakdown of testosterone already in circulation.)

Of course, a testosterone deficiency could also indicate a serious underlying condition. There are two main varieties of hypogonadism: primary (originating in the gonads) and secondary (originating in the endocrine system). The disorder may be congenital or acquired and can result from a wide variety of causes: damage to the testicles; chronic illnesses such as diabetes, obesity, or liver disease; a malfunctioning pituitary gland or hypothalamus; a genetic condition such as Kallmann syndrome; radiation or chemotherapy for cancer; or the side effects of various medications.

**BEFORE DECIDING** on a course of treatment for a patient with low testosterone, Dr. Alukal often collaborates with other specialists, such as cardiologist Howard Weintraub, MD, clinical director of the Center for the Prevention of Cardiovascular Disease. “Low testosterone is a risk factor for cardiac disease for the same reason that high cholesterol, hypertension, or diabetes are,” Dr. Weintraub explains. All these conditions impair vasodilation, the ability of the blood vessels to relax and allow increased flow. Vasodilation also enables erections, which is why erectile dysfunction can be a harbinger of heart disease. Some studies indicate that testosterone supplementation improves vasodilation. But additional measures may be needed to repair existing cardiovascular damage and to prevent further deterioration.

Another key to heart health, of course, is regular exercise—and by improving a patient’s mood and energy level, TRT can make getting off the couch less daunting. “I’ve had guys come back to me and say, ‘I’ve needed this stuff for a long time. I just didn’t realize it until I was on it,’” Dr. Alukal says.

One such patient is Robbie Donato. “I’m doing great,” he says. “I feel like I’m back to my old self again.”

That’s just the kind of result that Dr. Alukal hopes for. “Testosterone replacement doesn’t work for everybody,” he says, “but when it does, it can make a remarkable difference in a man’s life.”

Men with low testosterone are often referred to cardiologist Howard Weintraub, MD.
A growing body of research indicates that certain brain disorders in children are related to their father’s age.

BY KAREN HOPKIN AND AUBIN TYLER • ILLUSTRATION BY KEITH NEGLEY
AS A YOUNG CLINICAL research fellow at Columbia University in the early 1990s, Dolores Malaspina, MD, began searching for a genetic link in families with schizophrenia, an illness that had blighted a promising future for her younger sister, Eileen. To her surprise, she simply could not find enough subjects with a relevant family history. “Everyone talks about schizophrenia being a genetic disease, but the vast majority of people with schizophrenia have no family history,” she says.

How could schizophrenia persist if not through heredity? Science has long known that the illness tends to run in families. The risk of developing schizophrenia jumps from 1 percent among the general population to 10 percent if a primary family member, such as a sibling or parent, is affected. But conventional inheritance seemed to solve only a small piece of the puzzle. “Seeing the struggles of people like my sister, I felt there had to be better answers,” she says.

Dr. Malaspina, now the Anita Steckler and Joseph Steckler Professor of Psychiatry and director of the Institute for Social and Psychiatric Initiatives at NYU Langone Medical Center, resolved to find them. In 2000 she teamed up with epidemiologist Susan Harlap, MD, research professor of psychiatry, obstetrics/gynecology, and environmental medicine, to analyze data from the Jerusalem Perinatal Study, a massive health survey based on 92,408 babies born in Jerusalem between 1964 and 1976 and followed into adulthood, along with 83,000 parents. When the researchers anonymously matched records of individuals who were eventually diagnosed with schizophrenia, they discovered a startling trend: The risk of developing schizophrenia increased steadily with the age of the father. It doubled among offspring whose fathers were 40 years old when they were born and tripled in those whose fathers were older than 45.

Publishing their results in the Archives of General Psychiatry, Dr. Malaspina and Dr. Harlap theorized that the passage of years increased the number of spontaneous, or de novo, mutations passed along to offspring via the fathers’ sperm. Unlike women, who possess their full complement of eggs at birth, men make sperm throughout life, a process that becomes more error prone as men age. Males, from the time they reach puberty at 13 or 14, make sperm every 16 days or so. By age 20, a man’s spermatogonia, the stem cells that give rise to sperm, have divided more than 150 times; by age 50, those cells have divided more than 850 times, with each division increasing the likelihood of error.

The researchers knew that the idea of a ticking male biological clock was not new. A century ago, an observant obstetrician named Wilhelm Weinberg noted that of the thousands of babies he had delivered in Stuttgart, Germany, the later-born children were more frequently afflicted with certain disorders—including achondroplasia, a form of dwarfism—than their first-born siblings. Weinberg ascribed this enhanced susceptibility to the advanced age of the parents. Decades later, pioneering British geneticist L. S. Penrose conducted additional statistical analyses that pointed specifically toward the age of the father, not the mother, as the culprit. In 1947 the brilliant population geneticist J. B. S. Haldane speculated that sporadic cases of hemophilia that didn’t conform to known patterns of inheritance could be due to errors induced during sperm cell division.

“In evolution, genetic diversity is advantageous. So mutations in older men may be a way of saying, ‘Okay, let’s have some variety.’”

Yet the theory that Dr. Malaspina and Dr. Harlap put forth was met with great skepticism. “Many thought it was something about men who married later who may have had some constitutional problem, such as shyness or a social disability,” Dr. Malaspina recalls.

These doubts began to shrink, however, as the epidemiological evidence grew. In 2006 Dr. Malaspina collaborated with other researchers to study the Israeli data and discovered another brain disorder correlated with older fathers: autism. Their analysis found that men in their 40s were six times more likely to have children with autism than those under 30; for men over 50, the risk was ninefold. The risk rose steadily as fathers aged, a characteristic pattern of de novo mutations.

More recently, a rush of papers has offered compelling proof of a paternal link at the genetic level. Last spring three separate groups from Yale, Harvard, and the University of Washington published analyses of sequencing data on nearly 600 families with autism spectrum disorder in the journal Nature. Each team found de novo (spontaneous) mutations in the exome, a region of the genome thought to code for most human diseases. In the University of Washington study, for example, researchers sequenced
long strands of DNA containing more than 100 base pairs from both parents and affected offspring and were able to determine, in about a fifth of cases, which parent had contributed the DNA containing the new mutations in the child. The rate of new mutations from fathers, they found, was about four times that of mothers. And in all three studies, the mutation rate rose with advanced paternal age.

Another major paper followed in August, when Icelandic researchers announced in Nature that they had sequenced the entire genome of 78 families with either autism or schizophrenia and found, again, that fathers were the dominant source of new mutations in offspring. Moreover, those mutations doubled every 16.5 years, increasing eightfold in 50 years. In an accompanying editorial, University of Michigan geneticist Alexey Kondrashov, PhD, noted that if a 20-year-old father’s contribution is 25 mutations, a 40-year-old father transmits about 65, whereas the mother’s contribution remains at about 15, regardless of her age.

Spontaneous mutations are “some of the most interesting variants in the whole of genetics,” says Yale University’s Stephan Sanders, MD, lead author of one of the papers. “How else do you explain a child who has a disorder and parents who don’t?” He estimates that spontaneous mutations account for about 20 percent of autism cases, a figure in accord with Dr. Malaspina’s own estimates for both autism and schizophrenia. Of the 20,000 genes in the entire genome, about 1,000, or 1 in 20, may contribute to autism.

Triggers in the environment like pollution, stress, and diet can also induce heritable genetic changes by turning genes on and off and ultimately changing how they function, a phenomenon known as epigenetics. But paternal age is the dominant risk factor for spontaneous mutations. “It’s incontrovertible that new mutations arise largely based on paternal age,” Dr. Malaspina says.

With more evidence than ever before that mutations associated with paternal age underlie many cases of autism and schizophrenia, Dr. Malaspina and Dr. Harlap have now turned their attention to the question of which genes—and more specifically, which mutations within those genes—actually cause disease. In collaboration with geneticist Mary-Claire King, PhD, at the University of Washington, they have sequenced the coding region of genes in a dozen patients with schizophrenia and their parents. “The work is still in progress, but we’ve already found four new point mutations in an exciting set of novel genes,” Dr. Malaspina says.

These novel genes code for proteins that are found in some of the same cellular pathways associated with fibroblast growth factor receptor (FGFR) genes. Many of the other conditions related to paternal aging are caused by mutations in FGFR genes, Dr. Harlap explains. Moreover, certain point mutations in the genes result in more active protein as people age, contributing to many kinds of cancer. And, as men age, point mutations in testicular germ cells can accumulate, causing birth defects.

Why would evolution preserve such a destructive mechanism? Paradoxically, notes Dr. Harlap, the mutations in FGFR may confer an advantage to precursor sperm, helping them divide more efficiently and outcompete their neighbors, just as they do in cancer. In the testis, this phenomenon has been called the “selfish sperm” hypothesis. Nature’s effort to introduce variability into the gene pool occasionally and tragically produces human disease as well. “We don’t know that all progeny are disadvantaged by mutations, though those with autism certainly are,” Dr. Harlap adds. “In evolution, genetic diversity is advantageous. So mutations in older men may be nature’s way of saying, ‘OK, let’s have some variety.’”

Dr. Malaspina is quick to point out that the science does not suggest older men should forgo having children. “Most of the time, the child will not have one of these disorders, so I don’t think the data should suggest men not have children at a later age,” she says. But they do point to the need to rethink paternal health. “Before, we thought that sperm was not really dependent on the lifestyle of the man,” she says. “Now we have to say that it’s important.”

Above all, the researchers are hopeful that the windfall of data will lead to new diagnostics and therapies. “My own interest in all of this work is that it will change treatment,” says Dr. Malaspina. “That’s what I’m hoping to get to: treatment, prevention, and cure.”
A neuroscientist learns how zebra finches perfect their love song and, in the process, makes some surprising discoveries about how neurons hook up.

BY JIM SCHNABEL
PHOTOGRAPH BY GLORIA BAKER
Michael Long, PhD, studies the love song of Australian zebra finches to understand the basic neural logic of complex learned behaviors.
AustraliAn zebra finches

are popular pets that usually nestle together amiably on their perch or on the floor of their cage picking at seeds. Orange patches flanking bold streaks of white and black on their faces make them easy to identify, and they aren’t especially noisy. But when the time comes for courting, these small, dusty gray birds let out a song that has all the allure of a wheezing rubber duck. Amazingly, this repetitive, brraapping sound romances a female finch.

This raucous love song fascinates Michael A. Long, PhD, assistant professor of physiology and neuroscience and otolaryngology, because it is a complex learned behavior—mastering the precise melody with which to woo their avian mates takes considerable practice.

“We know surprisingly little about the neural underpinnings of such behaviors, despite their fundamental importance in our lives,” Dr. Long says. “The finch’s love song is a very good model for a complex learned behavior.”

A young male zebra finch spends several months learning the song from his father, and during this period will practice it several hundred thousand times. “The bird spends all day practicing this skill, just like a violinist or a tennis player must practice all day,” Dr. Long says. The resulting song varies widely from one bird to another but an individual reproduces it in an almost identical way each time—hundreds of times a day if a potential mate appears. Birds that fail to learn this special song produce a plaintive screech that leaves female finches cold, the songbird equivalent of leaving the bar alone. How the bird’s brain works at a song that has all the allure of a wheezing rubber duck.

To do this, he has invented a miniature microdrive half the weight of a penny that can be fastened to the bird’s head. Linked to specialized electronics by a short tether, it lowers a minuscule electrode into the finch’s HVC, which lies close to the surface of the brain, and positions the electrode within a single neuron at a precise depth. Then the electrode (one-thousandth the thickness of a human hair) measures how the voltage in that neuron changes over a song, and these groups appear to have enough internal redundancy to withstand minor losses without fumbling the tune—as one might expect, given the evolutionary consequences of failing to produce the correct song.

After earning his PhD in neuroscience at Brown University in 2003, Dr. Long moved to Cambridge, Massachusetts, to become a postdoc in the laboratory of MIT neuroscientist Michale Fee, PhD. They developed a miniature thermoelectric device that can cool tiny patches of the brain and used it to find the special spot that controls zebra finch song timing. When this spot, known as the HVC (high vocal center) nucleus, was cooled, the birds’ song slowed unmistakably. Scientists had known that multiple brain regions are involved in producing the zebra finch song, but they didn’t know whether all, some, or just one controlled the timing of the song’s individual sound bursts. “We showed that all the timing control is localized to this single nucleus of about 40,000 neurons,” Dr. Long says.

Nature published the finding in 2008, and soon after, Dr. Long joined the NYU School of Medicine. Today hundreds of twittering zebra finches fill his laboratory’s aviary. His chief aim is to determine how the neurons in the zebra finch’s HVC hook up to produce the precise sequence of brraapps and squeaks in a love song. “You can’t understand this by looking at the firing rate of an individual HVC neuron,” Dr. Long says. “You have to look at multiple neurons and see how they work together.”

Since the 1960s dozens of laboratories have studied the brains of zebra finches for clues to how birds in general learn to sing—and by analogy, how humans learn speech and other complex skills. But Dr. Long, who was recently named a Robertson Neuroscience Investigator by the New York Stem Cell Foundation and whose research is also supported in part by the Rita Allen Foundation and The Esther A. and Joseph Klingenstein Foundation, isn’t interested in the detailed workings of birdsong related to any specific animal or human skill; he wants to understand the basic neural logic of all learned behaviors—in other words, the rules by which neurons organize themselves to command precise sets of muscles in precise sequences.

“The finch is not the only game in town,” Dr. Long says, “but I think it’s the best for studying a manageable number of neurons that produce a clearly learned complex behavior.”
Dr. Long now plans to build a functional map of this HVC choir, at least for a meaningful segment of the zebra finch song, to study how it changes throughout the learning process. His graduate students Daniel Okobi and Sam Benezra are now training zebra finch males to sing while their heads are fixed beneath a large two-photon microscope. They expect to use the sophisticated microscope, which can peer deep into living brain tissue, to visualize and precisely time the activities of HVC neurons in one small part of the nucleus, then another, until they have data for a sufficiently large area. Postdoctoral researcher Daniela Vallentin, PhD, has also been refining the head-mounted microdrive device to enable longer and longer recordings from a given neuron. Her maximum single-neuron recording time in a finch brain so far is nearly four hours.

**Dr. Long’s Combination of Ambitious Neuroscience with Roll-up-your-sleeves Engineering is Influencing Research Well Beyond His Laboratory.**

In the finch brain, song is controlled by the high vocal center (HVC). A microdrive that measures the activity of neurons in the birds reveals that each group of these neurons is active for about 10 milliseconds during the song. Each group is likely connected to the next, like links in a chain, for sequential intervals. Each link signals downstream motor neurons (RA, robust nucleus of the arcopallium) that ultimately drive the vocal and respiratory muscles to produce the song.
A physician-scientist has devoted his life’s work to understanding the notorious bacterium *Staphylococcus aureus*. 

**STAPHYLOCOCCUS AUREUS INFECTS**

Some 1.2 million patients in hospitals each year. Notorious for causing a host of devastating infections from skin boils to toxic shock syndrome and for being especially difficult to treat, it has developed resistance to the most powerful antibiotics, including vancomycin, the drug of last resort. Richard Novick, MD (’59), the Recanati Family Professor of Science and a member of the Skirball Institute of Biomolecular Medicine, has dedicated his career to analyzing and combating the bacterium. His first major contribution to the field came in the early 1960s, when he found that a circular strand of DNA called a plasmid carried a staph gene responsible for antibiotic resistance. Dr. Novick’s discovery, along with others at the time, revolutionized scientists’ understanding of how bacteria manage their genes. He served on the faculty of Yale University, the National Institute for Medical Research in London, Vanderbilt University, Rockefeller University, Columbia University, and the Public Health Research Institute, and returned to NYU School of Medicine in 1993. He was elected to the National Academy of Sciences in 2006.

The exploitation of science, including the misuse of antibiotics, especially in animal feed, has concerned Dr. Novick throughout his career, and he is outspoken about his opposition to the development of biological weapons. An intrepid outdoorsman, Dr. Novick bikes to his lab from his Upper West Side apartment; he also hikes the Appalachian Trail as well as more demanding terrain in the Alps and Himalayas. On weekends at his home in Kent, Connecticut, Dr. Novick hunts for mushrooms and crafts bowls and vases out of wood.
When did you become interested in studying Staph?
I took a year out of medical training to do a mini PhD in Werner Maas’s lab, working on E. coli gene regulation. That got me interested in bacterial biology and genetics. My interest in Staph started during my postdoc in London with Martin Pollock. I spent the first year or two trying to see if we could get mutant varieties of Staph to attack methicillin, the new wonder drug. It was a rather dubious enterprise and it failed, but my research led to the discovery of the first plasmid found in Staphylococcus and I have stuck with staphylococcal research ever since.

Staph can inhabit our bodies without harm, but it can also cause deadly infections. How can it be so benign and so toxic?
That’s the $64 billion question. Thirty percent of people carry Staph, primarily in the nose, where it resides without penetrating the nasal tissues, raising two big questions: When the organism is living in the nose, does it interact with the immune system? Are the genes that cause infection being expressed? I think these questions are very well worth looking into.

You have a collection of close to 12,000 Staph strains. How did you acquire them and what distinguishes one from another?
We started collecting them when I was in England in the 1960s. Many are clinical isolates, obtained from patients. The others are research strains, which we’ve constructed by changing, adding, and subtracting genes. We’re trying to answer questions about how the bacteria are organized and how they regulate and transfer their genes.

Do you believe it will ever be possible to develop an effective antibiotic against this highly resistant bug?
Absolutely. We’re working on one. In the late ’80s, we cloned the gene for lysostaphin, an enzyme that dissolves Staphylococcus. Lots of people have studied it and shown that it is absolutely unparalleled for wiping out Staph in infected animals. A company we founded to produce it for clinical applications didn’t work out. Now we’re again trying to find an angle to make it commercially viable.

What other approaches are you taking?
There’s been a lot of interest in treating bacterial infections by inhibiting the expression of virulence genes. We discovered an inhibitory peptide that does just that to block a staphylococcal infection. We’re working out the details of that strategy, which, although it is effective in animal models, has yet to be tried in humans. We’re also trying to do something to interfere with biofilms, aggregations of bacteria and other organisms that attach to surfaces and are largely impermeable to antibiotics. Staph biofilms are a big problem in surgical implants for this very reason. I’m also working on an antistaphylococcal vaccine, the basis of which is top secret for the moment.

How would you define the path of your career?
I have to confess, I’m largely an opportunist in science. Some scientists might set out to answer a certain question and devote their entire lives to it. Good examples would be Fred Sanger, who set out to determine the sequences of nucleic acids, and John Kendrew, who wanted to know the structure of a protein. I never did that. I fell into Staphylococcus, because during my postdoc in London, I was asked to work on a problem of antibiotic resistance in Staph. Another case is toxic shock syndrome, caused by a staphylococcal toxin known as TSST-1. We were invited by Procter & Gamble to clone the TSST-1 gene, which led us to a new class of mobile genetic elements based on their carriage of this gene. That discovery has ballooned into a really cool project. That’s the way it has always happened in my career.

When did you start hunting for mushrooms and what’s your favorite variety?
It started in England. I noticed a big white puffball on the lawn where we were working. I knew it was edible—I don’t know how—so I picked and ate it and it was pretty good. My wife and I have eaten 30 species or more, but she’s gotten fussy lately. She’ll only eat three or four of the most highly regarded species.

“For young scientists, I’d say study what the great scientists have done. Learn about the world, look at history, look around you.”

Our favorite is probably the black trumpet, Craterellus cornucopioides.

When did you learn to work with wood?
It goes back 20 years and involves mostly wood turning, using a lathe. Although I love the idea of doing sculpture, I’m completely incompetent when it comes to doing anything freehand. If it’s constricted to something round, I can handle it.

What worries you most about medicine and science today?
One of my big concerns is the way medical care is being done. First, medicine should not be for profit. Period. Medicine for profit has been nothing but a disaster in every respect. Second, medicine should not be run by insurance companies. These two aspects of medicine as practiced in the United States have led to a god-awful mess. I’m an environmentalist and I think humans are overrunning the planet in ways that are destructive long-term. Fisheries are being depleted. Fossil fuels are being exploited, the planet is heating up. I’m terrified about what’s going to happen, because commercial interests are very rich and powerful, and very shortsighted.

What are you most optimistic about?
I certainly have a lot of hope for medical progress and for the success of science in solving problems. I’m excited about that. After all, that’s what I do as a lifework.

Where do you look for inspiration?
I used to look for it through historical insights. At the moment, my inspirations are generated internally. I’ve been around long enough. For young scientists, I’d say study what the great scientists have done. Learn about the world, look at history, look around you. Look at some phenomenon that everyone takes for granted and nobody knows about and ask, “What is that all about?”
Honoring Three Masters and a Major Benefactor on DEAN’S HONORS DAY

NYU SCHOOL OF MEDICINE’s 11th annual Dean’s Honors Day was held on Tuesday, October 2, 2012, at Farkas Auditorium to honor achievement, commemorate accomplishment, and celebrate excellence with the granting of tenures, promotions, chair appointments, and other distinctions to worthy faculty members and others. The NYU Brass Quintet opened the event and Dean Robert I. Grossman, MD, led a platform that included Kenneth Langone, chairman of the board of trustees, NYU Langone Medical Center; John Sexton, PhD, JD, president, New York University; and Steven B. Abramson, MD, vice dean for education, faculty and academic affairs. Three distinguished faculty received the honor of the highest-profile awards: Master Clinician, Master Educator, and Master Researcher.

“The three people honored this year have woven together powerful intellect, sustained effort, steadfast achievement, and greatness of spirit,” Dean Grossman said. “They remind us that excellence is an instantly recognizable absolute and, at the same time, a deeply individual achievement. They shine in very different but equally spectacular ways.”

Philip K. Moskowitz, MD, the Mamdouha S. Bobst Associate Professor of Internal Medicine, was named Master Clinician. Dean Grossman lauded Dr. Moskowitz for “embodying all the caring, skill, and expertise that would define such recognition,” characterizing him as an outstanding clinician and dedicated teacher and calling him a “doctor’s doctor” who has been “a pillar of NYU Langone Medical Center for nearly 50 years.” A member of the executive committee for medical school admissions, Dr. Moskowitz directed the House Staff Teaching Program for 15 years and has been faculty director of development for the past decade. Lori Fink, a trustee of NYU Langone Medical Center and board chair of the Cancer Institute at the Medical Center, and her husband Larry Fink, also a trustee, recently endowed The Philip K. Moskowitz, MD, Professor and Chair of the Department of Neurology. Steven L. Galetta, MD, was named to the endowed chair.

Danny Reinberg, PhD, professor of biochemistry and molecular pharmacology and a Howard Hughes Medical Institute investigator, received the Master Scientist Award. A National Institutes of Health Merit Award recipient, Dr. Reinberg and his collaborators have made fundamental discoveries in gene transcription and the mechanism by which information from DNA is transferred to the RNA that directs protein production. Most significantly, he has identified some of the key enzymes that control access to DNA in its cellular form, where it is curled tightly around proteins called histones. Among his laboratory’s major breakthroughs was the development of a powerful new methodology for studying the unwinding of DNA required for gene activation. This finding, based on seven years of research, allows scientists to investigate the discrete steps necessary to turn genes on and off at the proper time and in the proper place. Dr. Reinberg is a co-founder of Constellation Pharmaceuticals, a chromatin therapeutics company, based in Cambridge, Massachusetts.

Linda R. Tewksbury, MD (’90), assistant
professor of pediatrics and an influential advocate for scholarship in medical education, received the award for Master Educator and Mentor. “Mentors shape lives, not just career choices,” Dean Grossman said. “And in so doing, they also make lasting contributions to the quality and effectiveness of our entire profession.” Dr. Tewksbury coordinates the advisory program for pediatric program applicants and was among the first cohort of 10 Master Scholars Advisors chosen for the School’s advisory program. The graduating class of 2011 elected her Distinguished Teacher in the Clinical Sciences.

Larry A. Silverstein accepted the 2012 Valentine Mott Founders Award in recognition of extraordinary support of the School of Medicine’s academic mission. A 1952 alumnus of the New York University College of Arts and Science, trustee of New York University’s board since 1976 and of the Medical Center and School since 1998, Mr. Silverstein, along with his wife, Klara, recently established the Silverstein Scholarship Fund for medical students with an endowment of $5.25 million. He is president and CEO of Silverstein Properties, Inc., a Manhattan-based real estate development and investment firm. In July 2001 Mr. Silverstein signed a 99-year lease for the World Trade Center for $3.25 billion dollars. Six weeks later, the Twin Towers were attacked. Today, he is the driving force behind the site’s redevelopment.

**DR. LITTMAN ELECTED TO INSTITUTE OF MEDICINE**

**DAN LITTMAN, MD, PHD,**

the Helen L. and Martin S. Kimmel Professor of Molecular Immunology, professor of pathology and microbiology, and a member of the Skirball Institute of Biomolecular Medicine, was elected to the Institute of Medicine (IOM). Dr. Littman is widely recognized for his seminal contributions to understanding the molecular basis of immune recognition, HIV pathogenesis, T-cell differentiation and selection, and, most recently, the role of commensal bacteria in immune system development and regulation. Election to the IOM is considered one of the highest accolades for outstanding professional achievement and commitment to service in the fields of medicine and health.

**DR. TSIEN RECEIVES NEUROSCIENCE AWARD**

RICHARD W. TSIEN, DPHIL, Druckennill Professor of Neuroscience, chair of the Department of Physiology and Neuroscience, and director of the Neuroscience Institute at NYU Langone Medical Center, received the Julius Axelrod Prize from the Society for Neuroscience during its annual meeting. The prize recognizes exceptional achievement in neuropharmacology or a related field and exemplary efforts in mentoring young scientists. It is supported by the Eli Lilly and Company Foundation and includes a $25,000 award. One of the world’s leading neuroscientists, Dr. Tsien has devoted his career to understanding signaling within the brain and the heart; he is best known for his studies of calcium channels, which drive a multitude of critical processes in the body.

**Dr. Llinás Honored**

**RODOLFO LLINÁS, MD, PHD,**

the Thomas and Suzanne Murphy Professor of Neuroscience, University Professor, and former chair of the Department of Physiology and Neuroscience at NYU School of Medicine, was awarded the Gold Medal for Science by the Spanish National Research Council (CSIC), the highest distinction the organization offers. The award recognizes the many contributions he has made to the neurosciences over the course of his career.

Dr. Llinás is known worldwide for pioneering magnetoencephalography, a highly sensitive, noninvasive technology for measuring the brain’s electrical activity, and for elucidating how certain brain diseases arise from thalamocortical dysrhythmia, the disruption of connections between the thalamus and the cortex.

The CSIC is the largest public institution dedicated to research in Spain and the third largest in Europe.
ROBERT PORGES, MD

ROBERT F. PORGES, MD, professor of obstetrics and gynecology, who twice served as chair of NYU Langone Medical Center’s Department of Obstetrics and Gynecology in a career spanning more than 50 years, died on November 1. Dr. Porges, who was 82, had battled lymphoma for several years.

Roberta Porges, MD

Dr. Porges (above) and with his wife, Felicia Axelrod, MD, at 2012 Medical Alumni Day.

“Dr. Porges was the quintessential old-school physician: humble, graceful, and elegant,” David Keefe, MD, the Stanley H. Kaplan Professor of Obstetrics and Gynecology and chair of the Department of Obstetrics and Gynecology, told Every Mother Counts, an organization devoted to making pregnancy and childbirth safer in the developing world. “Even in his 80s, he was considered the best surgeon for the most difficult cases. He trained generations of medical students and delivered generations of mothers and babies with his always-kind, always-compassionate manner.”

Scores of patients and their families who mourned the loss of Dr. Porges shared these sentiments. “This wonderful, intelligent, caring doctor delivered our daughter and became a close friend for life. Our family mourns the loss of this extraordinary person who was a true gentleman: elegant, kind, and compassionate,” wrote Lorraine and Herbert Podell in an online guest book accompanying Dr. Porges’s obituary in The New York Times.

A masterful surgeon, Dr. Porges was director of the Division of Urogynecology and Reconstructive Pelvic Surgery. In 2003 he was named Distinguished Surgeon by the Society of Gynecologic Surgeons. Even during the final weeks of his life, physicians sought his advice and requested his presence in the operating room to assist them with challenging cases.

Born in Vienna, Austria, on September 11, 1930, he immigrated to the United States with his family when he was eight years old. A third-generation physician, Dr. Porges graduated from Dartmouth College and earned his MD from the State University of New York (SUNY) Downstate Medical School. After an internship at Beth Israel Medical Center in New York—where his father was also on staff—Dr. Porges finished his residency training at Jacobi Hospital in the Bronx. Dr. Porges served for two years as a staff obstetrician and gynecologist in the U.S. Air Force, stationed at Wilford Hall Hospital in San Antonio, Texas.

Dr. Porges came to NYU Langone in 1962, and never left. It was here that he met his wife, Felicia Axelrod, MD—then a medical student and now a professor of pediatrics and neurology and director of NYU Langone’s Familial Dysautonomia Program—to whom he was married for 47 years.

At 78, Dr. Porges returned to school to earn a master’s degree in public health with an emphasis on global women’s health. He traveled to Uganda to spend 14-hour days surgically repairing the fistulas and pelvic organ prolapses that many women there endure after multiple difficult deliveries. At NYU Langone, he established the Division of Global Women’s Health, collaborating with partners around the world—particularly in sub-Saharan Africa and the Americas—to improve maternal health in local communities.

In late October, as Hurricane Sandy approached, Dr. Porges was a patient in Tisch Hospital’s Critical Care Unit, gravely ill from a relapse of lymphoma. “He and his family decided he’d go home,” says Dr. Keefe. “The power was out at home, but he had his family by his side.”

In addition to his wife, Felicia, Dr. Porges is survived by his son, John, an attorney, and his daughter, Vicki, clinical instructor in pediatrics at NYU Langone, as well as four grandchildren. •
One patient at a time. When you include a bequest in your will to NYU Langone Medical Center you help us deliver outstanding health care to the many patients and families who rely upon us to improve their lives. Superb physicians, an award-winning nursing staff and internationally ranked scientists make the difference. Join our community, and create your legacy today.

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