STANFORD MEDICINE

Summer 2013

special report

ENVIRONMENTAL IMPACT
The health effect

After Hurricane Sandy
Lessons learned

Water, water *not* everywhere
A Q&A with Gary White and Matt Damon

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S T A N F O R D

M E D I C I N E

Summer 2013

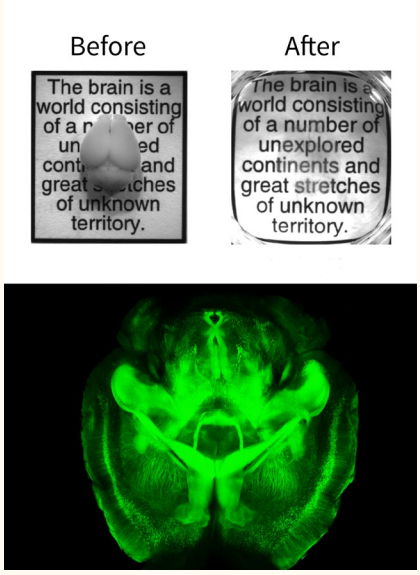
A CLEAR VIEW

HOW TO MAKE A LUCID BRAIN

How do you turn a brain transparent? And more to the point, why would you want to? • Stanford researchers answered both of these questions in April when they published a recipe in *Nature* for rendering a mouse brain completely clear.

It's a big break for neuroscientists, who have struggled to fully understand how the brain works and why sometimes it doesn't. Part of the difficulty has been the limitations of available research techniques. To discern a brain's cellular circuitry, researchers thinly slice the organ and then reconstruct three-dimensional models: a laborious and inexact science, at best.

The new method, dubbed CLARITY, keeps the postmortem brain whole — not sliced or sectioned in any way — with its entire three-dimensional complexity of fine wiring and molecular structures completely intact and able to be measured and probed at will with visible light and chemicals.



JELLIED BRAIN
Top: A mouse brain before and after the transparency treatment. In the "after" image, the brain is only faintly visible, blurring the words "number," "unexplored," "continents" and "stretches." Below: A stained transparent mouse brain, seen from below.

The technique is the result of a six-year effort to extract the opaque lipids from a brain while preserving other important features. Lipids are fatty molecules that help form cell membranes and give the brain much of its structure, but that make the brain largely impermeable both to chemicals and to light, hindering research. Removing the lipids, however, causes the remaining tissue to fall apart.

"We thought that if we could remove the lipids nondestructively, we might be able to get both light and macromolecules to penetrate deep into tissue, allowing not only 3-D imaging, but also 3-D molecular analysis of the intact brain," says Karl Deisseroth, MD, PhD, a professor of bioengineering and of psychiatry, who led the project.

Deisseroth's method replaces lipids with a hydrogel. Neuroscientists soak the brain in a watery suspension of short, individual hydrogel molecules. Then, when warmed sufficiently, the hydrogel molecules congeal into long polymer chains, forming an invisible mesh that holds the brain together and yet, as if by magic, does not bind to the lipids, which can then be extracted in a separate process.

What remains is a transparent brain with all of its important neurons, axons, dendrites, synapses, proteins, nucleic acids and other components precisely in place.

Researchers are able to repeatedly stain, destain and restain the clarified brain with fluorescent antibodies to explore distinct molecular targets. The different data sets can be aligned with one another to create complex and stunningly detailed structural maps of brain circuitry and structures.

While the *Nature* study was conducted on a mouse brain, the researchers have used the same method on an entire zebrafish and on preserved human brain samples, establishing a path for studies of other organisms.

"Of particular interest are intrasystem relationships, not only in the mammalian brain but also in other tissues or diseases for which full understanding is only possible through analysis of single, intact systems," says Deisseroth, who is one of 15 experts on the "dream team" that will map out goals for President Obama's $100 million brain research initiative.

"CLARITY may be applicable to any biological system," says Deisseroth, "and it will be interesting to see how other branches of biology may put it to use." — ANDREW MYERS

WEB EXTRA Watch an interview about this new way to see inside brains: http://stan.md/18HyyxJ

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DEPARTMENTS

COVER: BRIAN CRONIN

letter from the dean

In the midst of the fast-paced genetic revolution in health care, generating both basic science discoveries and treatment advances, it's easy to think that DNA is, in fact, destiny.

But it's increasingly obvious that the environment — the world outside our bodies — has a significant impact on health in ways that we're only now discovering. It's no surprise that air thick with pollutants can be deadly for a person with asthma. But now we know that bad air can cause harm in utero — breathing traffic pollution during early pregnancy is linked to serious birth defects, as pediatrics professor Gary Shaw showed in a recent study.

One way the outside environment can influence our health is by leading to mutations in our DNA sequences, as is the case with cigarette smoke. But another way is by turning certain genes on or off without affecting DNA sequences — a phenomenon called epigenetics. Our external environment sometimes sets epigenetic changes in motion. These effects can be far-reaching. In fact, recent research by associate professor of genetics Anne Brunet demonstrated for the first time that even longevity can be handed down through epigenetic inheritance.

Fortunately, there's a growing recognition in medicine of the importance of looking at the totality of an individual — in his or her environment — as an indicator of health and as a guide to treatment. It's not always just test results or the symptoms presented in the clinic that matter, but an individual's physical environment, socioeconomic status and access to social support.

In fact, many studies have found that health-care spending directed at disease intervention addresses only about one-quarter of the determinants of health. In a study with Stanford economist Victor Fuchs, professor Mark Cullen found that education and family structure are better indicators of life expectancy than access to health care.

For an academic medical center, this is sobering news. It means that preventing and treating disease will take more than groundbreaking research and the best treatments; it will require tackling the underlying environmental factors — be they social, physical or behavioral — that make us sick. It means that health requires a lot more than outstanding doctors and hospitals.

I'd like to thank the Stanford Woods Institute for the Environment for partnering with us on this issue of the magazine and for helping to remind us that health is about more than DNA and medical care. It's also about the environment.

Sincerely,
Lloyd B. Minor, MD
Carl and Elizabeth Naumann Dean of the School of Medicine
Professor of Otolaryngology-Head and Neck Surgery

GLENN MATSUMURA

upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD UNIVERSITY MEDICAL CENTER

TB hideout

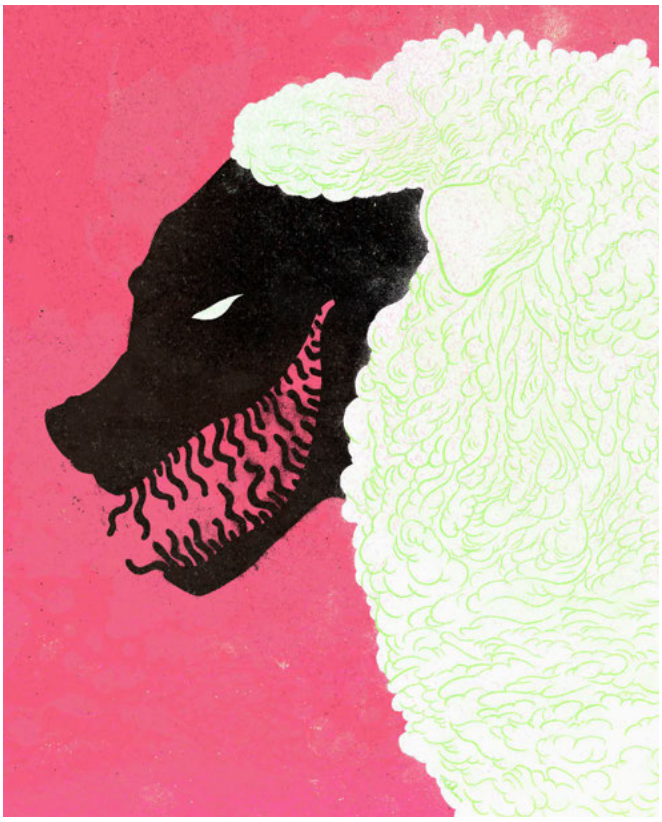
RESISTANCE TO THERAPEUTIC DRUGS? Check. A free pass from the immune system? Check. A stable living environment? Check.

When it comes to hunkering down, tuberculosis bacteria choose a uniquely qualified lodging site in the body: stem cells in the bone marrow. Here the bacteria nestle, hassle-free, in a dormancy that can last decades before erupting to spread and kill millions of people each year.

Using some of the body's most precious cells as a hideout? It's unashamedly devious, undeniably successful and completely unexpected. Stanford postdoctoral scholar Bikul Das, MBBS, PhD, and oncologist Dean Felsher, MD, PhD, were the first to report this wolf-in-stem-cell-clothing tactic in *Science Translational Medicine*.

"Self-renewing stem cells like these in the bone marrow have properties — such as natural drug resistance, infrequent division and a privileged immune status — that make them resistant to many types of treatment," says Felsher. "Now it turns out that this ancient organism figured out a long time ago that, for the same reasons, these cells are ideal hosts to invade and in which to hide."

Das first noticed tuberculosis bacteria in bone marrow biopsies of dormantly infected patients during his years as a physician in India. "We now need to learn how the bacteria find and infect this tiny population of stem cells, and what triggers them to reactivate years or decades after successful treatment of the disease," he says. — KRISTA CONGER



JACOB THOMAS

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School of Medicine faculty are investigators for the Howard Hughes Medical Institute. Read more at http://stan.md/10r7Oy4.

IUD appeal

INTRAUTERINE DEVICES have been an unpopular form of birth control in developing countries. Negative perceptions and barriers to access mean that just 7.6 percent of women in developing countries use IUDs compared with 14.5 percent in developed ones.

Research from Stanford's Paul Blumenthal, MD, and Population Services International suggests IUD use can be boosted through better education about — and access to — family planning options. The group detailed in a *Contraception* paper how this approach helped get IUDs to more than 500,000 women in 13 countries over two years. — MICHELLE L. BRANDT

upfront

Tailing stem cells

REPAIRING DAMAGED HEARTS by infusing them with stem cells in the hope that these cells will replace worn-out or damaged tissue hasn't yet met with clinical success. This might partly reflect faulty initial placement, says Sam Gambhir, PhD, MD, professor and chair of radiology and director of the Molecular Imaging Program at Stanford.

"You can use ultrasound to visualize the needle through which you deliver those stem cells. But once they leave the needle, you've lost track of them," he says. Did the cells get to the heart wall? Did they stay there? How long did they stay alive? You don't know, largely due to a dearth of decent imaging tools.

But Gambhir and his team developed a sensitive visualization technique, described in a study published in *Science Translational Medicine*, that lets researchers observe in real time where stem cells they've injected are going and monitor them for weeks afterward.

They designed nanoparticles whose chief constituent, silica, is visible to ultrasound. The nanoparticles are doped with gadolinium, an MRI contrast agent. In the study, mesenchymal stem cells — often used in heart-regeneration research because they can differentiate into beating heart cells — gobbled up the nanoparticles without complications and then, infused into healthy mouse hearts, could be viewed immediately afterward with ultrasound and with MRI two weeks later. — BRUCE GOLDMAN

BUILDING BEGINS

ABOUT 400 ADMINISTRATORS, donors and community members gathered May 1 to watch as shiny red shovels were put to ceremonial dirt, marking the formal start of construction of the new Stanford Hospital. • Scheduled to open to patients in 2018, the new building will optimize the hospital's services and infrastructure, adding beds, private rooms, operating suites, expanded emergency services and the flexibility to adapt to advancing technologies and more streamlined services.

The 824,000-square-foot hospital will increase patient capacity to 600 beds and feature 368 individual patient rooms, an enlarged level-1 trauma center and an emergency department with nearly three times the current capacity.

It's designed to enhance both physical and emotional healing with the latest in medical, surgical and diagnostic technology. Individual patient rooms will include accommodations for family members to visit and spend the night. A roof garden will create a retreat for patients and families. The building will also incorporate innovations in green technology to reduce the hospital's environmental impact.

The new hospital is part of the $5 billion Stanford University Medical Center Renewal Project that will bring facilities to current seismic safety standards and support the growth of the medical center. — BY RUTH SCHECHTER

Self-taught CPR

IF A CHILD'S HEART STOPS, quick and skillful CPR can keep oxygen flowing to the child's brain until paramedics arrive. But in the past, helping parents of high-risk pediatric patients learn CPR in the hospital was challenging.

Now, new research from Lucile Packard Children's Hospital shows that a self-instructional kit can teach families CPR. The kits, which included a video and mannequin for CPR practice, were distributed in the hospital and taken home for practice after discharge. Six months later, most parents studied were confident in their CPR skills.

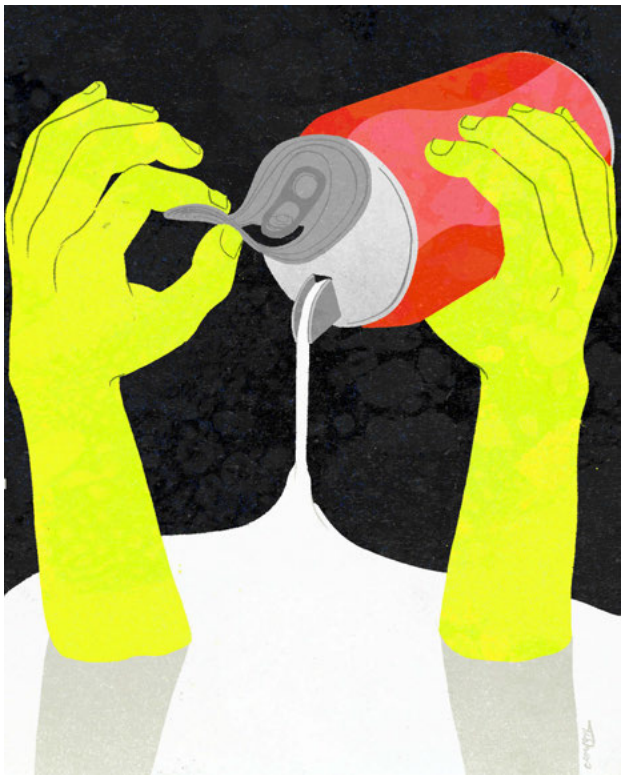
"It allowed them to feel relieved that they would know what to do if something ever happened and their child required CPR after they left the hospital," says resuscitation educator Lynda Knight, RN, who led the study. The findings were published in the *Journal for Healthcare Quality*. — ERIN DIGITALE

Not so sweet

DOES EATING SUGAR CAUSE DIABETES? For years, scientists have said "not exactly." Eating too much of any food, including sugar, can cause weight gain; the resulting obesity predisposes people to diabetes, says the prevailing theory.

But now a large epidemiological study suggests sugar also has a direct link to diabetes. Researchers examined sugar availability and diabetes rates in 175 countries over the past decade. The data the team used did not distinguish between type-1 and type-2 diabetes, though type-2, the form previously associated with obesity, accounts for around 90 percent of cases worldwide. After accounting for obesity and several other factors, increased sugar in a population's food supply was linked to higher diabetes rates, independent of obesity rates. An extra 12-oz. soda's worth of sugar per person per day raised diabetes rates by 1 percent. The study was published in *PLOS ONE*.

"It was quite a surprise," says lead author Sanjay Basu, MD, PhD, assistant professor of medicine. The study gives the first large-scale evidence that a sugar calorie may be more than just a calorie when it comes to diabetes risk. — ERIN DIGITALE



LET THEM EAT DIRT?

A TEAM LED BY MARK DAVIS, PHD, director of Stanford's Institute for Immunity, Transplantation and Infection, found that over the course of our lives, key immune cells somehow acquire a "memory" of microbes that have never entered our bodies.

So-called CD4 cells hang out in our circulatory system, on the lookout for pathogens that have found their way into the blood or lymph tissue. Our bodies have diverse inventories of these cells, each with its own narrow capacity to recognize a single pathogenic "body part"— or so it's been thought. If such contact occurs, a CD4 whirrs into a hyperactive state vital to the immune response. CD4 cells fall into two categories:"naïve" cells that randomly target pathogens they haven't encountered yet, and long-lived "memory" cells that, having had a run-in with a pathogen, are ultra-responsive to it.

In a study published in *Immunity*, Davis' team exposed immune-cell-rich blood from 26 healthy adults and from two newborns' umbilical cords to several nasty viral strains. Nearly all the adult blood samples contained cells responsive to those viruses. More surprising was that about half of the virus-responsive CD4 cells in adult samples were in the "memory" state — even though sensitive tests ruled out participants' exposure to any of those viruses in real life.

Another surprise: About one-fifth of the samples boasted "cross-reactive" memory CD4 cells responsive to both the nasty viruses and other harmless environmental microbes. This implies that exposure to common bugs in the dirt and in our homes may reduce our susceptibility to dangerous pathogens. — BRUCE GOLDMAN

JACOB THOMAS

Drug searches

AFTER TAKING A NEW MEDICATION you feel sweaty, so you go online and search for possible side effects. If there were multiple searches for the same information, could they serve as an early alert to previously unreported side effects?

That appears to be the case, based on a study in the *Journal of the American Medical Informatics Association*. Researchers at the School of Medicine and at Microsoft Research analyzed search histories from Internet users who agreed to share anonymized logs of their Web searches, and pinpointed an interaction between two drugs that was unknown at the time of data collection.

"Seeking health information is a major use of the Internet," Altman says.

"Patients are telling us lots of things about drugs, and we need to figure out ways to listen," says co-author Russ Altman, MD, PhD, professor of medicine.

— SARAH C.P. WILLIAMS

HIDING IN PLAIN SIGHT

THE ENVIRONMENTAL FACTOR

It's right before your eyes: The water you drink, the air you breathe, your neighborhood — in other words, your environment — can make or break your health. • A healthy environment is critical to human health: One recent study estimates that air, water and soil pollution cause up to 40 percent of worldwide deaths each year, as well as countless illnesses. • Yet the environment is often left out of medical conversations, in part because the problems are so big and so complicated. • "Because these are societal problems, no one individual can solve the problem on his or her own," says Barton "Buzz" Thompson, PhD, co-director of the Stanford Woods Institute for the Environment. "And because the problems are complex, no single discipline can solve the problem on its own." • The good news is that support for interdisciplinary environmental research and advances in technology to carry out that research are bearing fruit. • "The environment is intimately connected to human health. That's why the Stanford Woods Institute fosters collaborations between researchers in medical fields and other disciplines," says the institute's other director, Jeff Koseff, PhD. "Their work is leading to solutions of some of the world's most serious health issues." • Read on to discover how teams are tackling a few of the world's environmental problems for the sake of our health.

ILLUSTRATION BY BRIAN CRONIN


ONE WAY

priming the pumps debugging dhaka's water

By Ruthann Richter

PHOTOGRAPHY BY AMY PICKERING

RIGHT: DHAKA'S WATER
A flimsy municipal pipe carries water from a polluted lake to this compound's washing area, where residents clean their dishes and clothes.

AMY PICKERING, PHD, STOOD AT THE EDGE OF THE RIVER, THE WATER BLACKENED BY WASTE AND DEBRIS, AS THE FERRYMAN BECKONED TO HER FROM HIS FRAGILE WOODEN SKIFF, THE ONLY MEANS TO THE OTHER SIDE. IT WAS FEBRUARY 2011, THE START OF PICKERING'S FIRST VISIT TO DHAKA, BANGLADESH, AND SHE WAS GETTING HER FIRST GOOD LOOK AT THE CHALLENGE AHEAD: FLIMSY PIPES SUCKED IN FOUL RIVER WATER, WHICH WOULD BE DISPENSED THROUGH COMMUNAL PUMPS FOR SLUM DWELLERS TO DRINK.

Pickering, a postdoctoral researcher in civil and environmental engineering at Stanford, would spend the next few weeks in Dhaka, a city with the distinction of being the most densely populated and — because of its poor infrastructure, inadequate health care and polluted environment — ranked by *The Economist* as least livable in the world. She was there to lay the groundwork for a project proposing a simple, low-cost method for purifying Dhaka's contaminated water supplies and improving the health of the city's estimated 10 million residents. The method, an ingenious chlorination system, is a radical departure from previous approaches to providing clean water. If

the method is proven in Dhaka, she and her colleagues would like to see it applied across the developing world.

The project grew out of the despair of an American doctor working in Bangladesh. Stephen Luby, MD, now a professor of medicine at Stanford and principal investigator for the project, had spent eight years in Dhaka as the director for the U.S. Centers for Disease Control and Prevention in Bangladesh before coming to Stanford in September 2012. While in Dhaka, he also worked with the International Center for Diarrheal Disease Research, whose Dhaka hospital admits more than 100,000 people every year for diarrhea, much of it caused by drinking contaminated water. He estimates fewer than 20 percent of people in Bangladesh have access to water that is free of contamination.

As an infectious disease specialist, Luby was acutely aware of the many waterborne risks to local health, including cholera and typhoid, as well as diarrheal diseases caused by microbes such as rotavirus, *E. coli* and shigella. Rotavirus, which causes severe, watery diarrhea, is one of the biggest threats, responsible for the death every year of more than 15,000 children under the age of 5 in Bangladesh, according to a 2008 study in the journal *Vaccine*. More than half a million children worldwide die each year of rotavirus infection, which is one of the primary causes of diarrhea in young people. Those who are infected shed the virus in their feces. It then spreads through hand-to-mouth contact with contaminated material or through drinking tainted water.

"If you talk to people in these communities, almost all of them will be able to tell you about somebody they know who has died of diarrhea," particularly infants and young children, Luby says. "So mothers are very familiar with the problem."

Finding a solution became a nagging issue for Luby. So he turned his attention to Dhaka's water supply and began pondering new ways to clean it up. Unlike developed countries, which rely on large water-treatment plants to purify water, developing nations for the most part put the onus on residents to boil, filter or chlorinate their home water supplies. But fewer than 10 percent are willing or able to take these steps, even if the water they drink could put them — or their children — at risk for serious illness and death, Luby says.

"You're asking poor people to set up a water treatment plant in their home. Many people don't," says Luby, who is also a fellow at Stanford's Woods Institute for the Environment. He reached the conclusion that clean water would never reach those at highest risk of diarrhea and other serious, water-related ailments without an entirely new approach.

Three years ago, before he came to Stanford, he met Pickering, then a Stanford graduate student, at a scientific meeting in Berkeley. He had reviewed one of her papers and was impressed with her thoroughness and careful scientific reasoning. He saw her again in 2010, at the American Society of Tropical Medicine and Hygiene conference in Atlanta, and talked with her about the water issues in Dhaka, asking if she might come up with a fresh approach — some mid-level solution between a costly treatment plant and a home purification system, which he viewed as a failed strategy.

So Pickering headed to the burgeoning South Asian city on a scouting mission, stepping gingerly into that shaky-looking skiff to arrive at Korail, one of the nearly 5,000 slums scattered around the city. About 40 percent of Dhaka's people — an estimated 4 million residents — are wedged into these slum neighborhoods, where families live chockablock in sin-

Collecting water
SLUM DWELLERS USE ALUMINUM POTS KNOWS AS KOLSHIS AND PLASTIC BOTTLES TO GATHER THEIR WATER.

The pump at work
A HAND PUMP WITH A STANFORD PROTOTYPE DEVICE DELIVERS CHLORINATED WATER FOR DRINKING AND WASHING.

gle-room tin shacks. Pickering says she loves to travel and has worked in slums in both India and Africa, but had never encountered a place like Dhaka. Its slums, 33 times more densely populated than San Francisco, are a chaotic environment where people compete for every inch of space, dodging rickshaws, bicycles or other obstacles on pockmarked roads.

"I have to say Dhaka is the most intense place I've ever worked," says Pickering, who has visited the city several times. "Living and working there requires a sense of internal calm and focus."

Air pollution has draped a layer of soot over the city, while rains routinely flood the many homes perched unsteadily along the city's vast network of waterways.

"There's open sewage everywhere," she says. "There's not a well-functioning sewer system to remove feces from the communities. The kids are playing in it, and it's very unsafe."

Water supplies are conveyed through these neighborhoods via PVC pipes resembling backyard garden hoses, which are often cracked and leaky, and exposed to runoff from pit latrines, holes in the ground that serve as communal toilets. Because the city's water flow is intermittent, it creates a negative pressure in the pipes, which then suck in the surrounding sewage. Tests done by Stanford and the diarrheal research center showed that 80 percent of water samples were contaminated with bacteria from human waste, Luby says.

On her scouting mission, Pickering made a key observation. Most slum dwellers, she noticed, were collecting water at communal hand pumps, which were shared by 10 to 50 families. Women typically rose early, at 4 or 5 a.m., squatting in their colorful salwar kameez (loose-fitting pants and long tunics) to collect the water in plastic buckets or metal vases known as kolshis for use and storage at home.

Pickering had a thought: What if she and her colleagues could find a way to infuse chlorine into the water at these shared sites? A few drops of the chemical, which kills viruses and bacteria and most diarrhea-causing pathogens, would purify the water and spare residents the trouble of doing it themselves. If successful, it would be the first automated chlorine disinfection system for use in low-income areas.

The beauty of the approach is that it doesn't require people to change their behavior — one of the major impediments to many current water-purification programs, says Jenna Davis, PhD, an associate professor of civil and environmental engineering and a member of the project team. Studies show that when people are given the tools to purify water at home, they are initially enthusiastic and rates of diarrhea decline, she says. But once researchers leave, old habits set in, and progress stops.

For instance, Shaila Arman, a scientist at the diarrheal research center and a Dhaka resident, was involved in one

coming to a sprinkler near you

in america, reused water on tap

Not only developing countries such as Bangladesh struggle with their water supplies. In the United States, population pressures, growing energy costs and climate change uncertainties threaten a future of municipal water shortages, particularly in the arid West. Water reuse — the use of treated wastewater — will likely be key to meeting future water needs. • According to the most recent data available from the U.S. Environmental Protection Agency, Americans use 1.7 billion gallons of reused water every day. While that's a lot of water, it's less than 1 percent of U.S. daily water use. • Stanford civil and environmental engineering professor Richard Luthy, PhD, is leading the charge to increase water reuse. Luthy is the director of ReNUWIt, a $20 million National Science Foundation multi-institutional research center focused on ensuring that communities have dependable water supplies and designing systems to manage and reuse that water. Water treatment as we know it is energy-intensive and resource-inefficient. "We need to be thinking differently," says Luthy, the Silas H. Palmer Professor of Civil Engineering and a senior fellow at the Woods Institute for the Environment. • As part of their work for the center, Luthy and his colleagues are planning a test-bed facility on Stanford's campus — the first of its kind in the United States — where researchers from around the world will experiment with technologies including some that have the potential to reclaim water while producing clean energy. • Luthy and other Stanford experts say that reused water can be as safe as what flows today from the kitchen faucet — a 2012 report by the National Research Council pronounced reclaimed water safe as ordinary drinking water. But they warn that unless chemical waste is curbed, the safety of any type of water will be in jeopardy.

Even with today's technology, reused water compares well with drinking water. Regarding pathogens, the research council's report states, "Although there is a great degree of uncertainty, the risk from potable reuse does not appear to be any higher, and may be orders of magnitude lower, than currently experienced in at least some current (and approved) drinking water treatment systems." Part of the reason for this is that many municipal water supplies contain "de facto" reused water — for example, river water that receives discharge from sewage treatment plants.

The report says that tests "have documented the presence of wastewater-derived contaminants in watersheds throughout the country" and that, according to a recent study of drinking water supplies, "one or more prescription drugs was detected in approximately 25 percent of samples collected at the intakes of drinking water treatment plants in 25 states and Puerto Rico."

So in simple terms, ordinary drinking water already contains reused water to some extent, as well as some of the chemicals it carries. Which brings us to what professor of medicine Stephen Luby, MD, says is the real issue. It's not contaminants in reused water, it's the massive quantity of chemicals we manufacture and release into the environment at large. "Where is this stuff going to go?" asks Luby, an expert on waterborne illness and a senior fellow at Woods and at the Freeman Spogli Institute for International Studies.

"We live in this environment. We can't escape it," says Luby. "We are a chemical world. I know the toxicologists say it's all in the dose, but it does concern me."

Craig Criddle, PhD, a professor of civil and environmental engineering and a senior fellow at Woods, echoes Luby's concern, saying more focus should be given to green chemistry and replacing chemicals that are nearly impossible to remove completely from water sources.

The national Safe Drinking Water Act sets maximum exposure levels for many chemicals in municipal drinking water, but does not establish standards for many applications of recycled water, such as toilet flushing, cooling and irrigation, where water of lesser quality may be suitable and less expensive to produce. It also does not set standards for unregulated chemicals, trace amounts of which are sometimes present in reused water.

That means water treatment strategies should be robust, says Luthy. He calls for the use of multiple treatment methods, careful monitoring for equipment malfunction and operator error, and better federal water reuse regulations to rectify non-uniform state rules.

Today only a few municipal systems — including areas of Southern California and Texas — replenish their reservoirs or groundwater basins with treated wastewater, and only about one-tenth of 1 percent of municipal wastewater nationally is recycled into local drinking supplies.

But that will increase, Luthy says.

"Locally sourced water supplies — from water reuse, stormwater capture and better groundwater management — are the future," he says.

— ROB JORDAN

community water-chlorination project that failed because people could not adapt to a new, seemingly complex technology, especially since they didn't consider water contamination a serious health threat. She says most people were less concerned with pathogens in the water than with its smell and appearance. Moreover, taking on a new habit, she says, is hard when people are struggling to get by day to day.

"People are worried a lot about the demands of life, so they are not as concerned about diarrhea, which in the scheme of things is not perceived as so serious," Arman says.

Before Pickering left Bangladesh, she visited a hardware store and spent $30 on what would become a crucial piece of research equipment for the project: a bright green, 70-pound iron pump, just like those used in the slums. With a colleague's help, she stuffed the 2-foot pump into her hard-shell suitcase and padded it with her T-shirts and socks. "I was lucky the guy who checked me didn't bother to weigh it," she says with a smile. "I was pretty excited about it. I was also worried that it wouldn't arrive, as our luggage flying to Bangladesh is often lost."

But arrive it did, and the rusty pump now sits on a makeshift wooden platform in the environmental engineering lab in Stanford's Y2E2 environment and energy research building, an anomaly among the pristine, sophisticated equipment on neighborhing lab benches. Pickering says she was hoping to find an off-the-shelf device that could easily attach to the pump and dispense an appropriate amount of chlorine into the water, but it was not to be.

"I found there was no technology out there that took into account that there was no access to electricity," she says. "It would also have to work with a non-continuous water supply and be able to use liquid chlorine, which can be bought very cheaply in Dhaka in the form of household bleach."

Fortunately, a dedicated group of Stanford students in civil and environmental engineering soon came together, willing to spend countless hours in the lab — and in the field in Dhaka — designing and testing different prototypes. Graduate student Yoshika Crider cobbled together the first in 2011 in a pink bathtub in the Dhaka apartment she shared with two other students. She used pieces of plastic to fashion a rectangular mixing chamber, connected by a hose to a mesh bag of bleach powder. The device, designed with the same principles as a pool chlorinator, was held together by duct tape, "the roughest of prototypes," she says.

Crider and a few other students later proposed it as a project for a class, Engineers for a Sustainable World, and the effort gathered steam. The team since has gone through at least 20 other iterations, all stowed in a bucket in the lab that graduate student Keegan Cooke calls "the prototype graveyard." Some of the prototypes weren't durable enough for

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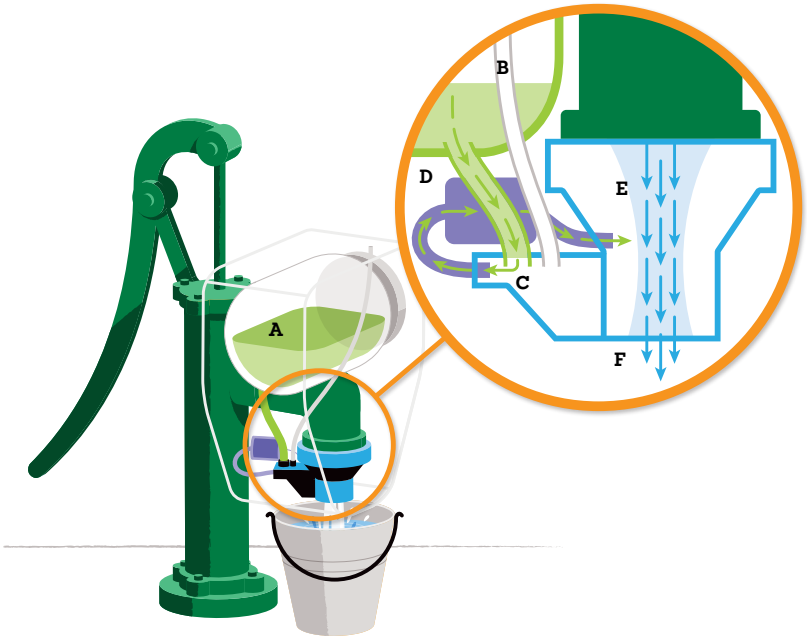
Chlorination at the pump

IN THE LATEST PROTOTYPE OF THE STANFORD TEAM'S CHLORINE DOSER, TINY AMOUNTS OF BLEACH FLOW THROUGH A PRESSURE STABILIZER AND A DOSE REGULATOR AND ARE THEN INJECTED INTO THE WATER STREAM.



A The chlorine reservoir holds ordinary bleach.

B An air tube helps balance the pressure.

C The chlorine travels through a pressure stabilizer.

D The chlorine travels through a regulator to control the flow, just a few drops per liter of water.

E Water flows through a restriction to create the Venturi effect, which reduces fluid pressure and draws in the chlorine.

F Water exits the pump safely chlorinated.

RON CHAN

close encounters

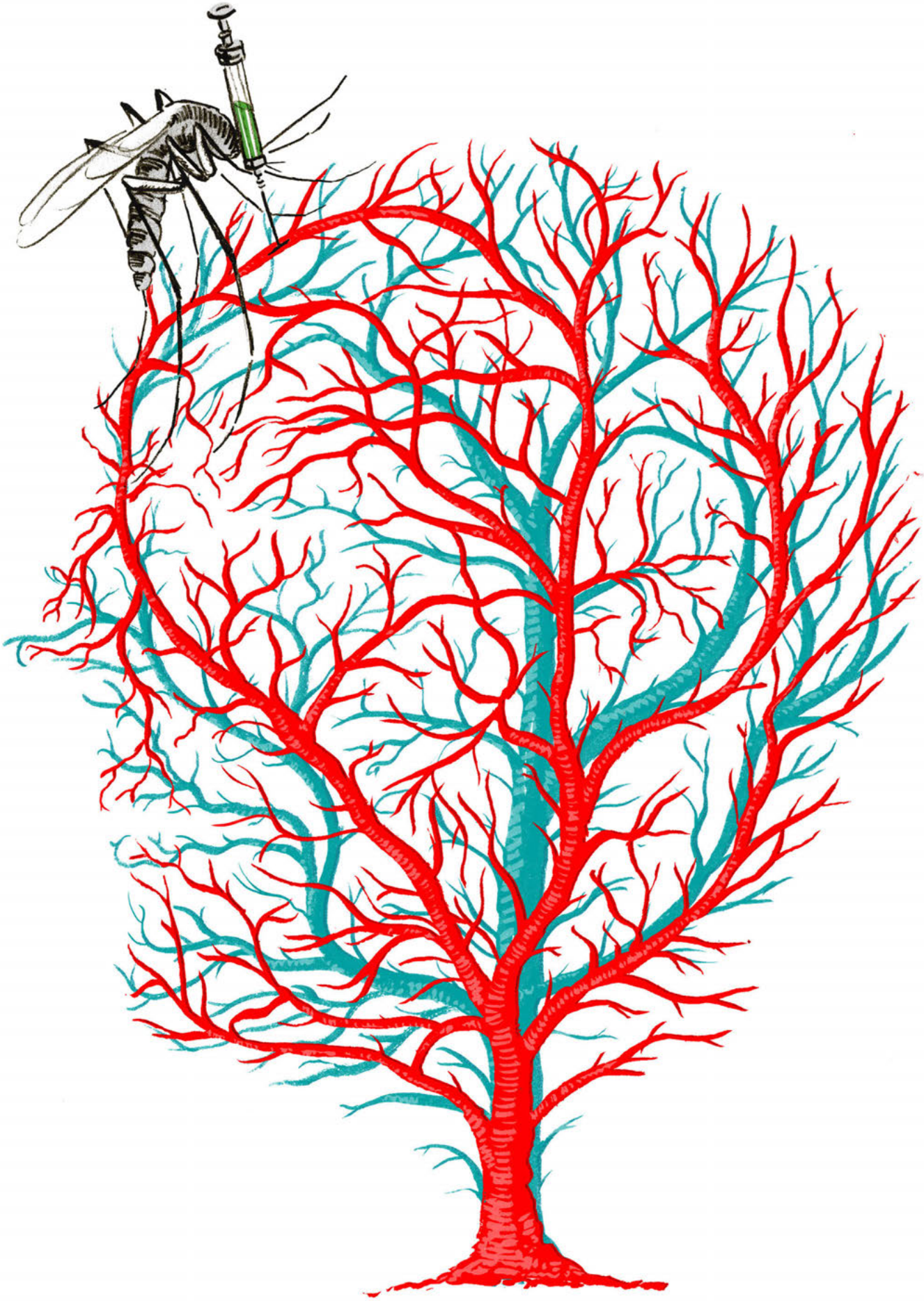
HOW WE'RE CROSSING PATHS WITH DISEASE-BEARING PESTS

By Bruce Goldman

ILLUSTRATION BY DANIEL HOROWITZ

Microbes don't own wings or legs, but they can rent them. Mosquitos transmit the agents behind malaria and dengue, two of the world's great tropical scourges.

Fleas carry *Yersinia pestis*, the menace behind the bubonic, pneumonic and septicemic plagues, collectively known in medieval times as Black Death. • While what mosquitoes, fleas, ticks and many other pests carry may vary, they all share a penchant for pawning off their infectious cargo on other animals, including us. In epidemiologic parlance, they're vectors, from the Latin word meaning "carrier." • Still, it takes two to tango. For every biter, there has to be a bitee. "We also come to them," says Eric Lambin, PhD, a Stanford professor of environmental earth system science who calls himself a "landscape epidemiologist." He tracks, among other things, how our shifting land-use patterns may be rendering us more (or less) prone to vector-borne diseases. • For the past eight years, Lambin, a senior fellow at the Woods Institute for the Environment, has been combining satellite mapping with house-to-house surveys and using computer analysis to crunch all the data thus obtained. The results — reports of the "spatialization" of risk factors for disease spread by animals — could lead to more precise predictions of infectious threats and help guide policymakers in infrastructure and emergency-response planning. • This matters because human activities are modifying large areas of the Earth, causing formerly cryptic pathogens to seemingly pop up out of nowhere. "Epidemiological approaches have often assumed the environment to be an unchanging space," says Lambin. But that's not the case. • New diseases have been emerging from swamps, forests and riversides at a rate of about one a year over the past four decades, according to the World Health Organization, which carefully tracks them. We have no genetically based resistance to these new diseases. Meanwhile, long-dormant epidemics have been awakening from their slumber, and some of those aren't exactly a walk in the park, either.



Not only landscapes but our connection to those landscapes have been transformed by hunting, farming and trading, not to mention high-speed transportation, global migration, urbanization, suburbanization and outdoor recreation: in short, civilization. Any change we make in where we go and when we go there in our daily lives can put us in some vector's path.

To get a more accurate understanding of the bridges that close the transmission gap between the pathogens and us, Lambin, now the George and Setsuko Ishiyama Provostial Professor in the School of Earth Sciences, became one of the first researchers to combine ground-level data with newly available satellite images of Earth in time segments of 10 years — an approach about a dozen other teams now pursue. It's how he found himself in Thailand eight years ago, peeking in water containers for mosquito larvae and getting the fish eye from opium-poppy farmers.

ZOOMING IN

Mosquitoes don't pollinate anything. They don't crowd out even more obnoxious competitors. Their only known utility is as food for other animal species about which the best that can be said is that they eat mosquitoes. Mosquitoes stink.

But each species of mosquito stinks in its own way. Mosquitoes of the genus *Anopheles* spread malaria. Those of the genus *Aedes* transmit dengue fever.

By far the world's most ravaging tropical parasitic disease is malaria. According to WHO, in 2010 there were some 219 million clinical cases of malaria and an estimated 660,000 deaths, mostly among African children.

Dengue fever, also transmitted by mosquitoes, is a flu-like disease widely spread throughout developing countries. While initial infection often proves asymptomatic or mild, it can be quite severe and multiple infections more so. WHO estimates 50 million cases of dengue infection occur each year.

In rapidly developing parts of the world, widespread land-use changes have had a notable impact on the resident mosquito population. In the mid-2000s, Lambin, in collaboration with colleagues including entomologists and epidemiologists, measured that impact in northern Thailand.

The study's location was ideal for investigating the relationships between land use, mosquito populations and disease transmission: a region encompassing three provinces in far northwestern Thailand where between 1989 and 2000 large areas of forest were cleared for slash-and-burn farming or for permanent fields (mostly orchards) and intensive irrigation farming. Interestingly, the study showed that the slashing of local forest ecosystems might simultaneously increase some mosquito populations and decrease others, thereby cutting down on one disease while abetting another's rise.

The investigators collected nearly 800 mosquito larvae in and around seven villages, pairing each sample with a description of its larval habitat, collection date and GPS-derived geographic coordinates accurate to within 10 meters. The researchers also inspected water-filled containers for mosquito larvae, which they preserved in alcohol and sent off to a molecular-analysis lab at the University of Leeds in England to be typed by species.

In each village, Lambin and his colleagues obtained epidemiological data for both malaria and dengue. Nearly 2,000 villagers volunteered blood samples and information on their sex, age, profession, birthplace, daytime and evening locations, housing conditions and use of preventive measures such as window screens and bed nets.

Not everyone was willing to talk, Lambin recalls. "As we were analyzing the satellite images in the hills northwest of Chiang Mai, we were detecting small forest clearings, far away from roads and villages, that were obviously cultivated. We were intrigued by this pattern, but found that whenever we interrogated local farmers about it they would shut down and, sometimes, walk away from the interview. We finally realized that these were opium-poppy fields — a small remnant of the old days when the Chiang Mai area was known as 'the Golden Triangle.'"

The incidence of malaria was so low that the scientists had to discard their data for that disease. But dengue incidence was climbing. Mosquitoes that transmit malaria need dense forests, which villagers had cut down and replaced with orchards. The ones that transmit dengue breed well (and their larvae thrive) in the standing water found in artificial containers villagers liked to use.

All this info, when crunched, allowed Lambin and his colleagues to develop a conceptual model representing interactions between people, the landscape and mosquitoes. According to the model, halving the density of artificial containers in villages during the wet season could significantly reduce the number of infective bites people would receive.

The model further predicted that improved disease-risk awareness and investments in preventive measures, like window screens and bed nets, could influence disease transmission at least as strongly as changes in mosquito populations. Using such prevention measures could counter even a doubling in total orchard area, resulting in the complete suppression of all bites by dengue-transmitting mosquitoes. (The local health agency subsequently promoted these simple preventive measures, but not many residents of remote, poor areas made changes.)

stanford woods institute

A HUB FOR ENVIRONMENTAL RESEARCH

HEALTHY PEOPLE AND COMMUNITIES need a healthy planet to sustain them. This fundamental understanding drives Stanford researchers who are seeking out solutions to the world's most pressing environmental challenges. • Several of the researchers featured in this issue, along with 145 other researchers and faculty members representing all of Stanford's seven schools — are pursuing environmental solutions as fellows and affiliates of the Stanford Woods Institute for the Environment.

THE INSTITUTE WAS ESTABLISHED IN 2006 with a gift from Stanford alumnus Ward Woods, '64, and his wife, Priscilla, to find ways to protect and nurture our planet, and to develop environmental leaders. The institute's programs emphasize interdisciplinary research targeting the most critical, complex environmental and sustainability challenges. The institute also convenes global experts and stakeholders to advance informed decisions about important environmental topics. • In June, the institute announced its latest round of grants through its Environmental Ventures Program, which provides seed funding to catalyze research in one or more of the Woods focal areas: climate, ecosystem services and conservation, food security, freshwater, oceans, public health and sustainable development. Each project receives funding of up to $100,000 per year for one or two years. Since the annual program began in 2002, it has awarded more than $7.2 million in seed grants to more than 50 projects. These initial grants have led to $39 million in follow-on funding from other sources.

Read more about these and other Stanford Woods Institute projects at: http://woods.stanford.edu/.

Lambin's expertise in tying observations from the sky to what can be seen only at ground level made him an ideal collaborator for a project that was to unfold on an other continent.

CHECKERBOARD JUNGLE

In 2012, the Kenyan Wildlife Service reported, Kenya lost approximately 360 elephants to poaching, up from 289 the year before. But an even bigger threat to big wildlife — and to us — is posed by rising human population densities and the conversion of land for growing crops.

If you look at a satellite image of the Amazon basin, says biology professor Rodolfo Dirzo, PhD, the Bing Professor in Environmental Sciences and director of Stanford's Center for Latin American Studies, you see dramatic disappearances of forested land. This civilization-driven deforestation is happening in Africa and East Asia as well, Dirzo says.

"But satellite imagery won't tell you anything about another rapid disappearing act going on in many parts of the world," he says. "And that is the disappearance of large and medium-sized animals. In the Brazilian Amazon, 15 million big animals are being lost each year."

This phenomenon is called defaunation. Dirzo has been doing fieldwork for decades, mostly in Latin America and mostly in tropical rainforests where human actions have reduced populations of peccaries, tapirs, giant anteaters, monkeys and jaguars. "When there's gradual loss of rainforest due to human encroachment, what's left is often not contiguous. Instead, you have little fragments, remnant islands of forest too isolated to maintain big animals. To be genetically viable, a jaguar population needs to consist of at least hundreds of individuals, and this implies an area of tens of thousands of acres."

We humans worry more about elephants, zebras, jaguars, camels, tapirs, hippos, giraffes and so forth than about their wimpier little mammalian cousins the rodents or, certainly, even less hirsute species from toads to nematodes. But from a pure health standpoint, does the relative abundance of big mammals actually matter to us?

The answer, it turns out, is yes. Defaunation changes the vegetation.

"Grasses grow, shrubs become more abundant," Dirzo says. Fewer large mammals also means more little ones. "When the big animals go, the population of small rodents tends to increase. Now throw in human habitation, and you have more grain, more shelter" — and, of course, a lower likelihood of getting stomped on. "Those rodents are about to have a wonderful life!"

Dirzo is the principal investigator for an interdisciplinary research project focused on Kenya. The study involves Lambin as well as Michele Barry, MD, professor of medicine, senior fellow at the Woods Institute and senior associate dean for global health in the School of Medicine.

"Studying how increased animal-human contact can facilitate the transfer of pathogens to humans could have huge public-health ramifications," says Barry.

At Mpala Research Center in Kenya's Nanyuki District, researchers from UC-Davis have set up "exclosures" surrounded by electrified fences that prevent a piece of a wildlife preserve in the savannah from being trampled by big animals. This simulates defaunation, Dirzo says. On other "control" patches, large animals are not excluded.

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ENVIRONMENTAL IMPACT

street smarts

USING CITIZEN-SCIENTISTS TO FIGHT FOR HEALTHIER NEIGHBORHOODS

Feliciana Jimenez, an 80-year-old with nine children, squints with a critical eye at the camera window of a tablet computer. Through this lens, she sees her street in a whole new light. She takes pictures of crumbling sidewalks and a construction worker's hose, coiled like a snake at her feet. She hits the record button on the tablet to describe how these hazards could cause seniors to trip and fall. She captures images of clogged sewer drains covered in stagnant water that could breed mosquitoes. As each hazard is recorded, the tablet saves its precise location on a map, using the device's built-in geographic positioning system. • Jimenez lives in North Fair Oaks, Calif., nicknamed Little Mexico by locals. It is a working-class community within Silicon Valley that has been passed over by the tech-driven gentrification that has lined streets of neighboring towns with shade trees, sidewalk cafes and farmers' markets. • To fight for a safer, healthier neighborhood, Jimenez volunteered to test two new devices — a customized tablet computer and a wearable camera — both of which can be used to notify city planners about things that need to be fixed and improved, from hardscapes to landscapes. • The benefits of these changes in the

By Kris Newby

PHOTO BY LESLIE WILLIAMSON

RIGHT: FELICIANA JIMENEZ

Documenting hazards in her neighborhood.


Custom
Catalytic conver
Stainless mufflers
2701

"built environment" — the man-made structures that define a place — go well beyond aesthetics: People who live in places that promote walking, socializing and eating fresh foods are physically and mentally healthier than those who do not.

Abby King, PhD, a Stanford professor of health research and policy and of medicine, initially developed the customized tablet for documenting neighborhood hazards as a way of helping San Mateo County with its Grand Boulevard Initiative, which aims to improve the safety and aesthetics of El Camino Real, the busy retail thoroughfare that runs through the county. As part of the new project, King and her team at the Stanford Prevention Research Center are creating a social blueprint for teaching residents and grassroots organizations how to persuasively communicate these community needs to city planners.

But in this era of government gridlock and dwindling funds, reworking the car-centric urban landscapes of the last century isn't going to be easy.

As Jimenez walks down her street, two Stanford researchers observe how she interacts with the tablet computer, looking for ways to improve it. Called the Stanford Healthy Neighborhood Discovery Tool, the simple-to-use tablet is loaded with software developed by King's team to track users' walking routes and geographically tag hazard locations, linking them with audio narratives and photographs. Afterward, it leads the user through a questionnaire about the walk.

As Jimenez stops to snap pictures of graffiti and an overflowing trash bin, the two researchers — Sandra Jane Winter, PhD, a Stanford postdoctoral scholar, and Priscilla Padilla Romero, MPH, MPP, a community partner from San Mateo Medical Center — take a few moments to show her how to verbally record her impressions of each neighborhood feature. They notice that the slick plastic tablet is hard for her to grasp, and that the tablet's screen is difficult to read in the bright sunlight.

After the walk, hazard images and location coordinates

the custom software tracks users' walking routes and geographically TAGS HAZARD LOCATIONS, LINKING THEM WITH AUDIO NARRATIVES AND PHOTOGRAPHS.

JIMENEZ'S STREET is lined with boxcar rows of postwar houses adorned with cast-iron grates on windows, brick fences and plaster lawn ornaments. Homes are mixed in with light industry — an auto repair shop, a welder and a cabinetmaker. Around the corner are small retail stores selling Mexican groceries, piñatas and quinceañera gowns in Easter-egg colors.

While most of the houses in the neighborhood are tidy and well-maintained, at midday the neighborhood has a glaring, hard edge to it. Looking at an aerial view of North Fair Oaks via Google's satellite map, it's obvious why — there are very few trees. North Fair Oaks' concrete-colored grid of streets forms a visible line against the emerald-green border of neighboring Atherton, the second most expensive real estate market in America, known for its meandering lanes shaded by live oak canopies.

can be uploaded to an online map, which can be shared with researchers, city planners, policymakers or others involved in the project. The walking routes of all participants are overlaid on the map, making it easy to identify the more frequently walked routes where repairs need to be made first.

Jimenez also wears a Microsoft SenseCam camera around her neck; it automatically snaps a picture of everything in her field of vision every 12 seconds. Later these images will be analyzed using software developed by King's collaborators at the British Heart Foundation Health Promotion Research Group in Oxford, England. The image-analysis software organizes these photos into discrete, time-coded activities, adding another layer of understanding to how people interact with their environment. For the purposes of King's studies, the camera's built-in GPS function provides information on distances and walkability to food sources, jobs and local

transportation. It also allows researchers to identify hazards that participants might have overlooked.

King's dream is that her tablet-based tool will provide a low-cost way for community advocates in places like North Fair Oaks to work with city officials to improve their neighborhoods. But before she launches it into the world, she and her Healthy Aging Research & Technology Solutions team need to collect more evidence to not only improve the tool, but to teach community groups how to use it.

KING FIRST became interested in ways to improve the quality of life for seniors while studying clinical psychology at Virginia Tech. As she began her postdoctoral work at Stanford University, she watched a beloved grandfather grow frail and slowly die. It motivated her to abandon her plan to work one-on-one with patients, and instead to look for ways to alleviate the suffering of aging populations on a larger scale.

"From when I first met her, Abby was passionate about getting older adults out there exercising as a way of preventing chronic disease," says Marcia Stefanick, PhD, professor of medicine and of obstetrics and gynecology, who has worked with King at Stanford since the early 1980s. "And since then she's been researching the best ways to leverage principles of human behavior to get people off the couch and out doing healthy things."

Recently King has been exploring the use of mobile technologies to encourage people to exercise more. Last year she developed a mobile phone app that appeals to the social nature of users, allowing participants to motivate each other to increase their walking throughout the day and to compare their team's performance to other teams'. Another app appeals to nurturing instincts by allowing users to adopt a virtual pet bird that exhibits either good health or bad, based on the daily healthy habits of its owner.

Behind King's latest idea, using the tablet to document neighborhood hazards, is growing evidence that improving a town's built environment results in happier, healthier residents. A key tactic is to get people out of their cars.

How to do that? Urban planners suggest clustering retail stores near mass transportation hubs, adding bike lanes and changing zoning rules to encourage more sidewalk cafes and fewer drive-through restaurants. Adding public squares, benches, farmers' markets and dog and people parks forges social connections, which in turn reduces crime and isolation-driven depression.

Enhancing the aesthetics of the pedestrian experience can also motivate people to walk more. Some proven strategies include widening sidewalks, adding pedestrian-oriented street lighting and creating green barriers to buffer the impact of traffic on shoppers. In addition, reducing the number of lanes can slow traffic and make crossing the street safer.

The health benefits of neighborhood walkability have been documented in a number of recent studies. For example, a 2004 study published in the *American Journal of Preventive Medicine* by Lawrence Franks, PhD, found that for each hour spent in a car each day, a commuter has a 6 percent greater chance of being obese than non-commuters. He also found that people who lived within walking distance of shops and businesses were 7 percent less likely to be obese.

Notably, another study involving regular exercisers (defined as those who exercised at least 2.5 hours per week), found that, even among this reasonably active group, those with long car commutes gained an average of 4.8 pounds over four years, 2 pounds more than their non-driving peers. This study by Takemi Sugiyama, PhD, was published in the February 2013 issue of the *American Journal of Preventive Medicine*.

ABOUT A YEAR AGO, King and her team tested the precursor to the tablet within a population of 400 seniors in East Palo Alto, a town 5 miles from North Fair Oaks. This study looked at ways to better inform city planners about the physical barriers to fresh-food sources. Both North Fair Oaks and East Palo Alto have median household incomes of about $50,000, below the California average. These cash-strapped cities with lower tax bases haven't had the luxury of investing in as many infrastructure improvements as their wealthier Silicon Valley towns, and the health of their populations has suffered.

In February, King's team celebrated its first success, after being contacted by Brent Butler, planning manager for East Palo Alto.

"Some of the street issues that this Stanford study brought to our attention have been added to our comprehensive sidewalk inventory and repair program," says Butler.

These suggestions were influential in the city's addition of countdown timers to crosswalks on its main thoroughfare, University Avenue, to ensure that seniors and children allow enough time to cross. The study also helped the city document sidewalk obstacles that impede movement of people using wheelchairs, walkers and strollers.

Some of these future improvements may be funded by an unexpected patron, the new kid in the 'hood, Mark Zuckerberg,

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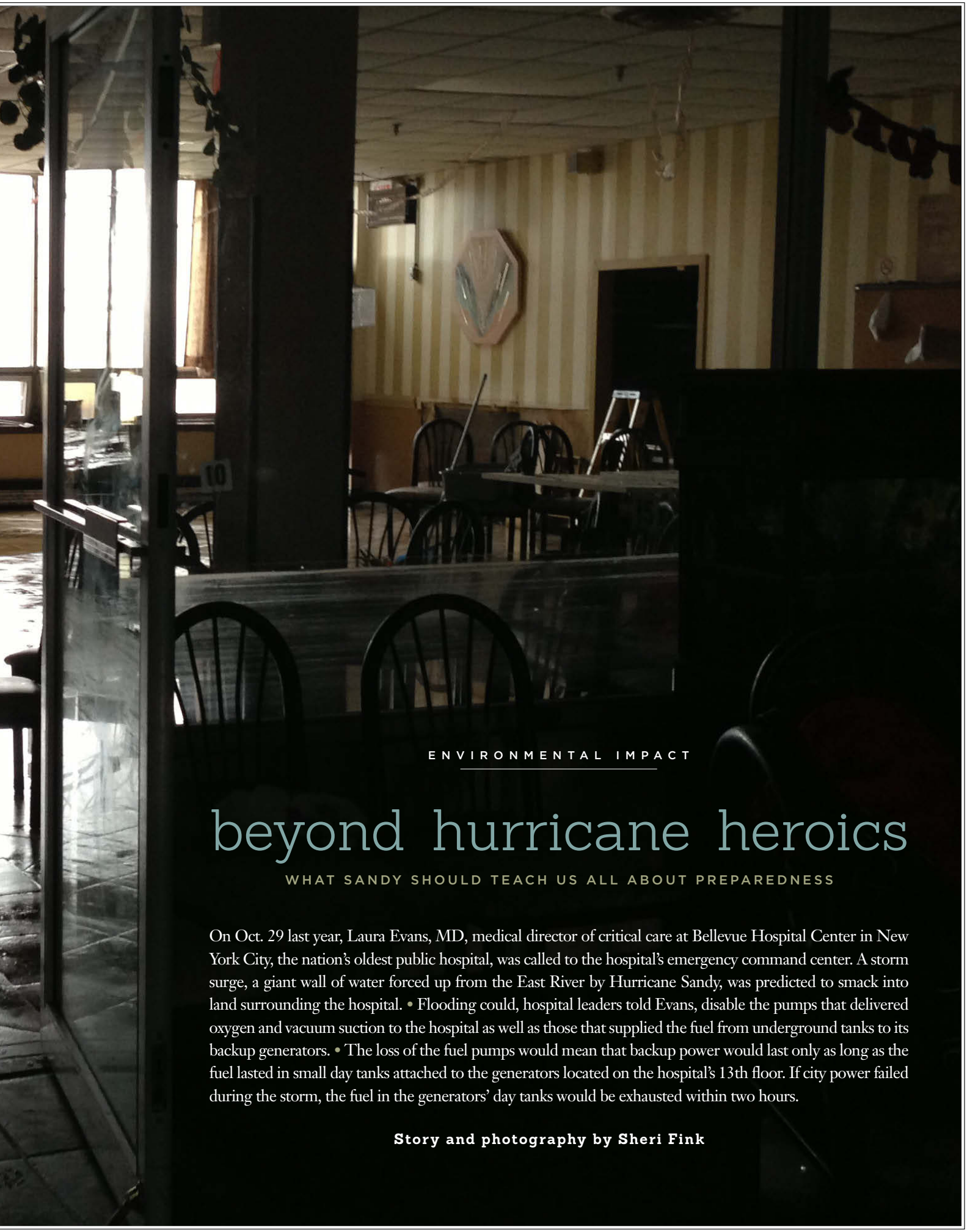
INSIDE THE SEAVIEW MANOR HOME FOR ADULTS
in Far Rockaway, Queens, on Oct. 30, 2012, as the home prepared to evacuate its 124 residents.



ENVIRONMENTAL IMPACT

beyond hurricane heroics

WHAT SANDY SHOULD TEACH US ALL ABOUT PREPAREDNESS

On Oct. 29 last year, Laura Evans, MD, medical director of critical care at Bellevue Hospital Center in New York City, the nation's oldest public hospital, was called to the hospital's emergency command center. A storm surge, a giant wall of water forced up from the East River by Hurricane Sandy, was predicted to smack into land surrounding the hospital. • Flooding could, hospital leaders told Evans, disable the pumps that delivered oxygen and vacuum suction to the hospital as well as those that supplied the fuel from underground tanks to its backup generators. • The loss of the fuel pumps would mean that backup power would last only as long as the fuel lasted in small day tanks attached to the generators located on the hospital's 13th floor. If city power failed during the storm, the fuel in the generators' day tanks would be exhausted within two hours.

Story and photography by Sheri Fink

Clockwise from top left: Sand-filled entryway of Promenade Rehabilitation & Health Center in Rockaway Park, Queens, after Sandy; National Guard soldiers carry a patient down a stairwell at Bellevue Hospital on Nov. 1, 2012; water gushes out of a pump at Bellevue as ambulances idle and wait for patients during the evacuation on Nov. 1.

Nearly all of the patients in Evans' 56-bed adult intensive care unit relied on equipment that ran on electricity. Many were on life support, or had intravenous drips that regulated their heartbeats and blood pressure. Some had intra-aortic balloon pumps that helped keep their blood flowing. "It was really terrifying," Evans says.

The command team had limited good news. They believed the generator in the building next door, supplied by a separate fuel pump, would continue functioning. They could use it to power exactly six outlets in the intensive care unit. Hospital leaders turned to Evans. They would continue looking for a way to keep all vital equipment powered — but if they failed, which of her very sick patients should be given access to one of the precious six power outlets?

"Laura," one hospital official said, "we need a list."

PROFESSIONALS, PATIENTS and their loved ones in New York City hospitals, nursing homes and adult-care facilities might reasonably have believed they were safe as Hurricane Sandy approached. While many of the facilities sat beside tidal rivers and the ocean in low-lying "Zone A" areas of the city, Mayor Michael Bloomberg had exempted them from his pre-storm evacuation order for the general population. They could, instead, "shelter in place."

But anyone following the recent history of how hospitals and nursing homes have fared in American disasters had ample reason for concern. The images of the hurricane spinning toward my city, and the knowledge that thousands of New York's most fragile residents would be left in its path, in facilities that were not hardened to withstand significant flooding or power outages, made my stomach sink.

In many New Orleans hospitals after Hurricane Katrina in 2005, floodwaters knocked out vulnerable backup power systems. A day later, still awaiting rescue in intense summer heat, doctors at Memorial Medical Center were so desperate, they intentionally hastened the deaths of some patients by injecting them with morphine and midazolam, one or both detected in at least 18 of the 45 bodies ultimately found at the hospital.

How could other hospitals in a

Over the past five years, I've reported on the impact of disasters on hospitals and medical systems, from Hurricanes Katrina, Gustav and Isaac in New Orleans to Tropical Storm Irene in New York. I've just written a book about this subject, *Five Days at Memorial: Life and Death in a Storm Ravaged Hospital* (Crown) — due out this September. When Hurricane Sandy approached, I reported from New York City's hospitals and nursing homes. One question stuck with me: After everything we've learned about those horrific days in New Orleans, how could other hospitals in a major American city end up without power, their workers fighting to keep alive their most desperately sick patients?

I came away with the firm belief that America's medical infrastructure remains extremely vulnerable to natural hazards, and there is an urgent need for disaster planners to involve the larger community in deciding how resources are allocated — both in preparing for disasters and in responding to extreme triage scenarios like the ones faced by Evans and by the physicians who served after Hurricane Katrina.

LESSONS FROM THE LAST BATTLE?

The health commissioners for New York state and New York City are hands-on leaders with substantial experience. City health commissioner Thomas Farley, MD, was working in New Orleans at Tulane University at the time of Hurricane Katrina. New York state's commissioner of health Nirav Shah, MD, based himself with the team at New York City's emergency operations center.

Before Tropical Storm Irene struck in 2011, Farley and Shah helped oversee the transfer of roughly 10,000 patients from seven New York City acute-care hospitals and 39 nursing, psychiatric and adult-care homes in partnership with the city agencies and public and private medical organizations.

"We were not confident any could withstand flooding on the first floor without a loss of power and an inability for them to be rescued quickly," Farley told me at the time, in September 2011. "Our assessment was it was safer for them to evacuate than stay in place."

Shah's stance was similar. "It was the right decision," he told me just after the 2011 storm passed, even though the health facilities did not end up flooding and the move turned out not to have been necessary. "Imagine what would have happened if there was an 8-foot surge? All those places would have been under water and would have been really on little islands right now."

As Sandy was churning up the coast, I asked both men why a different decision was being made, with the storm surge expected to be even higher. Health officials elsewhere in New York and in other states mandated that patients be moved away from the water. Shah said he felt confident that if anything should go wrong, the city was ready to respond quickly. The commissioner of the city's Office of Emergency Management, Joseph Bruno, sounded similarly sanguine. "I'm very confident in the way it's been handled," he said.

The officials had instructed vulnerable nursing homes to move residents to higher floors and to transfer roughly 100 residents who required mechanical ventilators to help them breathe. The state also ordered nursing homes to staff their facilities at more than 50 percent higher than usual. Health and emergency officials surveyed the facilities before the storm "to eyeball generators," watch them be turned on, and assess fuel and food supplies, Shah said.

However, they did not check whether the generators were vulnerable or protected against the floodwaters that might be unleashed by a storm surge. And they did not advise evacuation for any of the dozens of facilities where, state databases show, deficiencies had been noted in nursing home backup generators, wiring, maintenance and preparedness measures, including evacuation plans.

Shah pointed to the substantial risks involved in pre-storm evacuations for vulnerable patients. "It's extremely agitating," he said. "We learned there's a risk-benefit of moving people versus sheltering in place."

It's true there have been fatalities in pre-storm evacuations. A bus carrying nursing home residents away from Houston in advance of Hurricane Rita in 2005 overheated and burst into flames, igniting oxygen tanks and killing 23 people. When New Orleans implemented citywide hospital and nursing home evacuations prior to Hurricane Gustav in 2008, many patients were transferred to Baton Rouge, which was harder hit by power outages from the storm, necessitating the re-transfer of a number of patients. More research needs to be done on the health effects of evacuation, particularly comparing those transferred in a controlled way prior to a storm and power loss, versus those moved in the chaotic midst of a disaster.

major American city find their workers fighting to keep alive their most desperately sick patients?

Some observers suspected another factor might have been considered. It is expensive for hospitals and nursing homes to shut their doors proactively. New York City health-care facilities were, at the time of Sandy's approach, awaiting reimbursements in the millions of dollars for the ultimately unnecessary evacuations the city and state had mandated before Irene. The thought that this could occur again was, at the least, an unpleasant one. Shah said financial considerations played no part in the evacuation decision-making.

THE IMPACT

Three major hospitals in New York City lost power and had to be evacuated during or after the storm, including Bel-

levue and Coney Island hospitals, both run by the city, and the private New York University Langone Medical Center. The Veterans Affairs New York Harbor Healthcare System evacuated in an orderly fashion before the storm arrived.

At least 29 nursing and adult-care facilities in Queens and Brooklyn were severely flooded. Generators failed or were absent. At Horizon Care Center in Arverne, near the Atlantic Ocean, the water rose to knee height on the first floor within a span of five minutes, according to administrator Nicole Markowitz. The backup generator worked for only about 10 minutes after the power failed. Overnight, it was hard to change patient diapers in the dark. The next morning, elderly residents sat in chairs in chilly, dim, foul-smelling hallways.

In all, more than 4,000 nursing home and 1,500 adult home residents in New York City endured up to three days in cold, dark surroundings before being rescued, often hauled down staircases on disaster sleds carried by first responders.

The long-term health effects on vulnerable patients remain to be calculated. Officials have not examined whether the death rate increased in residents who scattered across the region. One member of a team of researchers who wish to study these issues said this spring that she had not yet been given access to needed data by state officials.

MAKING SENSE OF THE DECISIONS

"It's worth looking at what would be the costs and advantages of making hospitals a little more capable of withstanding a flood of a certain height," Commissioner Farley told me after Tropical Storm Irene. But it took until June 2013 for the city to release a comprehensive plan to protect health infrastructure — part of a $20 billion proposal to prepare New York for future storms — and most improvements would not need to be in place until 2030.

The question is: Who pays to harden the systems? Many hospitals were built years ago to different building codes and then expanded with additions. Hospital wiring diagrams I've reviewed in Katrina hospital-liability cases look like masses of spaghetti.

Raising generators above flood level is just the first step in protecting a hospital's backup power. Often, transfer switches and other elements of the electrical systems and fuel and water pumps need to be moved or made submersible as well.

Some say flood-proofing these systems should be considered public investments. Others argue it is unreasonable to expect hospitals to gird against all foreseeable, but unlikely, catastrophes.

Ironically, only now is the New York City Health and Hospital Corp. eligible to receive substantial federal funding to make those improvements to its disaster-struck hospitals and health-care facilities. According to corporation president Alan Aviles, the costs of repair and improvements will exceed $800 million — much higher, presumably, than the cost of prevention.

Perhaps hospital accreditation standards and electrical codes should also be tightened. Currently, hospital backup generator system codes and standards are more oriented to short-term power losses like those that might occur when a tree branch falls and cuts off city power for a few hours. Generators must be tested under load for only short periods. There is no dress rehearsal for the days-long outages that are likely to follow a severe disaster like a hurricane. Often it takes a real crisis for hospital engineers to discover problems — for example, difficulty switching back from generator load to city electricity.

Even if backup systems ran for longer periods, at many hospitals, they are not designed to power critical functions, particularly heat, air conditioning and ventilation. Hospital standards do not require this and are "not always sufficient" in major catastrophes, according to a post-Katrina warning issued by the largest hospital accreditation body, the Joint Commission.

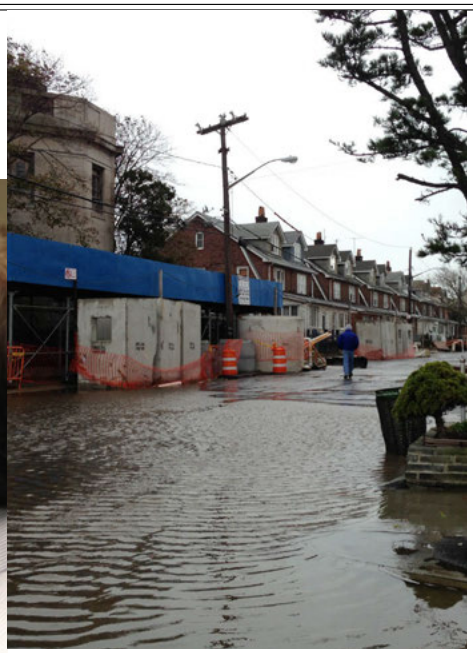
Nor is there a standard for how the flow of information is to be handled. In New York there was no central place for relatives of hospital patients and nursing home residents to find out where their loved ones were or whether they were safe. Many endured a prolonged, tortured limbo.

Hospital backup generator system standards are more oriented
There is no dress rehearsal for days-long outages.

DOING BETTER

At a Hurricane Sandy medical meeting sponsored by the Institute of Medicine and the New York Academy of Medicine in April, many speakers noted the ingenuity, hard work and willingness to endure hardship on the part of the city's medical professionals. "The amount of heroism that arises during situations like this cannot be overstated," Irwin Redlener, MD, head of the National Center for Disaster Preparedness at Columbia University, said.

Clockwise from top left: Scott Strauss, North Shore-LIJ Health System's director of corporate security and emergency management, left, and Mark Solazzo, chief operating officer, at the health system's command center, Oct. 30, 2012; a street in the Rockaways, Oct. 30; preparing to cut power to Ocean Promenade Nursing Center to repair transfer switches corroded by seawater.



But Redlener saw a problem with that. "We need to wonder why we needed so much heroism," he said.

From my observations of multiple disasters, health system preparedness needs to occur on multiple levels: the physical, organizational and personal. This might involve investing in infrastructure improvements, purchasing a stock of emergency ventilators, or planning for alternate care spaces where patients can quickly be moved and treated. It can mean looking at what disposable equipment can be reused in an emergency, making sure there are redundant communications for when the cell phone towers go down, and having contingency plans for reaching home-based patients and stocking them with everything they might need before a crisis.

to short-term power losses.

Preparedness might include setting up a quiet space and a schedule of sleeping shifts and insisting that staff members get enough rest to be able to function. Plans are needed to ensure that even when the very fundamental technologies fail, the medical staff maintains the rhythm of patient care, the best possible sense of normalcy in a most abnormal situation.

Above all, a good response requires flexibility and situational awareness: making sure actions match up with the actual conditions, not just the plan.

THINKING CREATIVELY

As Sandy intensified outside of Bellevue Hospital, Laura Evans, the critical care medical director, brought news of the expected power outage back to her ICU staff. Choices had to be made about which patients would have access to the six power outlets that might keep working even if every other outlet died. Evans had studied New York state draft guidelines on how to allocate ventilators in a severe respiratory pandemic using a scoring system that estimates how severely ill someone is. She repurposed these plans to help guide the decision-making.

Evans pulled together an ad hoc committee to make the choices. "This isn't a role for one person," Evans told hospital leaders. Her committee was composed of professionals who had no patients that would be affected by the decisions. In this way, direct providers would be free to do what their ethical duty required. "If you're the primary doctor," Evans says, "it's your job to advocate for your patient." The committee, by contrast, could take a wider range of factors into account and choose fairly according to transparent scoring guidelines. The committee included not only doctors, but also ethicists and nurses. It did not, however, include representatives of patients or their families.

The decisions about the power outlets and the reasons for them were communicated to fellow providers. Some chal-

Clockwise from top left: A grounded boat on Cross Bay Blvd. in Broad Channel, Queens; Hurricane Sandy's storm surge pushed part of a boardwalk against Promenade Rehabilitation & Health Center in Rockaway Park, Queens; author Sheri Fink.

lenged the choices, but in the end they accepted them. All of this was accomplished — a list of patients, moving them between beds — within about two hours.

As she prepared the plan, Evans thought about how she would feel the next day if it had to be implemented. She wanted, she said, to "have a process that we can describe, that is transparent," that was applied to all patients the same way, "as fair and equitable as it can be." She wanted to look back and be able to justify the decisions they were making, to maintain the trust of the larger society that might examine them. Medical professionals are used to the illusion of control, she said, and "having a system and procedures gave us a sense we had some control of the situation."

That night, as Evans and her colleagues were completing their list, the lights flicked out. City utility power had failed. It took about seven terrifying seconds for power from the backup generators to kick in and get things functioning again. Soon after, Evans received a call from the hospital's command center. Except for those six outlets, all power would be lost in the next hour to 90 minutes, hospital leaders believed. Millions of gallons of floodwaters were filling the basement of the 25-story hospital to what would reportedly reach a height of more than 4 feet and more than double that in some areas. Water gushed into elevator pits with enough force to remove elevator doors from their moorings.

Evans and her colleagues stationed two health professionals at the bedsides of all patients who relied on ventilators, preparing to squeeze oxygen into their lungs manually with flexible Ambu-bags. Bright orange extension cords connected to the backup generator system snaked through patient corridors. Nurses counted drops on IV pumps, so that if everything failed, they could go "old school" and give vasopressors by drops per minute.

At several hospitals across the city, doctors and other staff were scrambling, too, contemplating and preparing for the possibility of a complete power outage — a scenario that they had not, in some cases, fully anticipated in previous disaster drills and plans. At the emergency command center for the North Shore-Long Island Jewish Health System, doctors took to a white board to sketch out clinical priorities ("cohort patients," "establish clinical command structure," "triage") for two threatened hospitals as waters rose around them.

Evans wanted to look back and be

At Bellevue, communicating about the triage decisions with patients and their family members was the most challenging aspect of the scenario, Evans said. She and her colleagues could not imagine how to inform those who would not get power outlets, and they put off the task. Looking back, Evans feels the families had a right to know. Preparing for such communication is a high priority for the future. Rarely do triage protocols or standards of care offer guidance on how and whether to inform viable, aware patients or the

PORTRAIT OF SHERI FINK BY JEN DESSINGER

family members of patients who are triaged not to receive potentially life-sustaining resources. Also, the staff did not think about asking whether any of the selected patients or their families might wish to volunteer to give up a power outlet so that it could be provided to someone else. "It wasn't even on my radar," Evans says.

Some guidance does exist on questions of resource allocation in disasters, now commonly called "crisis standards of care." These are guidelines that lay out which patients should — and should not — receive hospital resources that are in short supply in an emergency.

For example, should the most ill be prioritized, because they are more dependent on medical technology? Or should the less seriously ill patients be prioritized? They could arguably endure more hardship, but they might have better survival chances, making saving them a more efficient way of doing good. What about neonatal intensive care unit babies who are fragile and have, if they survive, a whole life ahead of them? Or the elderly with multiple medical problems and poor prognoses, but who were the wise family matriarchs and patriarchs who inform and inspire, who have served others throughout their lives?

What of medical professionals themselves who may be exposed to higher risks and whose work may be so needed after a disaster? Should they be prioritized? What about support staff? What about hospital supply delivery truck drivers? Where to draw the line?

Clearly these are questions of values as much as they are of medicine. Disaster planners are increasingly realizing that the larger community must be involved in answering them — as an example, in 2012 the Institute of Medicine released extensive community planning guidance for engaging the public in the development of crisis standards of care. Some existing protocols even call for removing patients from ventilators if they do not improve after a certain trial period when ventilators are in extremely short supply. But there hasn't been much research on this. Based on data from recent flu seasons, a few small studies have found that most patients who would have been assigned a lower triage priority if the protocols had been implemented actually recovered and survived when they received full treatment. In other words, there was slim if any evidence that the traumatic prospect of taking away ventilators or other resources from patients with a lower triage priority actually would have saved more lives.

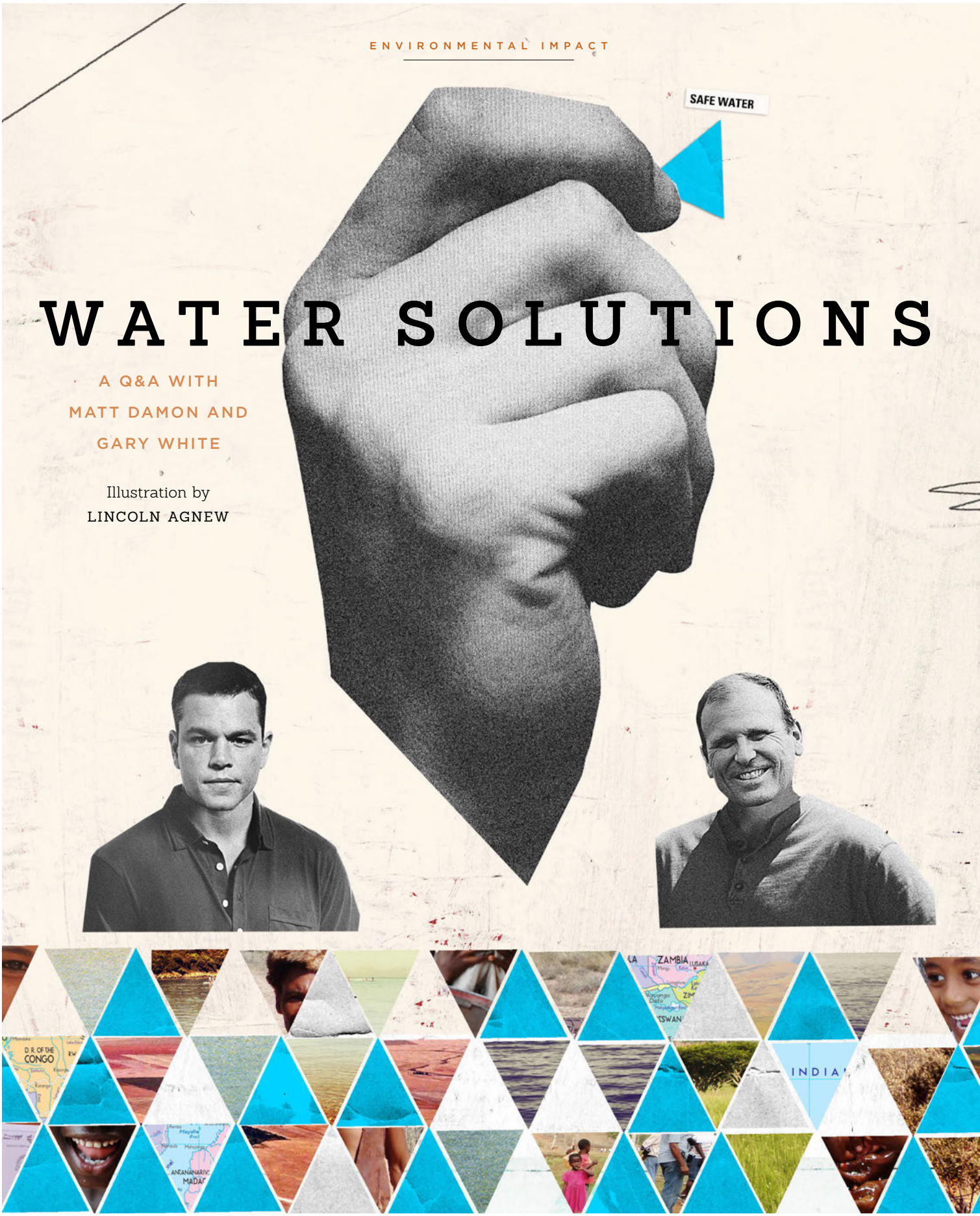
Sometimes the most important aspect of triage is remaining alert to the possibility that rationing won't be necessary, or can be minimized — doing everything possible to avoid the need to make such wrenching decisions. In the end, it was improvisation that made the biggest difference at Bellevue after the generator fuel pumps failed. Volunteers, soon replaced by National Guard soldiers, formed a chain and hand-carried fuel up 13 flights of stairs to feed the generators manually until everyone could be transferred out of the hospital. Swift thinking prevented the backup power from failing. It prevented those horrible choices from having to be made. Evans' patients were all maintained on backup power until they were transferred to other hospitals.

Hours later, climbing one of Bellevue's long staircases, I passed personnel in blue scrubs carrying a baby in a transport incubator down to a waiting ambulance. Other staff huffed and puffed up the steps with supplies. The smell of diesel wafted into patient corridors. The situation balanced just on the edge of control. Fortunately, dramatic scenes like this do not occur often. But being in New York for Sandy was a reminder that disasters can arise anywhere, at any time, and that they can change the lives of medical professionals, their patients and their families forever. Across the country many hospitals in flood zones have electrical backup power systems in their basements. Others, in earthquake zones, were constructed before modern building codes. Others are simply situated in tornado alley. We need to think more about the dilemmas we might face and how we can prevent or minimize them. It benefits everyone to prepare.

able to justify the decisions, to maintain the trust of the larger society that might examine them.

Sheri Fink, MD, PhD, a graduate of Stanford's School of Medicine, won a 2010 Pulitzer Prize in Investigative Reporting for her story The Deadly Choices at Memorial *(co-published by* The New York Times *and* ProPublica*) about decisions made by the medical staff of a New Orleans hospital in Hurricane Katrina's aftermath. Her forthcoming book is* Five Days at Memorial: Life and Death in a Storm-Ravaged Hospital *(Crown, 2013).*

An earlier version of this story appeared on ProPublica: "*In Hurricane's Wake, Decisions Not to Evacuate Hospitals Raise Questions,*" *Nov. 1, 2012. — Contact Sheri Fink at medmag@stanford.edu; follow her on Twitter at @sherifink.*



WATER SOLUTIONS

A Q&A WITH MATT DAMON AND GARY WHITE

Illustration by LINCOLN AGNEW

"Water, water, every where,
And all the boards did shrink;
Water, water, every where,
Nor any drop to drink."

THE RHIME OF THE ANCIENT MARINER

Remember that iconic poem you read in high school? The poet, Samuel Taylor Coleridge, was musing then about sailors lost at sea. But those words written in 1834 could also be speaking about a crisis in the world today.

Globally, 780 million people have no access to safe water, and 2.5 billion lack access to toilets and sanitation. Overwhelmingly, women and girls in the developing world are most severely impacted by this crisis. That's why Water.org, the nonprofit co-founded by actor Matt Damon and civil engineer and water specialist Gary White, uses a gender lens when designing solutions — prioritizing women as the change agents in their communities.

When you travel to some of the world's poorest countries, it's women who are walking the dusty roads carrying water jugs. And it's because women bear the main responsibility for keeping their households supplied with water, caring for the sick, maintaining a hygienic home environment and bringing up healthy children that Water.org says women are a critical part of developing comprehensive solutions.

Paul Costello, *Stanford Medicine*'s executive editor, hosted this Q&A with Water.org's co-founders to find out how they intend to solve the global water crisis.

COSTELLO: Matt, you could have chosen any issue to get involved in. What was it about water that stirred your passion?

DAMON: The enormity of it. Water underpins everything. My personal moment came in early 2000 on a trip to Zambia. I went on a water collection with a 14-year-old girl from a village I was visiting. It was a long walk, and we talked about her hopes and plans; she said she was going to go and live in the big city and become a nurse. After she told me about her plans, I realized that if someone had not possessed the foresight to sink a bore well near where she lived, she wouldn't have been able to go to school and she would have spent most of her time scavenging for water. It just hit me how profound an impact access to safe water has on an individual, a family and an entire community. I just can't think of a cause that has a larger impact than access to safe drinking water and basic sanitation — especially for women and girls.

COSTELLO: Why especially women and girls?

DAMON: Women and girls spend about 200 million hours a day securing supplies of water resulting in significant losses in productivity. In addition, inadequate sanitation — lack of toilets — in schools leads to significant absenteeism of young girls. When not in school, girls often have to seek sanitation in the early morning or late at night to gain a small amount of privacy, risking their personal safety.

COSTELLO: Currently there are 780 million people without access to safe water and 2.5 billion without access to sanitation. Gary, what's the human cost?

WHITE: Every 21 seconds a child under 5 succumbs to a preventable, waterborne illness. Solving the water and sanitation crisis is the single most cross-cutting investment opportunity to alleviate poverty, increase women's empowerment, advance early childhood education and improve basic public health. According to the World Health Organization's *The World Health Report 2002*, halving the proportion of those globally without access to safe drinking water and adequate sanitation by 2015 would result in an estimated 272 million more school attendance days a year, and the value of deaths averted, based on discounted future earnings, would amount to $3.6 billion a year.

COSTELLO: What are biggest challenges related to water and sanitation globally?

WHITE: Lack of awareness or understanding of the crisis is one obstacle. It is difficult for people who are accustomed to reach out and turn on a tap when they want a drink of water to fully grasp the magnitude of the crisis. In industrialized countries, the richness of our water security is nearly invisible — while in many developing countries, a real-time tragedy is unfolding.

Another obstacle is the traditional model of charity itself. It would require $200 billion in capital to solve the global water and sanitation crisis in the next five years. The total per year of external investment and aid flowing to the developing world is about $9 billion. One of the challenges is that much of these investments are made in the form of aid and subsidies that bypass those living in poverty. The situation is compounded by the fact that most non-governmental organizations do not segment the market — everyone is viewed as equally poor and requiring aid. Given the inverse relationship between the level of subsidy and sustainability of water infrastructure, this type of approach has no real prospect of driving scalable and sustainable solutions. Therefore we must think carefully about how to deploy charity and where market-based models can really make a permanent difference.

"WHEN YOU SEE THE DIFFERENCE THAT WATER can make in a community, that feeling of pure joy — there's nothing really that can compete with that in my day job." — MATT DAMON

COSTELLO: Is the problem that there's just not enough water?

WHITE: Ultimately, there is enough water on the planet for everyone. If every person in the world who currently lacks a safe water supply secured 50 liters of water for basic daily use, it would take a mere fraction of 1 percent of the world's water resources to provide it.

CONTINUES ON PAGE 45

FROM STUDIES OF FRUIT FLY EMBRYOS,
A SKIN CANCER TREATMENT

WINNIE'S TALE

THREE YEARS AGO, 101-YEAR-OLD WINNIE BAZURTO NOTICED A STRANGE GROWTH ON HER LOWER EYELID. She didn't worry about it initially, but in 2012 it started getting bigger, fast — doubling in size every two weeks and growing into the orbit of her right eye, restricting her vision. • Diagnosed as basal cell carcinoma, the most common skin cancer, her main concern was that the painful growth would infiltrate the eyeball, possibly causing blindness. Bazurto's options for treatment didn't look good. Although still healthy, her age meant she was not a candidate for the eight-hour surgery necessary to remove the growth, or the alternative — six weeks of radiation treatment. But she was reluctant to lose the sight in her right eye and, along with it, much of her independence — not to mention her ability to watch a fastball on the television set. • Then a third option emerged: a new drug approved by the U.S. Food and Drug Administration in January 2012 called vismodegib (brand name Erivedge) to treat inoperable basal cell carcinomas. • Like most patients prescribed a new drug, Bazurto knew little about the story behind its origins. The Genentech-developed drug is the first class of drugs approved by the FDA that works by inhibiting one of the key regulators in human development: the hedgehog molecular signaling pathway. • Considered a landmark in cancer treatment, it's hoped there will be many more hedgehog-inhibiting drugs to come for the treatment of other invasive cancers — not just inoperable basal cell carcinomas like Bazurto's, but pancreatic, esophageal and ovarian cancers as well.

"That's the exciting part about this drug," says Anthony Oro, MD, PhD, a professor of dermatology at Stanford who was part of the original hedgehog cancer studies, and involved in the study that led to the approval of the drug, nicknamed vismo. "Now, hopefully, we will develop more of these types of drugs for other cancers in a faster cycle time." • Faster is the key word here, considering that more than 30 years of scientific research lie behind the development of the little pink-and-gray vismo pills offered to Bazurto by her dermatologist Jean Tang, MD, PhD, assistant professor of

By Tracie White

PHOTOGRAPHS BY LESLIE WILLIAMSON

WINNIE BAZURTO

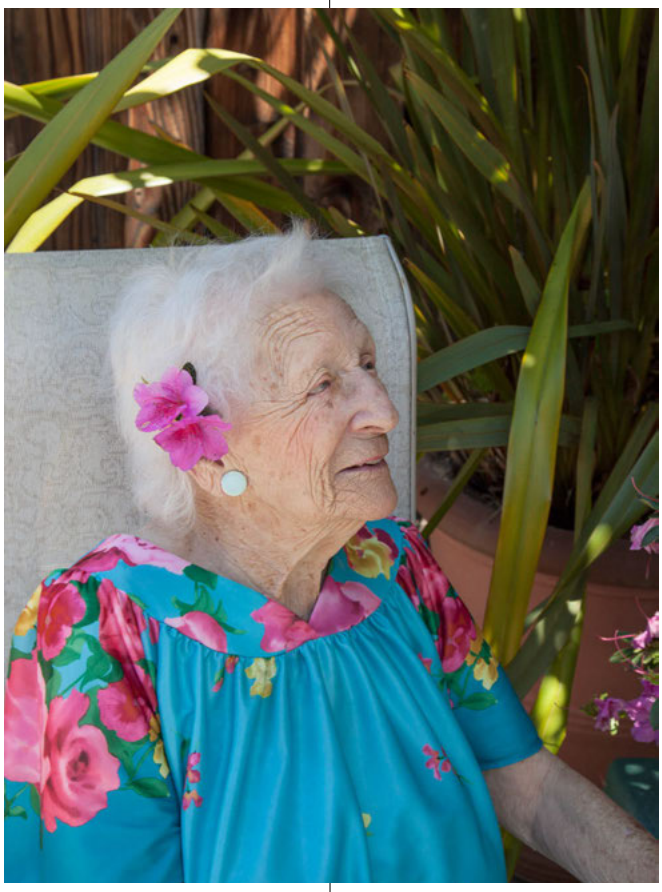
At 101, she has benefited from a cancer treatment decades in the making.

dermatology — one of the many scientists at Stanford and around the world involved in research that led to the drug's development.

For Bazurto, the new drug sounded like a good option. She agreed to give the pills a try.

The story behind the development of vismo is a 30-year history of scientific discoveries, one building upon the next, as they emerged from the laboratories of biologists who were working to understand how genetic pathways affect the development of life.

The drug's origins date back to a scientific quest in the 1970s to answer a crucial question of developmental biology. Scientists knew that a developing embryo started out as a ball of identical cells, but nobody yet understood how these cells knew when or where to grow body parts, such as arms and legs.



Scientists wanted to understand the mystery of embryogenesis.

It was the result of fruit fly studies by scientists Christiane Nüsslein-Volhard, Edward Lewis and Eric Wieschaus that eventually provided the answer — winning them the Nobel Prize. In their studies of thousands of newly created mutant fruit fly strains, the scientists identified more than 50 genes needed to control the formation of the embryo, including one they named hedgehog. The hedgehog gene was found to regulate the organization and pattern of fly body parts. (They named it hedgehog because, when mutated, the gene caused the flies to grow a coat of spines all over their undersides.) Remarkably, other researchers identified a similar gene in humans and other vertebrates, indicating that the gene had been present in common ancestors more than half a billion years ago.

These major discoveries excited the scientific community, triggering a new round of research to determine exactly how genes control the growth of animals. One of those scientists, who would prove to be a key player in the history of hedgehog research, was Matthew Scott, PhD, professor of developmental biology at Stanford.

"Scientists wanted to discover how all the molecular switches, gears, pipes, transport systems — all sorts of machinery — worked to control the organization of embryos during their development. The hardware — genes and proteins like hedgehog — is deployed somewhat differently in different animals, like species-specific software, to give rise to the vast diversity of animal forms," Scott says.

Sixteen years after the fruit fly discoveries, in 1996, Scott and a team at UC-San Francisco led by Ervin Epstein Jr., MD, professor of dermatology, made another huge discovery that would connect the hedgehog pathway and certain cancers. They discovered that defects in hedgehog or related genes were present in two cancers: basal cell carcinoma, the most common human cancer, and medulloblastoma, a highly malignant pediatric brain tumor.

"These genes, discovered first in flies, tell the cells of a growing embryo when and where they should divide," Scott says. "If the system breaks down, cells will divide when they should not, and that's cancer."

A new round of research took off. Scientists set out to discover therapies that could treat certain cancers by blocking the hedgehog pathway when it had gone awry.

SIXTEEN YEARS LATER, IN APRIL 2012, Bazurto, who lives in San Mateo, Calif., started taking the daily vismo pills with the hope of saving the sight in her right eye.

Bazurto has seven grandchildren, nine great-grandchildren and two great-great-grandchildren. She's survived the Depression, the recent recession and three husbands. She took the new treatment for skin cancer, and its side effects, in stride. Her appetite dampened a bit, she had some leg cramping. Most disturbing for her was some hair loss. She also developed an undocumented side effect — a squamous cell cancer, another non-melanoma skin cancer that looked like a small open wound on her arm.

But within just a few months, the basal cell carcinoma had shrunk significantly in size.

"All of the lesions pretty much disappeared four months after she started taking the pill," says her granddaughter, Gale Carli, a nurse from San Mateo. "It was amazing."

In August, Bazurto stopped taking the drug and had surgery to remove the remaining growth on her eye. The surgery took only an hour and a half and required no general anesthesia. A similar surgery was performed on the new growth on her arm, which healed up nicely. When she arrived in October for a post-surgical visit with Tang, her dermatologist, her hair was thinning, but her eye looked great.

"Oh you look so gorgeous!" said Tang when she walked into the examination room and first saw Bazurto seated in her wheelchair. Bazurto was joined by her daughter and granddaughter, all crowded into the small room at the Stanford Medicine Outpatient Center in Redwood City.

2013 have gone into fundamental research support for these Stanford labs. The hope is that their work will help lead to more new drugs, more quickly, Oro says.

"When vismo was approved, my son said, 'Dad, that was cool. Is it going to take you that long to find the next one?'" Oro says, laughing.

Both Oro and Tang were involved in the first clinical trials testing vismodegib on basal cell carcinoma tumors.

"If a patient only knew the whole story — how the happenstance of science led to their treatment," Tang says. "If they could go back to when this molecular pathway was first discovered in fruit flies, they'd be amazed. It's not until the dots are connected 30 years later that it begins to make sense."

For many of the basic scientists involved in this research, the clinical use of hedgehog-inhibiting drugs to treat patients like Bazurto — while not the original goal of their research — is the ultimate success.

"IF THEY COULD GO BACK to when this molecular pathway was **first discovered in fruit flies, they'd be amazed.**"

Bazurto rolled her eyes and laughed. She was wearing a floral dress with pearl earrings. Tang was dressed in a white lab coat. When they first met in April, Tang was very pregnant and Bazurto was losing her sight. Now Tang had a healthy baby boy, and Bazurto could see clearly out of her right eye.

"I can't seem to find a good wig maker," Bazurto said. "They don't think I'll live long enough to pay for it," she joked.

Tang ran her hands gently through Bazurto's thin, white hair. (In another month, it would all fall out but eventually grow back completely.) Then Tang gently tapped the skin next to her patient's eye, the site of the surgery.

"Is your vision OK?"

"Oh, certainly," Bazurto said.

"It's a little red at the bottom," Tang said.

"Oh, leave me alone," Bazurto said, rolling her eyes.

"She's been the toughest thing ever," Tang said, shaking her head with admiration.

Today, there are six or seven labs on the Stanford campus that conduct research in the hedgehog pathway. Tens of millions of National Institutes of Health dollars from 1996 to

"The FDA approval came out on my birthday, Jan. 30," Scott says. "I can't imagine a better birthday present. Even though I had nothing directly to do with vismodegib, to see the culmination of 30 years of research help patients live their lives better is enormously gratifying — and a testimony to basic science."

Bazurto, a small woman who loves baseball and football and has been known to occasionally wager on the 49ers, is today considered something of a rock star among hedgehog scientists in part because of her great response to the hedgehog-inhibiting drug and in part because of her advanced age. Back at Stanford for a post-op visit in October, Bazurto's surgeon, doctor and nurses all crammed into the exam room for photos with their VIP patient. She smiled widely and mentioned that a Genentech scientist had brought her flowers.

"He's the vice president of research at Genentech who has been studying the hedgehog pathway for 20 years," said Tang, describing Fredric de Sauvage, PhD. "I sent him your picture. He said it almost made him cry. I'm sure it was the crowning moment of his career." SM

— Contact Tracie White at traciew@stanford.edu

LEO AND FRIDA

THE DOCTOR AND THE ARTIST

Do you think it would be more dangerous to abort than to have a child?… If, on the contrary, you think having the child might improve my condition, then, in that case, I'd like you to tell me if it would be preferable for me to go to Mexico in August and have the baby there in the company of my mother and sisters, or whether it might be best to wait for it to be born here. … Doctorcito, you have no idea how embarrassed I am to bother you with these questions, but I see you not so much as my doctor as my best friend, and your opinion would help me more than you know.

Excerpt of a letter from Frida Kahlo,
in Detroit, to Stanford surgeon Leo Eloesser, MD, May 26, 1932.
From *Querido Doctorcito* (El Equilibrista, 2007).

She would later emerge as one of the world's greatest self-portraitists, but in December 1930 Frida Kahlo was unknown. She had come to San Francisco with her husband, the famous muralist Diego Rivera, who was there to paint frescoes, including one for the San Francisco Stock Exchange. Kahlo was 23, and this was her first visit to the United States. • Plagued by a chronically painful right foot, she consulted Leo Eloesser, MD, a noted thoracic and orthopedic surgeon at Stanford's medical school. He proposed little in the way of treatment beyond rest and healthy living, but Kahlo was grateful enough to paint his portrait. In it, the short, dark 49-year-old stands with his head jutting characteristically forward. Beside him is a model sailboat, emblematic of his passion for nighttime sailing on the bay. • With that gift of a painting, a loving friendship was born — one that would enhance two remarkable lives. • The letters and journals that Kahlo and Eloesser left behind reveal a bond that went far beyond the doctor-patient relationship. She wrote him passionate missives confiding not only

By Catherine Reef

RIGHT: LEO ELOESSER, PORTRAIT BY FRIDA KAHLO

Painting in oil in 1931 in Eloesser's home, Kahlo portrayed Eloesser with a model sailing ship named *Los Tres Amigos*, presumably in recognition of the friendship shared by the doctor, the artist and her husband, muralist Diego Rivera.

"I HATE DOMESTICITY," SAID LEO ELOESSER.

"CONVENTIONS WERE NO BOTHER TO LEO,"

WROTE HIS BIOGRAPHER. NEITHER WERE THEY TO FRIDA KAHLO.

her physical pains but also her deeply private emotional suffering. He was a ready listener, offering medical and moral support along with a generous dose of affection and playful wit. He even served as a go-between in her turbulent relationship with Rivera. He was awed by her talent, intelligence and audacity, and he found in her a kindred spirit, someone acutely interested in the world's cultures and in helping those who were less privileged.

KAHLO, A NATIVE OF MEXICO CITY, DISLIKED MOST OF THE AMERICANS SHE MET. "They are boring and they all have faces like unbaked rolls," she complained in a letter to a Mexican friend. Eloesser, however, seemed different. He spoke fluent Spanish and had an intensity and intelligence that attracted her, notes art historian Hayden Herrera in her biography *Frida* (Harper & Row, 1983). Also, his left-wing political views were compatible with hers, as she was an ardent communist.

Eloesser, for his part, "had a true love of art and artists," observed his friend and biographer, Harris Shumacker Jr., MD, in a 1984 article in the medical journal *The Pharos*. He took special pleasure in the company of painters and sculptors, calling them "a carefree lot, generous and liberal in recognition of their fellow artists as well as in their readiness to help," as noted in Shumacker's biography, *Leo Eloesser, M.D.: Eulogy for a Free Spirit*.

Eloesser was leading a full life when he and Kahlo crossed paths. He was chief of Stanford's surgical service at San Francisco County Hospital (now SF General) and clinical professor of surgery at Stanford's School of Medicine, which was then in San Francisco. A famed diagnostician, he had a thriving private practice and operated at five other city hospitals. "Leo was a workhorse. He had no concept of time, night or day," said a junior associate at the county hospital, according to *The History of the Surgical Service at San Francisco General Hospital* (2007). He played viola with members of the San Francisco Symphony in an ensemble that met in his apartment each Wednesday. He frequently took out his sloop, the *Flirt*, often with a companion, often female. He deflected questions about his single status with statements quoted in Shumacker's biography such as "I hate domesticity." Commented Shumacker, "Conventions were no bother to Leo."

Neither were they to Kahlo. She rejected current fashions, preferring the folkloric costumes and long skirts of the Tehuantepec region of Mexico, garments that tactfully hid her legs from view. Kahlo had spent long stretches as an invalid since the age of 6, when polio permanently weakened her right leg. As a teenager she survived a bus accident that all but shattered her skeleton. Her spine broke in three places, her right leg sustained 11 fractures, her right foot was crushed and a steel handrail skewered her pelvic region. In addition, Eloesser noted signs of a congenital condition — scoliosis according to some sources, spina bifida according to others. She was nonetheless an attractive woman in her own unconventional way. In his journal Eloesser described her as "a girl of unusual beauty" whose "hair was a lustrous black; her dark eyebrows almost met over her straight nose; her skin was of a faint, light-coral pink."

Kahlo started to paint while convalescing from the bus accident. As soon as she could walk again she tracked down the widely celebrated Rivera, who was at work on a series of 124 murals in Mexico's ministry of education. In no way intimidated, she demanded that he climb down from his scaffolding and look at her paintings. Rivera was taken with both the art and the artist, and in August 1929 the two married.

When Rivera finished the work that had brought him to San Francisco in 1930, he and Kahlo moved on to other U.S. cities where he had commissions. Kahlo's earliest missives to Eloesser from these places were chatty and entertaining, offering an outsider's irreverent impressions. New Yorkers, she wrote, were "irritable, as if they live in an enormous dirty chicken coop." Before long, however, her correspondence turned serious. She had a hard choice to make and needed frank advice. "I am now two months pregnant," she wrote from Detroit in May 1932. Although she welcomed motherhood, she worried that her body was too badly damaged to carry a child to term. Her Detroit physician assured her that she could safely continue the pregnancy, but Kahlo had serious doubts and was considering an abortion. "What I want to know is your opinion," she wrote, "because you know my situation better than anyone." Eloesser's reply has been lost,

FRIDA KAHLO

Photographed in 1944 in Mexico City.

BETTMANN/CORBIS

but what he wrote hardly mattered, because Kahlo decided on her own to keep the baby, with grave results. On July 4 she began hemorrhaging and was rushed to a Detroit hospital. She experienced a spontaneous miscarriage that necessitated 13 days of hospitalization.

Kahlo's grief over this disaster led her to a creative breakthrough. She painted *Henry Ford Hospital*, a dreamlike work in which she lies naked and bleeding on a hospital bed against a barren landscape. She holds strings — or umbilical cords — that connect her to an unborn child, a snail and other objects. Kahlo emerged from the ordeal as an artist who depicted her physical and psychological state in a rich allegorical language. "I paint my own reality," she told an interviewer in 1938. "She pierced through events and appearances to seize the deepest layers of that reality," wrote biographer Herrera.

Not everyone grasped this aspect of Kahlo the artist. When she wanted to paint her lost child, her Detroit physicians refused to lend her an obstetrical text, fearing the images might upset her. Rivera, knowing better, bought her one to use as a reference. "You are not dealing with an average person," he told the doctors, according to Herrera's book. In 1941, Eloesser presented her with a fetus preserved in formaldehyde, which she kept in her bedroom alongside her doll collection. It was a strange gift, but one in keeping with Kahlo's need to examine her life minutely. "Never did a painter, man or woman, so successfully transfer his (or her) emotions to canvas," Eloesser wrote in his journal.

THE 1930S WERE BUSY YEARS FOR ELOESSER. IN 1935 HE DESCRIBED the surgical technique for which he is best remembered. Designed to drain acute tuberculous empyema, an infection between the layers of membrane surrounding the lung, this "little piece of operative gadgetry," as he called it, involved making a U-shaped incision that permitted drainage while preventing air from entering the chest cavity. Antibiotics later eclipsed the need for the Eloesser flap, although it still has some value in chronic cases.

Eloesser also followed the leanings of his strong social conscience. He paid for round-the-clock nursing for a prisoner upon whom he performed surgery, and was known to give his Christmas dinner to indigent patients. In August 1937, he went to San Quentin State Prison to examine the political activist Tom Mooney, who was serving time for a 1916 bombing that killed 16 people in San Francisco. Mooney was then in the hospital with an inflamed gallbladder. Believing he had been wrongly convicted, the American left was monitoring Mooney's incarceration and treatment, so the prison physician wanted a politically liberal doctor to decide whether he needed surgery. Eloesser determined that the procedure could be postponed, and he performed it himself years later, after Mooney gained his freedom.

Also in 1937, Eloesser took a leave of absence from Stanford and went to Spain as a physician with the Abraham Lincoln Brigade, a unit of American volunteers fighting on the Loyalist side, against Franco, in the Spanish Civil War. He performed lifesaving surgeries behind the front lines in a makeshift hospital lacking heat and electricity, often examining wounds by candlelight. "When wounded begin to pour in, one has to take things as they are and make the best of them," he reported in January 1938 to the New York-based Medical Bureau to Aid Spanish Democracy.

He kept up his correspondence with Kahlo, now back in Mexico, whose condition was deteriorating despite surgeries, casts and corsets. "My foot continues to be sick," she wrote. "'Trophic ulcer,' what is that?" Eloesser, who questioned the value of the many procedures carried out by Kahlo's Mexican doctors, recommended a simple regimen of healthful habits. He particularly counseled Kahlo to limit her drinking, which had become habitual. At one point she assured him that she had given up "cocktailitos," writing, "I'm having a beer once a day and am a little stronger and in a better mood."

But the most striking aspect of their correspondence was unrelated to health. Wise, caring, trusted — and far away, Eloesser was the ideal confidant when Kahlo needed to unburden her heart. Rivera was perpetually unfaithful, having affairs with models, starlets and wealthy tourists. Among his lovers were the American sculptor Louise Nevelson and the Mexican film star María Félix. Although Kahlo, too, had been untrue, her husband's roaming pained her deeply, especially when he became involved with her own sister. "You have no idea what I suffer," she told her "*querido doctorcito*," her beloved little doctor. Life with Rivera became intolerable, and in 1939, when she was 32, they divorced.

Without the daily presence of the man she still loved, Kahlo entered a dark emotional state and drank more than ever. She painted herself wearing a necklace of thorns in one self-portrait, and with her heart exposed and dripping blood in another. And she was very ill. Her Mexican doctors put her in traction and suggested more surgery. In three months, she lost 15 pounds.

This time it was Rivera who consulted Eloesser. As luck would have it, Rivera was in San Francisco, painting a mural for the Golden Gate Exhibition. He was worried about Kahlo, so far away and unwell, and asked their friend the doctor for advice. Eloesser in turn telephoned Kahlo and urged her to come to San Francisco to put herself under his care. He followed up

MORE OMINOUSLY,

SHE WOKE ONE MORNING "TO FIND FOUR TOES

OF HER RIGHT FOOT BLACK ON THE ENDS." HE SCRIBBLED THE WORD "GANGRENE."

with a letter addressing the root cause of her suffering: "Diego loves you very much, and you love him." Acknowledging that Rivera "has never been, nor ever will be, monogamous," he went on to propose that she remarry him, accept him as he was and channel her energy into work. He closed by saying, "Reflect, dear Frida, and decide." Meanwhile, he convinced Rivera that remarriage would help safeguard Kahlo's fragile health, something the doctor honestly believed. "She really needs me," Rivera told one of his assistants, the American artist Emmy Lou Packard, Herrera wrote. He also admitted that a reconciliation would be better for him, too. Living apart "was having a bad effect upon both of us," he stated in *My Art, My Life*, the autobiography he wrote with Gladys March.

So in September 1940 Kahlo flew to San Francisco. Eloesser had her admitted to St. Luke's Hospital to rest and "dry out," and watched her health improve. During Rivera's visits to her hospital room, the couple discussed getting back together. Before anything could be settled, however, she took off for New York to meet with a gallery owner and, while there, had a whirlwind affair with a young German art lover. It was late November when Kahlo, still in New York, at last made up her mind to remarry Rivera — but the new marriage must be a union of two souls, she stipulated, with no physical intimacy. "I was so happy to have Frida back that I assented to everything," Rivera wrote in *My Art, My Life*. Kahlo returned to San Francisco and stayed in Eloesser's home until a brief marriage ceremony could be held in a city courtroom.

Again she expressed her thanks with a painting, this one a self-portrait dedicated to "Doctor Leo Eloesser, my physician, my best friend. With all my love." At home in Mexico she produced more self-portraits, painting herself in the company of parrots, monkeys and insects.

By 1945 Eloesser was ready for a change. He retired from Stanford and went to Nanjing, China, with the United Nations Relief and Rehabilitation Administration to train doctors in thoracic surgery. His Chinese colleagues noted his careful attention to patients' well-being before, during and after surgery, and his often-repeated rule, "If you don't respect the tissue, then the tissue won't respect you." He also wove basket-like bamboo prostheses for patients who had lost lower limbs. In 1949 he moved to New York to work with UNICEF.

Kahlo's life during these years was defined by unrelenting pain in her spine and right foot as her disability worsened. When Eloesser visited her in January 1950, she was about to enter Mexico City's English Hospital for a stay that would last a year. In his notes Eloesser recorded that Kahlo had consumed "No alcohol in three years." This was good news, but over the same period she had been taking "much Seconal." More ominously, she woke one morning "to find four toes of her right foot black on the ends." He scribbled the word "gangrene." By August 1953, the amputation of her leg below the knee could no longer be postponed. "This is going to kill her," Rivera rightly predicted. Kahlo lingered for an anguished year until July 13, 1954, when she died at 47. She had written in her journal, "I hope the exit is joyful — and I hope never to come back."

Eloesser, at 70, settled in Mexico with Joyce Campbell, a friend who also worked for UNICEF; she became his partner for the rest of his life. He operated a clinic in Tacámbaro, in the state of Michoacán, and concerned himself with rural health problems, especially tuberculosis and infant mortality. He trained rural midwives and published a manual on midwifery. He continued to see patients until his heart gave out on Oct. 4, 1976. He was 95, but his death took Campbell by surprise. "That morning he had been optimistic and even cheerful and I know he had no intention of dying," she wrote in a passage included in Shumacker's biography.

Eloesser had saved the letters he received from Kahlo. After his death, Campbell entrusted them to her friend Juan Pascoe, a literary printer. He in turn contacted María Isabel Grañén Porrúa, president of Apoyo de Desarrollo de Archivos y Bibliotecas de México, an organization dedicated to the recovery and preservation of historical documents. Curiosity impelled Grañén Porrúa to start a search of Kahlo's home outside Mexico City (now the Frida Kahlo Museum) for Eloesser's letters to her. Their discovery led to a 2005 exhibition at the Kahlo museum and a book, *Querido Doctorcito*, containing all the existing correspondence between Eloesser and the patient he held dear. SM

— Catherine Reef has written more than 40 books for children and adults, most of them works of biography and American history. Her book Frida and Diego: Art, Love, and Life *will be published in spring 2014 by Clarion Books/Houghton Mifflin Harcourt. Contact her at medmag@stanford.edu.*

FEATURE

Priming the pumps

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use in the field, had trouble with leaky valves or had backflow problems that caused the pipes to rust, among other issues.

One of the biggest challenges was to find a way to dose the right amount of chlorine, as the water pressure is highly variable in Dhaka. The students relied on principles of fluid dynamics to get the pump to draw in just the right amount, or about 0.5 to 1.5 parts per million, the acceptable range. Getting it right took many months and the help of an outside consultant who used customized software to create various fluid simulations.

The real testing began in the summer of 2012, when Crider brought one of the prototypes to Dhaka for a field trial at 10 different pump locations. In the first few days, she says, some residents complained of the chlorine taste, but then their complaints subsided. Some were particularly excited about the project, including one middle-aged mother who had plucked a leech out of the pump the week before.

"She seemed to think there was a difference in the water — that fewer people were getting sick," Crider says. "She is going to be a champion in the community for the system."

All of the residents, Crider says, were gracious and welcoming. On her last day there, a snack shop owner insisted on treating her to a lunch of fried potato and vegetable wraps, as a thank you for her help, she says. She says it's gratifying to see residents already benefiting from the project.

"We've already chlorinated people's water, which is the coolest thing. People are already affected by this technology. It's good work," says Crider, who left the device in place. Cooke is working to further optimize the technology, spending most days and many nights in the lab tweaking the design. He manufactured the latest prototype in his garage at home, using his own 3-D printer.

The current prototype, made of the same plastic used in Legos, resembles a kitchen funnel and has a silicone seal that secures it to the mouth of the pump. A slender tube connects the device to a reservoir, which holds up to about 5 liters of chlorine.

The device regulates the flow of the water, which otherwise pours out or sprays in bursts. After much trial and error, the students introduced the Venturi effect, a principle of fluid dynamics, to induce a low-pressure zone in the flowing water that draws in the chlorine. The device is designed to draw in chlorine according to the rate of flow; this ensures that the water is infused with just the right proportion of chlorine. The students also adapted a regulator used in medical IVs as another way to control the chlorine dose. Whoever manages the system can turn a dial to set the dose so it remains in a consistent, safe range. Ultimately the system will be enclosed so no one can tamper with it, Cooke says.

Cooke was an entrepreneur before he came to Stanford, having created his own company, Keego Technologies, which sells microbial fuel cell kits to schools, where they are used to teach students how microbes in the soil can generate electricity. As one of the few in the group with business experience, he is working on various business models that could help sustain the project over the long haul, a key to its success.

"In the water sanitation field, that's the hard part," says civil and environmental engineering faculty member Davis. "We have plenty of technology. We just haven't figured out how to deploy it on a sustainable basis."

One approach is to engage existing community-based organizations, which manage a variety of community projects, such as construction of new latrines or pipes, in collecting fees from landlords and other users to maintain the system, Cooke says. The community groups could hire residents for a small fee to periodically refill the chlorine reservoirs and make sure the devices are working properly. Landlords would have an incentive to contribute, as they could advertise their rental units as having clean water supplies. Another alternative could involve local entrepreneurs to maintain the devices, as there are many in Dhaka eager for a steady source of income, he says. He believes the device could be mass-produced for as little as $15 each.

Team members, including Cooke, Crider and Pickering, plan to go back to Bangladesh this summer to test the prototype and lay the groundwork for larger studies on its feasibility and health benefits. Pickering says they'll select 160 test sites, randomly assigning half to receive the chlorine doser, and compare rates of diarrhea and weight gain among the young children in the two groups.

Luby ultimately hopes to see the technology applied in communities across South Asia and Africa, where climate change, population growth and poor management practices have made clean water supplies — and water generally — an increasingly scarce commodity.

"Water is a very important resource that is not being well-managed, at the risk of all humanity," he says. For instance, in South Asia, agricultural interests are depleting the underground aquifers, so while crops are flourishing amid a green revolution, that productivity can't be sustained, he says. At the same time, surface water is being used as a garbage dump for sewage and industrial waste, compromising water quality and the entire ecosystem, he says.

Luby says he came to Stanford in September because of its collaborative, entrepreneurial spirit — something highly

visible in this particular global initiative.

"I spent 17 years working for the U.S. government, and I never had anyone say, 'Maybe I should create a start-up and make this go farther,' he says. "The fact is that we have been pushing ways of how we can get it out there. It's very exciting to work with people at Stanford who have that vision."

The project already is attracting some attention. The team won a $15,000 award in a U.S. Environmental Protection Agency student design competition for sustainability, and in April it won the 2013 American Society of Civil Engineers Sustainable Development Award, which came with a $1,000 prize. And last year the project won first prize, a $20,000 award, in the Social Entrepreneurship Challenge of the Business Association of Stanford Entrepreneurial Students. The project also is supported by grants from the U.S. Agency for International Development and the World Bank, which is funding the health impact evaluation.

As for Pickering, she says she realizes there is still a lot of work to be done to validate the technology and its financial viability. But she has high hopes this will be one of the paths to improved health for a large swath of people for whom clean water now is just a pipe dream.

"My biggest hope for the project is to develop a financially sustainable strategy for disinfecting water that can be adopted and scaled up in low-income, urban communities around the world to improve health," she says. **SM**

— *Contact Ruthann Richter at richter1@stanford.edu*

FEATURE

Close encounters

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Rat and mouse populations inside the exclosures greatly exceed those in the control plots, says Dirzo, who has invented his own term for this: rodentation. "We estimate a roughly 2.7 times greater abundance of rodents when big animals aren't around," he says.

The researchers didn't come up with that statistic by sitting in an air-conditioned office pecking at a keyboard. Here's a typical working day in the field: "In the afternoon, we go out to the field with lots of rectangular, aluminum traps baited with, say, peanut butter, and lay those traps on the ground spaced 10 meters apart in a large grid. If a rodent goes in, the trap closes, without harming the animal. Early the next morning, before the sun heats up the traps or ants discover the food inside them, we go check. If there's an animal in a trap, we note where in the grid that animal was collected."

Each caught animal is held in brief captivity. The scientists affix to its ear a numbered aluminum tag, so they'll recognize the rodent if they find it again. They weigh it. They draw blood and send it off to the Centers for Disease Control and Prevention for genetic analysis. Somebody — usually Dirzo — combs the animal for fleas, plopping them into an alcohol-filled container that is sent to a lab in the United States where they can be identified by species. Feces are collected to tell what the animal has eaten and what kinds of internal parasites it's infected with. The animal is then brought back to the exact spot where it was found, and let go. The next afternoon the scientists lay out traps all over again.

The UC-Davis plots in Nanyuki make for "a fantastic experimental setting," Dirzo says, "but it doesn't tell you exactly what you'll see in real life. To find out, we had to go where defaunation is most intense. And that's, of course, where humans are."

Dirzo's team located a nearby human settlement separated by a river from a big-animal conservancy site teeming with elephants, giraffes, zebras and more. In this much more realistic experimental setting, they repeated their laborious routines. "We also sampled inside homes. Some of our most successful trapping nights have been in homes."

In the human settlement, the researchers saw a 25-fold increase in rodent densities. "Rodents carry more human disease pathogens than large animals do," says Barry.

Now Lambin and his colleagues are combining remote-sensing-, field- and lab-based data with household-survey results to figure out which disease from which rodent lurks in what kind of geographic niche. "We've found," he says, "that specific types of land use determine what types of rodent species abound, and we've found some of the pathogens tend to be very specific to one rodent species. So, we can make intelligent predictions as to what kind of land use promotes what pathogen." In other words, they can tell which disease might pop up where.

In a small fraction of samples, the CDC has found serious pathogens including *Yersinia pestis*, the bacterial strain responsible for Black Death. Black Death pandemics decimated entire continents' populations several times between the sixth and 19th centuries, frequently killing two-thirds of infected people within four days.

There's no evidence of these pathogens being transferred to people. Yet.

NEXT?

This is where the expertise of a Michele Barry, who maintains good contacts with the local and mobile clinics that operate in Kenya, comes to the fore. Whitney Bagge, a graduate student whose advisers include Barry and Lambin, returned last summer from a three-week trip to Kenya, where she searched for cases of human rodent-associated disease and gathered ground-based mapping data to synchronize with satellite-based GPS imagery. In a search for lab-confirmed cases of rodent-

caused disease, she also visited private and public clinics, local dispensaries and district-level hospitals and spoke to mobile medical-services providers who bring residents of remote communities to these facilities.

"*Yersinia pestis* is awful," says Bagge. "But it's not just extreme examples that are of concern." Her medical-facilities legwork in and near Mpala has turned up several reports of a mysterious relapsing malarialike syndrome, marked by prolonged fever and malaise, that tests negative for malaria. "We're thinking the causal agent might potentially be rodent-borne," Bagge says.

At the moment, Bagge is back at Stanford assessing the data the study has yielded so far. But once the satellite, human-contact and animal-collection data are analyzed and the links between certain geographical niches, the species of rodents that infest them and the particular pathogens those rodent species carry have been drawn, "ideally we'll be able to use our analysis to extrapolate beyond the rodent-sampling sites we've actually studied to the entire region, and to assemble a 'risk map' depicting landscapes with likely higher prevalence of one disease or another. We can use that risk map to easily show people their risk for infection in entering a particular area."

Rodents haven't been thought of in this area as sources of diseases, so establishing that connection is important in itself. But they are recognized as a nuisance, so rodent-patrol squads already exist. "Knowing which rodents are prone to carrying serious pathogens and which particular landscape types are most likely to house those rodents could direct those rodent patrols to target these areas, for the sake of public health. That would be immediately helpful to medical professionals on the ground," Bagge says.

"The big, emerging pandemic pathogens we worry so much about primarily spill over to us from animal reservoirs," says Barry, citing the Nipah virus, featured (albeit in a fictional form) in the 2011 movie *Contagion*, as an excellent example. The real-life Nipah virus caused 105 deaths in an outbreak in Malaysia in 1999, and 55 more in India in 2001. "Pig farmers were putting their pigsties under mango trees where asymptomatic but virus-shedding, infected fruit bats were roosting. There was a spillover of bat virus to pigs, and then to pig farmers."

Nipah is just one name on a long list of emerging pathogens that nobody saw coming and re-emerging pathogens nobody expected to come around again. A combination of intensive field work and satellite imaging may help us get a handle on how we can keep them at bay — and, perhaps, establish public-health procedures responsive enough to get out in front of the pathogen we should always fear the most: Pathogen X, the one we don't know about yet. — *Contact Bruce Goldman at goldmanb@stanford.edu*

FEATURE

Street smarts

CONTINUED FROM PAGE 21

founder and CEO of Facebook. In July 2011, Facebook employees moved into the former headquarters of Sun Microsystems, a fortress-like quadrangle of buildings located between East Palo Alto, a six-lane freeway and the salt marshes of the San Francisco Bay. Because of its isolation, previous employees nicknamed the campus "Sun Quentin," after San Quentin State Prison.

The first thing that Facebook managers did was give the campus a built-environment makeover. They added a winding main street down the center of campus, and lined it with cafes, shade trees, coffee shops and racks of loaner bikes. The company has also pledged more than $800,000 annually to East Palo Alto and neighboring towns over the next 15 years to help improve traffic flow and create better pedestrian and bike paths.

This fortuitous collaboration with Facebook shows how valuable it is to have "shovel-ready" priorities documented when funding opportunities arise and how useful the discovery tool tablet can be for identifying those priorities. It's also an example of how some Silicon Valley companies, including Google and Apple, are building campuses that directly promote physical activity among their employees.

King, Winter and former Stanford Prevention Research Center postdoctoral scholar Matt Buman, PhD, now at Arizona State University, would like funding to refine the tool and teach community groups how to communicate their needs to city planners.

"In general, it's difficult to get funding for any research project in the current fiscal climate," says Buman, "but it's even harder for a project like this, because it doesn't fit neatly into National Institutes of Health funding categories. It's part prevention and public health, part behavioral science and part urban revitalization."

In Arizona, Buman has had volunteer shoppers use the tool at a farmers' market to provide feedback to the organizers on how to improve it.

To date, King and Winter have collected data from 15 of the 40 volunteers planned for the North Fair Oaks study, which is funded by the medical school's Office of Community Health by a seed grant from Spectrum, which oversees Stanford's NIH Clinical and Translational Science Award.

Next, they will organize a community advocacy meeting to help the study participants prioritize neighborhood issues by importance to the community and feasibility of being addressed. Together, these residents will develop an action plan and present the ideas to local health policymakers.

"This phase of the study is important because it ensures that the community members, not outside researchers, are advocating for change within their own neighborhoods," says Winter, who grew up near many poverty-stricken towns in South Africa. She is motivated to help these communities in a way that respects their unique cultures and needs. She also feels that changes that come directly from residents are more likely to be successfully implemented.

She adds, "The other benefit to this study is that it raises overall awareness about features of the environment — both the good and the bad — that affect our ability to live healthy lives."

As the team finishes this study, it's developing a software module for the discovery tool that will allow researchers to study how people access food in their neighborhoods and what drives their food choices. This new software will be tested in north San Mateo County and several neighborhoods in Mexico.

"Research shows that it is never too late to make healthy behavior changes and even small changes in the built environment can have a potentially big impact on critical health behaviors — including regular physical activity, healthful diets and avoiding tobacco use. These health behaviors are among the key drivers of the chronic diseases that are the nation's leading causes of death and disability," says King. "Chronic diseases, such as heart disease, cancer and diabetes, result in tremendous economic, societal and personal costs, both in the United States and globally, yet they are potentially avoidable. By simply making a town more walkable, we can help to enhance the health and quality of life for much of our population by a significant degree."

In this era when cities need to rethink their car-centric landscapes and to explore creative ways to control rising health-care costs, using citizen-scientists to lobby for more beautiful, walkable neighborhoods might be just what the doctor ordered. — *Contact Kris Newby at krisn@stanford.edu*

Q & A

Water solutions

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Inadequate distribution is a large part of what prevents people from accessing safe water. In urban slums, piping may run just beneath entire communities, bypassing them because the predominant thinking is that families living in poverty cannot afford to pay the connection fees to gain access to the water or sanitation systems. Through Water.org's WaterCredit initiative, we're demonstrating that this is not the case.

WaterCredit catalyzes small loans — typically $50 to $200 — to people in developing countries who lack access to traditional lenders and are in need of clean water and toilets. As loans are repaid, they can be redeployed to additional people in need of safe water, reducing the need for subsidies, which can then be freed up to help those who need it most.

COSTELLO: So paint the picture for us. What does the world look like when you realize there's truly progress out there?

WHITE: It looks like right now. We have made and are continuing to make tremendous progress. While it is true that today one child dies every 21 seconds from a water-related disease, only a few years ago this number was one every 15 seconds. This slight change saves 1,646 children every day. In early 2012, the United Nations announced that one of the Millennium Development Goals for water was met ahead of schedule. Between 1990 and 2010, 2 billion people gained access to improved drinking water [http://www.unwater.org/statistics_san.html]. We see this as an immense opportunity. Achieving universal access to safe water and the dignity of a toilet is within reach. We will need to remain focused and track and plan for new disruptions such as changes in climate that may detract from progress we've made. The answer to the crisis really comes down to mobilizing the global will, just as we did with the AIDS epidemic in Africa. **SM**

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BAD AIR

POLLUTION AND PREGNANCY

Breathing traffic pollution in early pregnancy is linked to higher risk for certain serious birth defects — a new finding that helps clarify a public health question that scientists have struggled with for more than a decade. • Prior studies of air pollution and birth defects date back as far as 2002, but their inconsistent methods produced a confusing picture: Researchers examined many different geographic regions and pollutants, most studies assessed only heart defects, and none evaluated what mothers were breathing during early pregnancy — the period when birth defects are most likely to develop. Results were mixed, with some but not all demonstrating a pollution-birth defect connection.

Enter a team of scientists from Stanford, the University of California-Berkeley and Sonoma Technology Inc. The UC-Berkeley researchers were already using data from federally mandated air-quality monitoring programs to examine links between traffic pollution and childhood asthma in California's smoggy San Joaquin Valley. Stanford's Gary Shaw, PhD, joined the team to add expertise from his work connecting birth defects to environmental factors such as maternal nutrition.

"Birth defects affect one in every 33 babies, and about two-thirds of these defects are due to unknown causes," says Shaw, the senior author of the new research. "When these babies are born, they bring into a family's life an amazing number of questions, many of which we can't answer." Shaw is a professor of pediatrics in neonatal and developmental medicine. His team looked at five birth defects and six measures of traffic-related air pollution.

"It's still unclear which birth defects may be associated with air pollution, so we started with the ones that we thought had the most potential impact from the environment," says the study's lead author, Amy Padula, PhD, a postdoctoral scholar in pediatrics at Stanford.

The team found a link between traffic-related pollution and brain and spine malformations. The research, published online March 28 in the *American Journal of Epidemiology*, evaluated 806 women who had a pregnancy affected by a birth defect between 1997 and 2006, and 849 women who had healthy babies during the same period.

All women studied resided in the San Joaquin Valley during the first eight weeks of their pregnancies, a window of time when many birth defects develop. Compared with women with the lowest carbon monoxide exposure, those who breathed the highest levels were nearly twice as likely to have a baby with anencephaly (the absence of a brain) or spina bifida (the failure of the spinal cord to close during development), which can lead to paralysis of the lower body and curvature of the spine, among other problems. Nitrogen oxide and nitrogen dioxide exposures were also linked to increased risk for these defects; women with the highest nitrogen oxide exposure had nearly three times the risk of having a pregnancy affected by anencephaly, for example. Further studies are needed to examine the combined effects of multiple pollutants, and to examine other pollutants.

The researchers are also hoping that policymakers will consider this study when they assess limits for air pollutants. This study offers new ammunition to fight for that, Shaw says. "Clearly there are multiple reasons to improve the air, but the well-being of our newborns is a fairly hot button to push." — ERIN DIGITALE

JACOB THOMAS

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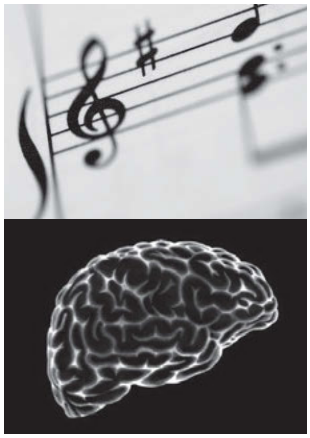
Music to our brains

A UNIVERSAL RESPONSE

The brains of different people listening to the same piece of music respond in the same way, which may help explain why music plays such a big role in our social existence.

"We spend a lot of time listening to music — often in groups, and often in conjunction with synchronized movement and dance," says Vinod Menon, PhD, a professor of psychiatry and behavioral sciences, who recently studied brains on music. "Here, we've shown for the first time that despite our individual differences in musical experiences and preferences, classical music elicits a highly consistent pattern of activity across individuals in several brain structures including those involved in movement planning, memory and attention."



Menon's team used functional magnetic resonance imaging to identify a distributed network of brain structures whose activity levels waxed and waned in a strikingly similar pattern among study participants as they listened to classical music they'd never heard before. The results were published in April in the *European Journal of Neuroscience*.

The team showed that the brain's motor-planning centers respond to music by foreshadowing movements that often accompany it: clapping, dancing, marching, singing or head-bobbing. The similarity of such patterns among participants may play a role in the social coordination of movement.

In addition, midbrain structures typically thought to passively relay auditory information to thinking-related centers higher in the brain are selective for musical stimuli, suggesting that the higher-level centers direct these relay stations to tune in to specifically musical sounds. Meanwhile, right-brain counterparts of two key structures in the brain's left hemisphere (Broca's and Geschwind's areas, crucial for speech and language interpretation) show synchronization from one study participant to the next. "These right-hemisphere brain areas track non-linguistic stimuli such as music in the same way that the left hemisphere tracks linguistic sequences," says Menon.

The notion that healthy subjects respond to complex sounds in the same way could provide insights into how individuals with language and speech disorders might listen to and track information differently from the rest of us.

"We are particularly interested in language and social communication in autism," Menon says. "Which brain regions are out of sync?" — BRUCE GOLDMAN

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