endeavors

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Winter 2012

BIG on the PIG: North Carolina's hog farming industry is one of the largest in the nation. Is it also making people sick?

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Endeavors engages its readers in the intellectual life of the University of North Carolina at Chapel Hill by conveying the excitement of creativity, discovery, and the rigors and risks of the quest for new knowledge.

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UNC RESEARCH

This is your last issue of *Endeavors.* I wish I could say it was because you let your subscription lapse, but of course you haven't. As you may have heard, state budget cuts have forced us to discontinue the print edition.

All is not lost, though: we're working to make our website the go-to spot for compelling stories, images, and videos of Carolina research and discovery. Those of you who receive the *Carolina Alumni Review* will continue to hear from us regularly, as our colleagues at that fine magazine have graciously agreed to set aside a bit of their print real estate for stories on Carolina research. We'll soon begin sending out a monthly digital newsletter with links to full-length stories and other features on our site (if you haven't already e-mailed us, you can sign up at the URL below). And we'll continue to publish some of our stories in outlets such as the UNC home page, www.unc.edu.

Thank you for reading *Endeavors* over the years, and thank you for being part of our story. If you'd like to comment, or if you have any questions, you may reach me at jdsmith@email.unc.edu.

—Jason Smith

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Biology grad student Lindsey Carr labels illegally caught sharks that the Galápagos National Park Service seized from an Ecuadorian fishing boat. Photo by John Bruno. Story on page 20.

overview

NUTRITION

Years of weight

by Susan Hardy

Don't wait until middle age to get in shape, says nutritionist June Stevens. The weight many people gain when they're young can shorten their lives even if they lose the extra pounds later.

Research in the past has linked being overweight as a young adult to a higher risk of premature death. But the studies that made those connections didn't look at whether the problem is being overweight when you're young, or *still* being overweight as you age. Those studies also didn't examine how weight gain affects young adults in different racial groups. Some research has suggested that having a higher body mass index (BMI) is more risky for whites than for blacks.

Stevens and her team looked at weight records of almost fourteen thousand people at age twenty-five and again sometime in middle age. They found that for most people, extra weight at twenty-five mattered. If someone had a BMI five points higher than normal at age twenty-five, it meant a 28 percent higher risk of dying sometime in the two decades after the second time the subjects were weighed.

The risk went up regardless of whether people had gained or lost weight, whether they smoked or drank, whether they exercised, and how many years of school they'd attended. The one group for whom this wasn't true was black men, whose length of life didn't seem to be related to their weight at twenty-five.

If you were overweight as a young adult, Stevens says, "you *can* lower your risk by losing weight later. Our research definitely supports that. But you may not be able to lower your risk back to where it could have been if you had not been heavy when you were twenty-five." The message is less that losing weight as an adult is too late, she says, and more that watching your weight in your teens and early twenties *isn't* too early.

Americans in their twenties are about twice as likely to be obese as they were two decades ago, according to the Centers for Disease Control. "The health-care system is trying to prepare for what will happen as a result of that increase," Stevens says. Her research suggests that in order to stop the trend toward more deaths from illnesses related to obesity, more young people will have to learn to eat healthfully and exercise.

Scientists should also pay closer attention to the relationship between race and weight, she says. The studies that said it might not be so bad to have a higher BMI if you're black may not have their stats right. Among Americans with normal BMIs, black people on average are not living as long as white people, Stevens says, and that makes it hard to compare the two groups' risk of dying from any one cause. Many studies of weight also don't recruit enough nonwhite subjects to get reliable data. Stevens used data from a large study of arterial hardening, in which about a quarter of the study subjects are black.

June Stevens is a professor of nutrition and epidemiology in the Gillings School of Global Public Health. The Atherosclerosis Risk in Communities Study is supported by the National Heart, Lung, and Blood Institute.

MEDICINE

The pain of aging

by Margarite Nathe

If you're seventy-five or older and have to make a trip to the emergency room because of pain, doctors are less likely to give pain medication to you than to a younger patient with the same complaint.

Results of a seven-year study of patient data from emergency rooms across the United States show that 68 percent of patients aged thirty-five to fifty-four received medications for their pain, while only 49 percent of patients aged seventy-five and over received the same treatment. UNC researchers focused only on patients who were in emergency rooms specifically because of pain, based on hospitals' standard reason-for-visit codes. The researchers made adjustments for patients' sex, ethnicity, and pain severity. (Sixty-seven percent of older adults who had severe pain received pain medication; the number was 79 percent for middle-aged patients.)

"We're not exactly sure why this happens," says Timothy Platts-Mills, who led the study. "It may be because physicians are more concerned about potential side effects in this population."

Patients sixty-five and older account for some twenty million emergency room visits every year. Almost half of these visits are for the evaluation and treatment of pain.

Platts-Mills and his colleagues at UNC are now investigating side effects of common pain medications and the impact of post-injury pain on physical function in older adults. "To us, the gap we observe in pain management for older patients highlights the need to better understand how best to manage pain in older patients and understand the barriers to doing this," he says. "All patients, regardless of age, deserve to have relief from pain, especially when it is severe."

Timothy Platts-Mills is an assistant professor of emergency medicine in the School of Medicine. UNC coauthors of the study are Denise A. Esserman, D. Levin Brown, Andrey V. Bortsov, and Samuel A. McLean, all from the School of Medicine, and Philip D. Sloane, from the Gillings School of Global Public Health and the Cecil G. Sheps Center for Health Services Research. The study, published in the Annals of Emergency Medicine, *was funded by the National Institutes of Health.*

CAROLINA FINDINGS

Cigarette smoke causes a 60 percent drop in the levels of a protein that helps lung cells stay hydrated. A three-month injury-prevention program for soccer players had only a temporary benefit, but improvements seen after a nine-month program persisted for months after the training ended. It is safe to cut and paste together different viruses in an effort to create the ultimate vehicle for gene therapy. The type of mortgage

Above: *Self Portrait with Poppies* by Taylor Lancaster, 2011.

MENTAL HEALTH

The healing arts

by Mark Derewicz

On the third floor of UNC's Neurosciences Hospital you can see art from some very talented people. All of it's for sale. And all of it was produced by people with mental illnesses.

The *Brushes with Life* gallery celebrates art as a release from the anxiety and pain associated with often-misunderstood diseases. Julie Pace, an occupational therapist at UNC, oversees the gallery, which contains more than one hundred paintings, sculptures, drawings, and mixed-media creations. She works with other volunteers for six weeks—twice a year—to collect the art, choose which pieces to feature, frame them, and place them on the walls. Pace and her colleagues give their time because they witness the power of art therapy in UNC's clinic every day. And Pace has watched some talented artists hone their craft over the years while managing their diseases.

Detail, *Egyptian Symbols,* anonymous.

"Too often people with mental illness are portrayed as unpredictable and violent," she says. UNC research has shown that people with mental illness are no more likely than anyone else to commit violent acts. "In fact," says Pace, "they're more likely to be victims."

What people with mental illness want, she says, is the same thing everyone wants—to find happiness and become productive members of society. Art helps. Some *Brushes with Life* artists studied fine art in college. Some are avid photographers. Some have been sketching for years. And some have no art background. But take a stroll through the gallery and you'll see that all of them are artists with voices, with personalities, and with stories.

Julie Pace is an occupational therapist who works with volunteers at the UNC Center for Excellence in Community Mental Health to install the gallery. The current exhibit was funded by a UNC Hospitals' Volunteer Services grant and an anonymous donor.

Kite by Claudia Moon, 2011.

Self Portrait with Mind by Taylor Lancaster, 2011.

a borrower has can have a greater impact on the borrower's ability to avoid foreclosure than income or credit history. Compared to pain-free individuals, people suffering from temporomandibular joint disorder are much more sensitive to mildly painful sensations, more aware of bodily sensations, and experience greater heart rate increases during mild physical and psychological stress. Over the past thirty years U.S. adults have been eating larger portions and eating more often.

ARCHAEOLOGY

Campus digs

by Mark Derewicz

The pig bones and broken dishes gave it away.

As construction workers dug a trench to replace a stormwater pipe at UNC's Vance Hall, they unearthed stuff they usually don't find. They stopped digging and archaeologists Brett Riggs and Stephen Davis started investigating.

For several days between November 14, 2011, and Thanksgiving, students working with Riggs and Davis used small tools to scrape dirt into buckets to reveal the past. Grad student David Cranford scraped loose a tooth, put it up to his lips, and made a funny face. "Pig incisor," Riggs says. "We've found a lot of pig bones." Another grad student, Mary Beth Fitts, found fragments of kitchen dishes. Some were locally made. Others had been made in England. She also found cellophane wrappers. That was odd. Clearly the wrappers didn't date back two hundred years. They kept digging.

Construction workers on a job near Vance Hall unearthed stuff they usually don't find: bones, fragments of dishes. Brett Riggs and Stephen Davis could dig it.

As the evidence piled up—glass, bricks, and more bones and dishes—Riggs and Davis realized they had probably uncovered a shallow cellar from the 1790s that had been part of a detached kitchen for a private residence.

Graduate student Mary Beth Fitts works carefully to remove dirt from around a fragment of a plate outside Vance Hall. Photo by Mark Derewicz.

On the other side of the excavation the students found a canal encased in large stones. Riggs says it's the remnants of a water drain or, more likely, a sewer from a private residence whose owners ran a store on the same property. The sewer, probably built in the 1820s, extends several meters into the quad, where it would have fed into a larger drain that runs from the south part of McCorkle Place north toward Franklin Street. The researchers took large stones off the top of the sewer that was stuffed with soil. There Fitts found more cellophane wrappers and the reason for them: a rat's nest. No one was home—just some trash. She also found more kitchenware from the 1830s and a cow bone.

"This is a study in urban archaeology," Riggs says. "We have feature upon feature upon feature. What brought this to our attention was all the stuff they dug up—nails, lots of glass, bone, china." On the other side of the pit there's the 1820s sewer. There's a lot of clay overlying the cellar and the sewer; the clay was probably added as fill when Vance Hall was built. Dividing the pit is a metal pipe sticking out from under the building. "No one seems to know what that conduit is," Riggs says. "Maybe it's an old gas line. Maybe there are live electrical wires in there." But the rusting pipe is definitely more modern than the artifacts. And now there's a new white stormwater pipe that construction workers put in place this fall.

The dig is the latest of several Davis has led across campus during the last twenty years. "Small projects like this one provide new information about the people who lived, worked, and studied in Chapel Hill during the university's earliest years," he says. "They also provide a convenient yet valuable opportunity for students to participate in archaeological fieldwork." Davis and Riggs will work with students in spring 2012 to analyze their findings.

Stephen Davis is the associate director of UNC's Research Laboratories of Archaeology, and Brett Riggs is a research archaeologist in the Research Laboratories of Archaeology.

VISUAL ARTS

Geoluminous

by Margarite Nathe

Michael Gurganus didn't use Photoshop to pretty-up any of these rocks. Instead he used an old-fashioned color processor—a piece of equipment most photographers think of as obsolete—and a collection of carefully chosen rocks, minerals, and gemstones to create his photographs. The technique draws a whole new depth, color, and light from the stones, he says.

Gurganus puts each rock face-down onto a sheet of photo negative paper and exposes it to the light. (There are no film negatives involved—the stones are the negatives.) As the light shines through and reflects off the stone's facets, the color processor creates a negative print that reveals details in the rock that are invisible to the naked eye. A chip of milky quartz may look dull and monochromatic at first, but the light exposes a whole array of surprising, luminous colors. The resulting prints invert the images and create their opposites—light shades appear dark, green turns to red, and so on.

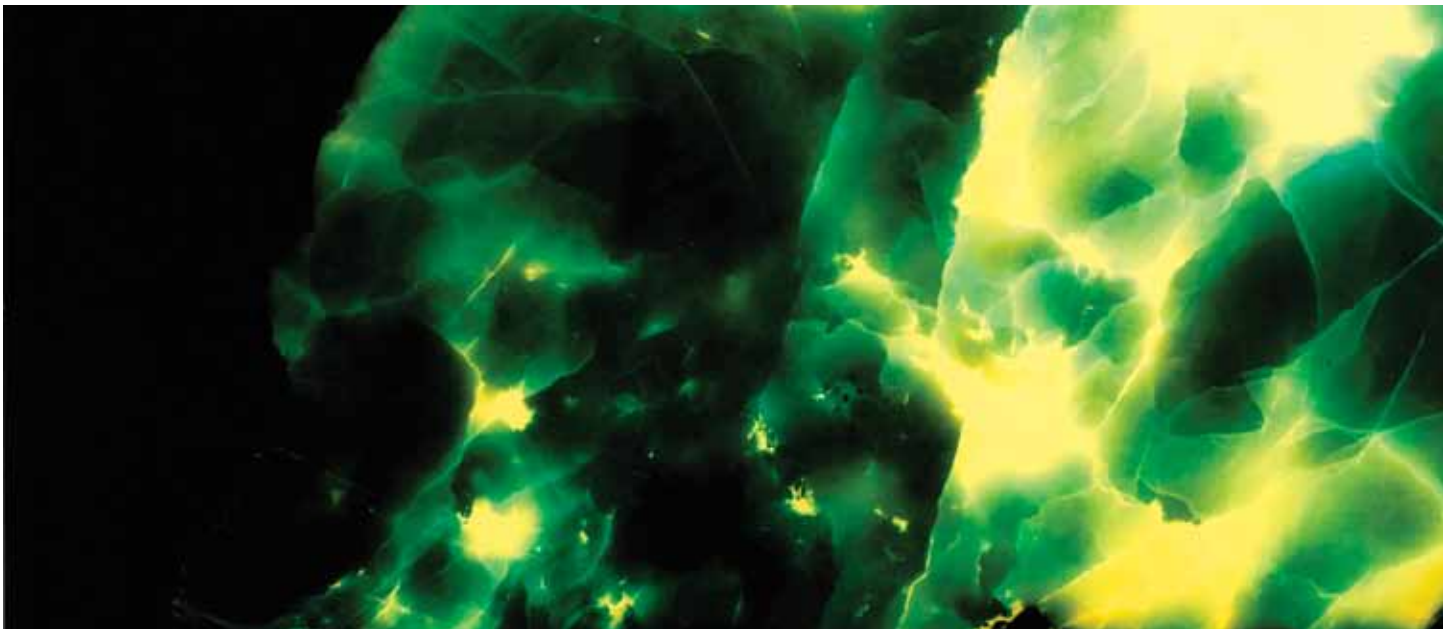
The color processor uses all the same chemicals that are involved in developing photos by hand, Gurganus says, but they're contained within the processor. By manipulating the settings on the machine, he can bring out colors from opposite ends of the color wheel and create all kinds of effects. But the color processor isn't a technology that's often used anymore, he says. UNC's Department of Art keeps the equipment as a teaching tool to help students learn about analog photography techniques before they move on to digital photography.

An old technique yields new depth, color, and light from stones.

Gurganus grew up in Durham, North Carolina, during the 1960s. He's been taking and developing photographs since he was seven years old.

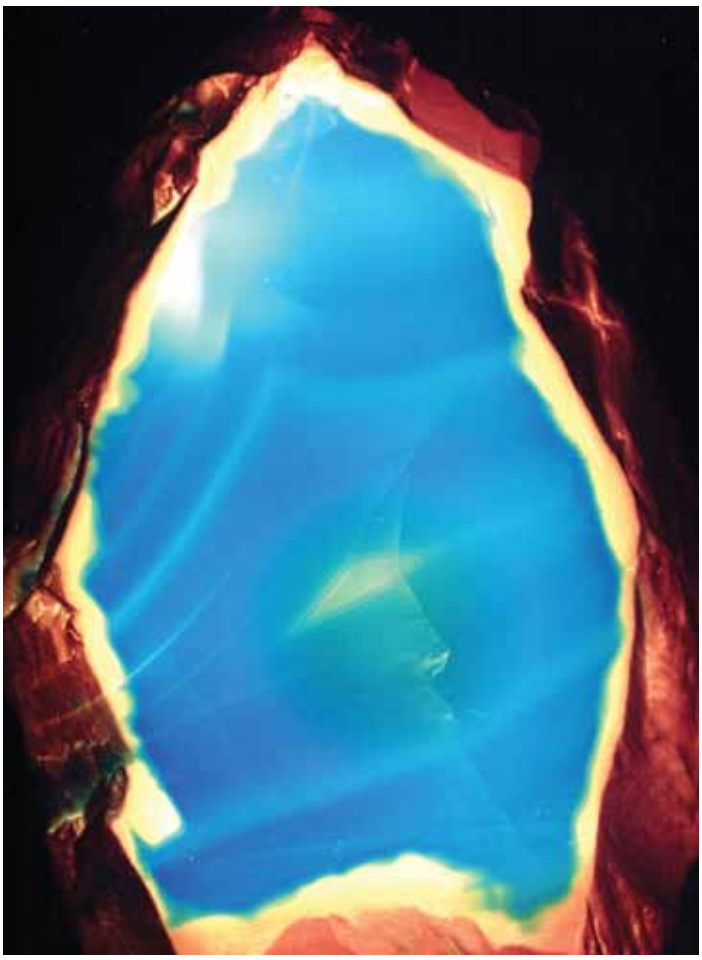
Michael Gurganus is a senior majoring in visual communications in Carolina's School of Journalism and Mass Communication. See more of his work at gurganusphotography.com.

A cellular protein called Shc plays a central role in the formation of new blood vessels. When compared to Caucasians, African Americans suffer higher rates of multiple large-joint osteoarthritis and knee osteoarthritis, but are less likely to be affected by hand osteoarthritis. Patients with high-risk nonmelanoma skin cancer of the head and neck may benefit from radiotherapy combined with chemotherapy. Only ten to twelve steps are necessary to synthesize the anticoagulant drug heparin



Gurganus puts the stone face-down onto photo negative paper and exposes it to the light. As the light shines through and reflects off the stone's facets, the color processor creates a negative print. Image by Michael Gurganus.

Gurganus collects geodes, or hollow stones that are filled with crystals. This one, he says, looks like fire. Image by Michael Gurganus.



Gurganus can manipulate the color processor to create all kinds of effects, he says, but it's not a technology that's often used anymore. Image by Michael Gurganus.

as a purer, less expensive drug with fewer side effects (existing methods use forty to fifty steps). Mexicans who migrate to the United States tend to eat more saturated fat, sugar, dessert, and salty snacks than they ate in Mexico. Obesity may make annual flu shots less effective. A protein called P-Rex1 is key to the movement of cells called melanoblasts. A protein called EWS-FLI1 alters the structure of DNA, leading to malignant bone and soft-tissue tumors in children and young adults.

THE PRICE OF PORK

North Carolina said no to new hog-waste lagoons.
Fifteen years later, the mess is still here.

by Susan Hardy ▪ photos by Donn Young

Let's say you're a North Carolina hog farmer.

Your father grew hogs. Maybe his father did, too. Or maybe they grew tobacco, back when it was subsidized. Either way, farming's what you know. So you're a hog farmer.

But this isn't your grandfather's farm. He owned the hogs he raised; yours belong to a corporation. The corporation told you how to build your barn and how to raise the animals. It owns the feed, the trucks, the veterinary supplies.

What do you own? The waste. You have three thousand hogs, each one producing several times the waste that a human being does. You're operating at a small margin; you don't have the money to experiment with an expensive new waste-management system. So you do what big hog farms have been doing since the 1970s: collect the waste, flush it into an open pit, and get rid of it by spraying it on your fields.

Maybe there's a school not far from one end of your property. Or maybe a well, or a creek that runs into the river in the next county. But your waste system was designed by engineers who said it was nondischarging, meaning that the waste and its effects stay on your land. The main thing on your mind is your contract with the corporation. It's going to be up soon, and you need it renewed—you've got a twenty-year mortgage to pay off on your barn. If you can't pay your mortgage, you'll lose your farm.

That's one side of the story.

Now let's say you're not the hog farmer; you're a woman living in a little house nearby. Chances are you don't have much money. Maybe your husband works on the hog farm. Maybe that's what puts food on the table right now. If it weren't for that farm, a lot of people you know would be out of a job.

But sometimes, when the wind is strong, you find a mist of hog waste on your windows and your car. Maybe one of your kids has asthma, and you notice that he wheezes more when you can smell the rotten-egg odor of waste in the air. Sometimes the stench is so bad it seeps into your curtains, your furniture, even your clothing. Your kids tell you they get teased at school for smelling like hog feces. You'd like to move somewhere where it's clean and the air smells sweet, but you don't have the money to pick up and start over. So you stay.

These are parts of the stories epidemiologist Steve Wing heard when he started visiting hog farming communities back in 1995. He's watched as some things have changed in the seventeen years since: in 1997 the North Carolina General Assembly placed a moratorium on building hog farms that use the traditional waste pits and spraying methods, and in 2007 the moratorium became law. The state and the industry have put money into studying hog-waste management and its environmental effects.

But North Carolina still has more than twenty-four hundred hog farms, built or permitted before the moratorium, that use the waste pits. And Wing and his colleagues are still uncovering damage to human health, and to the air and water, that they say can be traced back to the waste.

For Wing, it started with a phone call from the Concerned Citizens of Tillery in Halifax County. Help, they said. We know there are problems with the farms here, but without scientific evidence, no one can do anything about it.

His first response: "What's wrong with hog farming?" Wing lived in Chatham County. He knew people who raised hogs—small farms with twenty or a hundred head.

Come and find out, the people in Halifax County told him. So he went, and what he thought he knew about hog farming was upended. He heard the stories of corporations driving out independent farmers. Waste that doesn't just smell bad, but drifts on the air into homes and schools. People who are too afraid of the hog industry's influence, or of losing their jobs, to speak up.

He learned how the traditional hog-waste management system works. The floors of the barns are grated; waste drops into a trough and is then flushed into a pit covering several acres or more. The pit, called a lagoon, is usually open to the air, and it's full of waste much more concentrated than what you'd find at a city sewage plant, with higher levels of bacteria such as fecal coliforms and *Salmonella*. The waste also contains antibiotics the hogs were given—often the same kinds of antibiotics used to treat human disease.

The liquid waste sits in the lagoon for six months, and then it's sprayed onto fields where commercial crops and other plants take up nitrogen and phosphorus from the waste. The idea is for the farm to use up all the waste it produces.

Hog waste mixed with water drains from the barns into lagoons, where it sits for several months before being sprayed onto fields.

Residents of areas near hog farms are disproportionately poor and nonwhite.

When it rains on fields where hog waste is sprayed, bacteria and nutrients run off into nearby waterways, Mark Sobsey says.

One of the things Wing saw that hit him hardest wasn't pollution: it was a map. "It was at a black church," he says, "and they had a county map with red pins for the swine operations, green pins for the black schools, and yellow pins for the black churches." The group was trying to show that the farms had been built disproportionately in places where black people lived.

Wing put together census data from the areas around all of North Carolina's twenty-four hundred hog farms with waste lagoons. He found that yes, the areas of the state that are the least white—and that have the most poverty—are the areas that have the most hog farming. Also, hog farms are concentrated in places where people depend on wells for their drinking water. (We'll come back to the water later.)

NORTH CAROLINA HAS MORE THAN TWENTY-FOUR HUNDRED HOG FARMS THAT USE WASTE LAGOONS.

The next thing that people Wing talked to wanted to know was whether air pollution from the farms was causing some of their health problems. Wing's team and his community partners planned a survey of people around four sites: a big hog farm, two cattle operations, and a rural area that didn't have any large livestock operations. The researchers went to fifty homes within two miles of each of the farms and asked about symptoms that are often caused by air pollution—headaches, burning eyes, coughing. They also asked about symptoms that aren't typically related to air pollution, such as blurred vision and hearing problems. The researchers who did the interviews were accompanied by local people contracted to work on the study, Wing says, so residents were usually willing to talk to them.

The results backed up what anecdotes had suggested: people near the hog farm reported more symptoms than did people near cattle farms or away from big farming. And the symptoms they reported were the ones related to air pollution.

The study strongly *suggested* there was a problem with the air, Wing says, but he wanted to do something no one else had tried yet: track pollutants in air near the farms while tracking symptoms at the same time. In this study, residents in sixteen hog-farming communities measured their lung function twice a day with personal respiratory monitors. Wing and his team found that three things were happening at the same time: respiratory symptoms, decreased lung function, and pollutants such as fine particles present in the air.

Now the researchers are doing the same kind of study in schools. In the past, they've found more reports of asthma symptoms from middle school students in schools where staff report smelling hog odors inside more than twice per month. So the researchers decided to investigate air quality and respiratory symptoms in schools close to hog farms.

It isn't as unusual as you might think for a school to be near a big livestock operation, says land-use researcher David Salvesen. He and his collaborators have identified 79 North Carolina schools within one mile of big hog farms, and another 179 within two miles. In some cases the schools were built and the farms moved in later, he says, but in others the farms were actually there first.

"In some states you can't build a school close to a waste site," Salvesen says, "but North Carolina's Department of Public Instruction doesn't say anything about that. So school boards make these decisions without any guidance." Often they choose sites away from town, so schools can have more land, he says—more space means more buildings, more sports teams, more athletic fields.

Twenty-five years ago there were fifteen thousand North Carolina farms keeping hogs; now there are about three thousand. In 1992, there were a just over five million hogs in the state. Today, there are nine million.

These are the same rural areas where you'll find the big farms.

This would be okay if hog farms were keeping all of their own waste like they're supposed to. But waste pollutants are getting into more than just the air.

When Hurricane Floyd hit North Carolina in 1999, it flooded much of the eastern part of the state. The N.C. Department of Environment and Natural Resources reported that lagoons at forty-five hog farms overflowed during the flooding. But when Wing and two of his colleagues took satellite images of the flooded areas and overlaid them with a map of the state's hog farms, they found that more than two hundred other farms were in flooded areas.

That means that many more lagoons than were reported probably flooded, Wing says, and many barns with waste in them certainly flooded. By his analysis, more than half the households near farms in the flooded areas depended on well water. There was nothing to protect those wells from contamination if waste made it into the groundwater during the flood.

Floyd caused the worst flooding in North Carolina in five hundred years; the whole state, including the hog industry, was caught unprepared. But the rules for how much room farmers are supposed to leave in their waste lagoons are based on the heaviest rainfall scientists predict will occur in *twenty-five* years (up to nine inches of rain in twenty-four hours). This means that if a lagoon is in operation for more than twenty-five years, chances are high that it will encounter a storm it wasn't designed to handle. And that's if the farmer, whose operation is inspected by the Division of Water Quality once a year, is playing by the rules.

Floyd was the last of several major problems the North Carolina hog industry had in the 1990s with breached lagoons, contaminated waterways, and nutrients from waste stimulating fish-killing algae growth. This led N.C. Attorney General Mike Easley, then campaigning to be governor, to make a deal with North Carolina's biggest hog producers to replace the lagoon system with environmentally superior technologies. Smithfield Foods, the largest producer, by then had contracts with more than twelve hundred North Carolina farmers. The company promised to give the farmers money to convert to the new waste-management system.

The agreement sounded good—except that no one knew what that new waste-management system would be. Under the agreement, Smithfield funded research led by NC State University to find a good replacement for open lagoons and spray fields: something that would control odor, deal with nutrients such as nitrogen and phosphorus, and kill pathogens in the waste. The lead

researcher asked Mark Sobsey, a water quality expert at Carolina, to evaluate how well waste-management systems disposed of bacteria.

He and his collaborators found that the standard treatment—holding hog waste in a pit for six months—reduces the percentage of bacteria in waste by 90 to 99 percent. That sounds impressive, Sobsey says, but the concentration in the raw waste to begin with is up to a hundred million bacteria per quarter cup. "If you bring that down 99 percent," he says, "it's still several hundred thousand bacteria or more." Compare that to human waste, diluted with water and processed in a sewage treatment plant: it might end up with a few hundred bacteria in a quarter cup.

In theory, hog waste stays on the land where it's sprayed; in practice, Sobsey says, waste runs off into streams during rain. When Sobsey tests waterways and groundwater adjacent to hog farms, he finds higher-than-normal levels of *E. coli* and other bacteria. He's found unusual amounts of bacteria in the air downwind of hog farms, too, that he says escape into the open air when barns are ventilated.

It's not just the numbers of bacteria that concern Sobsey; it's the fact that these bacteria come from hogs that have been fed antibiotics that make the hogs grow faster. He's found antibiotic-resistant *E. coli* in groundwater on swine farms. These strains sometimes turn up on crop farms, too, but in much lower numbers.

Sobsey and his colleagues studied different waste-management systems—constructed wetlands, biofiltration, even a composting system that grows fly larvae for livestock feed—and found that several of the systems did much better than the lagoons at everything: controlling odor, recycling nutrients, killing pathogens. The best system overall, called Super Soil, separates waste into solids for fertilizer and liquid for irrigation and reuse in hog farms.

Super Soil works well, but so far it's been judged too expensive to fulfill the terms of the deal between the state attorney general and Smithfield. The designer of Super Soil is still working to bring down the cost, says School of Government professor Richard Whisnant, who led the committee to evaluate the economic impact of the technologies. If the system could be installed and maintained on most farms for a price that the North Carolina hog industry could recover from, the Smithfield Agreement might still be fulfilled.

Meanwhile, the N.C. General Assembly has outlawed new lagoons, saying that newly built farms, however they handle waste, will need to be more environmentally sound. But these standards don't apply to the old lagoons—some of which aren't even as old as the moratorium.

In 1997, North Carolina was home to about eight million hogs. Today, there are nine million. The industry has been able to keep growing in part by continuing to build on land that was bought and permitted before the lagoon moratorium took effect.

Hog farming now makes up almost a quarter of North Carolina's agricultural income. The old methods of waste management are deeply entrenched. Progress on cleaning up the industry seems to be at a standstill, but Sobsey is still publishing new research.

Left: Hog-waste lagoons can cover several acres and hold millions of gallons of waste.

Mark Sobsey and his colleagues studied several hog-waste management systems. The best overall, called Super Soil, separates waste into solids for fertilizer and liquid for irrigation and reuse in hog farms. It works well, but so far it's been judged too expensive to fulfill the terms of the deal between the state attorney general and Smithfield.

"We know that bacteria are getting off the farms," he says, "but we don't know yet how far they go, and exactly what the risks are."

He did a pilot study several years ago that showed that people who work on hog farms have more antibiotic-resistant bacteria in their digestive systems than people who work on crop farms. He hasn't been able to find money to follow up that study. Research on bacteria in livestock waste doesn't fit neatly into the aims of any major funding agency, he says. If he were just looking at problems *on* the farms, he'd go to the USDA or the FDA. If the research was all *off* the farms, he'd go to the EPA. But he's working in a gray area in between. There's no federal funding agency devoted to problems that affect the entire water cycle.

Steve Wing is helping start up a study of water in hog farming communities with microbiologist Jill Stewart, who tracks bacteria back to their source by examining their genetic codes. The Concerned Citizens of Tillery and other groups working with Wing are worried about their wells, many of which are shallow and susceptible to groundwater pollution.

IT'S NOT JUST THE NUMBERS OF BACTERIA THAT CONCERN SOBSEY; IT'S THE FACT THAT THESE BACTERIA COME FROM HOGS THAT HAVE BEEN FED ANTIBIOTICS THAT MAKE THE HOGS GROW FASTER.

And the hog farmer stuck with a mortgage? He may not even be in business anymore. Twenty-five years ago there were fifteen thousand N.C. farms keeping hogs; now there are about three thousand. Most of those are contractors for Smithfield Foods; a few are still independents. Some are using alternative waste-management systems. Many are struggling to survive. All the farmers are left not knowing when tougher regulation will come, or who will absorb the costs if it does.

Steve Wing is an associate professor of epidemiology, Mark Sobsey is a Kenan Distinguished Professor of Environmental Sciences and Engineering, and Jill Stewart is an assistant professor of environmental sciences and engineering, all in the Gillings School of Global Public Health. Wing's research was funded by the National Institute of Environmental Health Sciences and the N.C. Department of Health and Human Services. David Salvesen is a member of UNC's Institute for the Environment. Richard Whisnant is a professor of public law and government in the School of Government, and the former general counsel for the N.C. Department of Environment and Natural Resources.

This smog chamber helps William Vizuete and his colleagues at the UNC Gillings School of Global Public Health create nearly any kind of atmospheric concoction they can think up. They can pipe it into a lab and test the effects of pollution on human cells. Now they want to take their show on the road. Photo by Mark Derewicz.

A MATTER OF PARTICULATES

THERE'S A PROBLEM WITH HOW SCIENTISTS DETERMINE AIR QUALITY. WILLIAM VIZUETE THINKS HE KNOWS HOW TO SOLVE IT.

BY MARK DEREWICZ

Fifteen years ago, while driving west through southern California, I watched the brilliant blue sky turn ominous, an orangey-brown hue foreign to my eastern eyes. Was a storm approaching? Then it hit me; it was just Los Angeles.

Why did the sky look so gruesome? Car exhaust, I thought, and the fact that LA sits in a sun-drenched valley. But I was ignorant of the reason that smog is visible: particles. Smog is full of tiny toxic blobs that turn the horizon ugly as they bake in the sunlight. They can cause severe health problems from asthma attacks to lung cancer. That's why the EPA regulates those kinds of particles. But the methods scientists use to pinpoint the nastiest particles are far from perfect, according to chemical engineer William Vizuete. "We're not even sure what happens in our bodies when we breathe in the particles that wind up killing us," he says. To find out, scientists need better ways to study how particles interact with living cells. Vizuete thinks his team has built a better way—a device they can take on the road to test the air anywhere.

Burning wood, coal, gasoline, or just about anything else creates particles as byproducts. The particles combine with each other and gases attach to them. The two main sizes of particles, by the EPA's reckoning, are pm 2.5 and pm 10. The *pm* stands for particulate matter and the *2.5* means 2.5 micrometers in diameter. (A strand of human hair has a diameter of about 480 micrometers.) Researchers have found that particles smaller than 2.5 micrometers can lodge deep in our lungs and trigger disease. The larger particles can lodge in our upper airways and cause problems there.

Epidemiologists have found that hospital visits for respiratory ailments increase as air quality worsens. But in lab experi-

ments, toxicologists haven't been able to show why. They've tested the effects of automobile exhaust on live human lung cells, on mice, and directly on humans, but they haven't witnessed the same sort of adverse effects that epidemiologists find in hospital patients. "Toxicologists have to increase the particulate matter one hundredfold to get the same effect," Vizuete says.

There are probably a few reasons for this. People rarely inhale fresh car exhaust, he says. We breathe pollution that's been in the air a while, and that makes it different from pure car exhaust. Also, toxicology tests don't mirror reality. "When toxicologists run their experiments, they pump exhaust through a filter to capture particles," Vizuete says. "Then they scrape off the particles into a liquid solution and drip it onto lung cells or feed it to mice." Then they measure how the cells or mice respond. "The test is simple, cheap, and convenient," he says. "But we don't like it. The liquid causes the particles to cluster, losing their original size and shape. People don't breathe liquid, and that solution strips off a lot of stuff that had been attached to particles." Stuff such as gases, which can change how particles interact with live cells.

So UNC scientists created an alternative. They pump exhaust into a Teflon film chamber atop the Gillings School of Global Public Health and let the exhaust age in sunlight. Then, instead of using the standard liquid toxicology test, Vizuete and his colleagues use a more accurate system of their own devising.

In 2002, atmospheric chemist Harvey Jeffries wanted to build a better air quality testing system. He looked at a contraption in his house that uses an electrostatic field to filter out particulate matter. Jeffries wondered if he could mount a special plate on his device, put cells on that plate, and use the electrostatic field to force the particles onto the cells to see what happened. His colleague David Leith reminded him that there was a similar machine—an electrostatic precipitator—in a lab in Rosenau Hall. They dusted it off, replaced the electronics, and created a special receptacle to house the cells. "We still have this prototype," Jeffries says. "And it still works."

Jeffries, Leith, Vizuete, atmospheric chemist Ken Sexton, and others at UNC have used that piece of equipment to test the effects of bad air quality on lung cells. In one test, Jeffries and toxicologist Ilona Jaspers exposed lung cells to fresh diesel exhaust and found that the exhaust causes lung cells to secrete a signaling protein called interleukin-8, which is usually associated with inflammation. Then Jaspers decided to see what would happen to lung cells exposed to diesel exhaust that had been aged in sunlight over the course of a day. Turned out, aged exhaust caused an inflammatory response about five times greater than fresh exhaust did.

"THE IDEA IS TO PUT THE DEVICE IN SCHOOLS OR SELL IT TO ANYONE INTERESTED IN TESTING THE TOXICITY OF AIR," VIZUETE SAYS. COMMUNITIES CLOSE TO REFINERIES, HE SAYS, MIGHT LIKE TO KNOW IF THE AIR THERE IS LESS THAN OPTIMAL. VIZUETE AND OTHER RESEARCHERS NEED SUCH A SYSTEM SO THEY CAN FIGURE OUT HOW CERTAIN PARTICLES BECOME TOXIC, AND THEN STUDY WHAT THAT TOXICITY DOES TO DIFFERENT KINDS OF CELLS AND GENES.

UNC researchers are now using this technique to find out how different cell lines, various species of mice, and different human genes respond to toxic air. But all their tests have to be run at UNC using piped-in air from the rooftop chambers because the repurposed electrostatic precipitator is connected to equipment the size of a large refrigerator. It can't be hauled out to Los Angeles, for instance, to test the air there.

Vizuete had the idea to make a smaller, portable version. Something that could maintain a stable temperature and humidity level, like an incubator or a human body.

It took a few years, but Vizuete's team designed and built a working prototype. The size of a briefcase, it's a white plastic box with tubes and wires connected to disembodied electronics. The device sucks in air that flows through an ionic-charge field to charge the particles. Then the air flows beneath a plate of the same charge so that the particles are repelled downward onto a waiting tray of cells. Early tests have shown the patented device to be sixteen times more sensitive than the traditional liquid solution method. And Jaspers has used it to accurately replicate her experiment with aged exhaust and interleukin-8.

The prototype has gotten the attention of the EPA, which is letting Vizuete's team conduct field-site tests in Raleigh and might buy several prototypes for its researchers to experiment with. "The goal is to get feedback from them," Vizuete says, and then make any necessary modifications. If all goes well, Vizuete and colleagues will make the device commercially available through their startup company, BioDeptronix.

"The idea is to put the device in schools or sell it to anyone interested in testing the toxicity of air," Vizuete says. Communities close to refineries, he says, might like to know if the air there is less than optimal. Vizuete and other researchers need such a system so they can figure out how certain particles become toxic, and then study what that toxicity does to different kinds of cells and genes.

Vizuete's team has already used the device to see what nontoxic particles do to lung cells: very little. Then Vizuete put the nontoxic particles with gases found in a typical urban atmosphere and ran the mixture through the new exposure system. "We proved that the inert nontoxic particle was made toxic by these other gases," he says. The mass of the particle had nothing to do with the toxicity; it was all about the gases the particle was in.

"That's kind of scary," he says, "because our regulations are based on mass. That's the easiest and simplest to get at." But mass and size are only part of the story. e

William Vizuete is an assistant professor, Ilona Jaspers is an associate professor, and Harvey Jeffries is a professor emeritus of environmental sciences and engineering, all in the Gillings School of Global Public Health. Ilona Jaspers is also an associate professor in the Department of Pediatrics and the Department of Microbiology and Immunology in the School of Medicine. They received a Gillings Innovation Lab Grant and a small business grant from the National Institutes of Health and the U.S. Department of Defense to commercialize the device through BioDeptronix, LLC, the company they cofounded with Gillings School of Global Public Health professor David Leith and research assistant professor Ken Sexton.

SIGNAL TO NOISE

We know more about fragile X syndrome than any other piece of the autism puzzle. How close are we to a cure? ▪ by Margarite Nathe ▪ photos by Donn Young

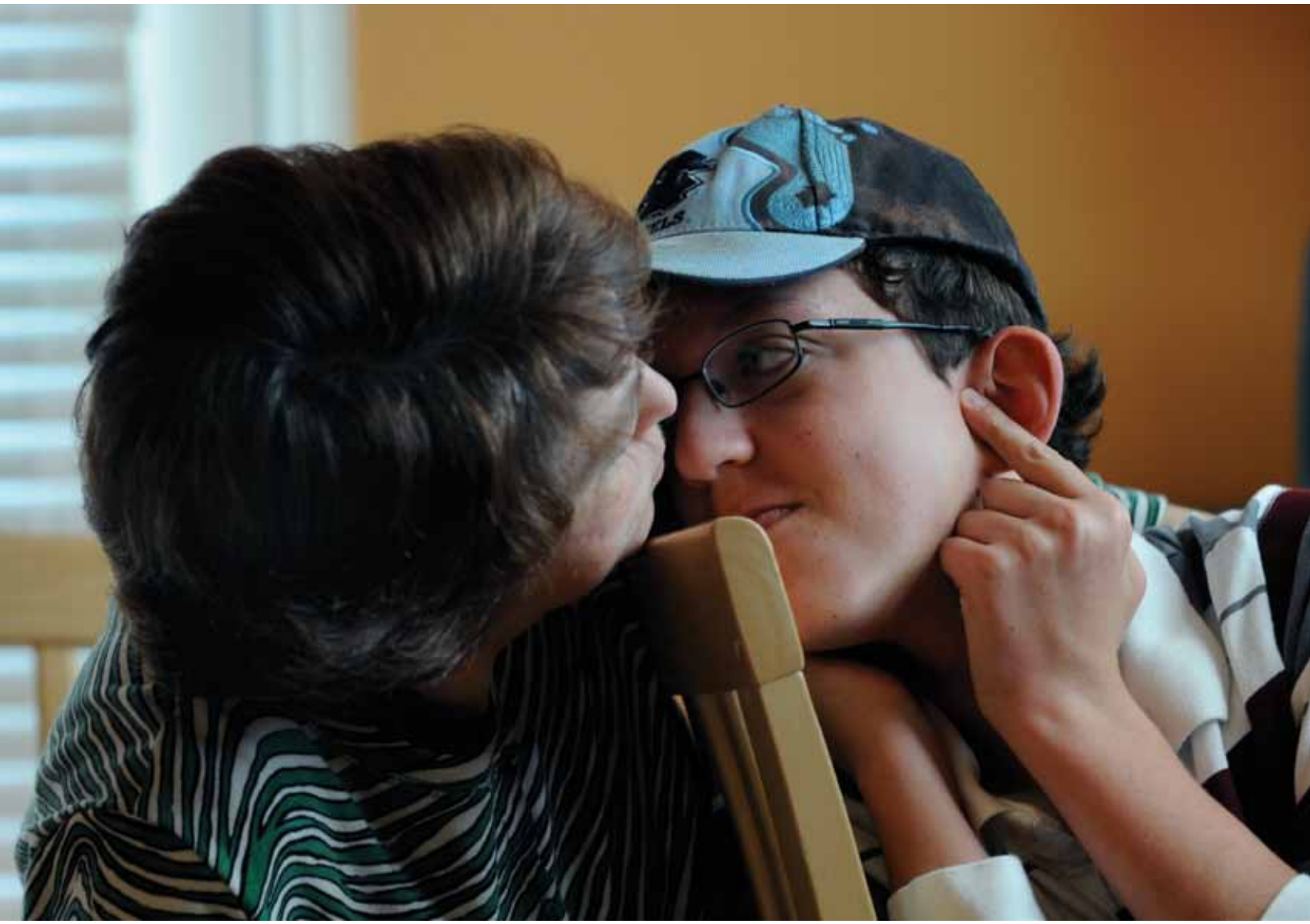
Imagine you're listening to the radio. You hear music. But there's a lot of static, too—noise that butts in from all over the place and muddies the signal. The static is distracting and frustrating and no matter how you mess with the dial, it won't go away. Now imagine you can't turn the radio off. That's sort of what it's like inside Adam Strom's brain.

Adam has fragile X syndrome, a genetic condition that can be synonymous with a lot of things: learning disabilities, intellectual disability, seizure disorders. A third of children diagnosed with fragile X, including Adam, also have autism. The syndrome is made up of a chaotic medley of symptoms that are different for each person. You could meet someone who has fragile X and never know it. That's one reason scientists have misunderstood it for so long.

One of Adam's symptoms is the static—the unending zap of stimulation from the sights and sounds around him, each of which demands the same attention from his brain regardless of importance. A typical human brain can tune out unimportant things in favor of more immediate concerns—an ongoing conversation, for example, rather than a squeaky door in the other room or a fly buzzing at the window.

Each of those things is a stimulus, a signal to the brain that sets off a flurry of synaptic activity and forges connections between nerve cells. When the brain recognizes a signal as something it doesn't need to pay attention to, the nerve cells calm down and stop producing the pay-attention protein they had begun to pump out. This synaptic

Right: Adam Strom with his mother, Teresa. It's hard for families to come to terms with having a genetic disability in the family, Adam's father Steve Strom says. "Everyone wants to have perfect genes and pass those on to their children. So there aren't a lot of conversations about it."



"A child with fragile X may not have any really, truly connected social conversations," says Linmarie Sikich, who runs clinical trials for developmental disorders and autism at UNC. "He may ask a lot of questions, like 'What are we going to do?' or repeat some piece of information over and over again, but he would still have a hard time answering questions like 'What did you do today?' or 'Are you happy?'"

activity is how we learn throughout our lives, and it's especially crucial for young, developing brains. But for children with fragile X syndrome, the cells don't calm down. The result is overstimulation, under-connectivity between nerve cells, and incessant static.

"There can be four things going on in a room, and Adam can't help but keep track of them all," says Steve Strom, Adam's dad. "He's aware of every detail of each of those things."

Adam started to show symptoms just after his first birthday, when he stopped learning new words and started losing muscle tone. "His skin got so loose, he looked like an old man," Steve says. Adam was still a happy baby, though, and didn't have a lot of the other developmental problems many babies with fragile X have—jerky movements, poor eye contact, incessant crying. There can be speechlessness, anxiety, aggression, hyperactivity, and tantrums that go on for hours. Some kids repeat phrases or sounds over and over again, rock back and forth, flap their hands, chew on themselves and their clothes. Some have what doctors call sensory defensiveness, which means, among other things, that they don't like to be touched. Then others, like Adam, are serial huggers.

Fragile X is the most common cause of inherited mental impairment. Symptoms can be similar to those of Down syndrome.

The "fragile X gene" that scientists talk about wasn't discovered until 1991, just a few years before Adam was born. "For many years in this business, we just sort of lumped children and people together as having developmental delay or intellectual disability," says Joe Piven, who studies the neural mechanisms involved in autism. "Being able to identify a gene that's responsible for this whole set of behavioral, cognitive, and medical problems really catapulted the whole field forward. Fragile X is a huge window of opportunity for understanding not only intellectual disability but also autism."

Researchers all over the world think

Teresa Strom now works as a social worker with foster and adoption agencies as an advocate for kids with developmental disabilities. She's a graduate of UNC's School of Social Work.

a fragile X cure—or the nearest thing to it—could be as little as ten years away. And researchers at UNC are getting closer to it.

In the family

Everyone has the fragile X gene, also known as FMR1—it's situated on the tip of the X chromosome. But an alteration in the gene can cause it to expand and mutate beyond its normal range, causing that spot on the chromosome to swell. Under a microscope, the tips of the X look fragile, like they're about to break off. This mutation is what leads to the syndrome.

Over a million people in the United States alone have the altered gene, although most of them don't know they're carriers. Other than a known family history of fragile X, there are few or no warning signs that lead people to get tested. Fragile X can hide in families for generations as carriers unknowingly pass the altered gene along to their children. But eventually, somewhere in the family, a baby is born who has a fully mutated version of the gene, which leads to the syndrome. That's what happened in Adam's mother's family.

Teresa Strom's grandparents were farmers in east Tennessee whose tenth child, Teresa's uncle, was known to be "a little slow." The doctors told his mother that it was probably because she'd had asthma during her pregnancy. Not until 1995, after Teresa's uncle was in his fifties, was he finally diagnosed. "He went to a new doctor for a change in his medication," Teresa says. "The doctor walked into the room and knew at first glance that he had fragile X."

Without the benefit of a blood test, many doctors don't recognize fragile X syndrome in babies or young children. Most kids who have it don't look different from others their age. But as kids with fragile X get older, they often develop a distinctive look: long faces, protruding ears, wide head circumferences.

No one in Teresa's family had ever heard of fragile X, but soon they learned that two of her first cousins also had it.

"We had been trying to get pregnant at that point," Teresa says. She'd had two miscarriages, which scientists now know are a common problem for women who are fragile X carriers. When she mentioned her newly discovered family history, her ob-gyn told her there was no reason to be concerned. But that was in the early days of fragile X research. There was a lot of misinformation going around.

Teresa found out she was a carrier (just like her father) around the time she found out she was pregnant with Adam. Then during the amniocentesis Teresa and Steve learned that, despite her doctor's reassurances, the child she was carrying had the full mutation. He would have fragile X syndrome when he was born.

Steve sighs. "That was agonizing," he says.

About 100,000 people in the United States have fragile X syndrome. Over a million are carriers, but most don't know it.

The autism link

No one really knows all the various causes of autism. But the discovery of the fragile X gene in 1991 changed everything for researchers all over the world. Suddenly they had an indisputable culprit for up to 6 percent of autism cases. Fragile X is now the most common known cause of autism.

"The issue with autism is that it's not one thing," Piven says. "We call it autism, but some people in the field are starting to call it 'the autisms.' Say somebody shows up at your doorstep and they're short of breath. You don't know if they've just run a race, or they just smoked a carton of cigarettes, or they have pneumonia, or they're having a heart attack. That's the situation with autism. We're now discovering that they don't all have the same thing."

Piven and his colleagues at UNC and Stanford just finished a study of brain images that show the differences between the developing brains of toddlers with autism caused by fragile X syndrome (like Adam) and toddlers who have autism with no known cause.

They looked at two MRI brain scans for each of fifty children, one at age two and another at age four. On an individual level, the MRIs didn't reveal much, says psychologist Heather Cody Hazlett, who worked on the study with Piven. To any radiologist, the

brains would look normal. But Hazlett and her colleagues used computers to process the images and convert them into quantitative data. That way Hazlett's team could measure the volume of various parts of the children's brains and compare the numbers across the group.

"With the two-year-olds," Piven says, "you wouldn't know the difference without a blood test. You might just think they had autism. Behaviorally, they were really similar." But the scans showed the real differences. The two-year-olds who had fragile X syndrome had larger-than-normal caudates, a part of the brain that is associated with repetitive behaviors. They also had smaller-than-normal amygdalae, which mediate social behaviors.

This is good news for researchers and for pharmaceutical companies. Knowing where in the brain the fragile X gene is expressed means scientists are one step closer to having a target for pharmaceutical treatments. Some of those treatments are in clinical trials now, including one at UNC.

Adam visits Linmarie Sikich on a regular basis while he takes part in a clinical trial for the drug Arbaclofen. Sikich has been running clinical trials for developmental disorders, autism, and early-onset schizophrenia for fourteen years. Arbaclofen can clear away some of the static for kids with fragile X, she says. UNC is one of a handful of hospitals across the country enrolling patients who want to try the drug.

Until about four years ago, most treatments for fragile X were behavior therapies and strictly controlled environments. "That was all we had to offer," Sikich says. Doctors tried to help by prescribing ADHD and anxiety drugs, but none have been quite right for fragile X patients. Now pharmaceutical companies are working to develop drugs specifically for fragile X, Sikich says, and Arbaclofen could be one of them. Sikich's trial may determine whether the drug improves patients' ability to learn, alleviates their irritable behaviors, eases their anxiety and repetitive tendencies, and—maybe most important—helps them function in social situations.

Interacting with others can be tough for kids with fragile X. Studies have shown that they have increased levels of cortisol—a stress hormone—during social interactions. Helping a child learn how to have a conversation can not only improve his cognitive functions (people tend to learn during social interactions) but also make things easier for the family. Here's an example, Sikich says: Say a family with a child with fragile X syndrome is going to a party. He might ask fifty times, "What are we going to do? Who are we going to see? When are we going to leave?" As his anxiety intensifies on the way to the party, so do his repetitive phrases and movements—rhythmic hugging, slapping, pushing, or crying. And once he gets to the party, the real overstimulation sets in. A meltdown becomes inevitable.

"Once they arrive, the child's repetitive behaviors are likely to become so intense

Some kids with fragile X repeat phrases or sounds over and over again, rock back and forth, flap their hands, chew on themselves and their clothes. Some have what doctors call sensory defensiveness: they don't like to be touched. Others, like Adam, are serial huggers.

and disruptive that the family has to leave abruptly," Sikich says. "But the same child, after treatment with Arbaclofen, may only ask 'What are we going to do?' five times instead of fifty. And he may have been able to talk to three or four people while they're at the party and even stay two hours without any meltdowns. In a couple of cases, there have been kids who have asked their parents for the first time, 'Do you want to play a game with me?' and kids who can provide a sentence or two in response to, 'What did you do in school today?' It's a huge difference for a family."

Opening doors

Developmental milestones loom large in many parents' minds. Baby should sit up at seven months, baby should babble at eight months, baby should use simple sentences by twenty-four months. Doctors often pooh-pooh first-time parents who get concerned if their baby is off-schedule. For babies with fragile X, this can have lifelong consequences *(read one mother's story at endeavors.unc.edu/brode)*. Steve and Teresa Strom were lucky. They knew that Adam had fragile X before he ever started to show symptoms. Most parents don't find out until their babies turn into toddlers.

As soon as Adam's symptoms started, his doctors helped Steve and Teresa enroll him in various therapies that were tailored to his needs. One was speech therapy, which helped Adam communicate through sign language. Steve says, "When I came home one day after work, Teresa said, 'Come here, I want to show you something.' She read a book to Adam, and Adam signed the word 'more,' telling her he wanted her to read it to him again. That opened a lot of doors for Adam."

Another was occupational therapy, the purpose of which for kids is the same as for adults: to help them function better at their jobs. A child's job is to play. It's how children learn, how they stimulate and understand their senses, and how they improve their motor skills. Adam's occupational therapist helped him play in a tire swing, which helped stop his muscle loss. Even today Adam loves to watch YouTube videos of other kids in occupational therapy sorting toys by color, scooting around on tricycles, playing on exercise balls. Sometimes he shows the videos to his own occupational therapist and asks for the same treatments.

Adam can now read several words. "Therapy" is one of them. He points out the word on a list of offices and departments that hangs next to the elevator in Medical School Wing D at UNC. Adam's father, Steve Strom, says, "Adam always wants to go to that floor. But we tell him no, he's going to see Dr. Sikich today."

All babies born in the United States are eligible for state-based early interventions—individualized therapy regimens that are tailored to each child's needs based on the severity of their impairments. Getting these therapies early, while a child's brain is in its crucial stages of development, can improve quality of life for children and their families for the rest of their lives. And although a simple blood test can screen babies for fragile X just after they're born, the testing isn't standard, so most families miss out on early treatments. At UNC Hospitals, researchers are now offering testing as part of the Fragile X Newborn Screening Study *(see "Screening for Fragile X," next page)*.

Animal models

"Adam was a jumper from early on," Steve Strom says. "He would stand up in his crib and jump and jump and jump." Eventually, after they upgraded from the crib to a bed, they bought Adam a mini trampoline to spare the new mattress. Sheryl Moy, who runs UNC's Mouse Behavior Phenotyping Laboratory, has seen the same kind of jumping in mice that were bred to have symptoms of autism and fragile X. One of her study videos shows a mouse vaulting up and down in the corner of its enclosure. "We call that jackhammer jumping," Moy says. "We counted up to eight hundred jumps during a single testing session. It's *extremely* athletic."

There are only two animal models for fragile X syndrome: mice and flies. In flies, the syndrome manifests itself mostly as a loss of circadian rhythm—the flies can't tell when it's day and when it's night. (Many kids with fragile X tend to wake up in the middle of the night.) Scientists can now completely eliminate symptoms in the fly model—in other words, cure them. Moy and her colleagues are now studying the more complex mouse model to see if we can do the same with them.

Teresa, Adam, and Steve Strom.

"Autism seems to be increasing in prevalence," Moy says, "and fragile X mice are one of the few genetic models that we can use to look at autism in a broader context. Of course, there's no way we'd be able to take something as complex as autism or fragile X syndrome and think that a mouse would show all of those symptoms, so we would never say, 'We have an autistic mouse.' But we can look at behaviors that are relevant." Figuring out how to treat symptoms and behaviors in the mouse models can teach us how to treat humans, she says.

Moy creates and runs behavioral tests for mice. She uses different strains of mice that were bred to have specific profiles and looks at how well they balance as they run along elevated beams, how they care for their young, where they like to sit in their enclosures. In the past, most tests for mouse social behavior were designed to look at aggression, sexual behavior, and maternal behavior. "But there wasn't a test to ask 'Does a mouse like social contact? Does it have social motivation?' And that's one of the problems with autism," she says. "It's not so much that the kids are aggressive. It's more that, in some cases, they're not interested in social interaction. They don't find it rewarding."

Moy and her colleagues created a test for the autism mice to find out whether they would rather be alone or with a mousy companion. The test—now standard in the field—begins when the mouse enters the middle room in a three-chambered box. From there it has three choices: it can a) stay in the middle room by itself; b) pass through a door to the left, where it will find another

mouse, referred to as the stranger, sitting inside a wire cage; or c) pass through a door on the right, where it will find an empty wire cage. (The empty cage is there to make sure the mouse isn't just drawn to the strange structure rather than the stranger inside it.) The chamber doors are equipped with photo beams that track how much time the mouse spends on each side and how many times it skitters back and forth.

The researchers found that most normal mice choose to hang out in the "social" chamber, where they can be with another mouse. They rear up, sniff at the cage, rattle their tails, or box (a show of aggression). "You can see the normal mice really seem to use this as an opportunity for social investigation," Moy says. The fragile X and autism mice generally don't show that social preference—they explore all the rooms equally.

Researchers also found that one strain of mice with autism-like behaviors, known as BALB/cJ, have smaller corpus callosums. This may be tied to their lack of social preference, Moy says, and it could provide a model for the same kind of brain under-connectivity that occurs in children with autism. She and other UNC researchers are now starting studies to find out if oxytocin, a hormone that's important in maternal behavior and social cognition, could promote social interaction. The researchers are still in the beginning stages, but tests so far suggest that mice treated with oxytocin spend more time sniffing and being sociable with other mice. "To us, this is extremely exciting," Moy says. "It suggests that this model could be used to develop therapeutic agents."

While clinical trials can offer hope and relief, not everyone has access to them. Teresa's uncle and cousins in Tennessee are five hours away from UNC Hospitals. And enrolling in a trial is a big commitment, Sikich says—it means frequent office visits, daily diaries, and the risk of being assigned a placebo rather than a new drug. But so far, the Arbaclofen has made a huge difference for Adam, Steve says. Adam is one of Sikich's long-term patients, so the Stroms will be among the first to know when new treatments become available.

"I'm not comfortable using the word 'cure' yet," Sikich says, "but I think we're very close to something that could modify the course of the disease. Not something that just slightly damps down symptoms, but that really changes learning, changes the anxiety. What can we do to provide the best treatments possible? How safe are the treatments? Unless we do the research at both the basic level and at the clinical-trial level, we'll never really know."

Adam is fourteen now. He's in eighth grade at a public school in Wake County where he's enrolled in an Autism 3 class. At school he goes to speech therapy, and outside of school he goes to occupational therapy and group singing therapy with Voices Together, a local nonprofit that serves people with developmental disabilities. "That's been fantastic for improving his performance in school," Steve says. "He's better at taking turns, answering questions, and helping other students. He's a trooper."

Joe Piven is Sarah Graham Kenan Professor of Psychiatry, Pediatrics, and Psychology and director of the Carolina Institute for Developmental Disabilities. Linmarie Sikich and Sheryl Moy are associate professors, and Heather Cody Hazlett is an assistant professor, all in the Department of Psychiatry in the School of Medicine. They're all investigators in the Carolina Institute for Developmental Disabilities, which brings together services for people with developmental disabilities, education/training for clinicians and scientists, and research. Steve Strom is executive director of The Arc of Wake County, which helps people who have developmental disabilities to live as independently as possible. Teresa Strom is a child welfare policy consultant with the N.C. Division of Social Services and a social worker whose experiences in child welfare, foster care, and adoption have allowed her to advocate for children with disabilities.

Web extra
Two of Pamela Brode's three sons were born with fragile X syndrome. Raising them while navigating a flawed health care system has been a wild ride, by turns terrifying, frustrating, and magical. Read about some of the things she's learned now that her boys are grown.
endeavors.unc.edu/brode

Screening for Fragile X

Fragile X screening is available to new parents at UNC Hospitals through the Fragile X Newborn Screening Study. If both parents agree, researchers will perform a simple heel-prick blood test just after the mother has given birth and before the parents leave the hospital.

Don Bailey and other UNC researchers in screening study are examining how parents make their choices about screening, and how those whose newborns test positive for fragile X deal with the news.

"So far, we've found that each family takes a different path," Bailey says. "Eventually they may consult with a medical geneticist and genetic counselor. They may go to the internet to read more about fragile X. They sometimes call the National Fragile X Foundation to learn more about what to expect. They inform other members of their family who may be at risk. They also start thinking about their other children and deciding whether to have them tested."

Early treatments can help the children and their families for the rest of their lives. But most babies with fragile X syndrome aren't diagnosed until they're toddlers. By then, their families have missed out on those early interventions.

The fragile X study touches on a larger controversy over genetic testing for newborns, Bailey says. Today newborns are routinely tested only for specific, treatable, life-threatening conditions. But some researchers say that whole-genome testing for newborns would be a far better way to help doctors find other serious health problems early, before symptoms even begin to show up. Would the benefits of foresight and early intervention outweigh the drawbacks? "With whole-genome screening for newborns, we'd be put in a really challenging position, because we'd learn hundreds of things about that baby," Bailey says. "And what do you disclose and what do you not disclose?"

Read more at: endeavors.unc.edu/fragile

Don Bailey is a research professor in the School of Education and the FPG Child Development Institute, and a distinguished fellow at RTI International.

JOHN BRUNO

TROUBLED WATERS

A marine massacre leads Carolina scientists to question the role of the ocean's most dangerous predator: humans. by Jason Smith

The bodies kept piling up. They were brought up one after another from the dark hold of the *Fer Mary I* and laid out on the deck, which was getting slippery from the water and blood. Ten bodies. Fifty. A hundred. Many had been gutted; some were beheaded. They were starting to get to John Bruno.

It was the largest illegal shark-fishing seizure the Galápagos National Park Service had ever carried out. As soon as Bruno heard that the boat had been seized, he petitioned the park service to let his team aboard. Not a lot is known about many of the shark species that live in the Galápagos, so Bruno asked if his team could identify, count, sex, and catalog the animals. A judge had to sign an eleventh-hour order approving Bruno's request. While the team waited, they rushed out to buy knives, gloves, coolers, a tape measure, and several thousand Ziploc bags. "But once we got out there," Bruno says, "we realized we were vastly unarmed for what we had to do."

The ship held 379 dead sharks. Their bodies, when totaled, weighed more than 48,000 pounds.

Bruno's team identified 303 bigeye thresh-ers (about half had their heads and tails cut off), 42 silkies, 24 blues, 5 smooth hammerheads (all had their hammers cut off), 2 tigers, 1 Galápagos shark, and 1 shortfin mako. The team couldn't identify one shark because the head, fins, tail, and part of the body were missing. Almost every shark's dorsal fin—what you picture slicing through the water when you think *shark*—had been severed. "This is what a marine massacre looks like," Bruno wrote the next day as he posted pictures on his blog. "It was one of the most depressing and intense days of my life. I felt like we were unearthing a mass grave in a war zone."

The team measured each animal, determined its sex, and removed the third through the fifth cervical vertebrae for genetic and population analysis. Then, in accordance with Ecuadorian law, they helped return the bodies to the ocean. To Bruno, it felt like a funeral at sea. "It was rough and windy and the sun was going down and all 379 sharks were dragged to a gap in the gunwale and eased in the water as the ship moved along," he told MSNBC. "They slowly sank, which

was for some reason the most powerful aspect of the whole day for a lot of people on board. Lots of tears were shed." The captain and two crew from the *Fer Mary I* were brought along so they could see that the researchers and the park service weren't themselves going to sell the sharks.

The *Fer Mary I*, which was based in Manta on the coast of Ecuador, had been longlining for sharks and swordfish. In the Galápagos Marine Reserve, that's illegal. Thirty fishermen were hauled off the boat to jail. Had they made it back home with their catch, they stood to make a killing: each shark's body, Bruno says, would have netted about two thousand dollars back in port. The animals' market value comes largely from their fins, which are used to make a soup that is popular in China.

Bruno and his team will use the vertebrae they removed to develop a kind of shark census for the area. Each vertebra contains growth rings, like those found in trees, that can help determine the age of each animal and how fast it grew. Each ring will also help the team determine the temperature of the water the animal was living in at the time. That will help the team establish habitat ranges for each individual and species, and will give them clues about where the animals live at different stages of their lives. And that information can help scientists and the park service figure out how to best protect them.

The team members were able to react to the ship's seizure so quickly because they were already stationed at Carolina's Galápagos Science Center on San Cristóbal Island. And when they put their normal research projects on hold to document the shark slaughter, it was all hands on deck—everyone who could help did. That's how Steve Walsh, who normally studies invasive plants and other land-use issues, found himself on a boat with rubber boots and gloves and a knife cutting vertebrae out of sharks. "It was horrific, gruesome, fascinating," he says. "We hope that something good might emerge from all of this: a greater understanding of sharks and their ecology. This contribution to scientific knowledge will benefit conservation in the Galápagos and beyond."

The ship held 379 dead sharks. Their bodies, when totaled, weighed more than 48,000 pounds.

All of the sharks on the *Fer Mary I* were species listed by the International Union for the Conservation of Nature as vulnerable or near-threatened. The ship's crew face three years in prison for fishing illegally and three more for capturing protected species. A judge released them to Ecuador, over six hundred miles from the scene of the crime, on the condition that they report every eight days to another judge in Manta. (The captain and chief engineer have to stay on San Cristóbal Island in the Galápagos until the end of the preliminary investigation.) In order for *any* of the fishermen to be prosecuted, they *all* have to show up in the Galápagos for their trial. Previous cases have suggested that that won't happen. "Without enforcement, legislation is meaningless," Bruno says. "For enforcement to work, the judicial system has to act as a partner."

On some level, Bruno understands why those fishermen were on the *Fer Mary I*. "People have to eat," he says. "People need jobs." Fishermen in the area have legally pulled so many sea cucumbers and lobsters out of the water that those fisheries are close to collapse. So now some people bait longlines for sharks.

But Bruno points out that many people have moved away from fishing and into jobs based on tourism. The ocean can still provide, he says, regardless of how you feel about sharks. "You don't have to care about the animals themselves," Bruno says. "But they're an economic resource to the area." He mentions that a globe-spanning study of shark-diving operations tagged the tourism value of each individual shark at a million dollars over the course of its lifetime. "The Galápagos Islands are one of the few places left that you can dive with sharks," he says. "Going to the Galápagos is like going to the Serengeti. You go to see wildlife, big predators. These marine animals need the same kinds of protection that terrestrial species have. They're worth far more alive and in their natural habitat than dead on a dinner plate or in a bowl of soup."

Workers from the Galápagos Science Center rest after hauling dozens of dead sharks from the hold of the *Fer Mary I*. Photo by John Bruno.

John Bruno is an associate professor of marine sciences in the College of Arts and Sciences. Follow his blog at www.theseamonster.net. Steve Walsh is the director of the UNC Center for Galápagos Studies, codirector of the Galápagos Science Center on San Cristóbal Island, and a professor of geography in the College of Arts and Sciences. Many of the shark vertebrae will be analyzed in Joel Fodrie's lab at UNC's Institute of Marine Sciences in Morehead City. The Galápagos Science Center, a joint effort between the University of North Carolina at Chapel Hill and Universidad San Francisco de Quito, promotes science and education that will help protect the Galápagos and enhance the lives of their inhabitants.

DAWN *of the* TREES

When did Earth's plants begin to stretch toward the sky? Patricia Gensel found the answer at a river's edge.

by Margarite Nathe

Say you've been scooped up and tossed four hundred million years back in time, back when the planet's landmasses are still huddled together and the deep, colossal ocean Panthalassa covers most of the globe. The Earth you've landed on is laboring through its Devonian Period, a stretch of history famous for its huge armored fishes, wandering tectonic plates, and plummeting levels of carbon dioxide. You're probably uncomfortably warm and the air probably stinks of iron sulfide.

Once you dust yourself off and take a look around, you'll see a swampy landscape and horizon jagged with volcanoes. There's some vegetation near the water's edge, but no trees or forests. The tallest plants in the world are only a few feet high and they have no leaves and no roots—basically, they're primitive, fleshy shoots that suck water from the mud directly beneath them.

Now look down, close to your feet. See that little plant that looks like a bunch of green spines sprouting out of the ground? Its stems are made up of what might be the very first traces of wood on Earth. And the next person to lay eyes on them, after you, will be biologist Patricia Gensel.

Left: If the fossils Gensel found had a modern-day counterpart, it would probably be this whisk fern.

In the mid-1990s, Gensel and her husband checked in to a summer cottage on the Restigouche River in New Brunswick, Canada. They'd been going there for years, armed with picks and shovels and geological hammers, and sometimes with a few students to help them dig. Together they would venture out to the shore to look for plant fossils.

"It's not light work," Gensel says. Summers there can be hot, and once the couple found a place near the shore to dig, they had to crack through the top layer of rock and lug the pieces aside. Then they would switch to crowbars. Hours later, if they were lucky, they were prying bits of fossilized plants out of the ground.

On this particular day, they were trying a new, little-known spot that some locals had pointed out to them. It didn't look too promising at first—a layer of small-pebble conglomerate doesn't usually make for well-preserved plant fossils, Gensel says. But once they dug through that, they found an obliging layer of undisturbed, finer-grain sediment. It was full of fossils. Some of them, she saw, blazed with an orange tinge. *Bingo*.

The color was a sign that the rocks were hiding pyrite, a mineral that turns to orange iron oxide when it starts to break down. And where there's pyrite, there are often well-preserved fossils.

To create the seal that will protect a plant over time, Gensel says, conditions have to have been just right back when the plant was buried. A certain pH and a lack of oxygen would help the cell walls of a decaying plant attract ions of some kind of mineral—usually silica, calcium carbonate, or pyrite. The cells would then fill with crystals, which can preserve the anatomy of a plant for hundreds of millions of years.

Gensel was excited. Intact fossilized plant anatomy doesn't come along every day. So they collected for hours and packed up the rocks to be sent back to her lab at UNC.

Eventually all the fossils were unpacked, sawed into sections, polished, mounted on slides, sealed in resin, and ready to be studied. When Gensel finally saw the ancient cell structures under her microscope, she was flabbergasted. Rows and rows of rigid, rectangular cells radiated outward from the center of the stem. She could almost have been looking at a cross-section of a modern-day pine sapling. But according to the spores present in the rock, her fossils were clearly four hundred million years old—a good ten million years older than the first plants scientists thought had developed woody structures.

The more Gensel studied the world's oldest wood samples, the more convinced she became that the main theory about why plants made the adaptation is wrong. It wasn't for strength, she says. It was for plumbing.

For the past hundred years, scientists have said that plants probably began to develop wood for structural support, to help them grow taller and stronger. "But these early plants were tiny," Gensel says. "In trees, secondary tissue and wood help provide additional support, but these little plants didn't need that. I think some of these changes in anatomy are related more to water use, or hydraulic conduction, than to support."

Plants were having a hard time staying hydrated enough to photosynthesize during the Devonian Period, mainly because carbon dioxide levels were plummeting. "The problem is that when the CO_2 levels drop, plants have to open their stomates longer to take up CO_2 for photosynthesis," Gensel says. (Stomates are pores on the surface of leaves and stems that allow for gas exchange in plants.) "And every time they open their stomates to take in CO_2, they lose water, because they're more hydrated inside than out." Plants needed more and better water conduction, and the elongated cells called tracheids that Gensel found in her fossils can do just that.

Some researchers say that temperatures in the Devonian were dropping along with carbon dioxide levels, stirring up glacial activity and periods of climatic waffling. We don't know all the specifics, but we do know that things were getting rough for plants. They had to adapt. "That's when most major plant structures evolved," Gensel says. "By the end of the Devonian, we had forests, big trees, leaves, and even early seed plants. Most of the kinds of reproduction we know in plants today were present by the end of the Devonian Period."

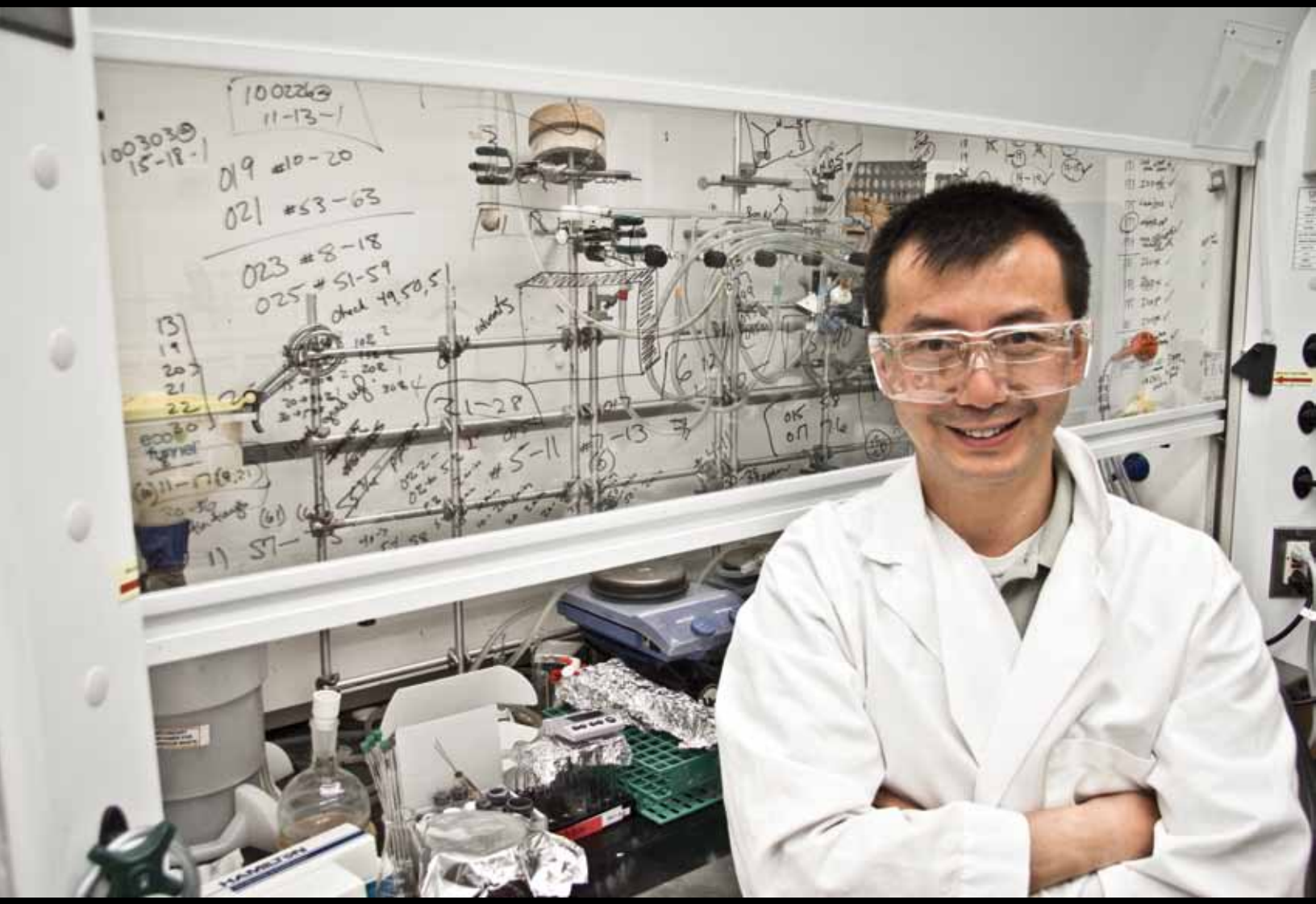
Earth's earliest wood. The cluster of wood cells is clear in this slide (just right of center). The more Gensel studied these samples, the more convinced she became that the main theory about why plants started producing wood is wrong. It wasn't for strength, she says. It was for plumbing. Photo by Patricia Gensel.

The fact that a woody structure gave plants more architectural support may have been just a happy accident. But all the changes together allowed Earth's flora to reach soaring heights, expand away from the shorelines, and spread inland to cover the planet.

While that was happening, the Devonian Period was coming to an end. It wasn't pretty, especially for the water-dwellers. Some unknown catastrophe triggered mass extinctions for various brachiopods, trilobites, jawless fish, and other reef-builders swimming in Panthalassa's waters, and brought the Age of the Fishes to an abrupt close. The organisms living topside, though, were just getting started.

Patricia Gensel is a professor of biology in the College of Arts and Sciences. She collaborated with Belgian colleagues Philippe Gerrienne, Philippe Steemans, and Cyrille Prestianni, and French colleagues Christine Strullu-Derrien and Hubert Lardeux. Their paper appeared in the August 12, 2011, issue of Science. *Gensel received funding for her work from the National Science Foundation and the New Brunswick Museum, where her fossils will go when her research is complete.*

MARK DEREWICZ



THE FORCE IS STRONG WITH THIS ONE

Chemist Jian Jin made a molecule to strike back against cancer, HIV, cocaine addiction, and more.

by Mark Derewicz

At the start of *The Empire Strikes Back*, a robotic probe lands on the ice planet Hoth, rises from the snow, and searches for the Rebellion's hideout. The long-limbed, metallic probe finds a specific structure and determines that it could be a field generator. Darth Vader orders the attack.

Now, put yourself in Vader's boots for a moment. He had long considered the Rebellion a cancer, a blight on the face of the galaxy. If he could have, he'd have blown the entire planet of Hoth to smithereens. Alas, the Empire's Death Star, which had a superlaser capable of such a task, had been destroyed in the previous *Star Wars* movie. So Lord Vader was forced to use a more precise method: he ordered a ground assault.

Okay, stay with me here.

Doctors want to help patients as best they can. Unfortunately, a lot of pharmaceuticals, such as chemotherapies, are too much like the Death Star's laser beam of annihilation and too little like a narrow assault on specific cancer cells. Some treatments wreak havoc throughout the body. And sometimes the drugs don't work well enough against cancer cells or tumors.

One reason for this: a lot of drugs, especially cancer drugs, are inhibitors; they prevent some cells from making certain proteins. When those proteins aren't expressed, cancer cells can't divide. Inhibitors, though, don't work perfectly. Many cancers and other diseases find ways to overcome the suppression. And because inhibitors are not selective, they don't just squash the proteins they target in cancer cells; they also blast other proteins in some healthy cells. This causes side effects, some of which are so severe that doctors can't give patients the most effective drug dosages. Scientists and doctors know all this, of course. They'd prefer a more precise approach. They'd prefer a probe and then a ground assault.

Unfortunately, a lot of drugs are too much like the Death Star's laser beam of annihilation and too little like a narrow assault on specific cancer cells.

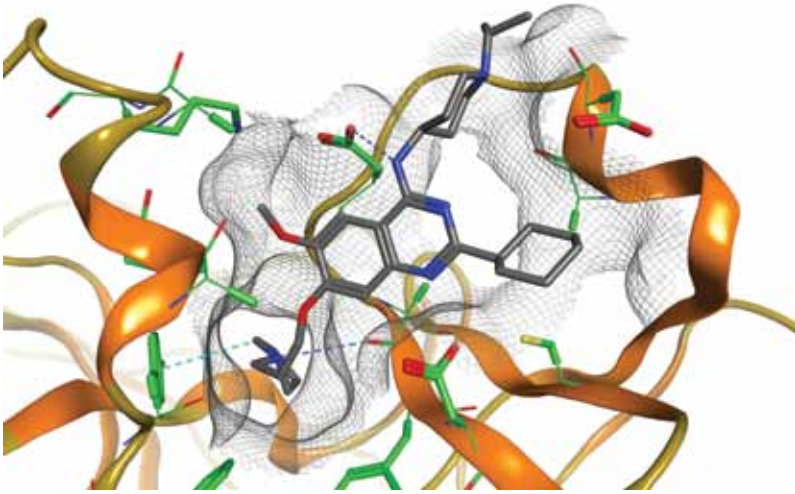
Medicinal chemist Jian Jin is nothing like Darth Vader, but he has created a probe and sent it out into the galaxy of biomedical researchers. It's strong, it's nontoxic, and it's allowing scientists to order attacks on ailments as varied as liver cancer, HIV, and cocaine addiction.

Jin, a soft-spoken scientist from China, spent ten years in the U.S. pharmaceutical industry discovering drug candidates for various targets before coming to UNC in 2008. When asked why he left Big Pharma, he smiles and pauses. "There are a lot of reasons," he says. "Mainly I wanted the freedom to pursue the science I'm most interested in." And that's molecular probes.

According to biomedical researchers, for a molecule to be classified as a probe it must meet certain criteria. It has to hit its target protein without messing up other proteins. It has to be robust; it can't work just some of the time. And the effect cannot be toxic. Drugs that are nonselective inhibitors, on the other hand, don't have to meet such stringent criteria.

"As long as a drug is safe and effective, you don't necessarily care how many proteins it might inhibit as long as its secondary effects are not *too* harmful," Jin says. But some of those secondary effects, such as digestive problems or liver scarring, are the result of changes at the cellular level. A nonselective inhibitor can cause a cascade of cellular effects, making it harder to discern the exact influence an inhibitor has on an individual protein.

"A probe can investigate the biological function of a single protein," Jin says. "It has to act cleanly, and only interact with the proteins it's designed to target." A lot of existing probes, though, are used as part of in vitro studies, but not in cells. The probes don't necessarily have to permeate cells or be viable for use in clinical trials.



Jian Jin's molecule, UNC0638, interacting with the protein G9a. The molecular probe will help researchers find out what role G9a and the related protein GLP play in such conditions as cocaine addiction, mental retardation, HIV latency, and various kinds of cancer.

Jin's probe, called UNC0638, is different. It targets two enzymes, proteins called G9a and GLP. They create the epigenetic code, which is full of protein and DNA modifications that determine which cells become brain cells or skin cells or lung cells. Some proteins are called writers—they create the modifications that make a liver cell a liver cell, for example. Others are called readers—they recognize those modifications. Others are called erasers—they remove the modifications. G9a and GLP are writers. But when they write too much, they cause problems. Scientists have found that both enzymes are overexpressed in many cancers, including leukemia, prostate cancer, lung cancer, and liver cancer. The two proteins have also been implicated in mental retardation, cocaine addiction, and HIV latency, the state where HIV remains in the bloodstream no matter how aggressive the treatment.

Scientists would love to know why G9a and GLP are overexpressed in these disparate conditions. That's where Jin's probe comes in. It suppresses *only* G9a and GLP so that researchers can study how the proteins affect human health.

Creating such a specific weapon took more than a year and several collaborations with scientists at UNC and elsewhere to get all the desired features into a single molecule. It started with a compound that had already been created and was commercially available for study. Unfortunately, that compound was kind of like the Death Star's laser beam of annihilation.

MARK DEREWICZ

Jin could have patented his probe. "But then no one would have access to it," he says. "We made it freely available to the scientific community even before we published our findings." Jin says that at least fifty researchers are now using his probe to investigate diseases.

In 2007, when Jin was still working in Big Pharma, other researchers published news that they had created a compound called BIX01294 that inhibited G9a. The only problem was that it was a bit toxic. How toxic? "Oh, it caused massive cell death," Jin says. "There was little separation between the compound's ability to suppress the proteins and its ability to destroy the cells outright." In 2009 scientists published a three-dimensional crystal structure of the compound and GLP. Jin and colleagues in Toronto took that structure and tried to remedy its flaws through a series of chemical modifications. They wanted to change that laser beam of annihilation into a harmless but much more effective probe.

"We improved the potency of that compound, as an inhibitor, by several hundredfold," Jin says. And those early alterations didn't result in massive cell death. That's because Jin's new compounds struggled to permeate cells at all. Over the course of a year Jin's team, including postdoc Feng Liu, kept altering the BIX compound, adding one chemical bond at a time so that the compound's properties and abilities changed until they met all the criteria to make BIX a robust probe. "We must have made hundreds of compounds," Jin says. Through months of trials and errors and successes, Jin's team came up with UNC0638, a molecular probe that permeates cells and does so in a robust, nontoxic way. Jin says, "We now have a great deal of biochemical and cellular data showing that it interacts only with the proteins it was meant to."

Jin could've kept his probe to himself, or at least kept it within the confines of UNC and Toronto. He could've patented it. "But then no one would have access to it," he says. "And that wouldn't increase our understanding of these targets. We made it freely available to the scientific community even before we published our findings. We want others to find new disease associations or to validate previously reported associations. *Then* companies can generate intellectual properties during their drug-discovery campaigns."

Jin's lab has given blueprints to Sigma-Aldrich, a company that sells chemical compounds to researchers, though Jin offers a cheaper route. "We'll make it for anyone," he says. "Now that we've developed two efficient ways to make UNC0638, it's easy. We can make grams of it in less than a month."

Mark Minden at the Ontario Cancer Institute is using Jin's probe to investigate the roles of G9a and GLP in leukemia. Rob Bristow, also at Ontario, is using it to study prostate cancer. James Ellis at the University of Toronto is using it to study how stem cells are reprogrammed. Angelique Whitehurst at UNC is studying how the probe and proteins interact with common chemotherapies. And David Margolis, also at UNC, is using the probe to study HIV latency. Jin says that at least fifty researchers are using his probe to investigate diseases. But he's about to lose track; most scientists now get the compound from Sigma-Aldrich.

All of those researchers are preparing individual ground assaults on some of our most common diseases. They're going to pin down G9a and GLP and find out whether these proteins are major players in the rebellion or just minor coconspirators. And if even one researcher comes up with a drug that works, maybe we'll call him a Jedi. *e*

Jian Jin is an associate director of medicinal chemistry at the Center for Integrative Chemical Biology and Drug Discovery at the Eshelman School of Pharmacy. Feng Liu is a postdoctoral fellow in Jin's lab. Their main collaborator was Cheryl Arrowsmith, chief scientist at the University of Toronto's Structural Genomics Consortium, which is committed to open access to its scientists' and collaborators' discoveries. Jin received funding from the National Institutes of Health and UNC's University Cancer Research Fund. Their work was published in the August 2011 issue of Nature Chemical Biology.

MICE IN SPACE

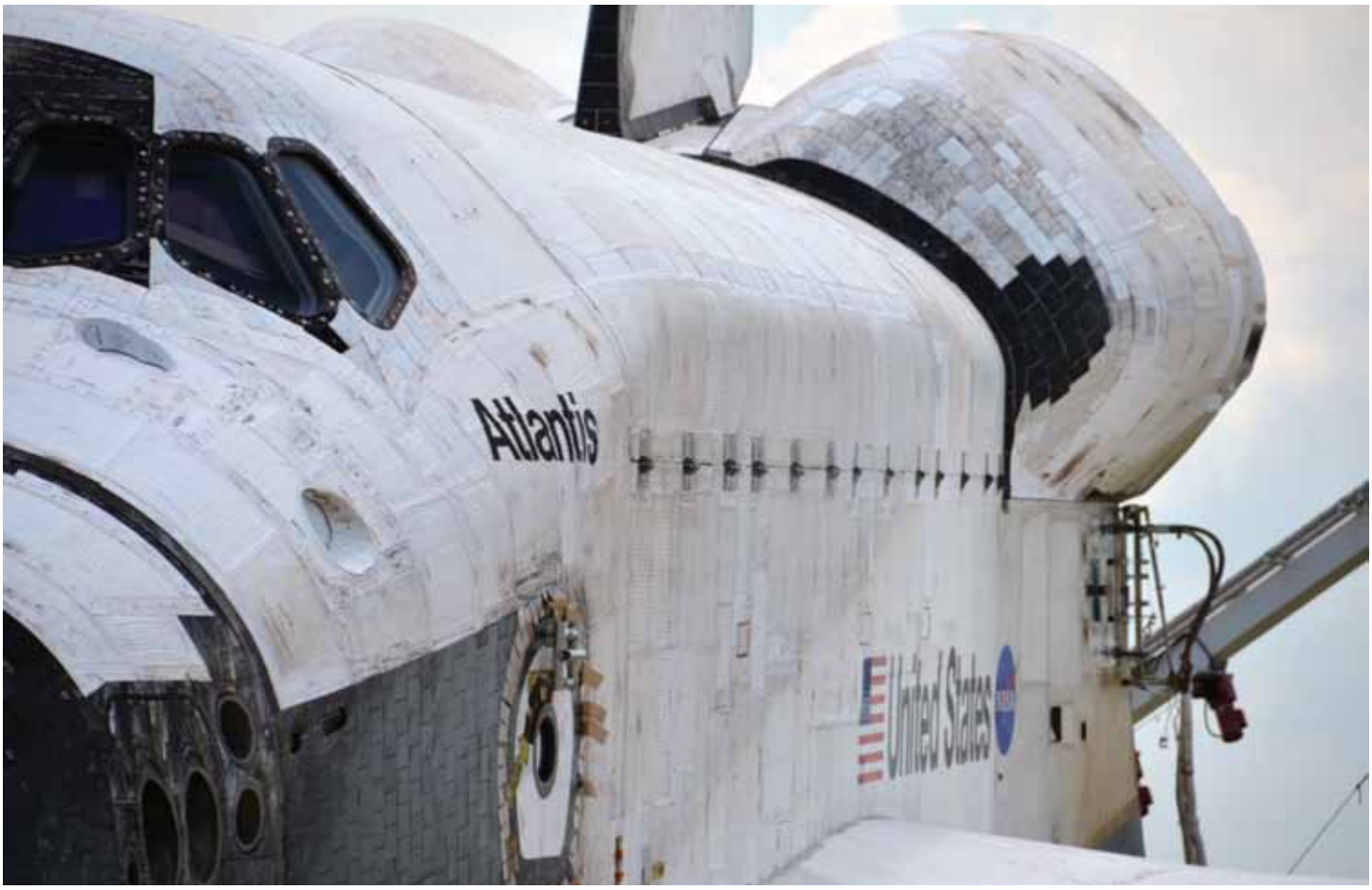
OR, TED'S EXCELLENT ADVENTURE

A Carolina scientist sent rodents into orbit to help humans who will never leave Earth.

BY MARK DEREWICZ

Before Ted Bateman became a space geek, he was a science nerd and proud of it. As a ten-year-old he delighted in dissecting the frogs and sheep lungs that his mom the biology teacher brought home from school. He once got a cat—already dead—from the Humane Society so he could bleach the bones and piece together the skeleton for an end-of-year project. And when he was twelve he designed his first mouse experiment at a science fair.

"I had three mice," he remembers. "I fed one normal lab chow, one soybeans, and one Frosted Flakes." Then for two weeks he ran them through a maze that he and his grandfather had built. The soybean mouse was always the clear winner. "It wasn't very scientific," Bateman admits. "But it was really cool."



Space Shuttle Atlantis, worn from years of traveling to the International Space Station, found a home at the Kennedy Space Center Visitor Complex. Photo by Anthony Lau.

Thirty years later, as a biomedical engineer, Bateman is still running experiments with mice. Except now he works with NASA, and his experiments have much more relevance to human health. He and colleagues around the country want to know what near-zero gravity does to bone density and whether new drugs can promote bone growth. Their research isn't just for the next generation of astronauts, but for the rest of us, too.

"Space flight is really a model for accelerated aging," Bateman says. "Many things astronauts experience in microgravity happen to us when we get older—muscle atrophy, bone loss, cardiovascular deconditioning, immune dysfunction."

And it turns out space flight is also a good model for radiation exposure. When cancer patients undergo radiation treatment, they lose bone mass. Bateman is trying to understand how that happens and what can be done about it.

In 1990 Bateman met his future. He was one of six physics majors at a small liberal arts college, but one of two from Fort Collins, Colorado. He befriended this fellow Coloradan, whose dad happened to work for NASA's Space Life Sciences Training Program, a six-week learn-a-thon for aspiring engineers. The father encouraged Bateman to apply; the next year, Bateman was accepted.

He listened to lectures from prominent scientists, learned how NASA operated, and saw how researchers designed animal experiments using sea urchins and rats. Bateman was sold. He enrolled in graduate school, where he helped design structures that astronauts could live in. Later he earned a doctorate in bioengineering and collaborated with BioServe Space Technologies at the University of Colorado, which conducted microgravity research and designed space-flight hardware.

"From then on my life has been kind of outlined by space shuttle flights," Bateman says. In 1996 he flew rats on STS-77 (that's the seventy-seventh mission of the space transportation system, a.k.a. the space shuttle.) Bateman helped design an experiment with NASA and the drug company Chiron to see if a hormone called insulin-like growth factor 1 increased bone growth. It did, but was never approved as a drug to grow bone tissue because it was too nonspecific. "Anything anabolic—anything that grows bone tissue—can potentially promote the growth of other things in the body," Bateman says. "Cancer cells, for instance."

That experiment, though, did yield fruit for Bateman. He wondered why NASA used rats for experiments instead of mice; most scientists preferred mice for their genetic variability. "Essentially NASA was wed to rats because rats don't smell as bad as mice," Bateman says. But he and colleagues proved that astronauts would have to put their noses right up against the glass mouse enclosures just to get a whiff of the furry little space-goers. And there was no reason for astronauts to do that; they barely even needed to check on the mice.

NASA relented. In December 2001, mice went on their first space odyssey. Bateman was in charge of every aspect of an experiment that took months to piece together with NASA, the biotechnology company Amgen, and other researchers. Its goal was to see if a protein called osteoprotegerin could keep mice from losing bone mass in space.

The mice were in orbit twelve days. A day before liftoff, Bateman's team injected some of them with the drug and some with a placebo. The mice were put on board twenty-two hours before the launch, and there they stayed. The astronauts hardly paid them any mind, except to visually check to make sure they were okay. They were. In microgravity, the mice could sprint up the wall, across the ceiling, and down the other side of their glass enclosure over and over. They nibbled on a big chunk of food affixed to the wall of their enclosure. To drink, they sucked on a nozzle attached to a spring-loaded water bag. The mice floated much like astronauts, using their forelimbs to maneuver around their habitats.

When the rodents returned, Bateman's team found that osteoprotegerin worked exceedingly well. Nine years later Amgen gained FDA approval for a drug astronauts have since used to prevent bone loss.

For the earthbound among us, though, preventing bone loss isn't always enough. Osteoporosis, for instance, often isn't diagnosed until bone density has already been depleted. One solution could be a drug that actually grows bone tissue. That fact was on Bateman's mind when STS-118 rolled around in 2007. That mission featured mice treated with a drug aimed at increasing muscle mass. It worked, and Bateman's team found that the drug also promoted bone growth. It's now in clinical trials.

"Space flight is really a model for accelerated aging," Bateman says. "Many things astronauts experience in microgravity happen to us when we get older—muscle atrophy, bone loss, cardiovascular deconditioning, immune dysfunction." Photo by Anthony Lau.

Bateman, by then a professor at Clemson, was making another connection between space travel and life on Earth. Astronauts are exposed to radiation, which can deplete bone tissue. "But that dose of radiation," he says, "is much lower than what cancer patients get during radiation therapy." Bateman wanted to find out what happened to these patients and, more specifically, what happened to their bone cells.

Bone tissue is composed of two major kinds of cells: osteoclasts, which limit bone growth, and osteoblasts, which promote bone growth. Together, they maintain proper bone density.

In 2007 Bateman teamed up with researchers at UC Irvine to measure how much bone mass cervical cancer patients lost after six weeks of radiation and what exactly the radiation did to osteoclasts and osteoblasts. The conventional theory was that radiation damages osteoblasts, resulting in a gradual decline in bone mass over time. But that's not what Bateman and his collaborators saw. They found that radiation turns on osteoclasts, which spurs the initial bone loss. Then, as radiation treatment continues, osteoblasts are suppressed. "We found that bone loss is incredibly rapid and just massive," he says.

Bateman thinks existing therapies that diminish osteoclast activity could help patients. As for drugs that promote bone growth, there's only one on the market. "It's very expensive and you have to get a daily injection," Bateman says. We should have better options, he says, and we should know what happens to patients with all kinds of cancers who undergo radiation treatment.

For that, Bateman, who came to Carolina in 2010, has teamed up with radiation oncologist Larry Marks to start clinical trials for lung cancer and prostate cancer patients. They've designed a study and have collaborators lined up, but they need funding. Bateman was working on that when NASA and Amgen approached him about participating in the final space shuttle flight.

"I was really too busy moving the lab to UNC to be involved with the mission," he says. "But my wife reminded me that I'd seriously regret not doing this. And she was right." So Bateman spent several months helping BioServe gather scientists from five universities and coordinate their work with NASA and Amgen to test a bone-promoting antibody on thirty mice.

In July 2011, BioServe and Bateman's team traveled to Cape Canaveral to participate in the launch festivities. They did what they always had done—prepped the mice, secured them in the shuttle's middeck locker, and made sure their enclosures were functioning properly. (Air must flow from the ceiling to the floor to make sure the mouse waste floats downward.) Thirteen days later the mice, men, and woman of Atlantis returned home safely.

The other labs have yet to report their findings, but Bateman's team found that the placebo mice lost bone mass as expected, and the drug-treated mice gained bone. The next step is to conduct clinical trials to see if the antibody can help prevent osteoporosis and bone fractures in humans. Or if it can help cancer patients maintain bone density.

As for Bateman's career as NASA's mice man, it might be over. There won't be any more space shuttle flights, and NASA won't be flying mice anytime soon.

Private rocket builders, though, could pick up the slack. One company will be ready to fly to the International Space Station next year. BioServe, Bateman's old stomping grounds, is slated to help design experiments with yeasts and bacteria on subsequent flights. Bateman thinks that animal experiments won't be far behind. Will he be the man in charge, wrangling researchers, rocket entrepreneurs, and drug companies?

"Organizing these flights is sort of like having a kid," Bateman says. "You forget how much work it is. You need enough time to pass. But let's just say that if I'm asked I'll have a tough time saying no."

Ted Bateman is an associate professor in UNC and NC State's Joint Department of Biomedical Engineering. He received funding from the National Space Biomedical Research Institute, NASA's Human Research Program, the National Institutes of Health, and Amgen, Inc.

in print

HISTORY

Life under Lee

by Mark Derewicz

General Lee's Army: From Victory to Collapse. By Joseph Glatthaar. Free Press, 600 pages, paperback, $20.00.

Soldiering in the Army of Northern Virginia: A Statistical Portrait of the Troops Who Served under Robert E. Lee. By Joseph Glatthaar. The University of North Carolina Press, 209 pages, cloth, $50.00.

Is there anything left to learn about Robert E. Lee and his Army of Northern Virginia? The short answer is yes. More interesting answers are in Joseph Glatthaar's two most recent books.

Historians have written thousands of books about Lee and his soldiers. Yet no one had written a narrative about the entire Civil War from the perspective of Lee's soldiers. To write that book, Glatthaar scoured thousands of primary sources; his bibliography in *General Lee's Army* is forty multicolumned pages. But to help him choose the right sources, Glatthaar did something else rare for Civil War historians: he turned to statistics.

There exists no single list of soldiers who served in the Army of Northern Virginia. So Glatthaar pieced one together. He made a chronological list of all the battles and organized each unit that participated by branch—artillery, cavalry, and infantry—and assigned a number to each unit for every branch. Then he selected units randomly. Finally he assigned a number to every soldier in those units and randomly selected numbers until he had a list of six hundred soldiers. He searched microfilm at the National Archives to find each soldier's service record, which led him to pension records, census records, and obituaries. Then he went back to the individual archives to find more about the soldiers and their comrades.

Glatthaar's method took years, but it allowed him to get a clearer sense of Lee's men and create a narrative based more on facts than a few scattered opinions.

The method Glatthaar used took years, but it allowed him to get a clearer sense of Lee's men and create a narrative based more on facts than a few scattered opinions.

"We've hit a point in history scholarship where people are cherry-picking evidence," Glatthaar says. "When you're dealing with so many Civil War soldiers, you can find a statement in their letters to justify any kind of argument."

Glatthaar's analysis also helped him debunk some long-held opinions about Lee's soldiers. Most weren't poor and most didn't desert for the reasons historians have long given.

Three Confederate soldiers taken as prisoners after the Battle of Gettysburg, July 1863. Photo courtesy of the Library of Congress.

A dead Confederate soldier in a trench he helped dig at Fort Mahone near Petersburg, Virginia, April 3, 1865. Robert E. Lee convinced his men to dig trenches and build fortifications as part of the strategy for wearing out Union troops. It nearly worked. Photo courtesy of the Library of Congress.

A dead Confederate soldier lies next to a fortification he helped build near Virginia's Spotsylvania Court House, May 19, 1864. Photo courtesy of the Library of Congress.

According to Glatthaar's analysis, 35.5 percent of Lee's troops were from wealthy families, even though just 24.7 percent of the South's citizens were considered wealthy. Twenty-three percent of Lee's soldiers were from the middle class; 27 percent of Southern citizens were considered middle class. Lastly, 41.7 percent of Lee's soldiers were from poor families, but 48.4 percent of citizens were considered poor.

"This negates the argument about 'rich man's war; poor man's fight,' doesn't it?" Glatthaar says. "The rich guys were actually overrepresented."

Glatthaar says most of the rich soldiers enlisted to preserve their way of life, which was dependent on slavery. Many of these soldiers said they joined the fight to protect their homes, their families, and their right to live how they always had. Once they were on the battlefield, though, their way of life turned into something completely different. "Soldiers thought they would just slug it out in the open field against the Yankees and rely on superior character and skills to win the day," Glatthaar says. "It never crossed their minds that they'd have to wield axes and shovels. That was work for slaves."

From the moment Lee took command he challenged that naïve perspective of warfare, Glatthaar says, and tried to inspire his officers to instill more discipline and a stronger work ethic.

"Our people are opposed to work," Lee wrote to Confederacy president Jefferson Davis in 1862. "Our troops, officers, community, and press all ridicule and resist it." Lee described how in ancient times Roman soldiers had dug trenches and built fortifications to protect themselves during battle campaigns. "There's

Glatthaar says that the Army of Northern Virginia was a fierce fighting force, but Robert E. Lee had to mold his men into the kind of disciplined soldiers who would do grunt work. Photo courtesy of the Library of Congress.

Throughout most of 1864, Lee's soldiers typically ate only a quarter-pound of meat and some cornmeal each day.

nothing so military as labor and nothing so important to our army as to save the lives of soldiers," he wrote.

Lee and his lieutenants got the men to dig trenches and to build fortifications and barracks. In fact, Lee got every last ounce out of his soldiers as they drove Union troops out of Virginia and won many battles against superior numbers. But the war plodded on. Federal troops maintained pressure, and Southern states couldn't get necessary supplies to Lee's men, leading to the war's desperate end.

Throughout most of 1864, according to Glatthaar, Lee's soldiers typically ate only a quarter-pound of meat and some cornmeal each day. "They weren't taking in enough good nutrition to break down the food they were actually eating," Glatthaar says.

Glatthaar wondered what the nutritional value of such food was. He called Boyd Switzer, a nutritional biochemist at UNC, who calculated that Lee's men consumed thirty-five to forty grams of protein a day, much less than they should've been eating. They consumed 6 percent of the recommended daily amount of vitamin A, 15 percent of the vitamin E, 3 percent of the vitamin K, 10 percent of the calcium, and 41 percent of the potassium, not to mention nowhere near enough vitamin B.

"They were getting about nine hundred calories a day," Glatthaar says. But their days were full of walking, fighting, and working. Today's soldiers, he says, eat four thousand calories a day just to maintain muscle mass.

It's been well known that Lee's soldiers suffered from dysentery, skin ailments, night blindness, anemia, scurvy, and diarrhea. Glatthaar's findings put the soldiers' suffering into even bleaker context—they were starving to death. Their challenge to survive and win battles became greater in the winter of 1864 and early 1865.

The men were forced to wear the same boots and clothes for so long that the fabric disintegrated. "There were times when soldiers would appear for inspection without pants or shoes," Glatthaar says. As the weather grew cold in late 1864, some of Lee's men said they were eager for a battle because winning meant they could take blankets, shoes, and clothes from Union soldiers. "This was mind-boggling," Glatthaar says. "I knew things were bad, but soldiers eager for battle so they could find an overcoat? I would never have anticipated that."

Despite the desperation, the Army of Northern Virginia inflicted heavy casualties on Union forces throughout 1864 even as Lee's best officers were killed and desertions increased.

Some scholars have found a correlation between soldiers' misery and desertion rates. But Glatthaar found a stronger motivation for desertion.

Married soldiers were 30 percent more likely than single soldiers to desert their units. And soldiers with kids were 80 percent more likely to desert. By far, the most desertions took place in February and March of 1865, when Lee's army lost a brigade—some one hundred men—every ten days. This was during Sherman's desolating march through the South. "Soldiers were just worried about their families," Glatthaar says. "Desertion, really, was all about their kids."

Deserters weren't cowards, he says. They hadn't lost faith in the Confederate cause. They left Lee's army for pretty much the same reason they had joined—to protect their homes, their families, and their way of life.

Joseph T. Glatthaar is the Stephenson Distinguished Professor of History in the College of Arts and Sciences.

At a glance: *a few more of Glaathar's findings about the soldiers in Lee's army.*

- Nearly 25 percent of all Confederate soldiers fought in Lee's Army of Northern Virginia.

- Nearly half were born in Virginia or North Carolina, and nearly half claimed Virginia or North Carolina as their prewar state of residence.

- Officers were three and a half times more likely to own slaves than were their enlisted troops.

- In 1860, 25 percent of Southern households had slaves, but 44 percent of soldiers' households owned slaves.

- A disproportionate share of soldiers who held slaves gravitated toward the cavalry. The artillery attracted the fewest slaveholders.

endview

Healthful snacks at the Sappony Heritage Youth Camp. Photo by Donn Young.

EATING RIGHT

Sappony kids can spend a week at the Sappony Heritage Youth Camp learning about their culture, including traditional ways of farming, cooking, and gardening. North Carolina tribes are working hard to improve nutrition in their communities and fight the disproportionate rates of diet-related diseases that afflict American Indians, including diabetes, heart disease, and obesity. Many tribal leaders have partnered with Sheila Fleischhacker and other UNC researchers with the American Indian Healthy Eating Project to improve nutrition and food access for the state's American Indians. Read the story and see more photos at: endeavors.unc.edu/healthy_eating_project

Sheila Fleischhacker is affiliated with UNC's Center for Health Promotion and Disease Prevention. The American Indian Healthy Eating Project is funded by Healthy Eating Research, a national program of the Robert Wood Johnson Foundation.

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**This is the final printed issue of *Endeavors*.
But you can still keep up with research and creative activity at Carolina. Details inside the front cover.**

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Why did Ted Bateman put mice on the space shuttle? Story on page 27. Photo by Anthony Lau.