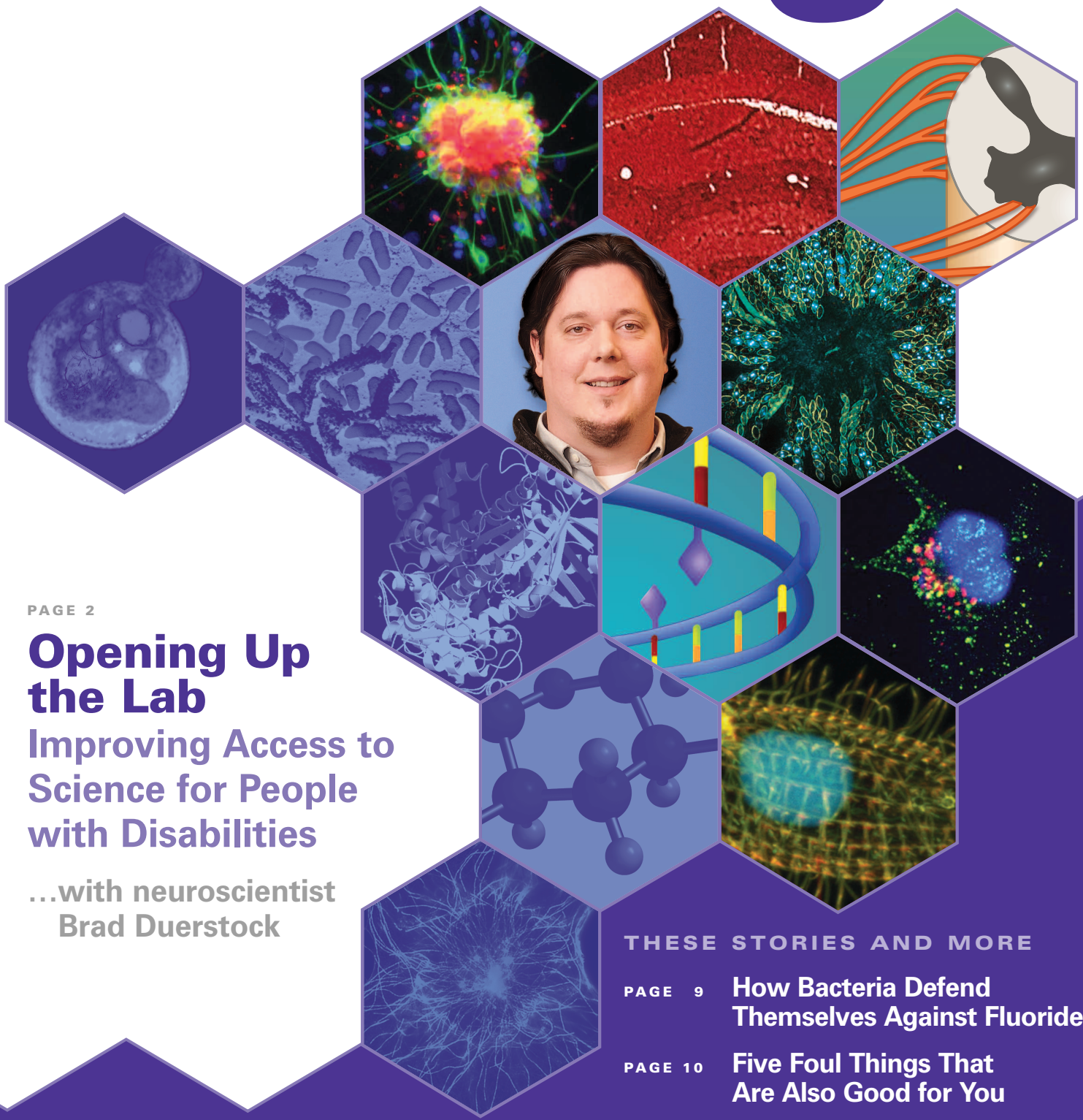
# Findings

SEPTEMBER 2012





THESE STORIES AND MORE



U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
National Institutes of Health
National Institute of General Medical Sciences

## Featuring



## Spotlights on Hot Science

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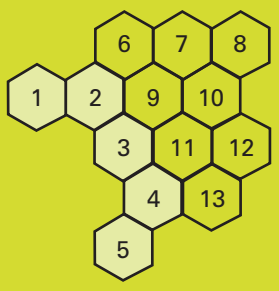
Produced by the Office of Communications and Public Liaison
National Institute of General Medical Sciences
National Institutes of Health
U.S. Department of Health and Human Services

http://www.nigms.nih.gov/findings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ANDREW HANCOCK, PURDUE UNIVERSITY

*Up Close With*

# Brad Duerstock

**NEUROSCIENTIST, ASSISTIVE TECHNOLOGY DESIGNER**

"The sense of discovery and the impact on others are big motivations for me."

**HOBBIES**

**Gadgetry, architectural design**

**FAVORITE MUSIC**

**Rock and roll, bluegrass**

**HISTORIC FURNITURE**

**Revolving bookstand like the one Thomas Jefferson used at Monticello**

**BIZARRE COLLECTIBLE**

**Ecuadorian shrunken head (replica made from goatskin)**

**FAVORITE GENRES**

**History, science fiction**

**FAVORITE CUISINES**

**Mexican, Japanese**


C500

ANDREW HANCOCK, PURDUE UNIVERSITY

# Opening Up the Lab

## Improving Access to Science for People with Disabilities

BY STEPHANIE DUTCHEN

A crash, then all goes black. When you come to, you can't feel part of your body. You will never move normally again.

Paralysis from accidents or medical conditions affects millions of Americans, forever changing their daily lives and future plans.

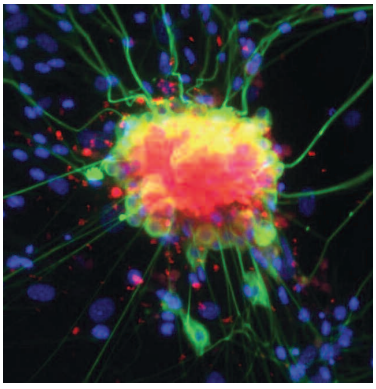
For those who want to work in labs, the road is being smoothed and widened by Brad Duerstock, a researcher at Purdue University in West Lafayette, Indiana.

Duerstock is building and modifying scientific equipment, adjusting the physical layout of labs and creating an online networking site. His goal is to encourage more people with impaired mobility or limited vision to pursue careers in science, technology, engineering and math fields.

"Science can be pretty inhospitable to people with disabilities. But that doesn't mean it's impossible," he says.

He speaks from experience. A quadriplegic since age 18 due to a spinal cord injury, Duerstock studies nerve injury and repair. Throughout his training and career, he's had to invent new ways to get the job done.

"It takes fortitude," he says. "You have to persevere. You have to be creative. You have to figure out your own solutions and make your own path."



LAWRENCE MARNETT, VANDERBILT UNIVERSITY

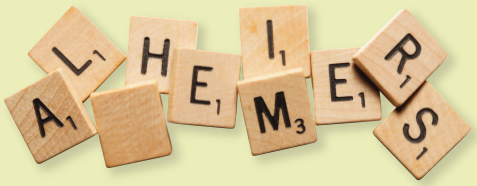
Spinal nerves (green) connect our skin and muscles to the spinal cord, allowing us to feel and react to our environment.

### A New Path

Duerstock grew up in Indiana in a family of teachers and principals. An excellent student interested in science and medicine—and a star member of his high school's swim team—he planned to become a physician.

About 3 months before graduation, during a swim practice at school, he had a diving accident.

"It happened so fast. I don't even remember hitting my head and breaking my neck," he says. "All of a sudden, I was floating face down and couldn't move my body."




# Does Cholesterol Play a Role in Alzheimer's?

Scientists have long known that cholesterol plays a number of roles—both good and bad—in the body. Now, they suspect it might also contribute to the development of Alzheimer's disease.

To visualize how this might happen, a team of researchers determined the structure of an Alzheimer's-related protein known as APP. To study the protein under normal conditions, the scientists placed it into laboratory-made membranes, which mimic its natural environment.

The scientists, led by Charles Sanders at Vanderbilt University Medical Center in Nashville, Tennessee, showed that APP can hook up with cholesterol in the artificial membranes. Based on other studies, the researchers believe that cholesterol then drives APP into specialized membrane areas known as lipid rafts. There, enzymes hack off pieces of APP, transforming it into a substance called amyloid beta, which accumulates in the brains of those with Alzheimer's.

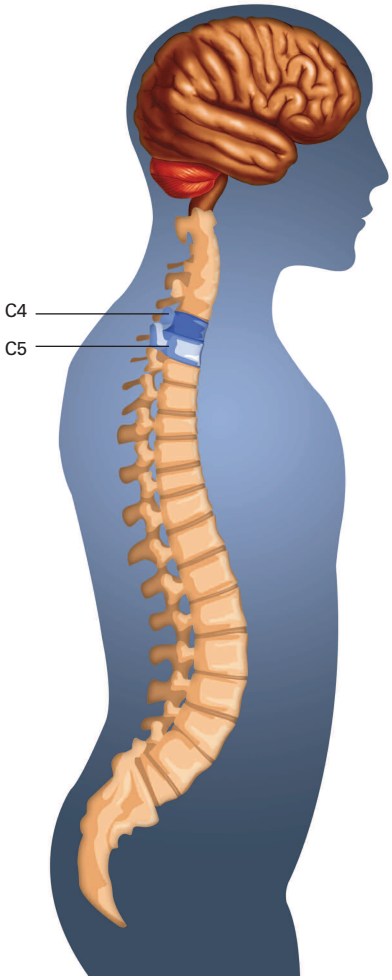
If this process promotes the disease, as the scientists believe, a drug that prevents APP from connecting to cholesterol might forestall Alzheimer's, a condition that affects up to 5 million people in the United States.

*—Alisa Zapp Machalek*

# I like being able to decide

Medically speaking, he had injured his spinal cord between the C4 and C5 vertebrae in his neck. He could no longer move his legs, arms, hands or wrists. He eventually recovered movement in his biceps and can rotate the lower portion of his right arm.

"I was a competitive swimmer for most of my life up to the accident. It was tough," he says. "But fortunately, I had other things to rely on. Academics were as important to me as athletics. When I couldn't compete athletically anymore, I competed academically."




Duerstock injured his spinal cord between the C4 and C5 vertebrae.

He also had to learn new ways to get around, eat, dress, bathe, open doors, check e-mail, talk on the phone, take notes, study and take exams.

Throughout his hospitalization and rehabilitation, Duerstock kept up with his schoolwork and maintained his high grades.

"My teachers were amazing," he remembers. "They would send me my assignments and make photocopies of handouts while I was in the hospital, and some would visit regularly to privately tutor me."

This commitment paid off. The first time Duerstock left the hospital was to deliver his high school commencement speech—as valedictorian of his class.

After the ceremony, he had to go back to the hospital.

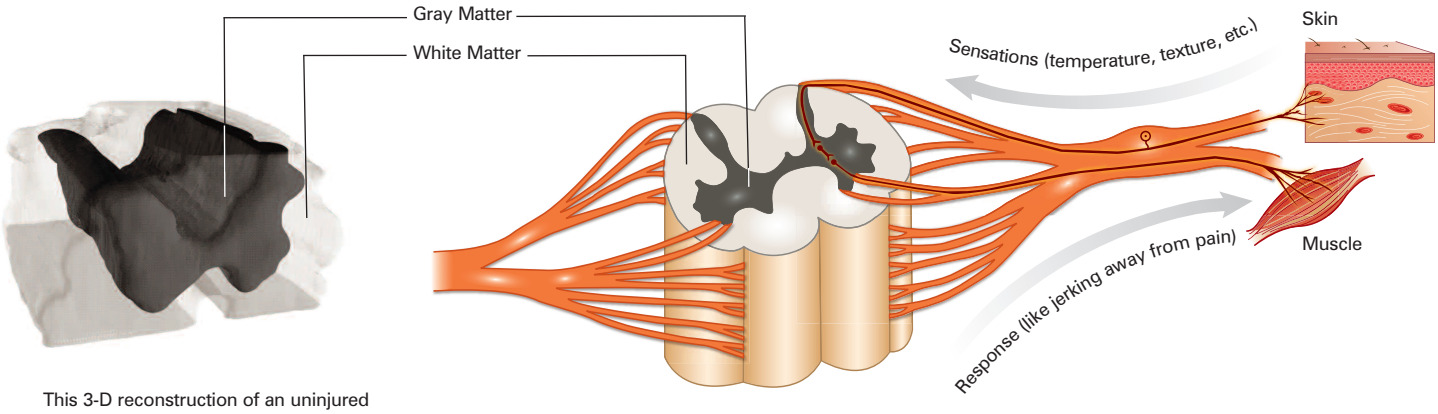
## College Choice

Despite his stellar academic record, some doors were still closed to him. He'd been appointed to West Point Military Academy, "but I quickly knew that wasn't going to happen," he says. West Point has strict physical requirements for its cadets.

So Duerstock decided to attend a nearby university, Purdue, which he knew was "famous for engineering." He switched his planned major from premed to an interdisciplinary engineering program focused on biomedical engineering.

At the time, "Purdue didn't have much in the way of accommodations," he remembers. "But they were working to comply [with the recently passed Americans with Disabilities Act of 1990] and wanted to find ways to accommodate me."

# what I want to research. That independence appeals to me.




This 3-D reconstruction of an uninjured section of rat spinal cord shows gray matter (dark gray) and white matter (transparent). Duerstock devised this technique to enable researchers to examine the center of the spinal cord.

BRAD DUERSTOCK

**Section of Spinal Cord**

Spinal nerves (orange) carry messages to and from the spinal cord.

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE, NATIONAL INSTITUTES OF HEALTH

Now, as a faculty member at his alma mater more than 20 years later, he helps accommodate students with disabilities by creating assistive technology for use at home, school or work.

## Investigating Injury

Duerstock first got a taste of research as a senior in college at Purdue's Center for Paralysis Research. He was fascinated by the work and went on to earn a Ph.D. in neuroscience. He now conducts his own research in areas ranging from neurotrauma to assistive technology.

"I like being able to decide what I want to research," he says. "I can look at whatever piques my interest. That independence appeals to me. It's very exciting."

A major focus of his research is on chronic (long-lasting) injuries to the spinal cord and central nervous system. What especially interests him is secondary injury.

Secondary injury is caused by the body's massive response to the initial trauma to nerves, bones and blood vessels. It includes a flood of white blood cells, inflammation, bleeding, tissue death from lack of oxygen and biochemically induced damage to nerve cells.

"There's a lot of things going on in secondary injury," Duerstock says. So many things, in fact, that "it's really hard to find the critical culprits."

Duerstock and his colleagues are hunting down these culprits using a variety of tactics. In one, they examine healthy and damaged nerve cells under a microscope to identify anatomical changes. Several years ago, they devised a way to computationally combine the images from many microscope slides to create a 3-D view of specific cells and molecules at the center of the spinal cord, where the most severe injuries occur.

They also look for molecules that cause or reveal secondary injury. Right now, they have their eyes on acrolein—the substance you smell when cooking oil burns. Acrolein increases dramatically after a spinal cord injury and fatally damages the nerves it touches. So it could be a major player in secondary injury.

In their search for treatments that lessen or repair nerve damage—or that stimulate the growth of new, healthy nerves—Duerstock and others are investigating a compound called polyethylene glycol or PEG, which is known to seal ruptured nerve cell membranes. In animal studies of spinal cord injury, PEG significantly reduced tissue damage and improved the animals' ability to move.

Duerstock realizes that his research could ultimately help not only the estimated 1.3 million people in the United States with spinal cord injuries, but also those with nerve damage from traumatic brain injury, diabetes, infections or neurodegenerative diseases like Alzheimer's and Parkinson's.

"The sense of discovery and the impact on others are big motivations for me," he says. "Being a researcher, you might have a broader impact on society than you would as a practicing physician."

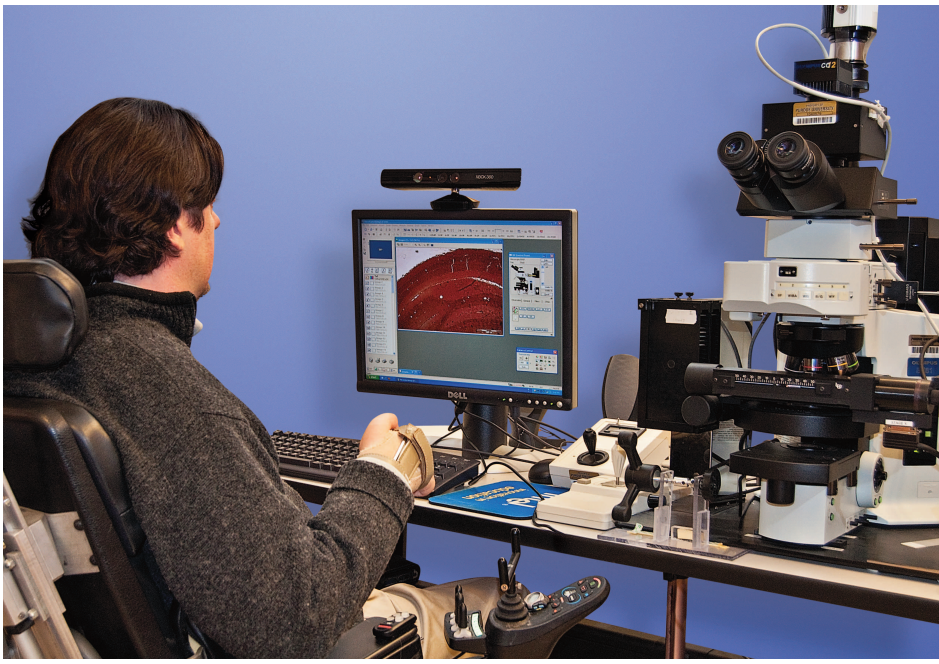
# Science needs people from different backgrounds to

## A Wider Scope

Duerstock always strives to be self-sufficient, conducting experiments and gathering data himself rather than relying on others in the lab. Often, that means creating new tools—like the accessible microscope he calls AccessScope.

"The light microscope is one of the fundamental pieces of equipment used in a biomedical lab. Having that tool available is critically important," he says. "AccessScope has allowed me to work for hours independently."

Duerstock started building AccessScope when he was a postdoctoral researcher. Although designed for people with upper-limb mobility impairments like his, it also turned out to help people with limited vision.



ANDREW HANCOCK, PURDUE UNIVERSITY

AccessScope is a high-tech light microscope that Duerstock modified to be accessible for people with limited hand and arm mobility, wheelchair users and those with impaired vision.

Devices that make life easier for people with disabilities often benefit others. Sidewalk ramps were created for wheelchair users, but they also help people pushing strollers, wheeling luggage or riding bicycles.

"Microscopes require you to perch and lean forward to peer into the eyepieces," Duerstock explains. "That's not something easily achieved by a wheelchair user." Nor is it easy for people with vision loss, he adds.

So, instead of using eyepieces, AccessScope displays images on a computer screen, where they can easily be enlarged to help all types of users.

Users who can't see the instrument readouts can use third-party screen-reading software to hear them.

Those with limited hand control due to paralysis, arthritis, carpal tunnel syndrome or other motor impairments can control an accessible slide loader to automatically place slides on the microscope stage. They can then adjust the microscope using a variety of methods, including keyboard, mouse or trackball.

Duerstock is also working to make AccessScope available to others remotely through his networking site. He envisions users logging in through a Web browser and performing microscopy from anywhere.

As Duerstock points out, assistive technology frequently has broader benefits than originally intended.

"Often what can be considered good assistive technology simply means creating a device that excels in user design or usability," he says.

look at problems in different ways.

**IAS—It's About Science**

Duerstock's most ambitious and far-reaching project yet is the $2 million Institute for Accessible Science, or IAS.

Based at Purdue and begun in 2010, it includes a fully accessible lab and the IAShub.org online networking site.

The hub is designed for people interested in improving accessibility for those pursuing science careers. It offers something Duerstock says he didn't have right after his injury—connection, inspiration and support from like-minded people. It serves as a virtual community where students, scientists, parents and teachers can share their experiences with overcoming obstacles.

The hub includes helpful articles and Web sites, participant profiles, a discussion forum and a blog. It also lists funding ideas for scientists who bring students with disabilities into their labs.

"[Mentoring such students] might take a little more work, but the funding and technologies are out there," he says. "And inclusion really has long-term benefits, not only for the individual with a disability, but also in bringing a greater diversity of people into science who have different perspectives to offer. Science needs individuals from different backgrounds to look at problems in different ways."

# DO-IT for Science

**Performing bypass surgery using sheep hearts.**
Touring Microsoft's headquarters. Working in a forensics lab.

High school students in the DO-IT Scholars program do these things and more during a 2-week sneak peek of college life at the University of Washington in Seattle.

DO-IT Scholars is a college-prep program in Washington state for students interested in careers in science, technology, engineering or math. But it's also much more.

DO-IT stands for Disabilities, Opportunities, Internetworking, and Technology. As you'll learn from the many videos posted on its site (http://www.uw.edu/doit), DO-IT Scholars describe it using words like fun, connection, learning and independence.

DO-IT Scholars have vision, hearing or mobility impairment; cerebral palsy; autism; or some other disability.

The 3-year program provides computer hardware and software, including any necessary assistive devices. It trains scholars to use technology to accomplish things they might never have thought possible.

The program hooks its participants into a broad, supportive and empowered network of other students with disabilities. It nurtures leadership skills, self-advocacy and lifelong friendships.

Many alumni continue to be involved in the program years after they've graduated by serving as mentors for younger scholars.

The DO-IT Scholars program began in 1993. It's been so successful that programs in Japan and South Korea have used it as a model for some of their own activities. —*Alisa Zapp Machalek*

# I'd like to think that after I leave the world, I've

## Access ABILity

To create the lab—dubbed the Accessible Biomedical Immersion Laboratory, or ABIL (sounds like "able")—Duerstock recruited an interdisciplinary team.

Engineers, ergonomics specialists, scientists, architectural designers and others renovated a standard "wet" lab to accommodate the needs and safety concerns of wheelchair users, people with vision loss and others who need to work in the lab.

Among ABIL's modifications:

- Wider doors and aisles so wheelchair users can enter and turn around without knocking into delicate equipment.
- Lower lab benches for common tasks like pipetting, creating slides and using microscopes.
- Lower, shallower sinks so people in wheelchairs can see and reach to the bottom.
- Faucets mounted on the side rather than the back of sinks so they are easier to reach. Ditto for the spray nozzle and distilled water dispenser.
- Easy-to-flip levers instead of round knobs that are harder to grasp.
- Emergency shower controls and eye wash centers adjusted for wheelchair users and easier for people with visual impairments to locate.

Other issues are harder to address.

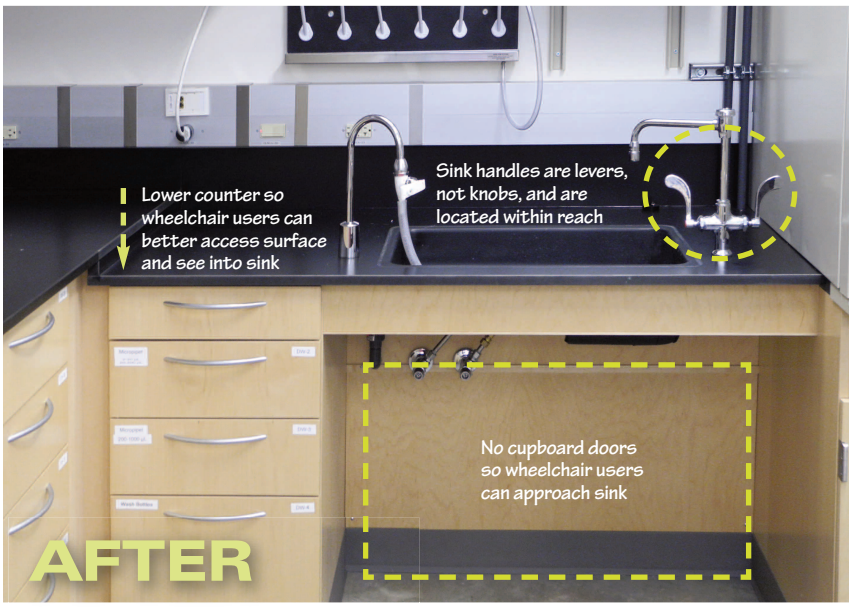
"Wheelchair users can't back away from a chemical spill easily or quickly," Duerstock points out. "Plus, you have a lap." Spills into the lap can go unnoticed for a while if you've lost feeling in your legs.

ABIL's first big test will come from a group of undergraduate students with mobility or vision limitations. Up to six students will use the lab and devise some of their own modifications while collaborating on research projects with Purdue scientists.

At the time of this writing, the students hadn't arrived yet. To find out what they had to say about their experience at ABIL, check online at http://publications.nigms.nih.gov/findings.


BRAD DUERSTOCK

When Duerstock looks at a laboratory, he easily envisions changes that would make the space more accessible to wheelchair users.




BRAD DUERSTOCK

# improved it in some small way.

### Bringing Lessons Home

Duerstock hasn't brought architectural innovations just to the lab. In 2001, he also designed his own accessible home.

"Architectural design interests me a lot," says Duerstock. "Before using a wheelchair, I had never thought much about it. But afterwards, when everything became inaccessible to me, one of my earliest desires was to be able to control my environment—to create my own space."

He designed each aspect of the house—from the thickness of the carpet to the automatic openers on interior doors—to make his life easier and more efficient.

He lives in the home with his wife, Li Hwa, and their dog, Luke, and cat, Xiao Hei.

Luke, a yellow Labrador retriever, is another sort of assistive technology. Duerstock got him several years ago from the Indiana Canine Assistant Network, an organization that arranges for prison inmates to train assistive dogs and then matches the dogs with owners.

For Duerstock, Luke is a big help opening sliding doors (he tugs on a rope tied around the handle), carrying things and picking up objects Duerstock drops.

"That used to be a big frustration—if I dropped my pen on the floor, it might as well have been on the moon, because I wasn't going to get it unless I had some assistance," says Duerstock.

In return, Duerstock devised some creative ways to give Luke the attention dogs crave. He plays fetch with Luke using a remote-controlled ball thrower, and he modified a candy dispenser to dole out kibble treats.

Occasionally, he brings Luke to work for extra petting—although he has to be careful, because the lab is not yet accessible for dogs with uncontrollably wagging tails.

While Duerstock doesn't know if there will be a cure for spinal cord injury and paralysis in his lifetime, he does hope to advance the field.

In the meantime, his assistive technology innovations and leadership of the IAS promise to make it easier for people with disabilities to work in labs and make discoveries of their own.

"I like knowing that what I do can ultimately impact others," Duerstock says. "That is very satisfying to me. I'd like to think that after I leave the world, I've improved it in some small way." ● ● ●

**FIND MORE** @

See Duerstock and Luke in action several times in a video from the Indiana Canine Assistant Network at http://tinyurl.com/caninenet

Check out the networking site Duerstock and others created at http://iashub.org

Read Duerstock's tips for building an accessible and energy-efficient home at http://web.ics.purdue.edu/~bsd/building.html

Learn how scientists can receive funding to support students with disabilities in their labs at http://www.nigms.nih.gov/Research/Mechanisms/PromoteDiversity.htm

## How Bacteria Defend Themselves Against Fluoride

For decades, people have prevented tooth decay using fluoride, which is found naturally in the environment and added to toothpaste, mouthwash and public water supplies. Fluoride works by strengthening tooth enamel and attacking the bacteria that cause cavities.

But scientists have recently discovered that many bacteria—including those that decay teeth—can defend themselves against fluoride.

A research team led by Ronald Breaker of Yale University in New Haven, Connecticut, found that bacteria use a bit of RNA called a riboswitch to sense and respond to high levels of fluoride. When fluoride attaches to it, the riboswitch activates specific genes that appear to encode proteins called fluoride transporters. The researchers suspect that bacteria use these transporters to rid themselves of fluoride, avoiding its effects.

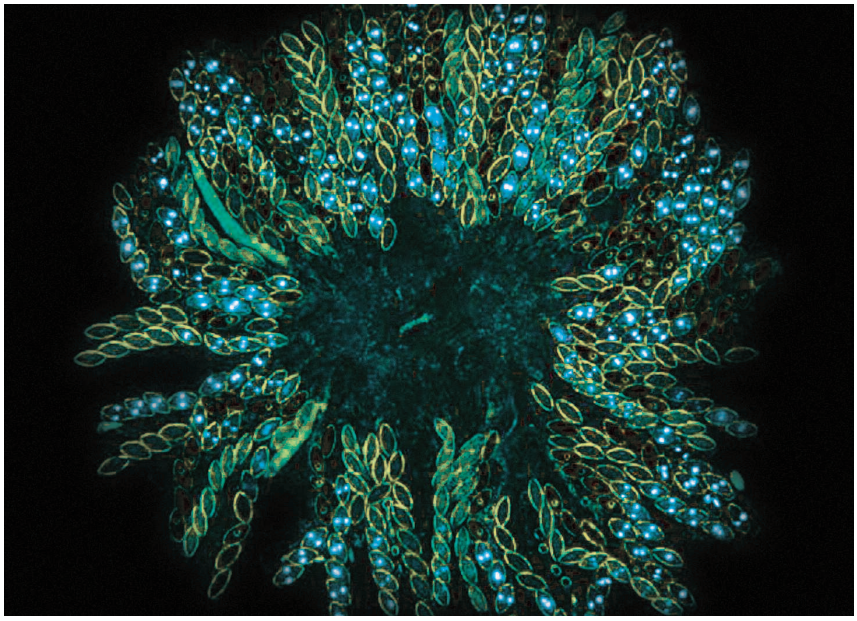
To parry this bacterial defense system, scientists could try to block the fluoride transporters or disable the fluoride riboswitch. Either way, the goal would be to stop bacteria from escaping a fluoride build-up.
*—Amber Dance*

Just Found Just Found Just Found Just Found

# Five Foul Things That Are Also Good for You

*By Emily Carlson*

**Usually, we think of mold, feces, nitric oxide, hydrogen** sulfide and rat poison as rank, toxic or both. But scientists funded by the National Institutes of Health (NIH) are learning more about the helpful roles these substances can play.



NAMBOORI B. RAJU, STANFORD UNIVERSITY

Bread mold (Neurospora crassa) is helping scientists learn about biological processes.

## Mold

If you're a homeowner, mold is definitely a four-letter word. But to scientists, it's a very important organism. The widely used antibiotic penicillin comes from a mold called Penicillium. This mold's bacteria-killing ability was discovered accidentally by Alexander Fleming in 1928 when it drifted in from another lab, landed on Fleming's petri dish and killed the bacteria on it.

Today, Neurospora crassa—a mold that can turn sandwich bread orange—is helping scientists answer questions about how species arise and adapt as well as how cells and tissues change their shapes in different environments. And because it produces spores on a 24-hour cycle, this bread mold is also useful for identifying the molecular timepieces that govern sleep, wakefulness and other rhythms of life.

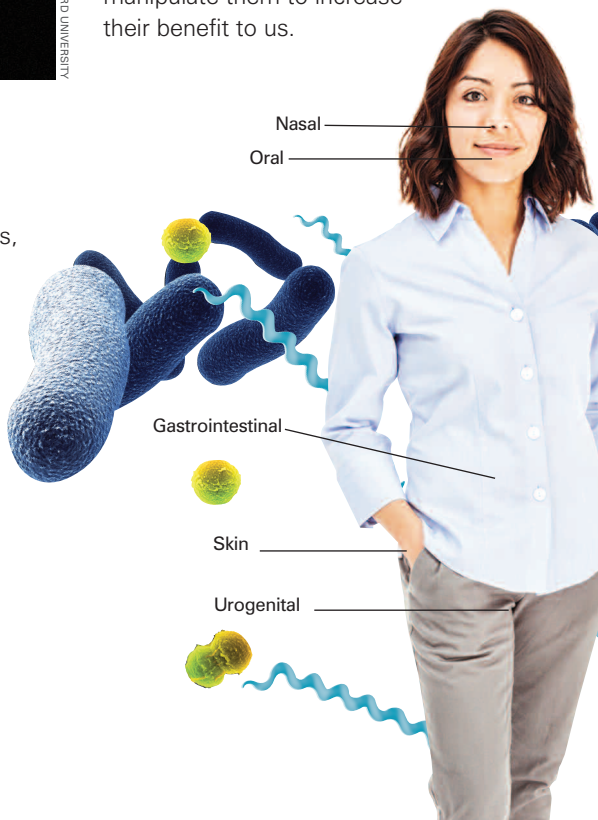
## Feces

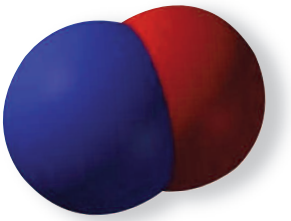
Our guts are host to many bacteria, and researchers are analyzing the bacterial colonies in our poop to better understand what they do.

Specifically, scientists involved in the NIH-led Human Microbiome Project (http://commonfund.nih.gov/Hmp) are using genomic tools to identify these communities in the gut and other hotspots—the nose, mouth, skin and vagina—to learn how they help maintain health or set the stage for disease.

In one study investigating the role of the gut's microorganisms in obesity, researchers obtained stool samples from pairs of female twins who were either both obese or both lean, as well as from their mothers. They found that each individual carried her own unique collection of bacteria. But the overall bacterial communities were more similar among family members than they were between unrelated people.

This information will contribute to a rapidly increasing body of knowledge about how microbes influence our physiology and how we might manipulate them to increase their benefit to us.





Nitric oxide.

BEN MILLS, WIKIPEDIA COMMONS

## Nitric Oxide

Nitric oxide is a toxic pollutant that we most often smell in car exhaust fumes, but it is critical to our cardiovascular health, brain function and immune system. It transmits signals in most living creatures to help dilate arteries, activate nerve cells and increase the number of white blood cells to kill invading bacteria and parasites.

Interestingly, Tibetans living at high elevations—where there's less oxygen in the air—have much more nitric oxide in their blood than do people living closer to sea level. Scientists believe that this extra nitric oxide dilates the Tibetans' blood vessels, increasing blood flow to ensure that sufficient oxygen gets to their tissues.

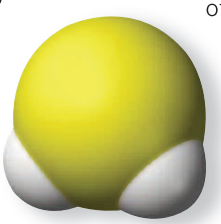
The discovery of nitric oxide's role in the body, particularly the cardiovascular system, netted a Nobel Prize in 1998.

## Hydrogen Sulfide

We generally associate hydrogen sulfide with the smell of rotting sewage. But some of our body's cells produce small quantities of this gas, and research indicates that this happens when their protein-making factories start churning out bad products.

The stinky gas seems to help cells slow down protein production or, if the situation is bad enough, stop production and commit suicide.

Understanding the normal role of hydrogen sulfide may help scientists develop treatments for diseases linked to excess cellular suicide like Alzheimer's and Parkinson's.



Hydrogen sulfide.

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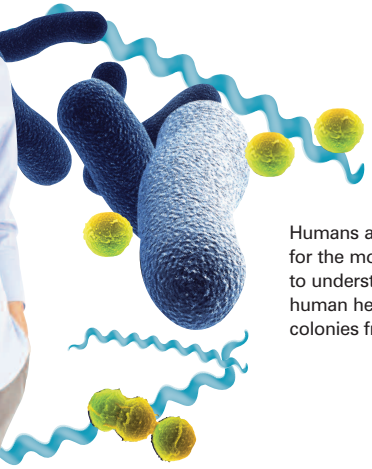


Humans and bacteria live together closely—and, for the most part, peaceably. Scientists are seeking to understand some of the roles bacteria play in human health and disease by analyzing bacterial colonies from a few microbial hotspots.


Warfarin, a commonly prescribed anticoagulant medicine, was initially marketed as a pesticide.

## Rat Poison

Warfarin, one of the world's most prescribed medicines, stems from a substance on spoiled sweet clover that caused cattle to mysteriously bleed to death in the 1920s.

Shortly afterward, researchers identified the cause of death—an anticoagulant molecule found naturally in the plant.

Chemically manufactured versions of the molecule were first marketed as rat poisons and later as a new class of drugs that now includes warfarin.

Each year, 2 million Americans start taking warfarin to prevent dangerous blood clots that can lead to heart attacks, strokes or even death. People might also take it after major surgery to avoid other clotting problems.

Prescribing the right dose of warfarin is tricky because, for genetic and other reasons, some people need higher doses and others need lower ones. Scientists are currently studying warfarin to better understand how a person's genetic makeup can affect his or her response to medicine. ●

# Chromosomal Caps in Sickness and in Health

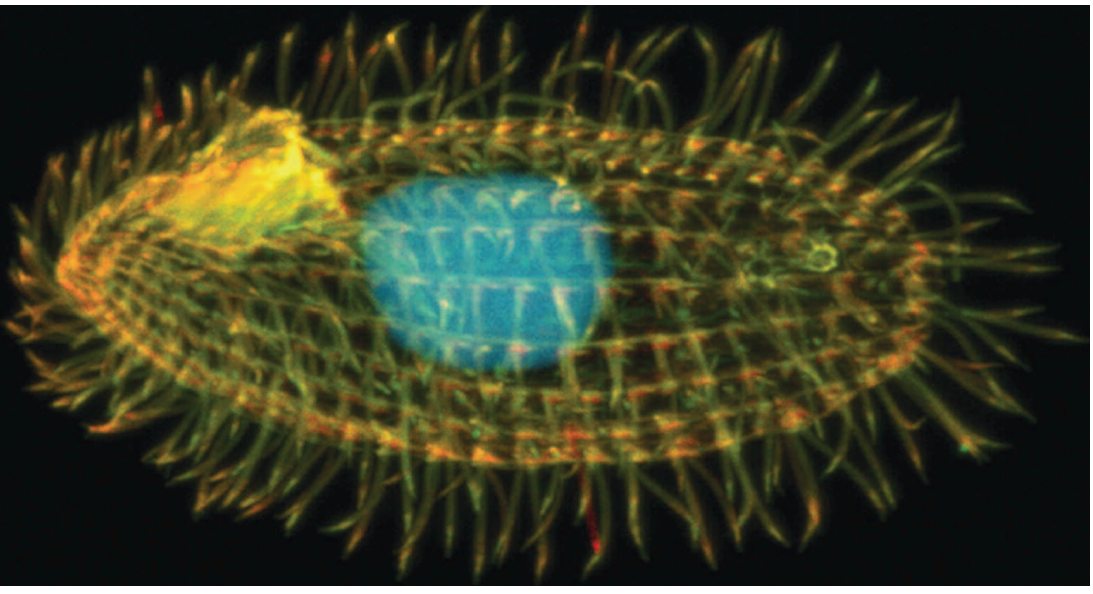
*By Amber Dance*

**Every cell in your body has its own Doomsday Clock,** ticking down the number of times it can safely divide. This clock takes the form of a cap, called a telomere, on the ends of each chromosome. Like the plastic aglets on the tips of shoelaces, telomeres keep chromosomes from fraying. But they get shorter every time the cell splits.

When its telomeres have shrunk to a certain point, a normal cell is supposed to die. But cancerous cells can avoid death by maintaining or even lengthening their telomeres.

Shortened telomeres have been linked to age-related diseases like arthritis, hypertension, stroke and diabetes, as well as the aging process itself. And some research suggests that chronic stress—both psychological and cellular—can also dramatically shrink telomeres.

If scientists could figure out how to control telomeres, they might be able to treat certain diseases of aging as well as cancer.



RUPAL THAZHATH AND JACEK GAERTIG, UNIVERSITY OF GEORGIA

The microscopic, single-celled swimmer Tetrahymena thermophila has about 20,000 chromosomes, each with telomeres on their ends. Human cells, in contrast, have a mere 46 chromosomes.

## Telomeres Aplenty

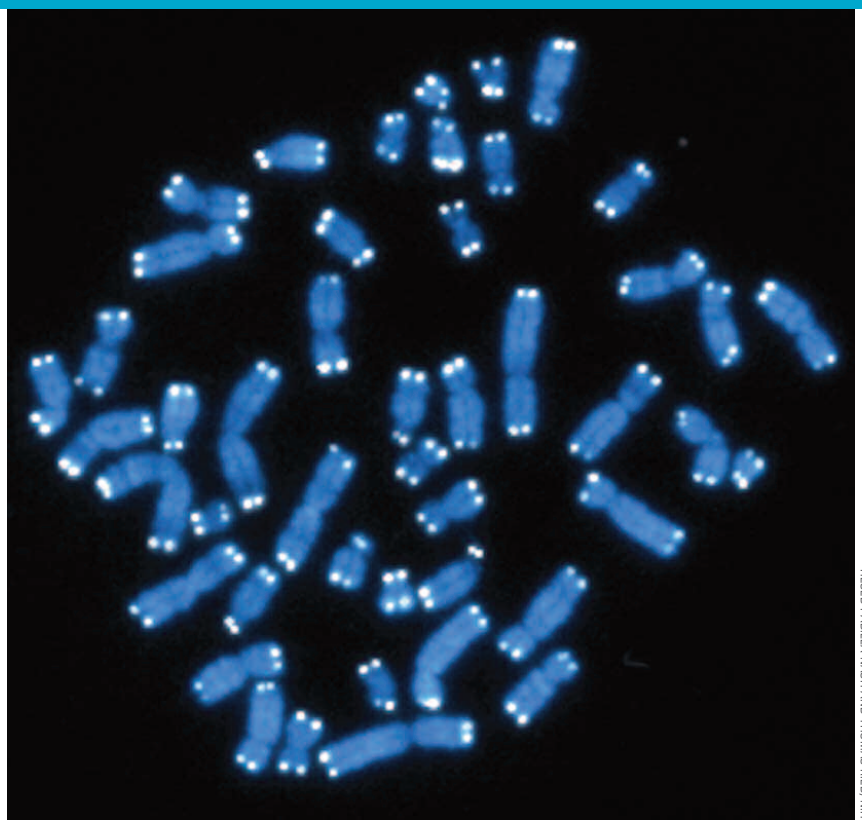
When a cell divides into two daughter cells, it has to copy its DNA. But the DNA replication machinery cannot reach the very ends of chromosomes, so each time a cell divides, its chromosomes lose 25 to 200 letters at their tips. Telomeres serve as dispensable DNA that buffers chromosomes from losing any vital genetic information. Telomeres also prevent chromosomes from sticking together.

Researchers have known since the 1930s that telomeres cap chromosomes, but it was not until the 1970s that they figured out what those caps are made of.

The team that solved this puzzle—and won a 2009 Nobel Prize for the work—was led by Elizabeth Blackburn at the University of California, San Francisco, and included Carol Greider, now at Johns Hopkins University in Baltimore, and Jack Szostak at Harvard Medical School in Boston.

Another key player was the model organism they used—a pond-dwelling creature called Tetrahymena that is an extraordinarily rich source of telomeres.

The scientists discovered that telomeres are long repeats of the same sequence of DNA. In people, they consist of the DNA sequence abbreviated TTAGGG repeated about 2,000 times.



HESED PADILLA-NASH AND THOMAS RIED, NIH

The 46 human chromosomes are shown in blue, with the telomeres appearing as white pinpoints. The DNA has already been copied, so each chromosome is actually made up of two identical lengths of DNA, each with its own two telomeres.

The researchers also discovered how cells can maintain the length of their telomeres: An enzyme called telomerase adds more of the TTAGGG sequence to the ends of chromosomes. This is important in a growing fetus, where cells are dividing rapidly. But in most adult body cells, telomerase is essentially dormant under most conditions. Certain cells can respond to temporary stresses by upping their production of telomerase, which prevent telomeres from shrinking prematurely.

## Telo Trouble

Malfunctioning telomeres and telomerase can cause diseases. For example, most cancers make lots of telomerase—as much as 10 to 20 times the normal amount. The cells don't stop dividing, and so they form tumors.

Scientists would like to turn off the telomerase in tumors, but first they need to learn more about telomerase. Juli Feigon of the University of California, Los Angeles, is working to describe the three-dimensional structure of the enzyme. Once scientists know the enzyme's detailed shape, they might be able to develop drugs to gum up the works and prevent cells from becoming cancerous.

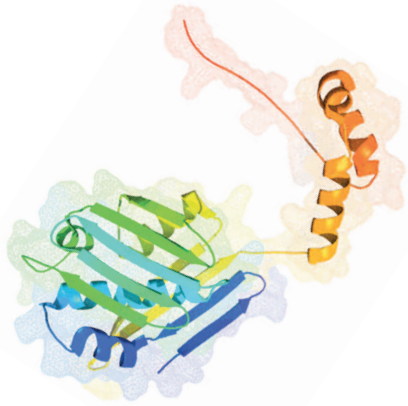
In Werner syndrome, people start aging rapidly during their 20s. They develop gray hair, cataracts in both eyes, hardening of the arteries and other diseases of old age. Jan Karlseder of the Salk Institute in La Jolla, California, found that people with Werner syndrome sometimes have missing telomeres or parts of one chromosome stuck to another. In a laboratory experiment using cells that originally came from a person with Werner syndrome, Karlseder found that when he provided extra telomerase to the cells, they ended up with less DNA damage than did identical cells that didn't receive telomerase.

Another rare disease, dyskeratosis congenita, happens when people can't maintain the telomeres in their bone marrow, which is where blood cells are manufactured. People with the disease die when their bone marrow can no longer produce enough healthy blood cells. Carol Greider continues her Nobel Prize-winning work by studying mice with broken telomerase, which mimics dyskeratosis congenita.

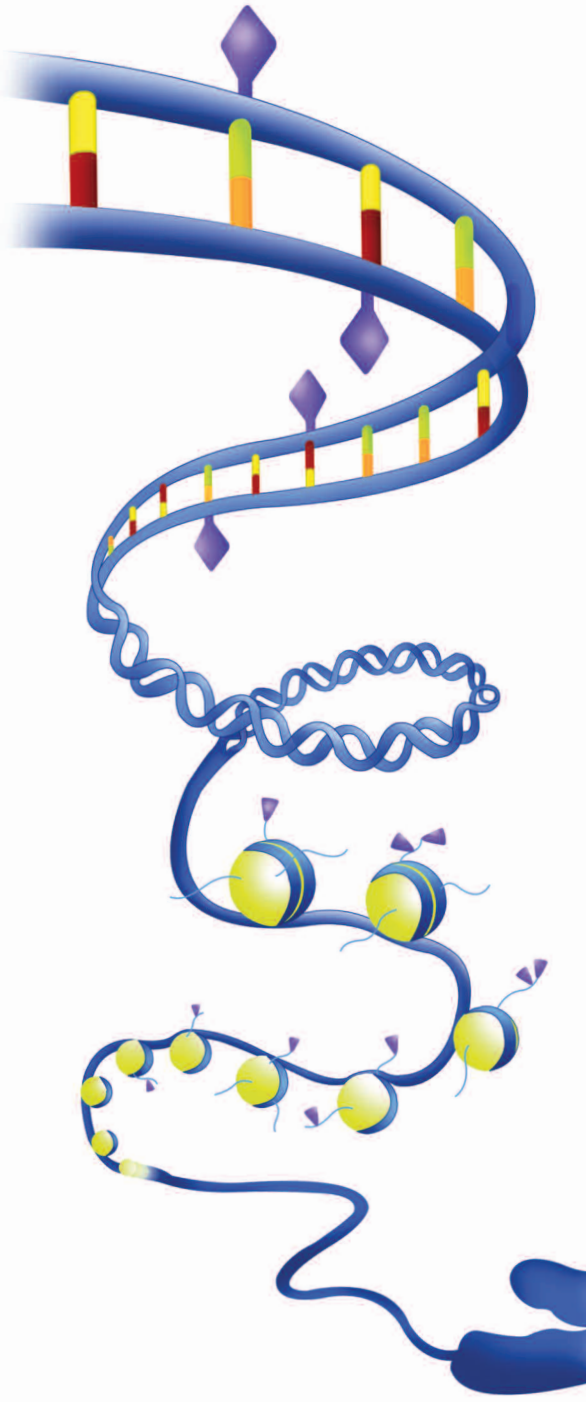
# Cellular Stress Relievers

*By Kirstie Saltsman and Emily Carlson*

**Your heart rate speeds up.** Your muscles tense. Your face may even blush. These are just a few ways you feel your body respond to stress. But stress also can seep into your cells. Rising temperatures, toxins, infections, resource shortages and other stressors threaten how cells function—and ultimately whether you're healthy. Scientists funded by NIH have learned a great deal about how cells respond to stress, and here are some examples.



This heat shock protein, Hsp33, wraps a protective arm around unfolded proteins.
URSULA JAKOB, UNIVERSITY OF MICHIGAN



## Protect Proteins

Heat can stress out cells. Warm them just three or four degrees, and their proteins begin to unravel and stop functioning. If the proteins unravel too much, they tangle up with each other and form a clump that can kill the cell. To prevent this catastrophe, cells rely on a set of molecules called heat shock proteins (or "chaperones") that work in many different ways. Some tuck the sticky, carbon-rich regions of unfolded proteins into a small pocket; others extend a protective arm around their unfolded neighbors or form barrels that sequester unraveled proteins away from any potential tangling partners. Once things cool down, heat shock proteins help their "clients" refold into proper shapes.

## Pass It On

Environmental stress can reach deep into a cell's interior and alter the genetic material held within its nucleus—and the changes can be inherited. A Swedish study showed that if a man didn't have enough to eat during his life, his *grandchildren* had a higher risk of diabetes, obesity and cardiovascular disease!

Subsequent research at the University of Massachusetts Medical School in Worcester showed that when male mice were fed a low-protein diet, the activity of hundreds of genes in the animals' offspring changed. In particular, genes that manufacture fats were more active. Although making more fats might be a protective stress response to starvation, when there's plenty to eat, it could lead to obesity and related diseases.

Genomic research suggests a potential link between these heritable changes in patterns of gene activity and changes in chemical markers, called epigenetic tags, affixed to certain genes. Scientists are trying to understand the nature of these changes and how they occur.

Chemical tags (purple diamonds) on certain DNA letters can change the activity of genes without altering the DNA sequence.

JUDITH STOFFER

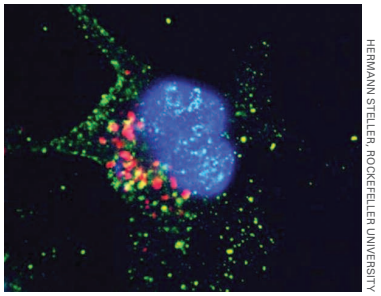
## Evolve

Cells use intricate mechanisms to maintain the stability of their genetic material. Under stressful conditions, however, they may relax these controls.

Allowing genomic instability creates a population of genomically diverse cells. Even if the original strain succumbs to the stress, there's a chance that at least one of other strains will survive.

Scientists tried out this theory in yeast, an organism commonly used as a model to study human genetics. When researchers at the Stowers Institute for Medical Research in Kansas City, Missouri, exposed yeast colonies to potentially toxic chemicals, the yeast cells quickly gained or lost entire chromosomes. After several generations of continued exposure, some of the yeast cells had evolved the ability to survive not only the original chemicals, but also others, including drugs that normally kill yeast.

In the future, scientists might be able to take advantage of this adaptive strategy to treat cancers, which typically involve cells with extra or missing chromosomes.



HERMANN STELLER, ROCKEFELLER UNIVERSITY

This cell is undergoing apoptosis, as indicated by the presence of caspase-3 (green), a key tool in the cell's destruction.

## Die

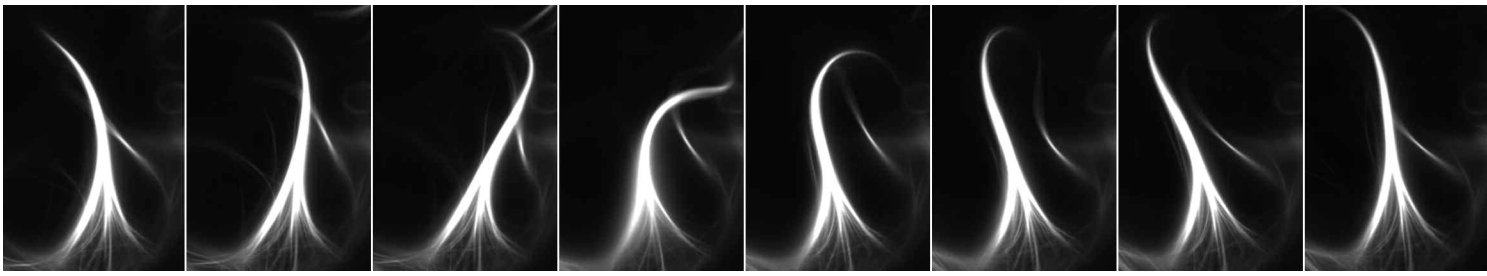
If all else fails, a cell may commit suicide via a pathway called apoptosis. This strategy sidesteps the destructive effects of a cell actually dying from the stressful conditions, which can damage or kill nearby healthy cells by triggering inflammation.

Scientists don't yet understand what causes a cell to abandon its attempts at self-preservation and commit to apoptosis. Some research suggests it has to do with the accumulation of unfolded proteins in a cellular compartment called the endoplasmic reticulum (ER). When stressful conditions, like exposure to a chemical, overwhelm the ER, molecules in its membrane may signal apoptosis to start.

Because cell death could play a role in a number of neurological and cardiovascular diseases, understanding how cells make their life-or-death decision might lead to ways to reduce the damage caused by these types of conditions.

# Cilia: Biology's Brooms

*By Amber Dance*



**These hairs are tiny,** but mighty. Cilia, lash-like structures on a cell's surface, sweep mucus from the lungs and circulate the fluid needed for proper brain function. They shepherd a woman's eggs from the ovaries to the uterus. And without the extra-long cilium called a flagellum, sperm would be tailless and unable to swim.

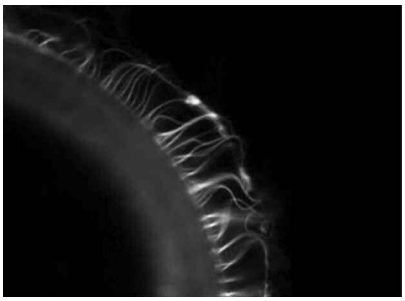
Scientists are learning more about basic cilia biology and gaining new insights into how problems with cilia cause diseases.

## Getting to Know Cilia

A single cilium is made up of some 600 protein pieces—more than many other cellular structures.

Frequently, many cilia work together, rippling like a hayfield in a breeze, to keep body fluids flowing properly.

Other cilia are non-moving loners. A single, antenna-like "primary cilium" sticks out of most cells, and scientists recently found that its job is to sense the environment around a cell and transmit signals into the cell.



See artificial cilia "do the wave" in a video at http://publications.nigms.nih.gov/multimedia/video/cilia.html.

## Cilia in Peril

More than a dozen rare but serious genetic disorders stem from cilia glitches.

For example, an error in one or another of several cilia genes can lead to primary ciliary dyskinesia, which affects one person out of 16,000. People with this syndrome have trouble keeping their lungs clear of mucus and sometimes are infertile.

Researchers have created artificial cilia that wave like the real thing. These lab-made cilia are revealing how the structures coordinate their movements and what happens when they don't move properly.

ZVONIMIR DOGIC LAB, BRANDEIS UNIVERSITY

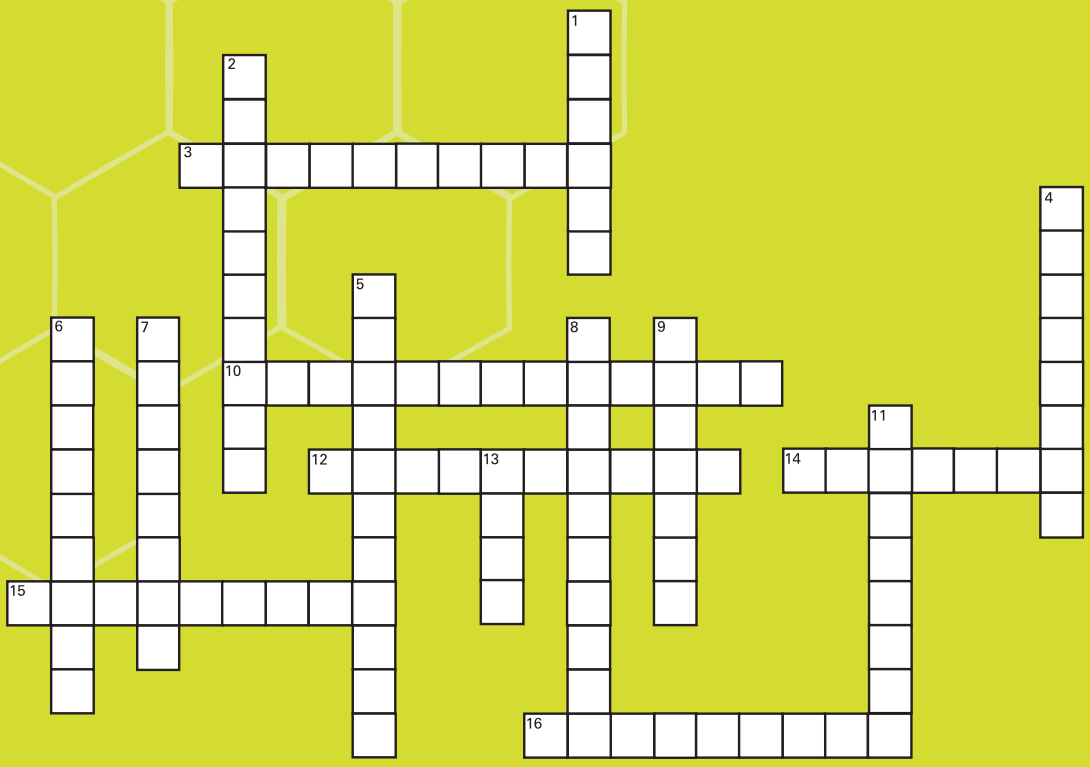
Bardet-Biedl syndrome is a genetic condition that occurs in approximately one in 150,000 people and can lead to obesity, blindness, kidney disease and extra fingers and toes. Researchers discovered that the disease is due, in part, to impairment of the primary cilium's communication abilities.

Could scientists come up with a cilia repair system to treat these diseases? One day they might be able to use gene therapies to fix mutations that cause malformed cilia. Or they might be able to learn to grow and transplant cilia into people who can't make the structures properly on their own.

**FIND MORE**

For more articles like those on pages 12–16, see http://publications.nigms.nih.gov/insidelifescience

EXPLORE IT **PUZZLE IT** FIND IT



## ACROSS

3. Bacteria use a bit of RNA called a _____ to sense and respond to high levels of fluoride.
10. The full name of the Seattle-based DO-IT program is Disabilities, _____, Internetworking, and Technology.
12. This enzyme lengthens telomeres.
14. As we age, telomeres _____.
15. Duerstock designs _____ technology for people with disabilities.
16. Nerve damage can include both primary and _____ injury.

## DOWN

1. An online networking site for people with disabilities.
2. Duerstock hopes to find ways to repair damage to this part of the body.
4. Nitric oxide increases blood flow by _____ arteries.
5. Scientists think _____ may play a role in Alzheimer's disease.
6. Cells commit suicide through a pathway known as _____.
7. This substance increases dramatically after a spinal cord injury.
8. One of Duerstock's inventions was an accessible _____.
9. Cancer cells often contain extra or _____ chromosomes.
11. Accessible tools can help people who have _____ or visual impairments—and everyone else, too.
13. Penicillin comes from _____.

**SOLVE IT ONLINE** An interactive version and answers can be found at http://www.nigms.nih.gov/findings.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NIH Publication No. 12-4932-02
September 2012
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