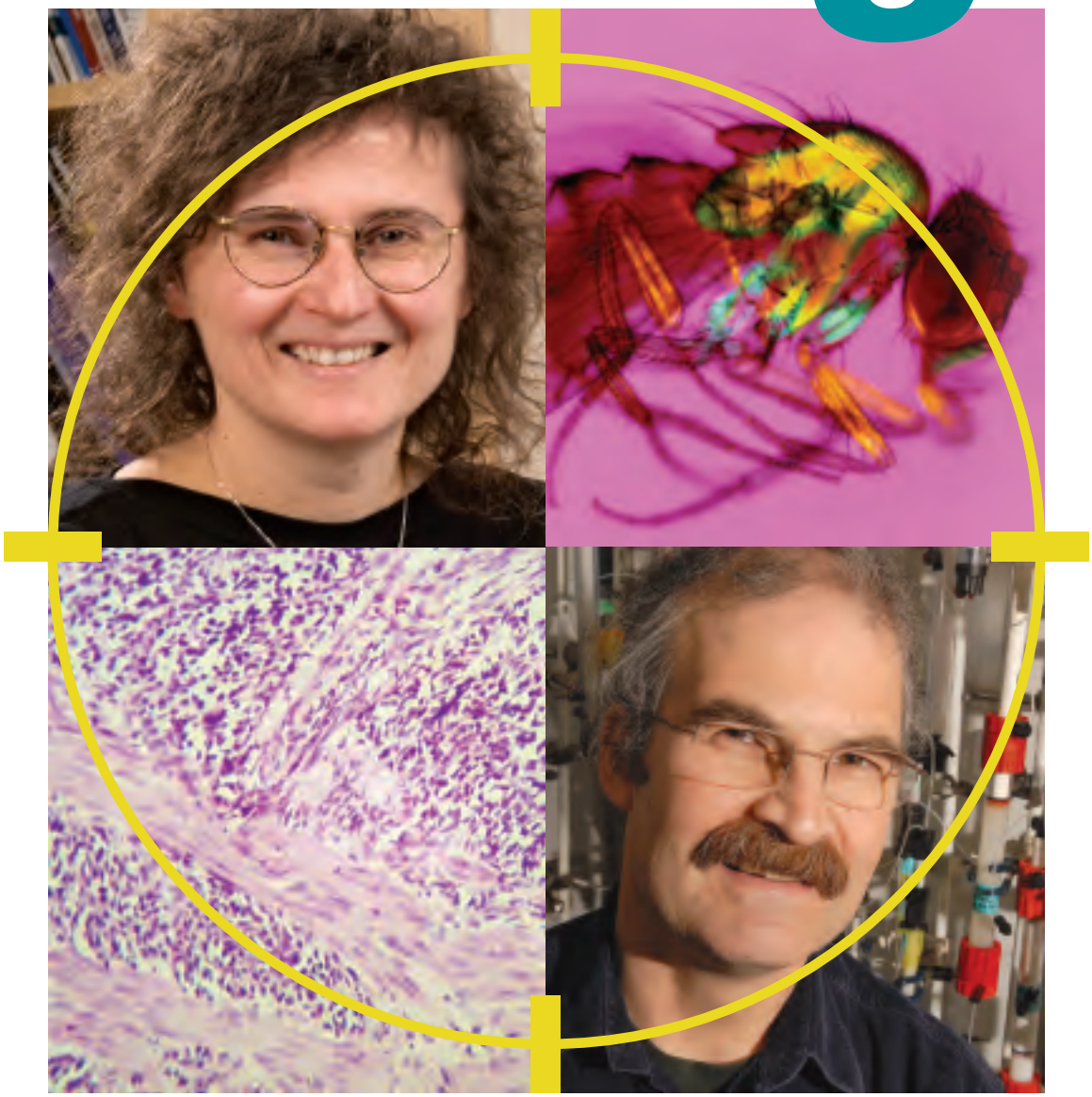
SEPTEMBER 2006

# Findings



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

Edited by Alison Davis under contract 263-MD-516060

Produced by the Office of Communications and Public Liaison
National Institute of General Medical Sciences
National Institutes of Health

**On the Cover**

**Chiara Cirelli:** ***Del Brown, Photographer***
Chiara Cirelli is a neuroscientist at the University of Wisconsin-Madison. Cirelli studies sleep using model organisms like fruit flies.

**Yuri Lazebnik:** ***Miriam Chua, Photographer***
Yuri Lazebnik is a cell biologist at Cold Spring Harbor Laboratory on Long Island, New York. He studies cell fusion.

# Editor's Note

Think you know your stuff when it comes to cells?

*Which organelle is known as the cell's "brain"?*

*Apoptosis is the popping sound cells make when they die. True or false?*

*What do mitochondria do?*

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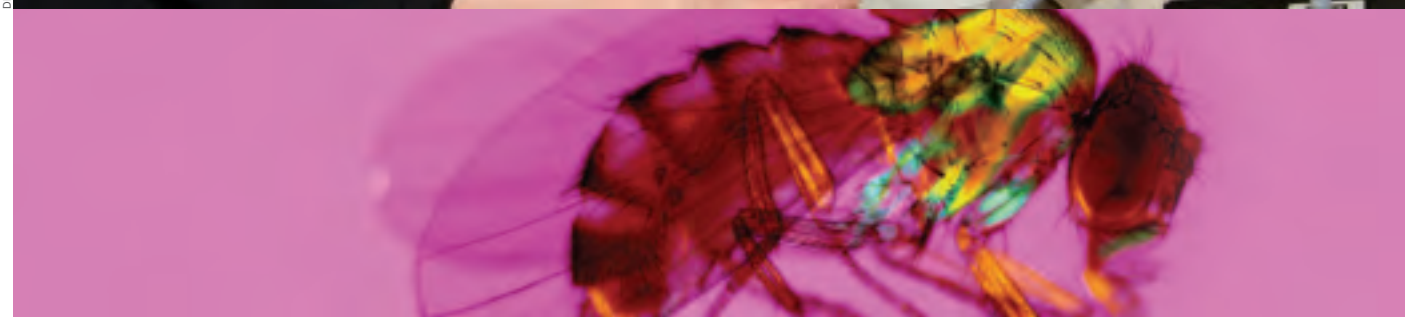
# Recipe for Sleep

DEL BROWN



BY EMILY CARLSON

## Do you like playing with your food?

Not molding it into sculptures, but experimenting with it—putting syrup instead of jelly on a peanut butter sandwich or microwaving marshmallows to see if they'll explode.

This creativity can have tasty results or teach you new kitchen tricks to show your friends. With the right utensils and training, you could even call yourself a chef…or a scientist.

Like chefs, scientists enjoy using their knowledge and tools of the trade to mix up lab recipes that can lead to new outcomes or ideas.

Or, you could be both. Take Chiara Cirelli, a neuroscientist at the University of Wisconsin-Madison. While her friends devour the fresh soups, pasta, and pizza that she creates at home, other researchers eat up the findings about sleep that she churns out in the lab.

## Settling Down

Born in a region of northern Italy famous for its first courses, Cirelli came to the United States 12 years ago for a research position in California. At that point, she already had M.D. and Ph.D. degrees. In 2001, she faced a tough decision: Should she stay in the United States, or return to Italy?

Cirelli, now 41, was being recruited by the University of Wisconsin to join a group of scientists who study the reasons we need shuteye. Without losing much sleep over the decision, she settled into a new life in the Midwest.

Today, she lives in a log cabin surrounded by woods and occasionally visited by white-tailed deer. "I grew up in cities, but I really like it here," says Cirelli.

The researcher, now a U.S. citizen, doesn't regret her choice to stay.

"The general attitude toward research is very different in Italy," Cirelli says, explaining that students in Italy typically get less experience teaching and sharing results with the public.

As Cirelli searches for answers about sleep—a quest she started as a graduate student in Pisa—she hopes that her work ultimately will lead to new sleep aids that might help people snooze more soundly.

"We have no good drugs that have the same restorative power as sleep," says Cirelli, suggesting that an ideal drug might be able to compress a night's sleep into a power nap.

## Sleeping Habits

All animals sleep—at least all those that scientists have studied. They don't necessarily do it the same way, though. Cows sleep standing up, armadillos snooze during daylight, and some birds nap with one eye open. Researchers have shown that dolphins sleep with one side of their brain still awake, probably because they need to be conscious to breathe.

▲ Why do we all need sleep?

Cirelli herself keeps a regular sleep schedule.

"I always get at least 7 hours," she says. She usually dozes off a few hours after dusk and rises before the sun—without an alarm clock.

"I wake up spontaneously," she adds. She doesn't nap, because she never feels sleep deprived, but she always encourages others to enjoy an afternoon siesta if they feel tired.

Cirelli sticks to this schedule no matter what may come up.

"I like to entertain and have people over for dinner, but at 9:30 p.m., I say 'goodbye.'" Her guests know that they're welcome to stay after their hostess hits the sack.

But still: Why do we sleep? From the savanna to the city, snoozing comes at a cost. A gazelle that's not keeping watch could get picked off by a hungry lion. For other species, like humans, sleep consumes valuable time that could be spent working, studying, or even partying.

Some researchers think that sleep gives the body a chance to repair itself, or that it provides the brain time to organize its thoughts. But Cirelli thinks something different.

**"Sleep is still very much a mystery."**

Her idea is that sleep helps us learn more the next day.

"When you're awake, you are always learning new things," she explains. As a result, the connections between the brain's neurons, called synapses, get stronger. The synapses also get bigger and need more fuel.

"We can't afford this in terms of space and energy," says Cirelli.

Research suggests that the slow brain activity produced during sleep shrinks your brain synapses, making you a more efficient learner in the morning.

Cirelli has been testing this hypothesis in rats. If proven true, she will be one step closer to explaining why we sleep.

## Slowing Down

Down a quiet hallway in an even quieter room that gets completely dark and stays a constant, cool temperature, 20 rats spend their days and nights. Tiny electrodes touching the rodents' brains record electrical activity, while other monitors record movement. Comparing the two helps Cirelli distinguish between a sleeping rat and one that's just lazing around.

The data translates into waves on a computer screen. For both brain and muscle activity, slow waves are usually tall and wide, whereas fast waves are short and narrow. As you get groggier, your brain starts producing slower waves. During the rapid-eye movement (REM) phase of sleep, when most dreams occur, the waves can be just as fast as they are during wakefulness.

Cirelli and her team run a variety of sleep experiments with the rodents.

To test the synaptic-strength hypothesis, they study the snoozing patterns of normal and "gifted" rats. While the average rats spend their time lounging around, the smarter ones get a mental workout in a more stimulating environment, where they're challenged by tasks like grabbing food pellets from a small opening.

The scientists analyze brain activity patterns of all the rats during sleep and wakefulness, and they look for physical differences in their actual brains during both states. Identifying dissimilarities between the two rat groups could point to a connection between learning and sleep.

## Fly by Night

For Cirelli, cooking and science share other common ingredients. Here's a hint: They're full of protein, but not particularly tasty.

Fruit flies! Yep, the same annoying pests that circle ripe peaches in the kitchen are a staple of the Cirelli lab. There, the flies go by their scientific (Latin) name, *Drosophila melanogaster*. Cirelli uses these insects to search for genes that may play a role in sleep.

At first, not everyone thought this genetic approach was a bright idea.

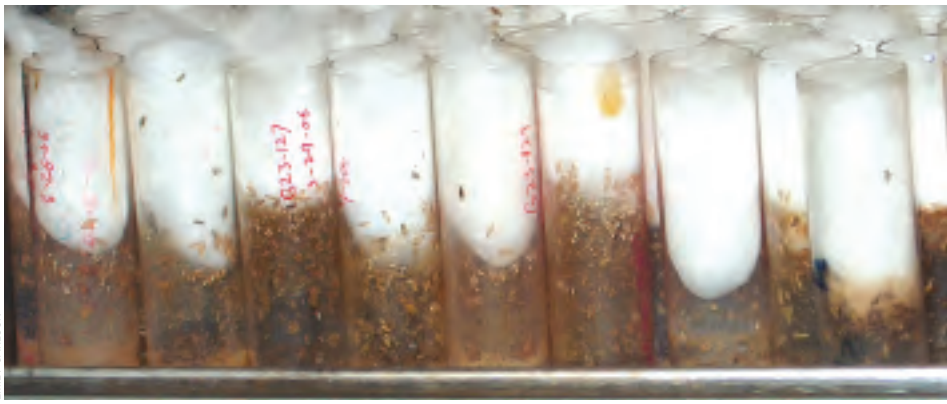
"In the research community, sleep was always considered something that happened only in mammals," says Cirelli. "The idea of studying sleep in flies was considered strange, to put it mildly!"

Lots of recent studies done by Cirelli and others confirm that fruit flies sleep. It might be hard to imagine a fruit fly (about the size of a rice grain) tucked into bed, but they get more sleep than we do—an average of 12 hours every night.

When flies sleep, they're completely still. Only loud noises or other disturbances wake them. If you give them medicines that induce sleep, they snooze longer. If you give them caffeine, they stay alert longer.

After sleep deprivation, the flies are more sluggish the next day and may need a nap to make up for it. Does any of this sound familiar?

Not only do flies sleep, they offer researchers a perfect tool for studying heredity, or genetics. With a fly life-span of just a few months, researchers can examine many generations of these organisms. Doing the same with humans would take hundreds of years!



EMILY CARLSON

In the lab, fruit flies bunk in glass vials stuffed with food.

Female flies lay eggs every day, making for a ready supply of flies. Plus, scientists know almost all the genes for about a dozen different species of *Drosophila*. That's important because by comparing the genes of related fly species, researchers can track changes in certain genes for a given behavior, like sleeping.

Cirelli searches for flies that can sleep less without becoming impaired. This trait, she explains, would probably come from a genetic mutation, a small change in a gene's DNA spelling that offspring can inherit. By locating the gene mutation, she and others could then explore its role in mammals, like mice, rats, and possibly humans.

Alternatively, the researchers could purposefully change a fly's genetic information and then look for any effect on sleep habits.

Before Cirelli and others proposed the idea of studying the molecular underpinnings of sleep, most sleep researchers focused primarily on brain activity. According to Cirelli, monitoring brain activity identified brain regions involved in sleep, but did little to explain what happens at the molecular level.

Cirelli wanted to figure out what genes and proteins contribute to normal sleep. So far, the researcher has identified several genes that appear to have a powerful effect on sleep and ultimately could lead to new clues about the causes of sleep disorders.

EMILY CARLSON

This contraption turns on its side like a carnival ride to keep the flies inside each vial awake.

## Sleepless in Madison

Unlike her research rats, Cirelli's flies sleep in a much noisier room. For the first part of a typical experiment, the insects bunk in a quiet closet, where each fly sleeps in its own glass vial stuffed with food. An infrared beam cuts through the "beds" to monitor movement. If a fly doesn't cross the light beam for 5 minutes, the monitor records that fly "asleep."

Next, Cirelli makes the flies really tired. She places the fly vials in a 4-foot-long robotic arm built by the campus machine shop. There, the flies try to sleep during what probably feels like a carnival ride. Every couple of minutes, the arm tilts and drops the frame containing the vials on its side.

This action not only changes the insects' orientation, it sends a rude awakening—the clank of metal against metal. Another sleep-depriving contraption includes a gadget that scrapes credit cards against the glass vials.

Before she had these gizmos, Cirelli herself kept the flies awake.

"It [used to be] me tapping on the glass or knocking the frames against my knee," she recalls, not very fondly.

Now tired, the flies return to the peaceful closet for a nap. At this point in the experiment, Cirelli looks for flies that spend less time catching up on lost sleep. These flies may have a genetic mutation that keeps them alert after sleep deprivation.

Normally, this type of genetic analysis can take years, and often researchers never find the mutation that causes the behavior they're studying.

"You need a lot of patience," Cirelli admits. "You also need a lot of luck."

Against these odds, her group hit the jackpot last year—they found the gene mutation that allows the "mini-sleeper" flies to get by on just a few hours of sleep each night without showing signs of sleep deprivation.

Working with another scientist who also studies *Drosophila*, Cirelli discovered that the minisleeper flies displayed another telltale inherited trait: They shook after being exposed to the anesthetic chemical ether.

**"The idea of studying sleep in flies was considered strange, to put it mildly!"**

"Only three or four genes in the entire set of *Drosophila* genes are known to cause shaking," Cirelli explains. Her team immediately knew where to find their needle in the gene haystack.

The information provided a shortcut to identifying the minisleeper gene, since genetic mutations that are physically close to each other on the same chromosome are often inherited together.

As it turns out, the mystery gene was one called "shaker," which encodes a protein that helps nerve cells transmit electrical signals. Because humans have a similar gene and protein, the finding offered a new target for drug development. But there's a problem: Minisleeper flies don't live nearly as long as the sleepier ones, so more work needs to be done to sort this out.

Despite her research successes, Cirelli says that it may be a long time before scientists completely understand the function of sleep.

"Sleep is still very much a mystery," she says. "But I'm optimistic we'll [have some answers] in my generation or the next."

## Espresso, Anyone?

While Cirelli likes to talk about her sleep research with family, friends, and coworkers during her regular dinner parties, the food she cooks is still the main attraction.

"She is the *best* at both molecular biology and cooking," says Ugo Faraguna, a visiting graduate student from Italy who was looking forward to joining Cirelli at her cabin for a lab dinner.

Faraguna's favorite dish is Cirelli's tortelloni alla zucca—homemade pasta stuffed with squash, most likely grown in Cirelli's own vegetable garden. Faraguna says that Cirelli's love for cooking is in part cultural.

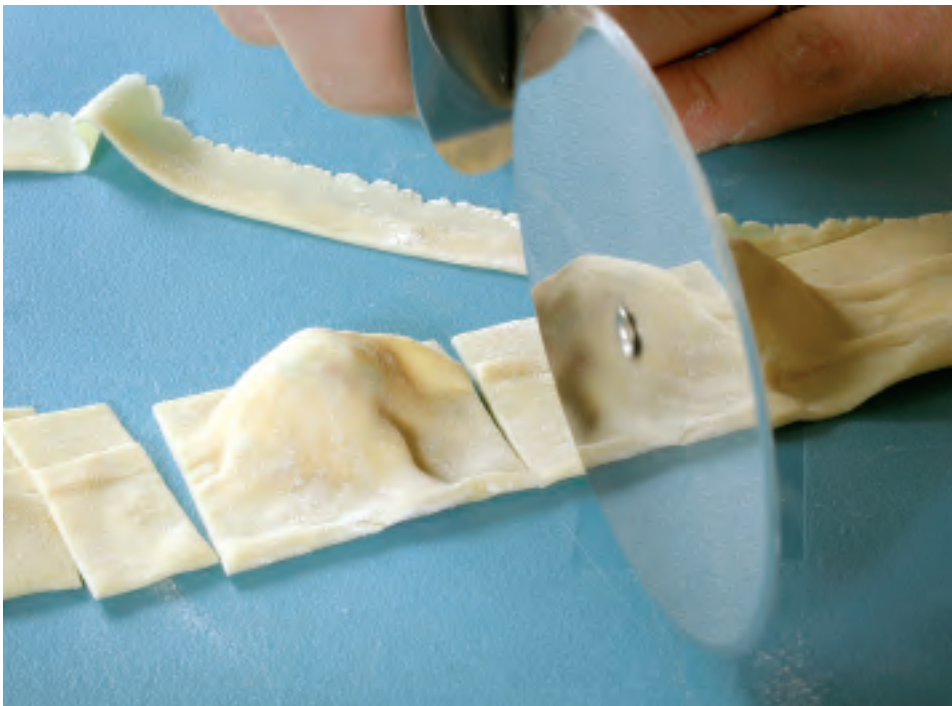
"In Italy, we spend hours and hours cooking. It's a ritual," he says. "Here, people think food is energy you put in your body, like the gas you put in a car."

When she's not working on lab or dinner recipes, Cirelli enjoys the outdoors. From April to October, she tends to her garden, hikes the trails near her house, or chops firewood for the winter months.

Once the Wisconsin winter brings frigid air and biting winds, Cirelli stays indoors. She reads or catches up on classic American movies—but not on television.

"I don't have a TV," she says matter-of-factly. Instead, she installed her own movie theater, complete with

Homemade pasta is a staple of Cirelli's Italian cooking.



a large screen, projector, and surround sound. Even though her friends tell her she should spend more time relaxing, Cirelli always says they have nothing to worry about.

"I absolutely love what I do!" she says.

Her colleagues can't complain: They enjoy Cirelli's company in the lab as much as they do at her dinner table.

"Chiara makes science fun," says Ruth Benca, a research psychiatrist who collaborates with Cirelli. According to Benca, Cirelli isn't interested in competing with other researchers, but instead prefers to work side-by-side with them.

"That's what science is all about," says Benca.

To her students, Cirelli is a fairy tale brought to life. Faraguna, who attends the same prestigious Italian university that Cirelli did, jokes that he came to the United States to find out if she was the "goddess" everyone said she was.

"She's a myth at our school [in Italy]," explains Faraguna, listing all her research accomplishments. "I love what I'm doing even more because of Chiara."

Given all that his teacher manages to accomplish, Faraguna lightheartedly wonders if Cirelli already has found the recipe for making more wakeful hours in a day.

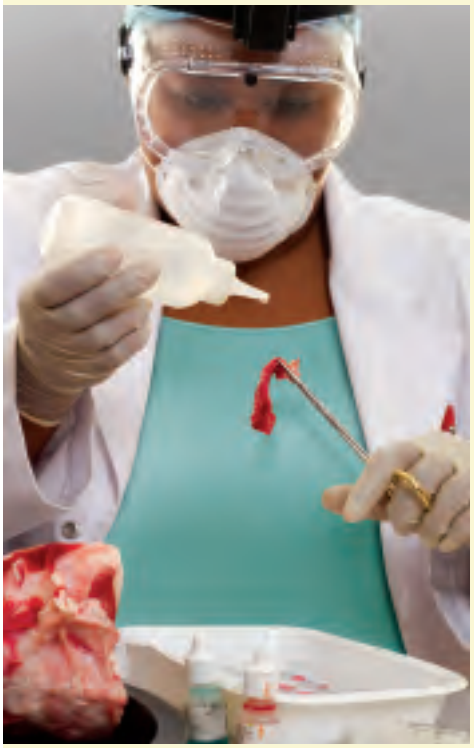
# Taste Tests

Take a bite of mushy peas or a sip of sour milk. Yuck, right? Well, maybe, but stop and consider that you just observed science in action!

When vegetables boil in water, the heat softens the rigid structure of the plants' cells. Milk, on the other hand, serves as its own chemical and biological laboratory. The few natural bacteria in milk that aren't killed during pasteurization can reproduce and generate enough acid to sour milk.

Scientists who study the properties and interactions of different ingredients are called food chemists. Their labs look like kitchens, with refrigerators, ovens, blenders, and other culinary tools. By concocting new recipes—their experiments—these scientists examine how different products or cooking techniques can change the flavor, smell, shelf life, or even color of what we eat.

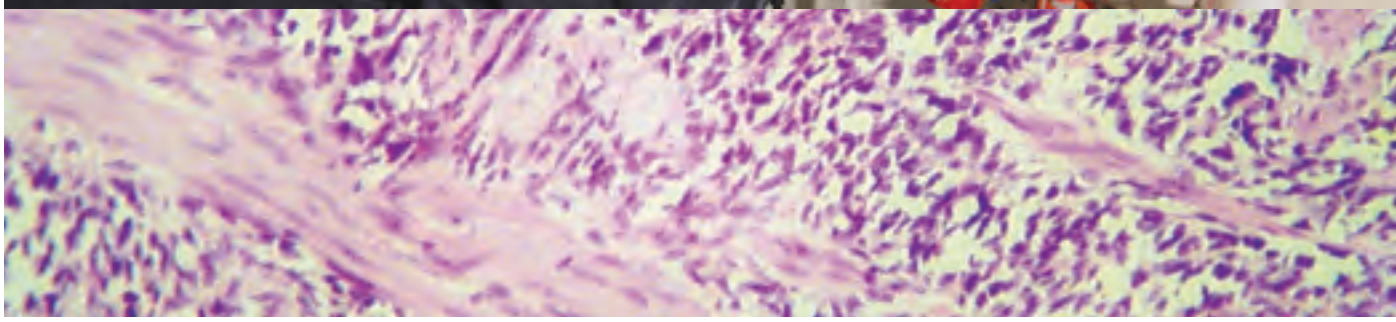
Besides knowing a lot about chemistry, these specialized researchers also know a lot about food, which is composed primarily of different combinations of water, proteins, fats, carbohydrates, and minerals. Water makes up 93 percent of an eggplant, for example, but only 3 percent of a peanut. Processing, however, can alter these compositions, changing a food's characteristics and its potential market appeal.



Since sampling the results is a key part of the food scientist's job, in this profession an above-average sense of smell and taste can be as important as scientific training. Sometimes, members of the public are invited to volunteer for taste tests. At the University of Wisconsin-Madison, food scientists who are trying to improve certain aspects of cheese and ice cream regularly call on a herd of experienced tasters to try their latest experiment.—*E.C.*

# Hunting a Killer

TOP: MIRIAM CHUA



BOTTOM: © 2004 AUGUSTINE G. DIGIOVANNA, SALISBURY UNIVERSITY—USED WITH PERMISSION

## A serial killer is on the loose, and scientists are hot on the trail.

BY ALISA ZAPP MACHALEK

That's because this killer is cancer, and among its pursuers is Yuri Lazebnik, 47, a cell biologist at Cold Spring Harbor Laboratory on Long Island, New York.

As a forensic scientist uses fingerprints and bloodstains, Lazebnik uses tools of cell biology to uncover the roots of cancer and help contribute to a cure.

## From Russia With Drive

Lazebnik grew up in St. Petersburg, Russia, raised by a single mother in a house that faced the department of mathematics and mechanics at the nearby university. When the students threw out parts of old computers or bits of broken machinery—knobs, switches, cables, and the like—Lazebnik and his friends would scamper over the fence, retrieve the discarded treasures, and transform them into rocket ships.

To earn money during college and graduate school at St. Petersburg State University, he held various odd jobs, working as a photographer, electrician, night-time store manager, and operator in a coal heating facility. At one point he even served as a cleaner of agricultural irrigation channels, which he remembers as backbreaking work that "involved a nice mixture of lumberjacking and ditch-digging."

One job that shaped the course of Lazebnik's career was working as a technician in a hospital.

"That's where you see the other side of life—people dying," he recalls. He was particularly moved by people who had cancer, especially kids.

Lazebnik resolved to study cancer and immigrated to the United States to do so.

## Guided By Surprise

*"The most exciting phrase to hear in science, the one that heralds new discoveries, is not 'Eureka!' (I found it!) but 'That's funny…'"*

*—Isaac Asimov*

The hallmark of cancer is its ability to spread. Rather than staying within their home tissue, cancer cells move aggressively into neighboring tissues, damaging or shutting down vital organs and often leading to death if left untreated.

**"You have the potential to discover something that could turn around your entire view of the world."**

Like many cell biologists who studied cancer in the early 1990s, Lazebnik initially focused on cell division, or mitosis, which goes haywire in cancer.

But a strange sight almost immediately pulled him in another direction. As he peered at dividing cells through a microscope, one of them looked "funny" to him. Its nucleus, normally a smooth, oval-shaped structure, looked like a bunch of grapes or a cluster of darkly colored plastic beads. He knew that whatever he was seeing, it wasn't mitosis.

As it turned out, Lazebnik had witnessed apoptosis, or cellular suicide. Our bodies use this process during normal development to sculpt the shape of our fingers and toes and streamline nerve connections in our brains. Apoptosis is also how the body removes old, worn-out cells throughout our lives.

At the time, few researchers studied apoptosis, and Lazebnik thought those who did were crazy, as most "rational" people didn't believe in apoptosis then, he says.

Nonetheless, Lazebnik followed the trail of where his research led him. Today, some 90,000 scientific papers have been written about apoptosis, and 10,000 new ones are published each year.

## Demonstrating Death

As an expert in the field, Lazebnik frequently speaks about apoptosis, both to researchers and to nonscientists. His talks are peppered with analogies, including a scene from the James Bond movie *The Spy Who Loved Me*, old film clips of an aikido master (see sidebar, page 13), and illustrations of bombs, collapsing houses, and a shark sliced up with its pieces rearranged.

Lazebnik saves his most vivid analogy for teaching high school students about proteases, the knifelike enzymes that carve up cells during apoptosis. In this demonstration, he first removes a scalpel from his right

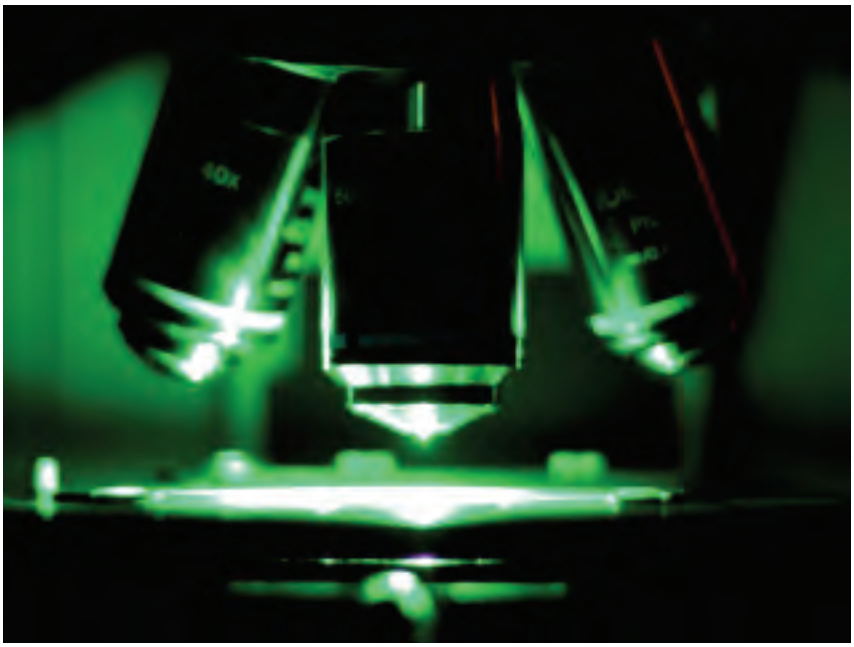
Lazebnik grew up in the Russian city of St. Petersburg.

pocket and shows it to the students. Then he extends his left arm and draws the knife straight across it.

Students gasp, but there's no blood. That's because the scalpel comes with a protective plastic sheath over the blade. Similarly, all cells contain proteases but keep them tucked away until they're needed, Lazebnik explains.

Next, he dramatically snaps off the protector. Every eye is locked on him as he raises the naked blade.

After a pause, he continues, "I take a piece of paper and slice it into many pieces. This shows the students what proteases do during apoptosis. The idea is impregnated into their minds."



By using a microscope to look at cells that have been marked with fluorescent dyes, Lazebnik is studying the roots of cancer.

## Fusion Confusion

A few years ago, biology stumped Lazebnik again. As before, finding the answer set him on a new research path.

The surprise finding was originally made by a high school student, David Rubenstein, who was working in Lazebnik's lab for a few months as part of Cold Spring Harbor Laboratory's Partners for the Future program, which Lazebnik directed for several years.

This program gives high school seniors a taste of the real world of biomedical research and helps debunk stereotypes about scientists.

For Rubenstein, it worked.

"I was very surprised seeing the head of the lab in a T-shirt and jeans," he says. *(He and others concede that, at one time, Lazebnik did have hair rather like Albert Einstein's.)*

Rubenstein set up what everyone in the lab thought would be a simple experiment. The results were anything but routine. Two human cell types—a cancer-prone type and a normal cell type—looked like they had somehow merged or fused together. Rubenstein's mentor, Dom Duelli, a postdoctoral researcher in the lab, was skeptical.

"At first I didn't believe him at all," Duelli confesses. "I thought he messed something up."

But Rubenstein repeated the experiment and got the same results, convincing Duelli and the others that he had stumbled across something else "funny."

To figure out what was going on, Lazebnik curled up with his computer to absorb everything that had been published about cell fusion.

He learned that the body keeps a tight rein on the process. In fact, there are only five known examples of healthy cell fusion: fertilization (when a sperm and an egg fuse), formation of part of the placenta, muscle development, bone remodeling, and a type of immune response.

And, Lazebnik learned, except for fertilized eggs, fused cells don't continue to divide—in stark contrast to tumor cells, which do so wildly.

Most telling of all, says Lazebnik, is that when healthy cells accidentally fuse, their reproductive lives screech to a halt—a clear demonstration of how seriously the body takes abnormal cell fusion.

Yet as is often the case, cancerous and cancer-prone cells play by different rules. Rather than avoiding cell fusion, these cells readily merge together and then continue to reproduce—at least in the tissue culture dishes Rubenstein and researchers worldwide use for lab experiments.

"It's called spontaneous cell fusion," says Lazebnik, "which basically means we have no clue [why] it happens."

The real question is: Does it happen in tumors inside people? And, if so, could it be a key to why tumors are so tough to kill?

## Viral Culprits

If cancer cells were all the same, we'd have cured the disease long ago. Instead, they vary widely. Even a single tumor can contain a mishmash of abnormal cells with unpredictable characteristics.

Fusion, which scrambles together different cell types, could cause the strange diversity within tumors, says Lazebnik. As he puts it, "It's like the merging of two companies—you could end up with something completely different in the end."

What makes cells fuse?

To find an answer, Lazebnik and Duelli thoroughly examined the genes and molecules in the fused cells. They discovered that, at least in this case, the culprit was a tiny particle squirted out by the cancer-prone cells. This particle seems to be the virus that causes an AIDS-like disease in monkeys.

The same virus is found in people, but doesn't cause disease. And it's not there alone. There's a family of viruses residing within us so commonly that the viral genetic material intertwines with our own, composing at least 8 percent of our genomes.

Yet just because these viruses are common and don't appear to cause disease doesn't mean they're harmless, cautions Lazebnik. The monkey virus clearly makes human cells fuse in plastic lab dishes, and no one really knows what trouble that might stir up.

Finding a virus that triggers cell fusion isn't new; a number of viruses can do this. In fact, large masses of merged cells, known as syncytia, are typical of infectious diseases like measles and mumps and are also seen in some types of cancer.

But syncytia don't continue to divide. They eventually die and are reabsorbed by the body.

Occasionally, only two or three cells fuse, rather than the hundreds typical of syncytia. In rare cases, these small masses survive and multiply. That's when the trouble starts, explains Lazebnik. The fused cells tend to develop genetic changes, or mutations, that are caused by the haphazard bumping and shuffling of the many different sets of chromosomes within them. Some of these mutations can chart a course toward cancer.

Whether any of that happens—and whether the mass eventually develops into cancer—depends on chance and time, Lazebnik says.

## Questions Continue

All of this raises some sobering questions, says Lazebnik.

Do viruses cause some of our cells to fuse? Does cell fusion cause, or contribute to, cancer?

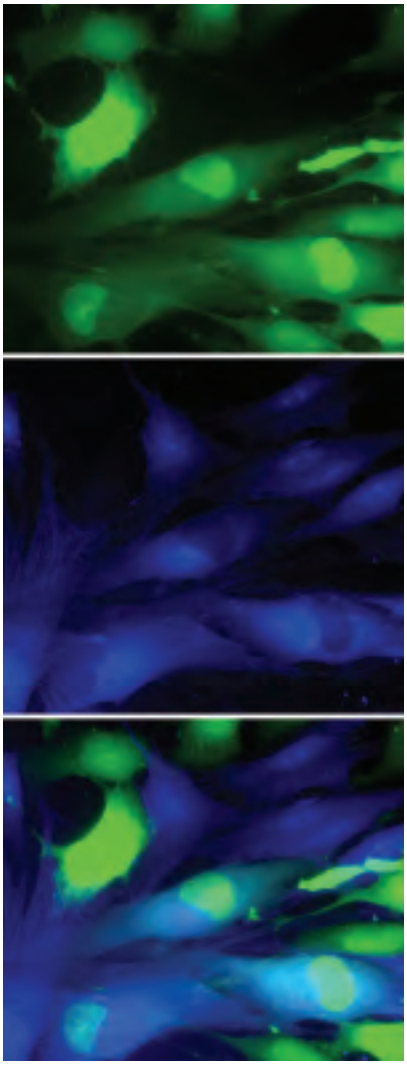
No one knows yet.

Scientists do know that at least 10 percent of cancers are caused, at least in part, by viruses. One example is human papillomavirus (HPV), which causes virtually every case of cervical cancer. Also, hepatitis B and C are strongly associated with liver cancer, and Epstein-Barr virus (which causes mononucleosis or "mono") is linked with some types of lymphoma.

If a virus causes a type of cancer, scientists may be able to prevent that cancer by developing a vaccine against the virus. The first vaccine of this sort targets hepatitis B. It has dramatically reduced the incidence of liver cancer.

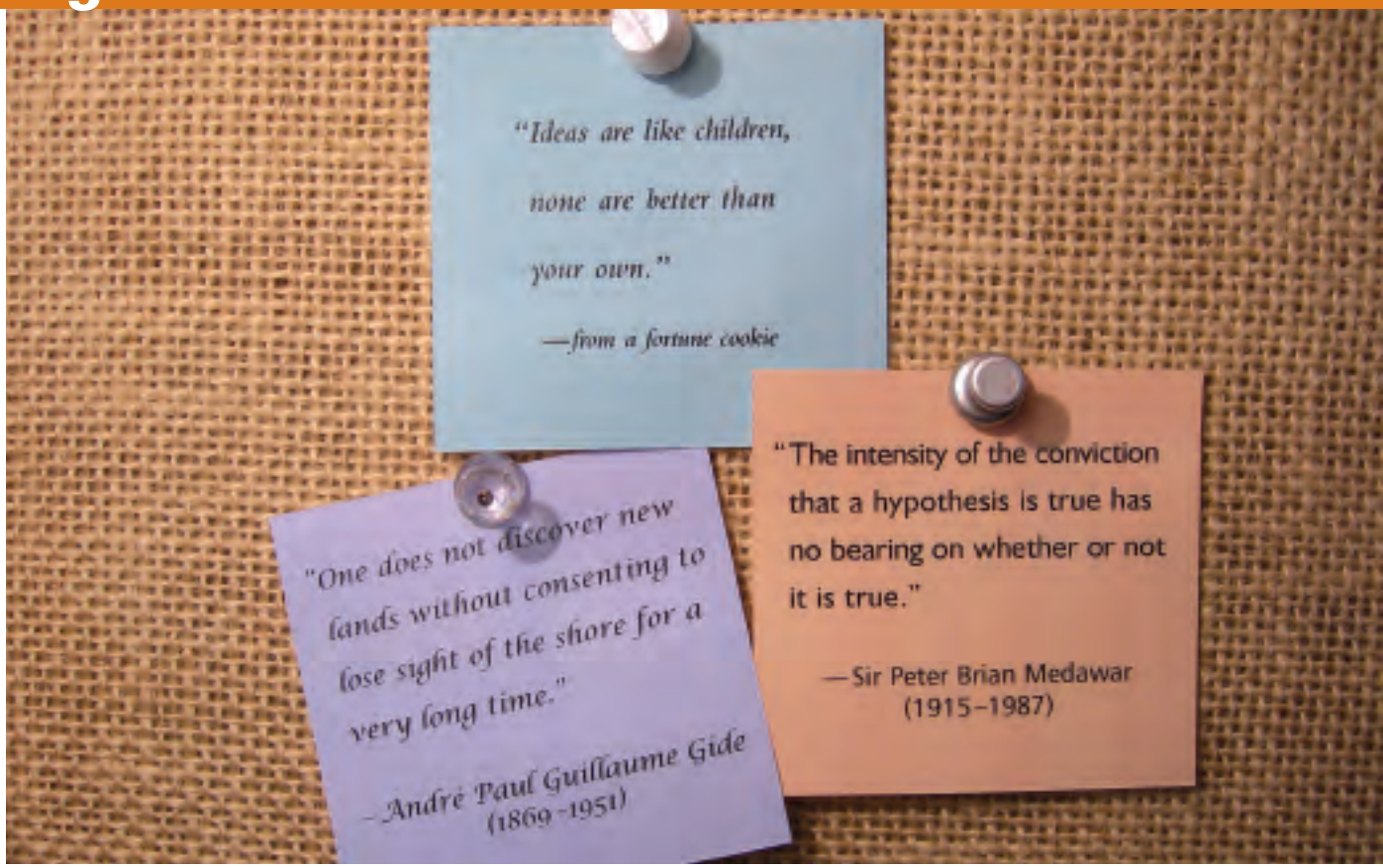
Another vaccine, against HPV, was approved by the Food and Drug Administration in June 2006 to prevent cervical cancer.

But viruses aren't the whole story. Only a few of the people infected with these viruses actually get cancer. Even in the case of HPV, only 1 or 2 percent of those with the virus develop invasive cervical cancer.



REPRODUCED FROM THE JOURNAL OF CELL BIOLOGY, 2005, VOL. 171, P. 494 BY COPYRIGHT PERMISSION OF THE ROCKEFELLER UNIVERSITY PRESS

Researchers label cells with different fluorescent dyes, then mix the cells. Those that contain both blue and green color have fused.




Quotations on the wall of Lazebnik's lab inspire students and other researchers.

So which other factors contribute to cancer? Lazebnik's data point to cell fusion.

This raises a concern about the notion of using viruses as vehicles to deliver genes or medications to specific tissues. The strategies rely on cell fusion, which might lead to bigger problems than the therapies were designed to solve, he says.

**"I was very surprised seeing the head of the lab in a T-shirt and jeans."**

As he seeks to understand the connections between cell fusion, viruses, and cancer, Lazebnik is in what he calls a "scientific wilderness." Although only a few other researchers are investigating whether cell fusion can contribute to cancer, Lazebnik is quick to point out that the idea is more than 100 years old. He cites papers published in 1887 and 1911 that propose the theory.

Although he admits that not all unusual ideas are correct, he also notes that some of the best ideas in science took years before they were commonly accepted. And he rattles off example after example.

## Stories and Histories

It's not only scientists whose ideas were scandalous at first that interest Lazebnik. He seems almost as well versed in the history of science as in science itself, flitting easily between quoting the ancient Greek philosopher Heraclitus, referencing the 17th-century mathematician and physicist Christiaan Huygens, and citing the 1914 paper on the cellular origin of cancer by developmental biologist Theodor Boveri *(which, Lazebnik points out, is sometimes still available—used—on the Internet)*.

Lazebnik's habit of quoting scientists, historians, and philosophers has infected his lab. Taped to walls are strips of paper containing many famous—and infamous—quotations.

After struggling with a series of experiments, one student working in the lab taped this note to her laboratory bench:

*"Success consists of going from failure to failure without loss of enthusiasm."*

*—Winston Churchill*

The next day, she added another strip of tape, similar to a quote commonly attributed to Albert Einstein:

*"Insanity: doing the same thing over and over again and expecting different results."*

If a pithy quote won't do the trick, Lazebnik pulls out a parable, often one from folklore. In one story, two frogs are trapped in a carafe of milk. One frog immediately dies in despair. The other keeps trying to escape. Eventually, the frog feels something hard under him and is able to jump out of the carafe. With his tireless jumping, he had churned the milk into butter. The moral? *Never give up.*

Even the way Lazebnik describes his interest in science is steeped in story. For example, he relates how the ancient Greeks observed that when amber is rubbed with a dry cloth, it becomes charged with an unknown force—now called static electricity—that attracts lightweight objects like dried leaves or bits of paper. The term *electron* is the Greek word for *amber*, he explains.

"What's out there that's comparable to the power of electricity, that we see every day, but that remains hidden?" Lazebnik asks.

That's what he's after. It's what keeps his passion for science alive.

"You have the potential to discover something that could turn around your entire view of the world."

And maybe in the process, you'll hunt down a serial killer.

# Killing Cancer With Aikido

合氣道

A black-and-white silent film shows an unfurnished room, in the center of which stands a petite, bald-headed Japanese man in his 80s. Suddenly, someone rushes at him from behind. The old man nimbly grabs the attacker's wrist and *swoosh!* The assailant's body slices through the air in an arc of black and white, then thuds on the padded floor. The elderly man, who never even turned to face his much younger opponent, remains standing.

Next, two assailants charge the man. He seizes their wrists, fashions a pretzel by twisting one opponent's head through the arms of the other, then flings them both to the ground.

A moment later, seven attackers engulf the man. The black-haired mob sways like a drunken beetle, then collapses. One figure remains standing: the wizened master, his arms outstretched, while a jumble of limbs in white tunics and black pants lies at his feet.

Those are scenes from a movie showing Morihei Ueshiba, who founded the martial art, aikido, in the 1940s.

JUN AKIYAMA, WWW.AIKIWEB.COM

"Ueshiba was a very tiny guy, even by Japanese standards—about 100 pounds and 5 feet tall. Yet what he could do is just incredible," marvels Yuri Lazebnik, a cell biologist and aikido aficionado.

Lazebnik plays the movie clip during his scientific talks as a visual metaphor for his research approach. He explains that aikido focuses on harnessing the power of your opponents and using it against them.

"By subtle moves and turns, a little person can make a big one flip over," he says. "This is very similar to what we're doing with oncogenes [genes that, when mutated, promote cancer]. Oncogenes have an energy that causes cells to grow and spread throughout the body as cancer. We're trying to reroute this energy to kill the cancer instead."

Lazebnik, who has studied martial arts for more than 20 years, recently earned his first belt in aikido. Aside from cultivating discipline, aikido inspires him by the way its masters appear to steer the laws of physics.

To him, this demonstrates not just one aspect of aikido, but a guiding life principle.

"If you gain and develop skills, you can make things happen that you didn't think were possible."—*A.Z.M.*

# Bench to Bedside

*These stories describe NIGMS-funded medical research projects. Although only the lead researchers are named, science is a team sport, and it's important to recognize that many researchers work together to carry out these studies.*

## Frogs Fighting Cancer

You might be surprised to learn that a carnivorous amphibian from Africa is helping scientists fight cancer. It's true—a clawed frog with the Latin name *Xenopus laevis* is teaching researchers about the genetics of Fanconi anemia, a rare, inherited condition that increases susceptibility to some forms of cancer.

Molecular biologist **Maureen Hoatlin** of the Oregon Health and Science University School of Medicine in Portland and her collaborator **Karlene Cimprich** of Stanford University in California used *Xenopus* eggs as incubators to understand how various genes and proteins might be involved in Fanconi anemia.

MICHAEL REDMER

Even though the enzymes that copy DNA as our cells grow and divide are extremely accurate, mistakes sometimes occur. Fortunately, repair proteins detect and fix virtually all of the errors. Researchers suspect that in the case of Fanconi anemia, a part of this DNA repair machine may be faulty.

The scientists showed that normal versions of the Fanconi anemia proteins do, in fact, prevent the accumulation of DNA errors in frog egg extracts. They think the proteins probably perform the same protective role in human cells.

That's because frog egg cells perform many of the same biochemical functions that human cells do.

Since *Xenopus* eggs are easy to grow and manipulate, scientists can use them to study DNA replication in a way that's difficult to do with mammalian cells. That quality is especially useful for Fanconi anemia research, because cells naturally stockpile the Fanconi proteins and others in preparation for the firestorm of DNA copying that occurs soon after an egg is fertilized.
—*Sarah Goforth*

## Marking Multiple Sclerosis

Multiple sclerosis (MS)—a chronic, often disabling disease affecting the brain and spinal cord—can be notoriously difficult to diagnose.

In MS the immune system attacks the protective coverings of nerves. These coverings, called myelin sheaths, normally speed electrical signals between nerves and organs. As the sheaths erode, however, people with MS can develop serious problems with movement, vision, and speech.

For the more than 10,000 Americans who will develop MS each year, spotting the disease promptly offers a chance for early treatment.

With that goal in mind, neurologist **Avindra Nath** and pharmacologist **Robert Cotter**, who both work at the Johns Hopkins School of Medicine in Baltimore, Maryland, searched for chemical markers of the disease in the fluid that surrounds the brain and spinal cord.

The researchers used a lab technique called mass spectrometry that can find a single type of protein in a complex mixture like spinal fluid. They examined this fluid in 29 people who had either MS or pre-MS symptoms and then compared the proteins found in their samples to the proteins found in spinal fluid taken from people with other conditions that impair neurological function.

Nath and Cotter discovered a single protein that was a lot more common in those with MS. If further studies confirm the protein's link to the disease, the work could lead to a simple test to diagnose MS much earlier than is currently possible.—*S.G.*

## Vitamin B12 Explained

Without enough vitamin B12, people can get sick with anemia or other illnesses. B12, which helps keep red blood cells healthy, is also a key ingredient in the building blocks of DNA.

We get the vitamin through our diet, either in animal protein containing the vitamin or in certain fortified foods like breakfast cereals. Strict vegetarians are at risk for illnesses caused by too little B12, as are people in countries where meat is scarce and nutrient-fortified foods aren't available.

B12 deficiency can also be a problem for older adults, whose bodies are sometimes less able to absorb the vitamin from food. Some studies even suggest a lack of B12 may contribute to Alzheimer's disease.

Researchers have studied vitamin B12 for decades, and the determination of its complicated structure earned English chemist Dorothy Crowfoot Hodgkin the 1964 Nobel Prize in chemistry. In addition, for years scientists have been studying how B12's elaborate chemical structure is assembled inside cells.

Yet some mysteries remain, and a big step toward solving them comes from the discovery of bacteria that can't synthesize B12 normally.

In the course of research to understand how bacteria cause disease, biologist **Graham Walker** of the Massachusetts Institute of Technology in Cambridge found that the bacteria he was studying were not behaving as expected.

Following up on this surprising observation, Walker learned that the bacteria were a mutant strain missing a key gene that is essential for B12 synthesis. He's now investigating whether B12 plays a role in bacteria-host interactions that can lead to infections in people.—*S.G.*

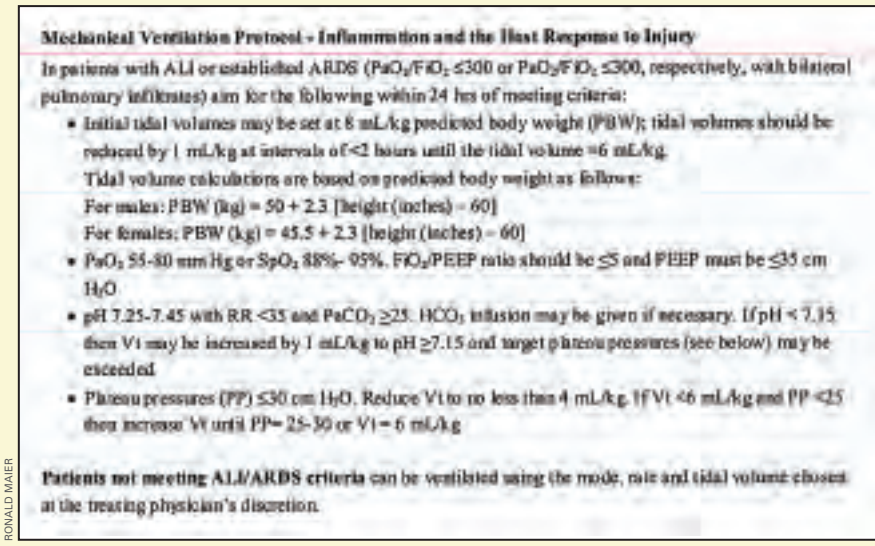
## Genes Affect Breast Cancer Drug Benefit

A common treatment for breast cancer is tamoxifen, which works by blocking the hormone estrogen from fueling tumor growth. But some people don't benefit from the drug, and new research shows that their genetic make-up plays a role.

Clinical pharmacologist **David Flockhart** of the Indiana University School of Medicine in Indianapolis discovered that of the roughly 210,000 people who develop breast cancer each year, about 10 percent have a genetic trait that causes them to metabolize, or break down, tamoxifen differently than others.

Because the drug is less effective in people with this trait, they have twice the chance that their cancer will return.

Finding this genetic link to drug response means that doctors could soon test a person's genes to predict response to tamoxifen and adjust prescriptions accordingly.—*S.G.*



**Mechanical Ventilation Protocol - Inflammation and the Host Response to Injury**

In patients with ALI or established ARDS ($PaO_2/FiO_2 \leq 300$ or $PaO_2/FIO_2 \leq 300$, respectively, with bilateral pulmonary infiltrates) aim for the following within 24 hrs of meeting criteria:

- Initial tidal volumes may be set at 8 mL/kg predicted body weight (PBW); tidal volumes should be reduced by 1 mL/kg at intervals of <2 hours until the tidal volume =6 mL/kg.
  Tidal volume calculations are based on predicted body weight as follows:
  For males: PBW (kg) = 50 + 2.3 [height (inches) – 60]
  For females: PBW (kg) = 45.5 + 2.3 [height (inches) – 60]
- $PaO_2$ 55-80 mm Hg or $SpO_2$ 88%- 95%. $FiO_2$/PEEP ratio should be $\leq 5$ and PEEP must be $\leq 35$ cm $H_2O$
- pH 7.25-7.45 with RR <35 and $PaCO_2 \geq 25$. $HCO_3$ infusion may be given if necessary. If pH < 7.15 then Vt may be increased by 1 mL/kg to pH $\geq 7.15$ and target plateau pressures (see below) may be exceeded.
- Plateau pressures (PP) $\leq 30$ cm $H_2O$. Reduce Vt to no less than 4 mL/kg. If Vt <6 mL/kg and PP <25 then increase Vt until PP= 25-30 or Vt = 6 mL/kg

**Patients not meeting ALI/ARDS criteria** can be ventilated using the mode, rate and tidal volume chosen at the treating physician's discretion.

RONALD MAIER

## Setting Standards

Emergency room doctors are famous for their ability to improvise under pressure. But the same creativity that allows doctors to cope with chaotic circumstances can actually work against efforts to determine which treatments are most effective.

That's where establishing standards of care for clinical research comes in. Setting guidelines for specific medical treatments can reduce the number of variables in research that involves patients, enabling physician-scientists to more clearly understand the impact of interventions.

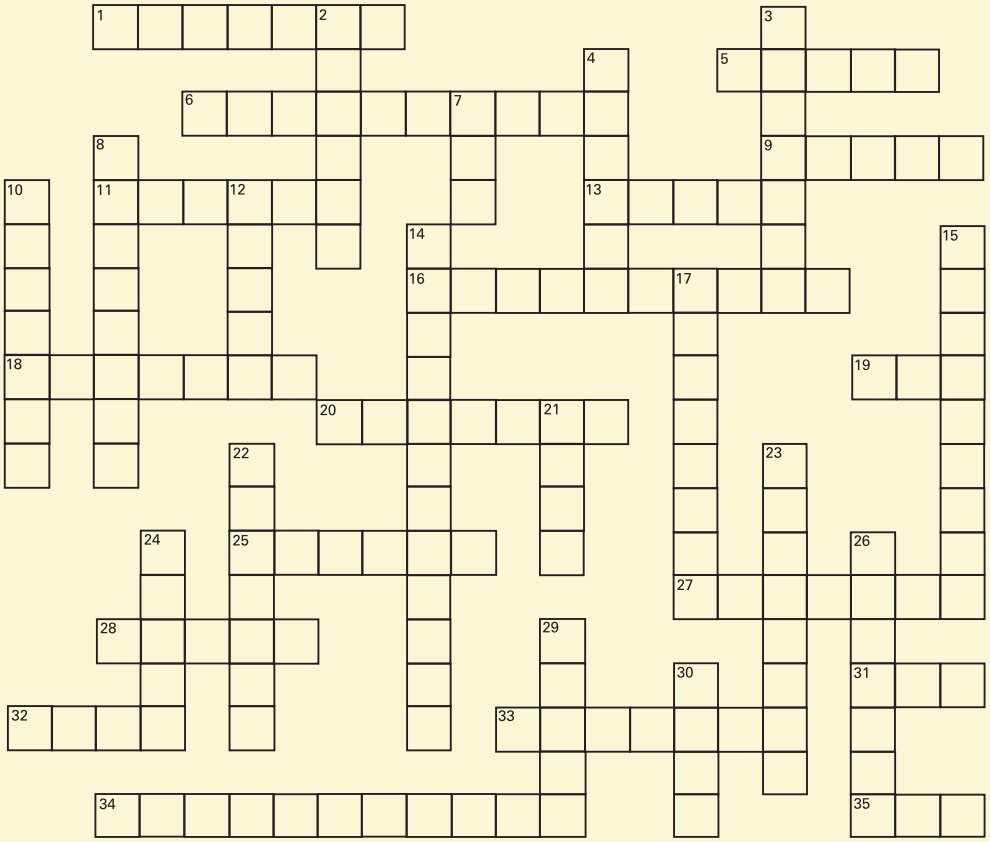
Such standards are already in place for many medical situations. Yet the treatment of patients with severe burns or other critical injuries varies widely from ER to ER. This confounds research to determine the best treatments for individual patients, whose bodies may react to injury, and respond to treatment, differently.

Recognizing this problem, a large team of scientists and doctors working to improve the care of severely injured patients banded together to develop a set of standardized treatment procedures.

As a result of this effort, doctors across the country can follow the same procedure for a given situation, advancing the research that ultimately improves patient care. In a step in that direction, the team has developed treatment summaries that fit on index cards and can be downloaded from the Internet for use as a bedside reference.

The team members acknowledge that, over time, the guidelines may need to be adjusted to reflect new research findings.—*S.G.*

# The Last Word



## ACROSS

1. tallest land animal
5. small particle that infects cells
6. fruit fly, in Latin
9. nimble
11. Lazebnik's martial art
13. after ice
16. test an idea
18. neuron connection
19. short snooze
20. science of living organisms
25. Yuri's native country
27. cell home for DNA
28. units of a living organism
31. half of two
32. journey
33. rare type of anemia
34. luck
35. gummy tree fluid

## DOWN

2. two cells make one
3. nutrient the body needs
4. uncontrolled cell division disease
7. primitive shelter
8. cell biologist Yuri
10. cell division
12. small islands
14. study of the nervous system
15. cellular suicide
17. genetic change
21. heredity unit
22. neuroscientist Chiara
23. merged cell masses
24. natural resting period
26. African clawed frog
29. Cirelli's first home
30. lend

Puzzle answers can be found at
http://www.nigms.nih.gov/findings/

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U.S. DEPARTMENT OF
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NIH Publication No. 06-4932
September 2006
http://www.nigms.nih.gov