U.S. DEP RTMENT OF HE LTH ND HUM N SERVICES
N TION L INSTITUTES OF HE LTH
N TION L INSTITUTE OF GENER L MEDIC L SCIENCES
45 CENTER DR RM 3 N32 MSC 200
ETHESD MD 20 2- 200

OFFICI L USINESS
PEN LTY FOR PRIV TE USE $300

FIRST CL SS PRESORTED
POST GE & FEES P ID
NIH/NIGMS
PERMIT NO. G- 13

NIH Publication No. 10–7661
September 2010
http://www.nigms.nih.gov

Printed on partially recycled paper.

Read, Share, Recycle.

Findings

SEPTEMBER 2010

PAGE 2

Fats and Flies

Insects Illuminate Human Disease

PAGE 10

For Janice

Legacy of a Short Life

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

Inside Science: Life in the Lab

1 *Up Close With:* **Estela Arrese**
2 **Fats and Flies**
6 Fruitful Work

9 *Up Close With:* **Kevin Tracey**
10 **For Janice: Legacy of a Short Life**
14 Cytokine Theory of Disease

Just Found: Quick Takes on Hot Science

5 A New Layer of Bacterial Defense
8 Tylenol® as Lifesaver?
13 A New View of the Flu
16 Rx: Genome Sequence

Edited by Alisa Zapp Machalek

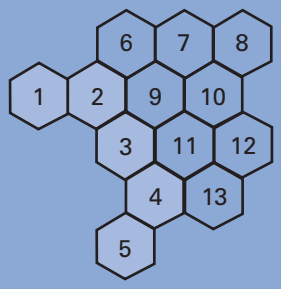
Contributing Writers
Emily Carlson
Stephanie Dutchen
Karin Jegalian
Alisa Zapp Machalek
Kirstie Saltsman
Janelle Weaver

Production Manager
Susan Athey

Online Editor
Jilliene Mitchell

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



On the Cover

1 **Scanning electron micrograph of cultured cells,** *Tina Carvalho, University of Hawaii*
2 **Crystals of trypsin protein,** *Alex McPherson, University of California, Irvine*
3 **Red blood cells,** *Tina Carvalho, University of Hawaii*
4 **Zinc finger,** *Jeremy M. Berg, National Institute of General Medical Sciences*
5 **Electron density map,** *The Southeast Collaboratory for Structural Genomics*
6 **Estela Arrese,** *Todd Johnson, Oklahoma State University Ag Communications*
7 **Lipid droplets,** *Estela Arrese, Oklahoma State University*
8 **Kidneys**
9 **White blood cell,** *Jim Ehrman, Digital Microscopy Facility, Mount Allison University*
10 **Managing the flu**
11 **Kevin Tracey,** *Adam Cooper, North Shore Long Island Jewish Health System*
12 **Bacterial spore,** *Adam Driks, Loyola University Chicago Stritch School of Medicine*
13 **Genome readout with stethoscope**

SEAN HUBBARD

Up Close With

Estela Arrese

BIOCHEMIST

"I really love what I do. You need that in almost everything you do in life."

PET DOGS

Two rescued Bichon Frises

FAVORITE AUTHORS

Jorge Luis Borges, Paulo Coelho, Isabel Allende, Gabriel Garcia Marquez

BEST THING ABOUT OKLAHOMA

"If you don't like the weather, …wait 5 minutes and it'll change" Will Rogers

FAVORITE VACATION SPOT

The beach

CAREER ALTERNATIVE

Nurse

SEAN HUBBARD

Fats and Flies

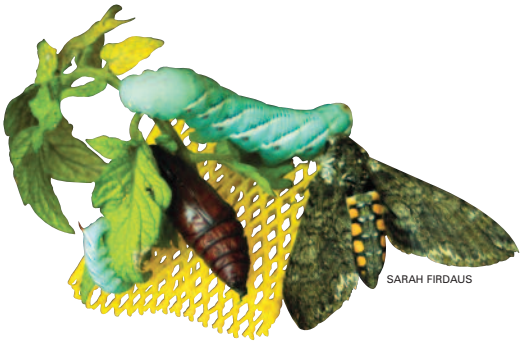
BY STEPHANIE DUTCHEN

The soft buzzing of mosquitoes fills the air while spotted moths with 4-inch wingspans flutter past. Blue-green caterpillars as thick as fingers crawl in a living carpet.

Summer picnic nightmare? Nope—this motley collection of insects lives inside plastic cages in Estela Arrese's biochemistry lab at Oklahoma State University (OSU).

Arrese studies these and other insects to learn how they—and we—store food as fat and later break it down for energy.

Her discoveries could lead to new ways for farmers to protect their crops from pests, and for health officials to combat mosquito-borne diseases like malaria and West Nile virus.



SARAH FIRDAUS

Arrese studies insects, including the tobacco hornworm shown here (counterclockwise from top) as a caterpillar, pupa and adult moth.

Not only that, but studying these little critters could one day improve our understanding of disorders like diabetes, obesity and heart disease, which relate to how we store and use fat.

Saying that we can learn about human biology from mosquitoes and moths "sounds kind of crazy," Arrese readily admits.

But the argument is hardly outrageous. Scientists have been studying insects to better understand human biology for more than 100 years (see "Fruitful Work," page 6). While we may not look alike, caterpillars, flies and humans use similar methods to regulate fat at the molecular level.

"It's very exciting," Arrese says of her work. "We are learning new things all the time. It's a good time to be in this field."

Fats Are Us

All creatures—people, insects, even plants—need fat to survive.

Most of the fats we eat are called triglycerides. Triglycerides give us more than twice as much energy as carbohydrates or proteins. But before we can use that energy, our bodies must break down the fats.

When we digest triglycerides, they get split into their component parts: three fatty acids and a carbohydrate. This splitting is called lipolysis (*lip-* for "lipid," or fat, and *-lysis* for "split"), and the enzymes that do the splitting are called lipases.

It's like an enormous, living puzzle.

Once they've been absorbed into our intestines, the fatty acids are recombined into triglycerides and shipped out to our cells through the bloodstream. Some of the fat gets used for energy right away. The rest is stored inside cells in blobs called lipid droplets.

Until the 1990s, researchers thought lipid droplets were just beads of oil passively floating around in cells. Then they discovered that the droplets are actually dynamic structures that help regulate when stored fat gets broken down for energy. Now, lipid droplets have taken center stage in fat research.

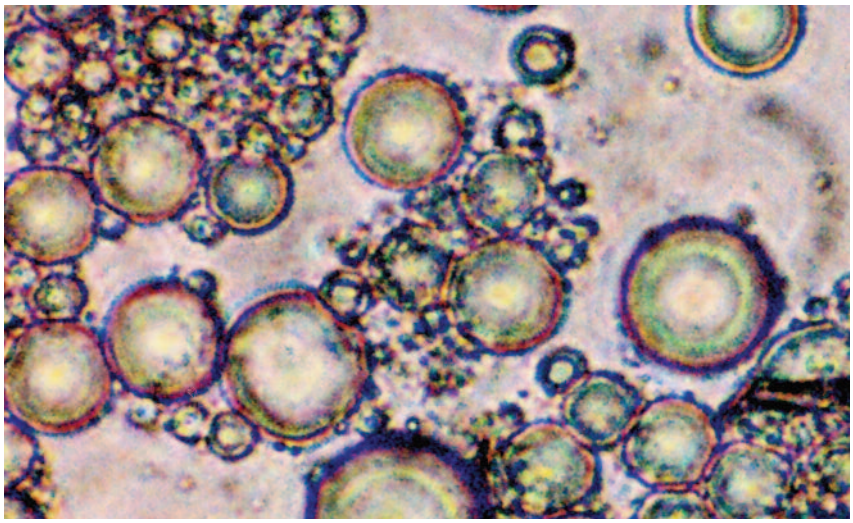
When the body needs extra energy —for instance, when we run a marathon — hormones direct lipases to break down the fats stored in lipid droplets and wash them back into the bloodstream.

The cycle of making, breaking, storing and mobilizing fats is at the core of how humans—and all animals—regulate their energy. An imbalance in any step can result in disease, including obesity and diabetes. Having too many triglycerides in our bloodstream raises our risk of clogged arteries, leading to heart attack and stroke.

Despite their importance, no one yet understands exactly how fat storage and mobilization work.

For instance, insects like silkworms and mosquitoes store up lots of fat when they're young by eating nectar or leaves. They use that fat later when they metamorphose into their adult forms and start flying.

They also burn fat when they lay their eggs. If researchers could block the movement of stored fat to the insects' ovaries, they could interfere with egg-laying and stop the bugs from reproducing. That could have an immense impact on pest and disease control.



ESTELA ARRESE

These lipid droplets store fat in the cells of the tobacco hornworm, *Manduca sexta.*

Protein Puzzle Pieces

But before any of that can happen, says Arrese, "We need to study a lot and have information at the molecular level."

It's like an enormous, living puzzle, and Arrese is trying to identify a few protein pieces and figure out how they fit together.

She has already discovered the function of a protein called Lsd1 found in lipid droplets.

Arrese also works with the main lipase involved in fat regulation in insects. Fittingly, it's called triglyceride lipase, or TGL. Now she's looking into how TGL works.

She has a lot of questions: Does TGL activate fat mobilization, block it or help another protein? Do other proteins help regulate TGL? What is the function of another lipase, called ATGL? How does the Lsd1 protein help control lipolysis, and is it a critical target for disease control? What does its sister protein, Lsd2, do?

"In a cell, there are so many proteins, it's hard to tell which protein really does the work," says physicist Donghua Zhou, one of Arrese's colleagues and collaborators at OSU.

To determine which proteins perform what jobs, biochemists like Arrese have to isolate and purify each one in a test tube before conducting extensive experiments.

And purifying proteins is not easy, explains José Luis Soulages, who collaborates with Arrese in the university's biochemistry department—and who also happens to be her husband.

"After a lifetime, you may say that you've found four key proteins," he says. "And there are probably 100 more. But their functions would never be known without the discovery of those first four."

'Shockingly Good'

It's especially tough to purify Arrese's proteins because they don't survive long outside cells and because they're found in oils. Most biochemistry tests are designed for water-based molecules—and as you know if you've ever shaken a bottle of salad dressing, oil and water don't get along.

That doesn't deter Arrese. Her lab was the first to purify TGL from fat tissue in insects as well as Lsd1 and Lsd2, and she continues to purify

proteins with a characteristic drive for perfection.

"When she brings me molecules, they are impeccable," says Steve Hartson, a biochemist at OSU who collaborates with Arrese.

An advantage to using insects like flies and caterpillars is that Arrese can raise hundreds of them in the lab and collect plenty of the proteins she wants—many more than she could from rats or people.

"It puts her on the edge of what's possible," explains Hartson.

Arrese aims to learn more about the proteins by examining their structures atom by atom.

But she can't use one of the most common protein imaging techniques, X-ray crystallography, because her proteins don't naturally form the needed crystal structures. Nor can she use the other common technique, called solution nuclear magnetic resonance (NMR), because the proteins are too big.

So Arrese collaborates with Zhou, who uses related technology called solid-state NMR. She hopes that soon, she will finally be able to see the structures of her proteins in 3-D.

It's definitely not a job for people with short attention spans.

Luckily, says Soulages, his wife is well-suited to the work—she has extraordinary concentration, keen powers of observation and a talent for planning efficient experiments. The combination of talent and commitment allows her to pursue a single scientific question for decades without losing focus.

"I think very few people can do that," he says. "In science, sometimes we are tempted to switch subjects or even fields because things get hard. She just puts in more hours and tries alternate approaches."

And it pays off. Hartson says, "She's a shockingly good biochemist. She does some incredible things with molecules."

Hartson recalls being "a little intimidated by her at first. She was very focused on doing science. But then she makes a discovery or [gets] key data and breaks into this radiant, beaming person. She's a real pleasure to work with."

Getting Her Hands Dirty

Arrese acquired her stringent work ethic as a young girl, when she spent summers on her family's farm in rural Pehuajo, Argentina.

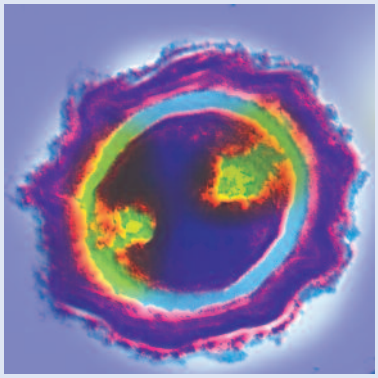
story continues on page 6

AMERICO ARRESE

Arrese as a child.

FIND MORE @

Learn about some of the surprising animals and plants used in research at http://publications.nigms.nih.gov/thenewgenetics/livinglab.html.



ADAM DRIKS

Bacterial spores have four outer layers that protect against harsh environmental conditions (color added).

A New Layer of Bacterial Defense

Bears hibernate in caves and toads burrow into the ground to protect themselves against harsh conditions. Bacteria take a different tack: They split off a small compartment called a spore. Spores are dormant structures that resist heat, chemicals, radiation and dehydration. When conditions become favorable, the bacterium exits the spore and grows again.

The structure of the spore's protective shell is key to its survival. This shell contains 70 different proteins in concentric layers. Until now, scientists didn't know how the proteins were arranged.

Biologist Patrick Eichenberger and his team at New York University used fluorescent green chemical tags, a microscope and computer analysis to build a map showing the location of spore proteins.

The scientists discovered that spores have four protective layers, including an outer crust never described before.

The soil bacterium the scientists studied doesn't cause any diseases, but its spores are structurally similar to those of the bacteria that cause botulism, tetanus and anthrax.

The research will improve our understanding of these organisms, perhaps leading to new ways to prevent the diseases they cause.
—*Janelle Weaver*

Fruitful Work

Strange but true: Mosquitoes, caterpillars and other creepy-crawlies can tell us about how humans store fat and call it into action when we need energy.

Obviously, insects aren't people. They aren't even mammals. But many insect species have hundreds of genes, proteins and biological processes so similar to ours that they're considered biochemically equivalent.

That means we can learn something about our own biology by studying insects. The creatures are smaller, simpler, shorter-lived and generally much easier to work with than people—even easier than mice and rats. A research project that might take a decade in humans could be finished in a month using insects.

Take the common fruit fly, *Drosophila melanogaster.* Since its 1910 debut in lab experiments, this fly has yielded insights into human traits as diverse as inheritance, circadian rhythms, drug addiction and Parkinson's disease. Geneticists estimate that 75 percent of the human genes known to contribute to disease have DNA equivalents in *Drosophila*.

Another popular research organism is the mosquito. While laboratories around the world study mosquitos to combat malaria and other diseases, Estela Arrese studies how the bugs store and utilize fat (see main story).

So don't be surprised if research on that buzzing barbecue nuisance provides clues about the fate of the fat in the burger you just ate.—*S.D.*

continued from page 5

"My father always wanted us to be busy doing useful things," she says.

For example, she and her brother were charged with taking care of a big vegetable garden.

Rather than resenting the work, Arrese says, "I realized I really liked it. I need that. I need to get my hands dirty."

It's still the case metaphorically in the lab, where she is always ready with a pair of rubber gloves if she needs to dive into the insect cages or help her students with an experiment.

It's also true at home, where she cultivates a thriving flower garden despite Oklahoma's unforgiving climate—dry summers, harsh winters, tornadoes and spring hail that drives Arrese outside to throw a protective tarp over her tulips and roses.

"Whatever it takes to have flowers, I will do it," says Arrese. "I don't care if it's a challenge. Because I was raised on that farm, I am used to a lot of work."

ESTELA ARRESE

Arrese has a thriving flower garden at her Oklahoma home.

study to look through microscopes a lot?

Dedication to Science

Arrese's father, a veterinarian, also raised her to love science.

She always felt comfortable in the lab he set up in their house, wandering amidst the pipettes and tubes, the microscope and canisters of liquid nitrogen. By the age of 10, she was helping her father and pretending to be a scientist herself.

Her favorite task was looking through the microscope. When she was in middle school, she asked her father, "What do I need to study to look through microscopes a lot?"

His answer: biochemistry.

"And that," she says, "is what I ended up doing."

The path wasn't an easy one.

She gave birth to her first child while she was still working on her Ph.D. thesis—just before her husband moved to the United States.

When she and her daughter joined her husband in Tucson, Arizona, she left behind her extended family, her language and her culture.

In Argentina, she had taught herself to read and write English with a dictionary in one hand and scientific journal articles in the other. But she arrived in the U.S. without knowing how to speak the language. She still struggles to speak as fluently—and as much—in English as she does in her native Spanish.

Despite the communication barrier, Arrese loves English. "It's more precise," she says. "I am 50—maybe when I retire, I will study it."

Experimenting in the Kitchen

Along with the lab, Arrese has always felt comfortable—and enjoys experimenting—in the kitchen.

When she has to follow a recipe, she says, "It's a disaster. I want to change it. I want to know what will happen if I add this or that."

ESTELA ARRESE

A sample of Arrese's cooking: the seafood dish paella.

Her husband agrees: "She has to see how people are cooking, and then she works it out on the bench—on the stove."

Some of her favorite dishes are cod and paella. Among her appreciative consumers are her husband, her two daughters and her students.

"I love cooking because I like good food, because I want to feed my family and also because I need that—to go and create something," says Arrese.

Growing up, she learned how to prepare not only an eclectic array of Argentine dishes, but also Spanish food from an aunt who was a chef and Italian meals from her immigrant grandmother.

When she relocated to Tucson, she promptly pestered a neighbor to teach her Mexican cuisine.

When the family moved again, this time to Oklahoma, a handful of graduate students from India joined her lab and helped her fulfill a decades-old desire to learn to cook Indian food. Whenever these students traveled home, they would bring back suitcases packed with spices for her.

Now Arrese has three graduate students from China, and she's looking forward to once again expanding her culinary horizons.

Extended Family

When she isn't grilling her students for cooking tips, Arrese cares for them as though they were her extended family.

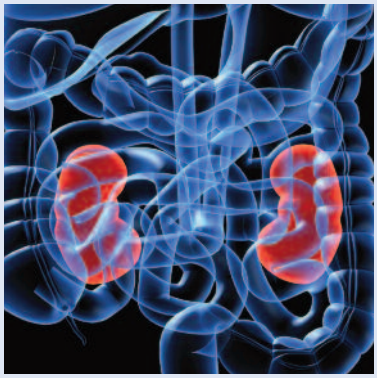
"She nurtures her students…in such a way that the excitement of science never wears off and critical thinking is developed," says Alisha Howard, who did undergraduate research in Arrese's lab before earning her Ph.D. with Soulages.

"She seems to be very invested in our future as scientists and as adults," agrees Zach Hager, a college senior in the lab.

Hager particularly appreciates Arrese's eagerness to work alongside her students at the bench.

Colleague Steve Hartson says that Arrese's "tremendous one-on-one mentoring and intellectual and moral support" are an inspiration to her

story continues on page 8



Acetaminophen, or Tylenol,® might prevent potentially fatal kidney damage in severely injured people.

Tylenol® as Lifesaver?

You might use acetaminophen, or Tylenol,® to treat aches and mild fevers. But this inexpensive medicine might also have a role in life-threatening situations like earthquakes, car accidents and war zones to counter a hidden danger—kidney damage.

When people survive major traumatic injuries, it's not uncommon for them to develop kidney failure. That's because when skeletal muscles are seriously injured, their cells burst and dump their contents into the bloodstream. The released contents include proteins, particularly one called myoglobin, that can severely damage the kidneys.

Researchers at Vanderbilt University in Nashville, Tennessee, discovered that if they gave acetaminophen to rats before or after muscle injury, it could alleviate such kidney damage. The doses that worked in rats are comparable to doses that are safe in humans.

If clinical trials prove that the treatment is safe and effective in people, acetaminophen might become a lifesaver in places that lack hospitals and medical equipment—like the sites of natural disasters. The researchers think it might also help prevent similar kidney and tissue damage caused by sickle cell disease, malaria and heart attacks. —*Karin Jegalian*

Identify [your] passion and follow it.

ESTELA ARRESE

Arrese (right, in blue) teaches her students to be efficient and excited about science.

continued from page 7

students and ensure that they achieve their potential. "They're excited by the science they're doing, and they go on to very successful careers," he reports.

Her students also admire the way she balances the jobs of lab head and mother (her daughters are now 13 and 20).

It helps to have her husband nearby. She and Soulages often take turns running long experiments or helping their kids with daily routines.

Her ultimate goals, she says, are to raise her children to be healthy and have good lives, and to find out what her handful of proteins do.

Soulages describes his wife's philosophy not as seeking an earth-shaking discovery, but as putting in her grains of sand, knowing they will last a long time. He could be talking as easily about her children and students as about her science.

For her part, Arrese gives the same advice to all:

"Identify [your] passion and follow it. When you really like what you do, it becomes easy. Live and work with passion and quality."

FIND MORE @

See all 40 scientists profiled so far in *Findings* magazine at http://publications.nigms.nih.gov/findings/issues.asp

ADAM COOPER

Up Close With

Kevin Tracey

NEUROSURGEON, IMMUNOLOGIST

"Doing science is just addictive. It is more like a hobby than a job."

SPECIAL MOMENT

Meeting the Dalai Lama

MOTTO

Carpe Diem (Seize the Day)

FAVORITE WEEKEND ACTIVITY

Cheering for his daughters at their soccer games

HOBBIES

Woodworking, deep sea fishing

WHO WOULD PLAY HIM IN A MOVIE

Harrison Ford

ADAM COOPER

For Janice: Legacy of a Short Life

BY EMILY CARLSON

After 4 years of medical school and 2 years of training to be a brain surgeon, Kevin Tracey had learned to control the emotions he felt for his patients. But everything changed on May 3, 1985, when he met Janice.

As part of his training, Tracey was working in the emergency room at Cornell University's hospital in New York City. At 6:45 p.m., paramedics brought in an 11-month-old female with severe burns. Tracey examined her and noted: burns on 75 percent of her body, no broken bones, no other injuries.

As he focused on his patient's needs, Tracey held back tears. Janice, who arrived wrapped in a teddy bear blanket, now writhed and sobbed on a metal gurney. Her once-soft skin was seared and peeling from her arms, legs and back. She had a 25 percent chance of surviving.

Just an hour before, Janice had been giggling on the kitchen floor while her grandma cooked spaghetti. When the grandma turned to drain a 10-quart pot of boiling noodles, she tripped and spilled the 212-degree water all over the baby. Sweet chuckles turned to inconsolable screams.

For the next 3 weeks, Tracey and others watched Janice ride a rollercoaster of recoveries and setbacks.

First, she went into a 5-hour surgery, where Tracey and his colleagues removed scalded skin and replaced it with thin layers shaved from Janice's bottom—an area that had been protected by her diaper. Everyone—her family and her medical team—sighed with relief once Janice opened her eyes and smiled.

The next night, though, her blood pressure dropped dangerously low, starving her brain, kidneys, lungs and other vital systems of much-needed oxygen. Her body was in septic shock. Tracey immediately pumped fluids and drugs into her veins to raise her blood pressure and prevent permanent tissue damage.

Despite these measures, Janice drifted into a coma. The next day, her organs began working again and she awoke.

But then she spiked a fever and her body swelled. Her kidneys—and soon her liver and other organs—stopped working. Janice was experiencing widespread inflammation, a life-threatening condition called sepsis. As before,

Her immune system had begun to destroy the

Tracey's infusion brought her back to life.

On May 28, Tracey celebrated with her family as Janice turned 1 year old. Instead of machines and monitors, balloons and streamers now filled her room.

But the very next day, Janice's heart stopped. This time, no medical feat could bring her back.

A New Path

Stunned by her sudden, unexpected death, Tracey set out to understand what caused it and to prevent the same thing from happening to anyone else.

During the next 2 years, he put his neurosurgery career on hold and focused on medical research.

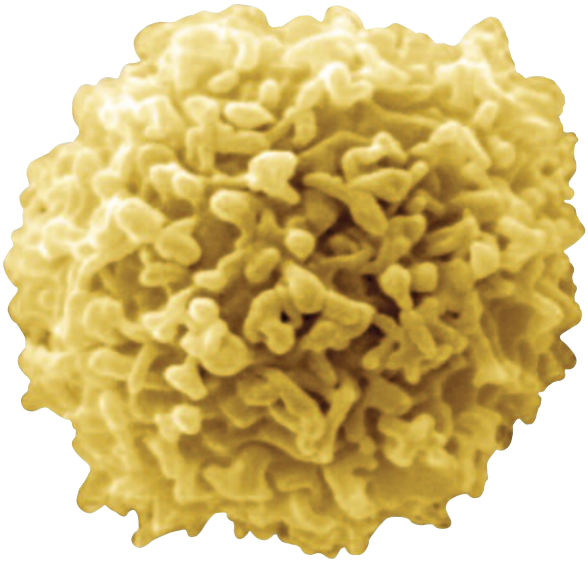
"Most doctors have a patient who affects their lives, who they really wish they could have done something more for," says Tracey. "Janice is my patient, and she has a lot to do with the path I've been on ever since."

Tracey was particularly curious to figure out why Janice's blood pressure had dropped so low. He knew her condition stemmed from septic shock, when the body's immune system reacts violently to a bacterial infection. But he had run all sorts of blood tests to locate an infection and had never found one.

If there was no infection, then what caused her immune system to rage out of control? The answer could overturn centuries of thinking about what makes us sick (see "Cytokine Theory of Disease," page 14).

Defense, Defense, Defense

The immune system is the body's natural defense against viruses, bacteria and other invaders. Its army is made up of more than 15 different types of white blood cells that produce molecules to defend and protect our bodies.



White blood cells, part of the immune system, protect us from viruses, bacteria and other invaders.

IMAGE COURTESY JIM EHRMAN, DIGITAL MICROSCOPY FACILITY, MOUNT ALLISON UNIVERSITY

Some white blood cells produce proteins called antibodies that bind to particular invaders and disable their actions. Others make proteins called cytokines that, when released into an infected area, help heal wounds and repair damaged tissue.

You can tell when your immune system is working because you get a fever, swollen lymph nodes in your neck, redness around a wound or even a rash or hives. These are the hallmarks of inflammation, an immune response designed to kill foreign invaders.

But for Janice, it had a different effect. Her immune system had begun to destroy the very thing it was supposed to protect. Tracey set out to discover why and how.

Cytokine Cures

Tracey's mentor and others had just identified a type of cytokine abbreviated TNF. Their research in mice suggested that TNF might play a role in infection.

Wondering whether TNF had been involved in Janice's case, Tracey injected rats with the cytokine. Almost immediately, their blood pressure plummeted and they went into septic shock.

Like Janice, the rats had a high white blood cell count, suggesting infection. But again, there was no bacterial infection—just an excess of TNF.

These experiments convinced Tracey that too much TNF can cause septic shock in rats. He further reasoned that, since rats and people are biologically similar, TNF probably does the same thing in humans.

Committed to finding a better treatment for patients, Tracey and his team created an antibody that could latch onto and immobilize TNF. It worked in laboratory dishes, but could it soak up excess TNF in living organisms? Could it stop septic shock, preventing harm to healthy organs and tissues?

very thing it was supposed to protect.

To find out, the scientists tested the antibody in baboons whose bloodstreams were filled with live bacteria, a condition known to cause septic shock.

Bingo! The antibody protected the animals.

While the anti-TNF antibody was never developed into a drug, other scientists built on Tracey's work and soon developed anti-TNF medicines that are now used to treat inflammation-triggered arthritis in millions of people.

Ulf Andersson, a doctor in Sweden, says he had been waiting decades for a medicine like this. He treats kids with inflammatory conditions like juvenile arthritis. When they come to him, many of his patients ache from inflamed joints in their arms and legs, making it difficult for them to move and even grow. The drug can dramatically improve the quality of their lives, Andersson reports.

"I have children who have been in wheelchairs for years who now play soccer again."

Compassion Cures

Andersson describes Tracey not only as a scientific collaborator but also as a close friend.

"I admire his human character as much as his genius," Andersson says.

After Andersson's wife died, Tracey flew from New York to Sweden to cheer up his friend. In the dead of winter, they put on special long skates and glided across parts of the Baltic Sea. Tracey's comfort and support, says Andersson, brought him back to life.

Andersson returns the favor twice a year, spending a week with Tracey, his wife and their four daughters.

"It is really amazing how he finds the time to perform first-class science and manage to be the best father and husband I have ever seen," says Andersson, who admits to copying some of his friend's family skills with his own children.

Tracey attends each of his daughters' soccer games and says he would attend every single practice if he could. He wants them to have fun, follow their passions and gain confidence in all that they do.

"Kevin is at his peak performance when he runs along the sidelines providing advice about how to play," says Andersson. "As an American, his understanding of soccer equals his lack of skill on the skates," he jokes.

When the weather is warm, Tracey packs up his family and heads into Long Island Sound to fish. Being a scientist, he studies the water and weather to find the best spot to drop the line. The family throws back most of what they catch.

"We all like being on the water," Tracey says. "A couple of hours feel like 2 days off."

The Octopus and the O.R.

Tracey decided on a career path when he was just 5 years old, right after his mother died. Sitting on his grandpa's lap, he asked what had

story continues on page 14

FIND MORE @

Play the Immune System Defender game (very basic) at http://nobelprize.org/educational/medicine/immunity or Immune Attack (more advanced and requires download) at http://www.immuneattack.org

Scientists who determined the 3-D structure of a flu protein suggest a way to make better anti-flu medicines.

A New View of the Flu

If you've ever gotten the flu, you know that we don't have many drugs to treat it. New information from scientists studying one anti-flu medicine, amantadine, may pave the way for designing more such drugs.

Biophysicists Mei Hong at Iowa State University and William DeGrado at the University of Pennsylvania discovered how amantadine interacts with a flu protein called M2. This protein launches infection by creating a channel between the flu virus and a healthy cell.

When the researchers determined the detailed, 3-D structure of amantadine bound to M2, they revealed that the drug plugs this channel, preventing infection. They also noticed that amantadine fits loosely inside M2, possibly leaving room for altered versions of the protein to wiggle free and go on to infect a cell. If virus particles containing this version of M2 multiplied, they could lead to a drug-resistant strain.

Already, many strains of the flu resist treatment by amantadine. The biophysicists think that designing drugs that fit into M2 more tightly than amantadine does could provide an effective treatment for the flu that is more difficult for the virus to resist. —*Kirstie Saltsman*

Cytokine Theory of Disease

When Kevin Tracey showed that our own immune systems produce molecules that can harm and even kill us (see main story), he called it the "cytokine theory of disease." This added a new chapter to the 2,000-year story about what makes us sick.

Prints depicting two of the four humors (choleric and sanguine) by Virgil Solis (1514–1562).

Dating back to the ancient Greeks, people and doctors alike believed that all human diseases, ailments and moods stemmed from an imbalance of the "four humors": blood, yellow bile, black bile and phlegm. Too much phlegm was thought to make a person tired and apathetic, while too much black bile caused delusions and depression.

This idea persisted in Western medicine until the 19th century. After showing that microscopic organisms can spoil food, French chemist Louis Pasteur hypothesized that the same organisms could cause diseases in animals and people. Building on this work, British surgeon Joseph Lister showed that sterilizing surgical tools reduced the number of postoperative infections. Finally, in 1890, the German doctor Robert Koch proved the "germ theory of disease."

Up until the 1980s, the majority of researchers focused on further demonstrating Pasteur's germ theory that viruses and bacteria make people sick and that our immune systems work to prevent this. Most weren't thinking about how the immune system itself could cause severe diseases. But as Tracey went on to show, the overproduction of cytokines can cause disabling and even life-threatening illnesses like arthritis and septic shock.

Tracey notes that his cytokine theory of disease actually echoes a key idea of the ancient Greeks' humoral theory of disease: Human illnesses aren't always caused by outside contagions—sometimes they stem from imbalances within.—*E.C.*

continued from page 13

happened to her and why. His grandpa said she had a tumor that, like an octopus, had spread its tentacles throughout her brain, making it impossible to remove. Right then, Tracey said he wanted to be a scientist so other kids didn't have to suffer like him.

He also liked caring for people, which steered him toward medicine.

Eventually, he decided to become a neurosurgeon—a specialty that allowed him to split his time between the operating room and the research lab. This dual career, he says, made him both a better doctor and a better scientist.

"Being a doctor is gratifying in part because of the experience that comes from helping one person at a time," he says. "But I was always excited about the possibility of discovering something that could help many, many people."

Also, he says, "Doing science is just addictive. It is more like a hobby than a job."

"For every 100 questions, there are another 100 questions. The churning of these questions and the development of new ideas are what drive scientific progress."

Surprise in the Lab

In 2000, Tracey left his medical practice to devote all his energy to the lab. He turned his attention again to creating an anti-TNF drug.

He and his team developed a chemical called CNI-1493. This compound, which could switch off TNF production, had the potential to treat cytokine-related disorders from sepsis and arthritis to stroke and digestive diseases.

Tracey knew the substance targeted immune cells. What surprised him was that it had an even more powerful effect on brain cells.

For every 100 questions, there are another 100 questions.

ADAM COOPER

For Tracey and coworkers, lively discussions often lead to new questions to explore and answer.

That's weird, Tracey thought. Why would something designed to target the immune system have an effect in the nervous system?

He discovered that CNI-1493 tells brain cells to activate a particular nerve, called the vagus nerve. Once activated, the nerve turns down TNF production.

The Wanderer

We know that the nervous system controls many important functions—from moving muscles to forming thoughts. But until quite recently, scientists believed that the immune system functioned independently.

Now it's clear that the brain and other parts of the nervous system—probably a whole lot of nerves, Tracey suspects—help direct our immune responses.

Tracey focused on the vagus nerve. This nerve, which means "wandering" in Latin, regulates our heart rate, digestion and other essential functions.

It meanders from the brain stem, across the neck and chest, down into the abdomen and ends up in our internal organs, including the spleen. Like the appendix, the spleen is an organ you probably think little about. But it's actually a major player in the immune system.

"Most of our circulating [white blood] cells pass through the spleen every 5 minutes," says Tracey.

The brain communicates with these white blood cells via the vagus. Electrical signals from the brain zip down the nerve and trigger its endings to release a molecule called acetylcholine into the spleen. When acetylcholine binds to special receptors on white blood cells, the cells stop making TNF. Less TNF means less inflammation.

Sketching Out an Idea

Since TNF causes septic shock, Tracey wondered how the brain limits production of the cytokine. To work out the answer, he turned to a trick he often uses to capture his thoughts: sketching.

When he first examined Janice, he diagrammed her burns and their severity. When he planned to build his daughters a two-story playhouse, he drew a blueprint on the back of a grocery bag. When he talked to middle school students about being a brain surgeon, he went to the blackboard and drew a drill with a spring to help the kids figure out how to bore through the skull without nicking the brain.

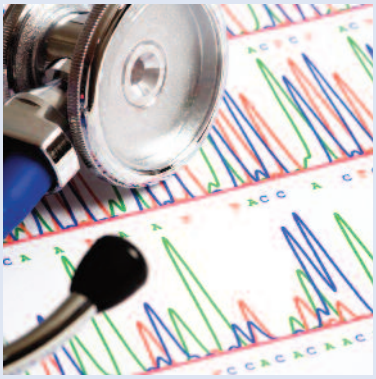
story continues on page 16

KEVIN TRACEY

Tracey designed and built this two-story playhouse for his daughters.

FIND MORE @

Watch a video of Tracey talking about his research at http://publications.nigms.nih.gov/multimedia/captions/tracey-captions.html



A person's complete genome sequence can yield clinically useful information.

Rx: Genome Sequence

You've probably heard that scientists have sequenced the entire human genome. But what does this mean for you? If your doctors knew the identity and order of all 3 billion letters in your genome, what could it tell them?

That's what researchers wanted to know. One of them, bioengineer Stephen Quake at Stanford University, volunteered his genome sequence for the study.

He and his colleagues used computer searches to find disease-related gene variants. They then analyzed his medical and family history. They even factored in statistical disease risks.

After all the number crunching, they found he had a higher-than-average risk for developing a handful of conditions, including heart attacks, thyroid disease, iron overload and certain cancers. Some of these run in his family and some don't. Also, he might respond poorly to certain heart medications—something good to know since he's at increased risk for heart problems.

With this study, the researchers have shown that a person's complete genome sequence can yield clinically useful information. But many challenges remain, including understanding the influence of a person's environment, which can change over time.

—*Alisa Zapp Machalek*

Her short life had a big impact.

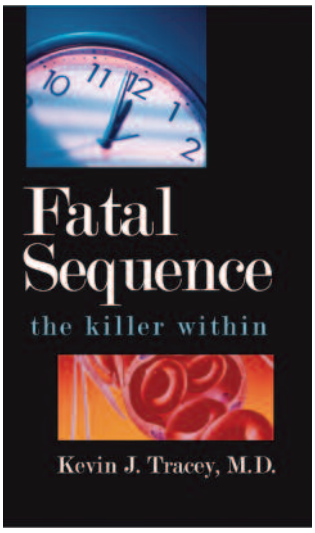
continued from page 15

Now using a whiteboard in his lab, Tracey sketched the brain, the spleen and the vagus nerve running between them.

The next day, he set up an experiment to see if, by stimulating the vagus nerve, he could dampen TNF production. He used an electrical device to activate the vagus nerve of rats. Within seconds, the animals produced less TNF.

Since then, he has shown that in animals, stimulating the vagus nerve can block arthritis, sepsis, shock, heart failure and inflammation of the colon and pancreas.

"The groundwork is being laid to try some of these approaches in humans, perhaps within the next year," he says.



COURTESY OF THE DANA FOUNDATION

Tracey's book describes Janice's life and what he and others have learned about septic shock.

Legacy of Life

When Janice died, Tracey didn't know exactly what happened or why.

"I had no good explanation for what the molecules in her body were doing," he says. "I know a tremendous amount more now."

He suspects that the baby's injury impaired her nervous system, which not only led to an overproduction of TNF but also to her heart failure. He also thinks that too much HMGB1—another type of cytokine discovered in his lab—likely triggered her sepsis.

More than 25 years later, Janice's story still influences Tracey every day.

"I tell everyone who will listen never to take anything out of the microwave with a baby in their arms," he says. "Never put hot food on a tablecloth that a child could pull down."

He created an invisible triangle that fills the space between his kitchen sink, stove and refrigerator. From an early age, his girls—now 7 to 15 years old—knew not to step inside it when unsupervised.

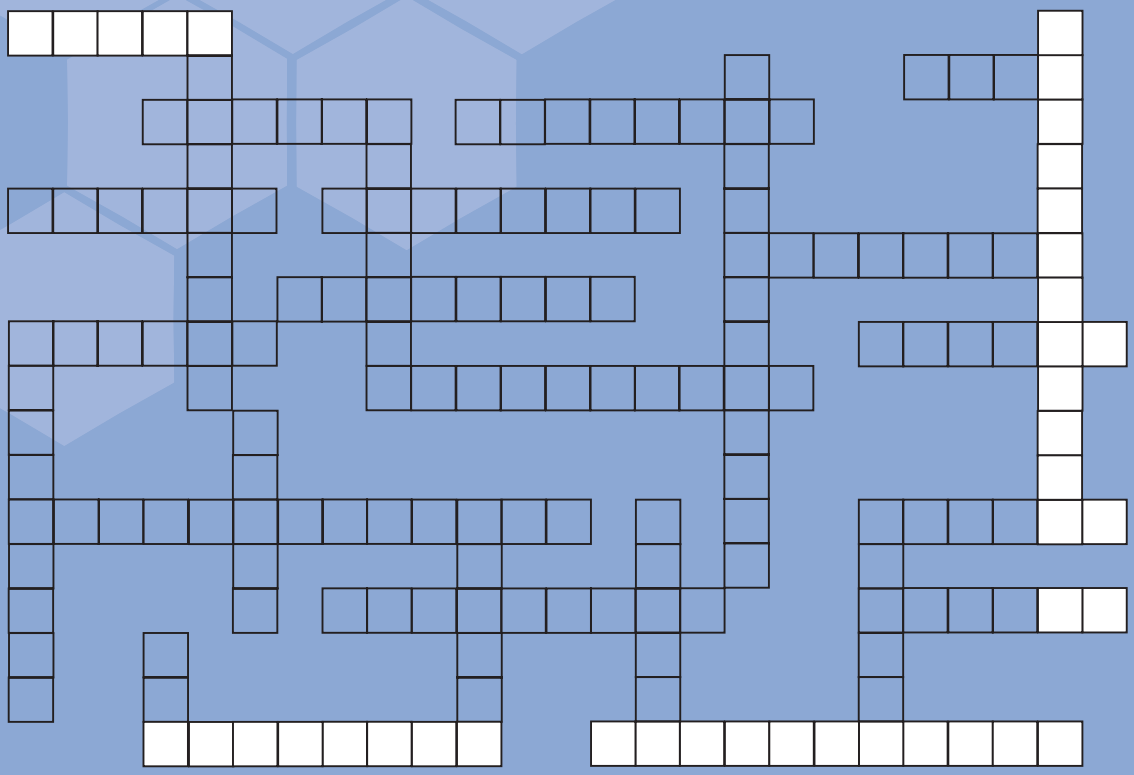
He even wrote a book called *Fatal Sequence: The Killer Within*. The title refers to septic shock caused by the immune system. The book describes Janice's life, how she changed Tracey's life and what he and others have learned—and applied to help patients—because of her.

Although she didn't live to see it, her short life had a big impact, says Tracey. "The people who receive drugs based either directly or indirectly on knowledge that came [because of] her—they're her legacy."

FIND MORE @

Read about a veterinarian who studies sepsis at
http://publications.nigms.nih.gov/findings/mar07/dogging.html

EXPLORE IT **PUZZLE IT** FIND IT



ACROSS

1. Nerve that influences the immune system
5. Number of Tracey's daughters
6. Scientific term for fats and oils
8. Normally helps heal wounds
9. Body's defense system
10. Insect that transmits malaria
11. Protein made by white blood cells
12. Studying fat metabolism in insects could teach us more about this human disease
13. Enzyme that breaks down fat for storage
14. Family member who influenced Arrese's work ethic
15. Signal sent by the brain
17. Where fats are stored
20. Organ involved in the immune system
21. Country where Arrese grew up
22. One of the four humors
24. Common name for *Drosophila melanogaster*
25. Condition that starves organs of oxygen

DOWN

2. Tracey's childhood dream job
3. A common type of fat we digest
4. Immune system response
7. Where fat molecules go when we don't need them right away
13. Process of breaking down fat for storage
16. Insects can be studied as _____ organisms for human biology
18. Stored fat is transformed into this when we need to use it
19. Patient who changed Tracey's life
20. Body-wide inflammation
23. Too much _____ can cause septic shock

SOLVE IT ONLINE

An interactive version and answers can be found at http://www.nigms.nih.gov/findings.

Discrimination Prohibited

Under provisions of applicable public laws enacted by Congress since 1964, no person in the United States shall, on the grounds of race, color, national origin, handicap, or age, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity (or, on the basis of sex, with respect to any education program or activity) receiving Federal financial assistance. In addition, Executive Order 11141 prohibits discrimination on the basis of age by contractors and subcontractors in the performance of Federal contracts, and Executive Order 11246 states that no federally funded contractor may discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. Therefore, the programs of the National Institute of General Medical Sciences must be operated in compliance with these laws and Executive Orders.

Accessibility

This publication can be made available in formats that are more accessible to people with disabilities. To request this material in a different format or to order additional copies, contact the NIGMS Office of Communications and Public Liaison at 301-496-7301; send e-mail to info@nigms.nih.gov; or write to the office at the following address: 45 Center Drive MSC 6200, Bethesda, MD 20892-6200. If you have questions or comments about this publication, you can use the same contact information to reach the editor, Alisa Zapp Machalek.

Free Publications

Browse and order NIGMS publications at http://publications.nigms.nih.gov/order.