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

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.

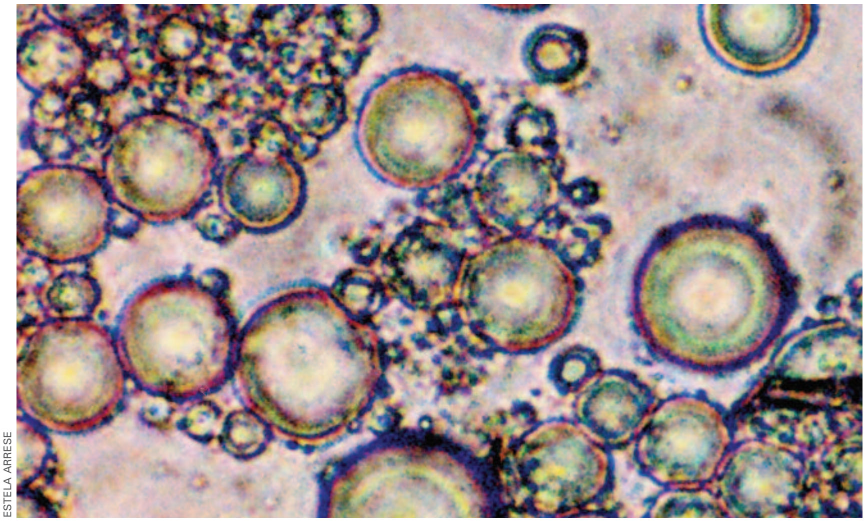
When the body needs extra energy —for instance, when we run a marathon — hormones direct lipases to break down the fats stored in lipid droplets and wash them back into the bloodstream.

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.

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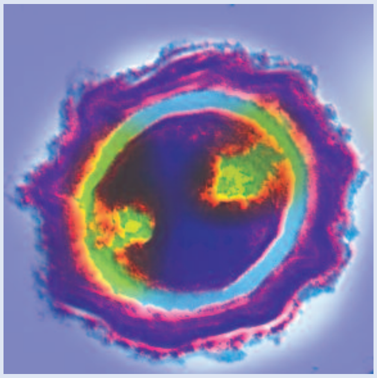
Learn about some of the surprising animals and plants used in research at http://publications.nigms.nih.gov/thenewgenetics/livinglab.html.



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.

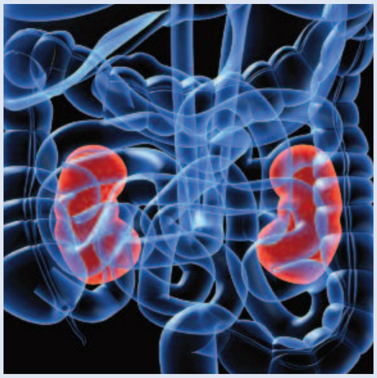
"She nurtures her students…in such a way that the excitement of science never wears off and critical thinking is developed," says Alisha Howard, who did undergraduate research in Arrese's lab before earning her Ph.D. with Soulages.

"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."

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