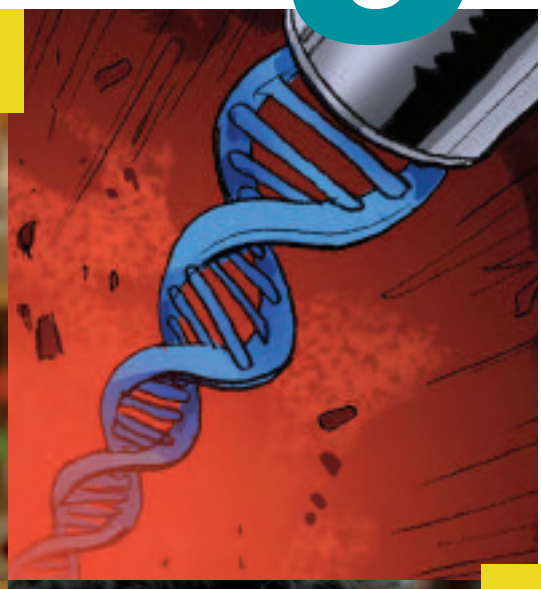
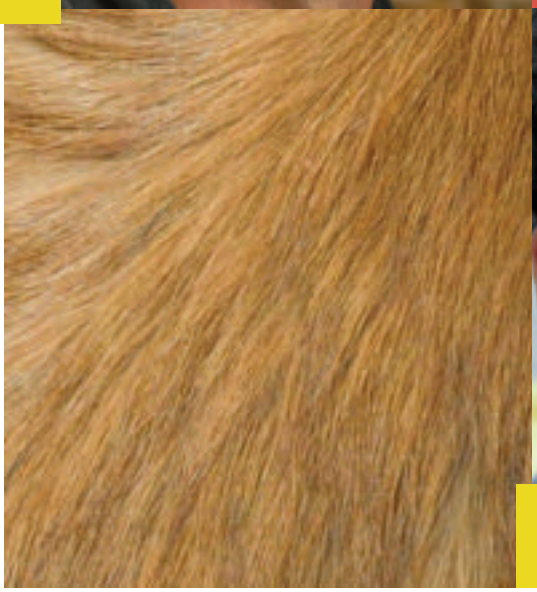
MARCH 2007

Findings





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On the Cover

Drew Endy: ***L. Barry Hetherington, Photographer***
Drew Endy is a synthetic biologist at the Massachusetts Institute of Technology in Cambridge. Endy combines science and engineering to design and build novel biological components, devices, and parts.

Cynthia Otto: ***Sabina Louise Pierce, Photographer***
Cynthia Otto is a research veterinarian at the University of Pennsylvania in Philadelphia. Otto studies the molecular basis of sepsis, a life-threatening, body-wide illness.

Editor's Note

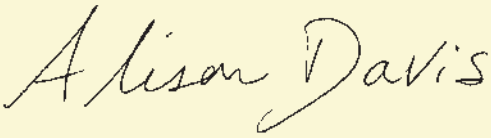
Some people just can't sit still. They'll scan a magazine while watching TV, stroking the cat, and digging into the popcorn bowl all at once. All the while, the phone's jammed between ear and shoulder.

Of course, all of us combine activities in our fast-paced, multidimensional world. We're used to it, and scientists are no different. In this issue of *Findings*, you'll meet two researchers who have taken the art of mixing to new levels.

Take Cynthia Otto. On page 8, read how her research is finding ways to heal critically ill animals—and ultimately people—faster and more reliably. While it's no surprise that this veterinarian loves animals, what's so unusual is how Otto combines that love with an investigative zeal to figure out why some patients don't make it out of the veterinary emergency room.

Another example is synthetic biologist Drew Endy (see page 2), whose quirky approach to communicating science to students yielded the comic book *Adventures in Synthetic Biology*. By blending biology and engineering in amazing ways, Endy is on a quest to make ordinary organisms do truly extraordinary things.

Read on…and don't forget the popcorn and the cat.



Alison Davis
Editor

davisa@nigms.nih.gov

http://www.nigms.nih.gov/findings

Do-It-Yourself

BOTTOM: DREW ENDY, ISADORA DEESE, CHUCK WADEY TOP: L. BARRY HETHERINGTON

In Drew Endy's world, things are a little different.

BY DAVID BOCHNER

There, bacteria run relay races, lie down to create a modern version of the Etch A Sketch® toy, and even work as photographic film.

Though it may sound like a weird world, Endy sees big promise in convincing living things to work as machines and perform useful tasks.

Endy, 35, is a synthetic biologist at the Massachusetts Institute of Technology (MIT) in Cambridge.

He and other researchers who work in this emerging area of science blend engineering, biology, and computer programming to find out how life works and how we can make it work for us.

Biology

"Biology is often thought of as [a mysterious process], where you don't actually know what's going on… or wet, goopy stuff that doesn't feel like it should be like a clock or something with gears and pistons and rods," he explains.

While biological materials and organisms may well be wet and goopy, to Endy they aren't all that different from engine parts. Not because of what they're made of, he says, but because of what they can do. The sheer capacity for innovation in biology is what makes it so cool to him.

And it's definitely cool to his students, as well: Every one of the bacterial tools mentioned above was dreamed up by a college student participating in the International Genetically Engineered Machines, or iGEM, competition that grew out of Endy's synthetic biology class at MIT.

Building Knowledge

Endy is by all accounts an engineer, in thinking and in training. He earned a bachelor's degree in civil engineering from Lehigh University in Bethlehem, Pennsylvania.

But even then, during a molecular genetics course, Endy's interest turned biological and he became fascinated with the nuts and bolts of living things.

He went on to earn a master's degree in environmental engineering 2 years later, also from Lehigh, and then a Ph.D. in biochemical engineering, this time from Dartmouth College in Hanover, New Hampshire.

Now, the building materials Endy works with are far from steel and concrete. The parts in his lab "shop" are made of DNA: Endy builds genomes.

Genome is the scientific term for all of the genetic material in an organism. By studying how genome organization creates templates for living things as diverse as people, penguins, and petunias, researchers can get clues about how genes affect health and disease.

"Building is a great way to learn."

For his research, Endy decided to focus on the tiny T7 bacteriophage, a virus that infects bacteria. The T7 genome has been intensively studied for years by researchers interested in questions about how information carried in DNA can cause a cell to reprogram itself, generating new products and behaviors.

To analyze any system, engineers begin by identifying all of its parts and then figuring out how they connect together to produce a functioning whole.

For T7, this work had been done. The organization of the T7 phage genome—or the order in which all of its genes string together—was already known. Scientists had figured out that the phage's genome has only 56 genes, which produce 60 proteins that direct various stages and types of infection.

The T7 genes cluster into several distinct classes, each of which is expressed at a specific point during infection. As the virus infects a bacterium, Endy explains, it has to switch from expressing one class of genes to another in order for the infection to continue and be successful.

One approach to understanding T7 would be to look at its genome and try to pry it apart piece by piece, to investigate the function of each individual gene. But Endy had a different idea.

"It's immediately obvious when you encounter [a] DNA sequence that this is a program, and that you could change it," Endy says.

But decoding the T7 phage "program" proved harder than he thought it would be. Endy's engineering background gave him a new strategy.

"The biological systems that we find in nature are not themselves designed by nature to be easy to understand. And so if I wanted to have biology that I understand," Endy recalls thinking, "I'd be better off building it myself."

AARON CHEVALIER (UT AUSTIN), JEFF TABOR (UCSF)

Bacteria can be genetically altered to produce a dark pigment in response to a flash of light. When researchers exposed a plastic dish of these bacteria to the black-and-white text, "Hello World," they created the world's first living photograph.

Bacteriophages are viruses that infect and destroy bacteria. Endy and other scientists study the genome of the T7 bacteriophage, shown in this drawing.

"You might try to understand a car, or a bicycle, by taking it apart and having the pieces all over your lawn," says Endy, "But you're going to have a much *better* understanding of a car or a bicycle if you take the bits and pieces and put them together to build one from scratch."

Programming Life

Synthetic biologists like Endy are driven by their desire to understand life's design rules, because this knowledge would make biological processes much more predictable.

In turn, the hope is, we'll all be better off. Knowing the rules of biology—and how the rules get broken in the early stages of disease—would provide the opportunity to implement health interventions well before symptoms appear, when the chance for cure is highest.

"How do we get to some future where the programming of living systems is as simple, understandable, and reliable as computers are today?" Endy asks.

It also doesn't hurt that Endy has a driving need to solve problems.

"When I don't understand how things work, I'm curious," he explains. "It bothers me."

So he went to work rebuilding the T7 genome from its parts. His goal was to construct a stripped-down, functional version of the genome that would be easy to understand.

The idea is that if he could build a version of T7 that works like the real thing, it would be a great step toward understanding the entire biological machine. And then Endy could simultaneously test each part of his synthetic, model genome.

When Endy thought about how to construct his own T7, he decided to equip it not only with the viral genes it needs to survive, but also with "cut-and-paste" sites in the DNA that would make it easy to change the phage's genetic program. That means scientists could add new DNA sequences, deactivate genes, or measure the activity or expression of any particular gene.

"Building is a great way to learn," says Endy, explaining that failure just means more experiments.

In 2005, Endy succeeded in partially redesigning the T7 phage. His lab creation, called T7.1, could perform just as well as the original.

Part of the effort, Endy explains, involved untangling some overlapping genes. This genetic handiwork, he says, will enable other scientists to manipulate parts of the T7 genome that could never before be separated in the real virus.

But in truth, T7.1 was only a partial redesign, because Endy was unsure of how many changes T7 could

MAUREEN GUNN

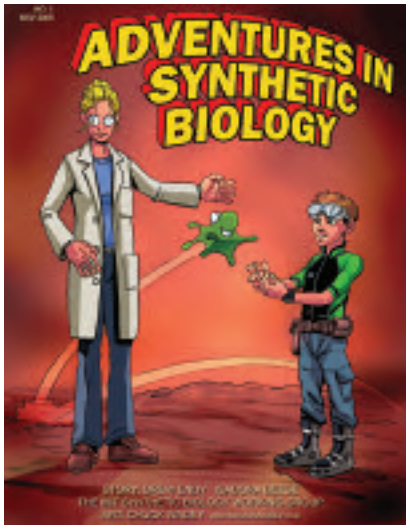
Endy has many adventurous interests outside the lab. In this photo taken in Kahului, Hawaii, Endy (back) kitesurfs with friends.

tolerate at one time. Following on the success of the first effort, researchers in Endy's lab are working on a new genome, T7.2. This one, he says, will have even more tools to make it user-friendly for other molecular builders.

For all his building enthusiasm and excitement for figuring out biology, Endy has other passions, unrelated to science.

What would he do if he weren't building genomes? To this, Endy simply shrugs.

"[I'd probably be] surfing…writing poetry and surfing. But probably in the other order."



DREW ENDY, ISADORA DEESE, CHUCK WADEY

▲ Endy created the comic book *Adventures in Synthetic Biology* to help explain his work to students and other scientists. The first page (right) shows "The Dude" scheming about how to get bacteria to work for him.

Communication Breakdown

As Endy continued his work retooling the T7 genome, he grew frustrated that biological engineering didn't seem to be evolving like other engineering disciplines. For example, a mechanical engineer can pick up a screw and know exactly what size and shape it is, he says, but many genetic devices are designed only to work in the research lab in which they were made.

"I don't see what I'm doing as work."

"It'd be like having an MP3 player that you could only hook up to your computer and your stereo," Endy explains, "whereas what you'd like is to have an MP3 player that could be hooked up to any computer and any stereo."

Through some trial-and-error efforts, Endy and his coworkers did discover a standardized way to get molecular machines to talk the same language. But what proved more difficult, he says, was trying to teach the language to new students.

The solution to this problem turned out to be, of all things, humor.

While attending a meeting in Los Angeles, California, Endy wore a name tag with a picture of one of his genetic gizmos. Out of the blue, one of the other attendees at the conference asked him to explain his image.

It didn't turn out quite as well as Endy might have hoped.

"I tell him the story about how a genetically encoded inverter works," Endy remembers. "I finish my story, and he goes, 'That sucks!'"

The man's harsh words took Endy by surprise until he realized that the guy had a point. The image needed way too much explanation to be understood clearly.

The man went on to suggest that a comic strip might get the message across. Endy laughingly recalls wondering at the time who in the world this person he was talking to might be.

As it turned out, the man who verbally accosted Endy was Larry Gonick, author of *The Cartoon Guide to Genetics*.

When Endy returned to Boston after the meeting, he got to work sketching a draft of the comic strip. But his assistant, who also happens to be a screenwriter, wasn't impressed. In fact, she responded with criticism similar to Gonick's.

"She happened to know the guy who does the storyboards for Spider-Man," remembers Endy, adding that they convinced the artist, Chuck Wadey, to do some drawings.

DREW ENDY

Endy created a database, the Registry of Standard Biological Parts, to store components of biological machines.

The result was the comic book *Adventures in Synthetic Biology*. In the first issue, boy scientist "The Dude" and his wisecracking teacher navigate the tricky terrain of synthetic biology and sum up all of its principles in living color.

On the Same Page

Endy's comic helped establish a way for scientists to talk the same synthetic biology language, but he knew that another key step would be finding a common place to keep all the parts so researchers could easily find and use them. It would not be an actual warehouse, but rather a common framework for organizing all the components of biological machines.

That amounts to a registry, or database, where everyone can find information and detailed descriptions about how to use that information. The Registry of Standard Biological Parts, which Endy helped to establish, keeps track of genetic components the way an engineer might keep track of machine parts or electrical circuit diagrams.

A single genetic "part" could be made up of several related and interacting genes. Endy's hope is that the tools for biological engineering become so advanced that someone with little or no biology background could still build a useful, living organism from off-the-shelf parts.

Endy likens the situation to household appliances.

Imagine if, in order to use a television, you had to know how every wire and tube functioned, and why only certain ones could connect to certain others.

Luckily for us, watching television is no more complicated than switching on the set.

"My motivation is that years from now, anybody who wants to [can] dream up a useful biological system and pull it off, without having to go through this whole big research process to do it," Endy explains.

Others have already begun to use the biological parts in the registry Endy set up: that's how students made the bacterial machines that create living photos and run relay races. Those projects emerged from the iGEM competition, which Endy helped launch in 2004.

In the summer of 2006, 37 different schools from around the world registered teams of undergraduates to engineer biological machines for the iGEM competition held last November. Participating students came not just from U.S. schools, but from all over the world. The contest hosted teams from the United Kingdom, Spain, India, Japan, and Slovenia, the 2006 grand-prize winners.

The Future Is Now

By bringing together undergraduates to engineer biology, the iGEM competition is a community teaching tool. It inspires students to try new combinations

MELISSA LI

Students from 37 countries gathered at MIT for the 2006 iGEM Jamboree.

and build amazing genetic machines with standard biological parts.

Endy says what's really neat about the living photographic film, for instance, isn't what it can do, but how it was made.

"[The bacterial film] was doubly cool because [the students] made the system out of some of the components that we already had…a novel combination of off-the-shelf parts."

In a cutting-edge field like synthetic biology, even the professors learn something new with each competition.

Endy continues to teach in innovative ways, and he has won awards for his creative educational approaches. Through his teaching and research, Endy aims to change the way biologists and engineers think about and use biology.

Basically, he wants engineers to see biology as just another way to build things.

"If you ask engineers what they want to do in their hearts, they want to make something," Endy says. He hopes to attract more engineers into synthetic biology by teaching them what they can make and how they can make it.

And as far as Endy's concerned, there's nowhere else he'd rather be.

"I'm doing what I want to be doing, and if I wasn't, I would change it," Endy says. "If at some point in the future, I'd rather be raising pheasants in southern France, or in northern France…or wherever they raise pheasants in France, I presume I would go do that."

"I don't see what I'm doing as work," he declares. ■

David Bochner, a Harvard University junior studying biology, was an intern at the National Institute of General Medical Sciences in summer 2006. He is an aspiring science writer who also writes for Harvard student publications.

Science and Society

Concerns about bioterrorism have led to calls for regulating synthetic biology and making it secure. If a scientist can easily make a virus from off-the-shelf parts, who else could?

MARSHA MILLER (UT AUSTIN)

Synthetic biologist Drew Endy thinks that the potential of biological engineering makes it worth pursuing (see main story), in conjunction with societal conversations about the technology's applications.

"There are lots of things we can imagine," Endy explains, offering examples of genomes designed to be understandable and genomes whose evolution is directed by researchers, as opposed to by nature.

Endy predicts that synthetic biology will evolve sort of like the Internet, through innovation and the widespread distribution of information. To him, spreading knowledge via the BioBricks Foundation, which he helped to establish in an effort to promote the free exchange of data and information, will encourage a revolution in the field of biological engineering. He doesn't see it putting power into the wrong hands.

Living machines are already better than their mechanical counterparts at a lot of tasks, Endy says.

"Biological systems are really good at material construction, chemical production, energy production, and information processing," he explains. The challenge is to find ways to make them work for us.

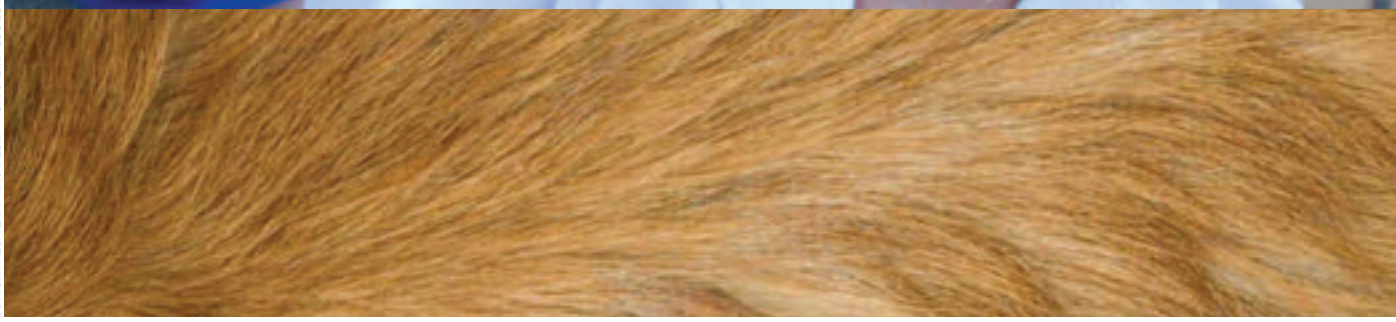
DREW ENDY

While some might claim that Endy and his colleagues are "playing God," Endy believes that he is simply realizing the human potential for innovation and imagination.

"Instead of just imagining the world as it exists, and as we inherit it from nature, I think it's becoming increasingly important that we understand how to imagine worlds that might be, how we would choose how to design and construct them."—*D.B.*

Dogging Sepsis

BOTTOM: ALISA ZAPP MACHALEK TOP: SABINA LOUISE PIERCE



BY ALISA ZAPP MACHALEK

"Sophie is one of the lucky ones."

That's according to veterinarian Cynthia Otto, pointing to a photo of a schnauzer mix amid the festive glow of holiday lights.

The photo, taken at an annual veterinary intensive care unit survivors' party, shows Sophie lounging in her owner's arms, greeting another partygoer with a friendly sniff. Just a month before, Sophie had been close to death after being hit by a car.

Otto saved the dog's life. Along with only 200 or so other people in the world, Otto is a certified expert in veterinary emergency and critical care medicine. She treats ill and injured dogs, cats, guinea pigs, ferrets, and anything else carried or carted into the veterinary hospital emergency room.

Otto, 45, also volunteers on two national-level disaster response teams. She competes with her dog

Dolce in flyball dog agility races. She loves gardening, gourmet cooking, and whitewater kayaking.

On top of all of that, she runs a research laboratory at the University of Pennsylvania School of Veterinary Medicine in Philadelphia.

Otto's scientific focus is sepsis, a dramatic, full-body reaction to an injury or illness. With Otto's help, Sophie averted sepsis. But many animals with similar injuries die from the syndrome.

Sepsis is a major killer in people as well as in animals. Every year, it strikes 750,000 Americans, most of whom are in intensive care units. About one-third of these people die—far more than the number of U.S. deaths from prostate cancer, breast cancer, and AIDS combined.

A Deadly Spiral

In response to an injury or infection, the immune system deploys an arsenal of biological and chemical weapons to annihilate bacteria or viruses. Immune cells called macrophages swarm into motion, devouring microbes and squirting out toxic substances to sterilize a wound. More cells pour in and continue to unleash lethal chemicals.

The crossfire damages healthy tissues, which become inflamed—red, hot, swollen, and painful. Still, this is normal collateral damage.

Sepsis goes way beyond normal. It is an immune system gone haywire.

Although it usually shadows serious infections or injuries, sepsis arises unpredictably. It is difficult to catch early and can quickly spiral into a life-threatening crisis that doctors are powerless to control.

As if using a machine gun to kill a cockroach, during sepsis the immune system sprays destruction throughout the body. Blood vessels, internal organs—eventually the entire body—become inflamed. Often before doctors suspect sepsis, blood pressure plummets, signaling shock. One by one, vital organs fail: the lungs, liver, kidneys, and, in the worst cases, the heart.

The chances of recovery range from 80 percent to less than 10 percent, depending on how many organs malfunction. In the most serious cases, death can come within hours.

"Sepsis is about the only medical condition that affects virtually every organ system—it's incredibly complicated," says Otto.

She sees a lot of sepsis in her animal patients. Trauma from a car accident can cause it, as can a variety of infections, including canine parvovirus, a disease that typically infects puppies between 6 weeks and 6 months of age. Otto's own dog had parvovirus when she adopted him.

BARRY ROSEN

Otto's dog Dolce, a former seriously ill patient who would have been euthanized, loves agility classes and flyball races.

"Sepsis is about the only medical condition that affects virtually every organ system."

NO Way Out

Otto is on a quest to find the cellular and molecular basis of sepsis.

Scientists think that a gaseous substance called nitric oxide (abbreviated NO) may be at the root of many of the complications of sepsis, but they haven't been able to prove it in human patients. They do know that at high levels, NO kills cells and inflames tissues.

But NO isn't all bad. In fact, in the right place at the right time, it is an important chemical messenger in a healthy body. Among other things, it helps regulate blood pressure by opening blood vessels. It is also on the front line of defense against bacteria and other invaders.

One of the first things that happens in sepsis is that microscopic blood clots form haphazardly throughout the body, blocking blood flow. Without a continual supply of fresh blood, tissues become starved for oxygen. This is called hypoxia.

CHRIS GREGERSON

For patients with sepsis or other serious injuries or illnesses, doctors can only provide supportive care, using mechanical ventilators (at right) and other medical devices.

Otto suspects that hypoxia sets the stage for a toxic blast of NO in sepsis patients. This rush of NO would cause a sudden and dangerous dip in blood pressure and a burst of inflammation, a hallmark of sepsis.

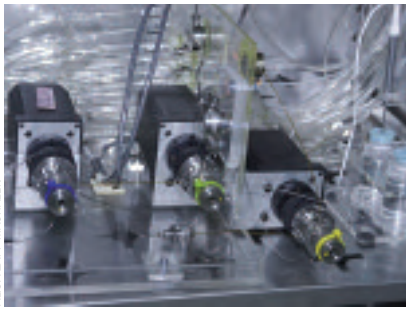
To begin investigating this idea, she tracked NO back to where it is produced—in macrophages. When these white blood cells encounter toxic bacterial products or when they are deprived of oxygen, both of which occur early in sepsis, they ramp up production of the enzyme that makes NO.

But this enzyme, which is called inducible nitric oxide synthase, or iNOS, needs oxygen to do its job. So when oxygen is scarce, Otto thinks, the inactive enzyme builds up inside macrophages. When oxygen levels are restored, the amassed iNOS would unleash a destructive flood of NO.

A good theory, but how could she test it?

Garage Gadget

Otto knew she couldn't use traditional petri-dish experiments because it is difficult to control how much oxygen gets into cells growing in a dish. She turned to her main collaborator, her husband James Baumgardner, who is a bioengineer and anesthesiologist (also at the University of Pennsylvania). Together, they designed and built a new contraption in their garage. They called it a forced-convection cell-culture system.



ALISA ZAPP MACHALEK

Otto and her husband built this forced-convection cell-culture system in their garage. Other hypoxia researchers are clamoring to use it.

Offering a new approach to cellular research on hypoxia, this system lets scientists accurately measure and control the amount of oxygen that passes over cells inside a glass tube. About a million cells form a layer on the inner surface of the fragile tube, which is about 4 inches long and thinner than angel hair pasta.

The homemade invention also includes a pump, calibrated gas tanks, two gas equilibrators, a computer-driven switching valve, electrodes that measure NO, and silicon tubing that connects it all. The setup is complicated and still being optimized, so to keep track of it, Otto posts an up-to-date schematic on a whiteboard next to the apparatus.

To tease out the connection between hypoxia and NO production, Otto's research team loaded macrophage-like cells into the slender glass tube.

Next, they set the machine to deliver normal amounts of oxygen to the cells for 90 seconds, then to deliver much lower oxygen levels (to mimic hypoxia) for 30 seconds. They continued this cycle, called intermittent hypoxia, for up to 18 hours.

At the end of these experiments, the team measured levels of NO and iNOS in the cells. The results, combined with other studies, suggest that intermittent hypoxia can indeed cause inflammation. That puts Otto another step closer to discovering the cellular factors that wreak havoc in sepsis patients.

Battle to Breathe

The lungs are an organ system that is particularly susceptible to damage from sepsis. In addition to her NO studies, Otto is also interested in finding out how lung damage is connected to hypoxia and inflammation.

When you inhale, air flows into your lungs, filling millions of microscopic air sacs called alveoli. Woven through this network of alveoli are billions of miniature blood vessels called capillaries, each 10 times narrower than a human hair.

Both alveoli and capillaries are encased in extremely thin membranes. Newly inhaled oxygen slips across these membranes from the alveoli into the capillaries. Once in the bloodstream, the oxygen is distributed to all parts of the body.

A serious injury or infection can rip, stretch, or irritate the delicate membrane around alveoli, allowing watery fluid to leak in. Flooded alveoli are less able to hold air, and some buckle under the pressure, leaving a person or an animal gasping for breath. Eventually, a large chunk of the lungs collapses. As more of the lungs cave in, breathing becomes impossible without mechanical ventilation.

Ironically, when patients with severe sepsis are put on breathing machines to support their failing lungs, the devices can actually worsen lung injury.

Otto wants to know how this unintended damage occurs.

Scientists have proposed many theories that attempt to explain ventilator-associated lung injury. But, because patients on ventilators have additional health problems and technical reasons make the research difficult, the root causes of this machine-associated injury have eluded scientists for decades.

One leading theory is that ventilators overinflate lungs, ripping open the tightly sealed connections between alveoli. Turning down ventilators to pump less air seems to reduce the damage.

When she began to examine the problem of ventilator-associated lung injury, Otto's first step was to determine how ventilators affect alveoli in a collapsed lung. Do they fully restore the structure of alveoli? Or do they only inflate alveoli with each puff, then allow the sacs to collapse again?

Her team, composed of Baumgardner and other physicians, veterinarians, and students, discovered the answer by studying an anesthetized rabbit on a ventilator.

Oxygen levels fluctuated wildly in the rabbit. In contrast, oxygen stays nearly constant in healthy lungs.

The research team concluded that the rabbit's alveoli snapped open and closed with each pump of the ventilator. In other words, the breathing machine could not maintain the inflated, semi-full structure typical of healthy animals or people.

The experiment adds weight to the theory that ventilators damage lungs by eroding their cellular fabric. The continual stress of expanding and deflating alveoli appears to wear them out, just like repeatedly stretching a rubber band weakens it until it breaks.

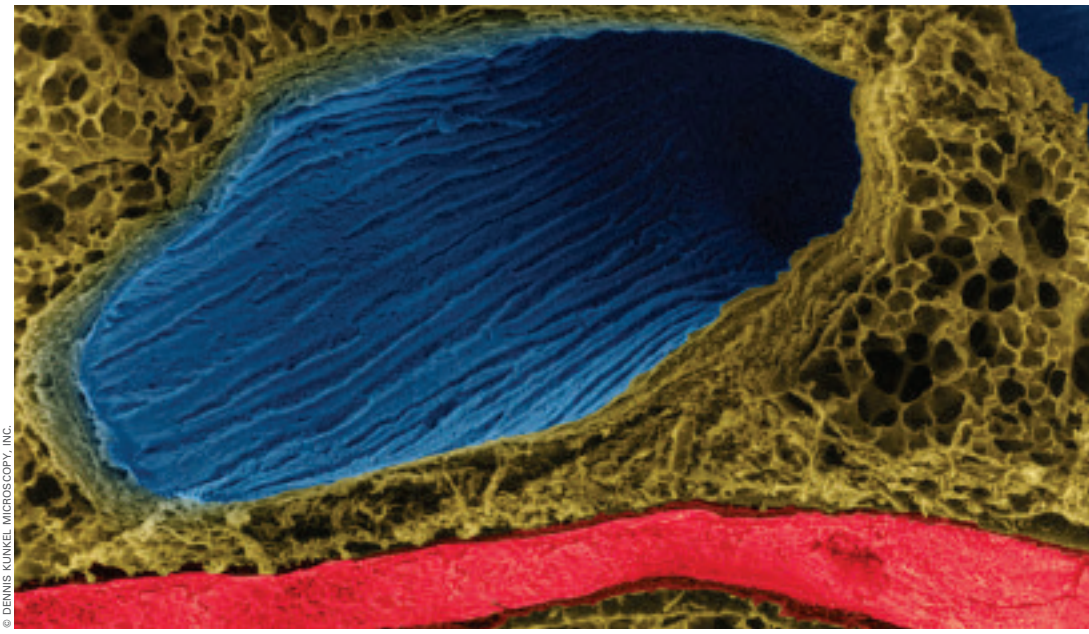
Dog Detectives

Otto's enthusiasm and drive are palpable to all those around her. "Cindy's great," says Mary Robinson, a graduate student in Otto's lab. "She has so much energy—she sweeps you up with it."

Or, as Otto puts it, "I have a short attention span, and I need constant shots of adrenaline!"

One of the ways she gets her adrenaline fix is by using her veterinary skills to assist rescue efforts when a disaster overwhelms local or state resources.

She serves on a veterinary medical assistance team that cares for animals in the same way that disaster medical assistance teams provide aid to human casualties. Most recently, her team looked for animal survivors after Hurricane Katrina.



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Take a breath. Oxygen just traveled through the branched passageways in your lungs (blue), through alveoli (yellow), and into blood vessels (red).

CALIFORNIA TASK FORCE 7 AND THE SEARCH DOG FOUNDATION

The search-and-rescue dogs that worked at the 9/11 terrorist attack sites were hailed as heroes. They continue to serve by participating in Otto's research on the health risks to rescue workers at the sites.

Otto is also a charter member of the Pennsylvania-based Federal Emergency Management Agency search-and-rescue team. Her job is to monitor and care for the search dogs—and, by default, other animals in the area. That's the team that took her to New York City's World Trade Center Ground Zero in September 2001.

Otto worked the night shift as search dogs sniffed through the huge pile of hot, twisted metal and concrete rubble. Every 30 to 45 minutes, she examined the dogs, rinsed the fine dust out of their eyes, and treated any minor cuts and burns.

"The biggest problem [for the search dogs] was dehydration, probably from overwork," says Otto.

She remembers the horrific scene as dusty, noisy, and surreal. It was eerily bathed in incredibly bright light—like a movie set, she says—while neighboring buildings were blacked out. Smoke and steam rose from smoldering debris.

The work was exhausting and frustrating for the dogs as well as for the humans. They had been trained that finding living people was a game. Because they found no survivors, they never got to win the game.

To buoy the dogs' spirits, Otto explains, workers hid themselves in nearby parks or near the disaster site so the animals could have a successful, live find. Otto says it was clear by the number of people willing to hide that the game was as therapeutic for the humans as it was for the dogs.

With their noses to the ground for much of their 12- to 15-hour shifts—and without benefit of the protective clothing and dust masks worn by their human counterparts—the search dogs were exposed to asbestos, diesel fumes, and countless other potentially carcinogenic compounds.

Since 2001, Otto has been monitoring the health of 97 dogs that worked at 9/11 disaster sites and 55 search dogs of similar breeds that were not deployed. Keeping tabs on the dogs' health will ensure that they get medical attention as soon as possible.

Also, because many forms of cancer progress faster in dogs than in humans, the animals could warn doctors of potential health problems in firefighters and other emergency workers, Otto says.

So far, the study shows no measurable medical or behavioral problems among the 9/11 dogs. "It's heartening, both for the animals and the human rescue workers," says Otto.

In 2002, the more than 300 search-and-rescue dogs that worked at Ground Zero and the Pentagon after the 9/11 terrorist attacks were awarded the Dickin Medal from the People's Dispensary for Sick Animals, a United Kingdom veterinary charity. The award honors the work of animals in war and is the animal equivalent to the U.S. Congressional Medal of Honor.

Finding Success

Stories about Otto's work have appeared in dozens of newspapers, including *The New York Times*, *The Washington Post*, and *USA Today*. She has also been covered by *CNN*, *Fox News Channel*, and media outlets in Europe.

But she wasn't always so well known.

SABINA LOUISE PIERCE

In 2002, the Pennsylvania Veterinary Medical Association named Otto "Veterinarian of the Year."

"I never stopped trying."

"During high school, I played sports, but spent most of my time on the bench," she says. "Every year, I ran for student council office and never won. I was strong academically, but I wasn't at the top of my class."

"Despite all of this, I never stopped trying, and I still find that I often don't succeed initially. [During] my first experience kayaking, I spent more time upside down than right side up. But this made me realize that I don't have to get it right the first time. And perhaps it is on the difficult path that we actually gain more than if the path was easy."

Otto's fulfilling personal life has been a key ingredient for her professional success.

"Without my passion for excitement and adventure [outside the lab], my passion for science and healing would not be as complete or as rewarding."

True to her blended background (see sidebar), Otto's ultimate goal is to translate laboratory discoveries into improved care for patients.

"What I'm especially passionate about is the ability to take what I'm doing in the lab, bring it into dogs, and eventually use it to treat people," she says. ■

A Rare Breed

Restarting the heart of a dog in cardiac arrest, discovering cellular secrets of sepsis, and lecturing around the globe are all part of the job for veterinarian Cynthia Otto (see main story). Otto is among a special group of scientists who conduct laboratory research and also treat patients.

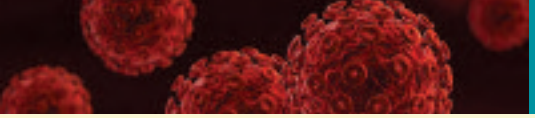
These health professionals blend the objective, rigorous methods of laboratory research with the intuition and experience necessary to practice medicine. Their integrated training and approach empower them to investigate an issue at many levels, deepening their understanding of the problem and its possible solutions.

"My work is translational," Otto says. "I look at the basic cellular level and take [that knowledge] all the way up to disease."

If Otto sees something mysterious in her patients, she knows how to design experiments that will shed light on the problem. Conversely, she can look at a research paper that seems esoteric to some physicians or veterinarians and know immediately what implications it could have for two- or four-legged patients.

Otto also thrives on the variety of two very different jobs. In the clinic, she gets instant gratification and an adrenaline rush, while her research provides the long-term satisfaction of helping to solve far-reaching medical problems.

"If I just did one, I think I'd go nuts," she says. "I need the balance of the two."—*A.Z.M.*



Bench to Bedside

These stories describe NIGMS-funded medical research projects. Although only the lead researchers are named, scientists work together in teams to carry out these studies.

Traumatized T Cells

Automobile accidents, gunshot wounds, and other forms of severe physical trauma make up the leading cause of death for Americans 40 and younger.

New research may improve recovery for people who suffer massive trauma.

Those who survive the initial injury can still suffer serious complications or die later. This is mainly because the human body does not have a reliable strategy for responding to massive trauma.

Most often, the trouble seems to be that the body's own protective immune system works too hard to recover from a serious injury. Researchers know that the resulting disruption of the healthy balance of immune system cells is a trigger for widespread disaster. T cells, in particular, shut down and cannot bolster the body's fight back to health.

Now, immunologist **Carol Miller-Graziano** of the University of Rochester Medical Center in New York has obtained results that help explain the T cells' rapid demise. Miller-Graziano and her team sampled blood from about 20 trauma patients whose organs were failing, as well as from the same number of healthy volunteers.

The scientists then separated T cells from other blood cells in order to identify changes specific to the vulnerable T-cell population. Using an automated approach that could map the activity of all T-cell genes simultaneously, Miller-Graziano found 338 that behaved quite differently in trauma patients.

The findings point to molecular signals after trauma that weaken T cells and send the immune system awry. Finding ways to reverse those signals may offer an opportunity to improve recovery from trauma. —*Alison Davis*

Resisting AIDS Resistance

Every year during the 1980s and early 1990s, AIDS claimed the lives of roughly half a million people between the ages of 25 and 44. The terrible death toll began to diminish in 1995, when scientists came up with a breakthrough treatment. The critical component of this life-saving therapy was a new drug called a protease inhibitor that targeted HIV, the virus that causes AIDS.

While this discovery was groundbreaking, it was only a partial fix, and a quarter century after the first cases of AIDS appeared, the disease still kills more than 15,000 Americans every year and millions more across the globe.

The problem is that HIV rapidly learned to "outsmart" protease inhibitors by constantly mutating, or shuffling, its genes. These genetic mutations alter the physical structure of the virus, which allows it to survive the effects of HIV-killing medicines.

Score another one for the scientists. Chemist **Arun Ghosh** of Purdue University in West Lafayette, Indiana, has crafted a drug that HIV cannot counterattack. Ghosh designed a molecule that attacks the HIV protease "backbone," a part of the virus structure that remains basically unchanged as the virus' genes mutate.

The drug was first tested in animals and then shown to be safe for use in human patients. In June 2006, the U.S. Food and Drug Administration approved it as an AIDS treatment, now marketed as Prezista™.

Ghosh's work provides a new treatment option for the 40 million people worldwide who are infected with HIV.—*A.D.*

Worm Sperm Illuminate Male Infertility

Problems with sperm are the most common causes of male infertility, which accounts for about 30 percent of all cases of reproductive failure in the United States.

Sperm may be immature, abnormally shaped, or unable to move properly. Sometimes, sperm are produced in very low numbers or not at all. Scientists do not understand the root causes of many of these issues that affect a man's ability to father a child.

Male infertility is often caused by abnormal sperm that cannot fertilize an egg.

In a study supported by a National Institute of General Medical

Sciences Minority Opportunities in Research program, San Francisco State University biologist **Diana Chu** and her team used roundworms to unravel the mystery. Like human sperm, worm sperm is packaged into bundles of protein and DNA.

Working with **Barbara Meyer** at the University of California, Berkeley, Chu used chemical techniques to isolate the worm sperm proteins, more than a thousand in all. Chu then used a powerful microscope to view the proteins that associate with worm sperm. After follow-up study, she found several that appear to be important for keeping the sperm healthy.

Chu and Meyer generated a list of 132 worm proteins that are critical for the worms' ability to reproduce. Over half of those proteins have human versions that have never before been tested for their roles in infertility.

The findings offer a promising resource for finding new infertility treatments and birth control approaches for men.—*A.D.*

Protein Linked to Cleft Lip and Palate

A developing child's face takes shape in early pregnancy, as the upper lip and palate (the roof of the mouth) grow together on either side of the tongue. When these tissues don't meet up properly, a gap remains. This is called cleft lip and/or cleft palate.

Surgery can often repair the facial structure of a child born with this condition. However, scarring can be a problem, as can difficulties with eating and speech.

Researchers believe that, like many birth defects, cleft lip and cleft palate are caused by both hereditary and environmental factors, and scientists have already identified several suspect genes. Now, geneticists **Cynthia Morton** and **Richard Maas** of Brigham and Women's Hospital in Boston, Massachusetts, have provided an important clue that may help explain previous findings.

Morton and her team examined DNA from a blood sample obtained from a 5-year-old child born with a cleft lip and palate but no other known health problems. The scientists noticed an abnormal chromosome in the child's cells; it contained a gene that had been split. Since genes provide the instructions for making proteins that do important jobs in the body, a broken gene usually results in a protein that doesn't work properly or at all.

More experiments revealed that this gene normally produces a protein that acts as an activation switch for other proteins known to be important for formation of the lip and palate.

Further study of how these proteins interact to produce the birth defect will help scientists better understand, diagnose, and treat it.—*A.D.*

Will Fight for Food

From birth to death, our lives follow a complicated recipe of nature and nurture. While heredity affects our personality and health, how we live—our environment—plays a huge role as well. Nonetheless, identifying genetic traits that influence our actions may help us learn how to manage unhealthy behaviors.

ED KRAVITZ

"High aggression" fruit flies resort to boxing over territory and food.

One way researchers are studying genes and behavior is by using model organisms that have similar genes and biochemistry to people. Recently, behavioral geneticist **Trudy Mackay** of North Carolina State University in Raleigh used fruit flies to look for genes that might be linked to aggression.

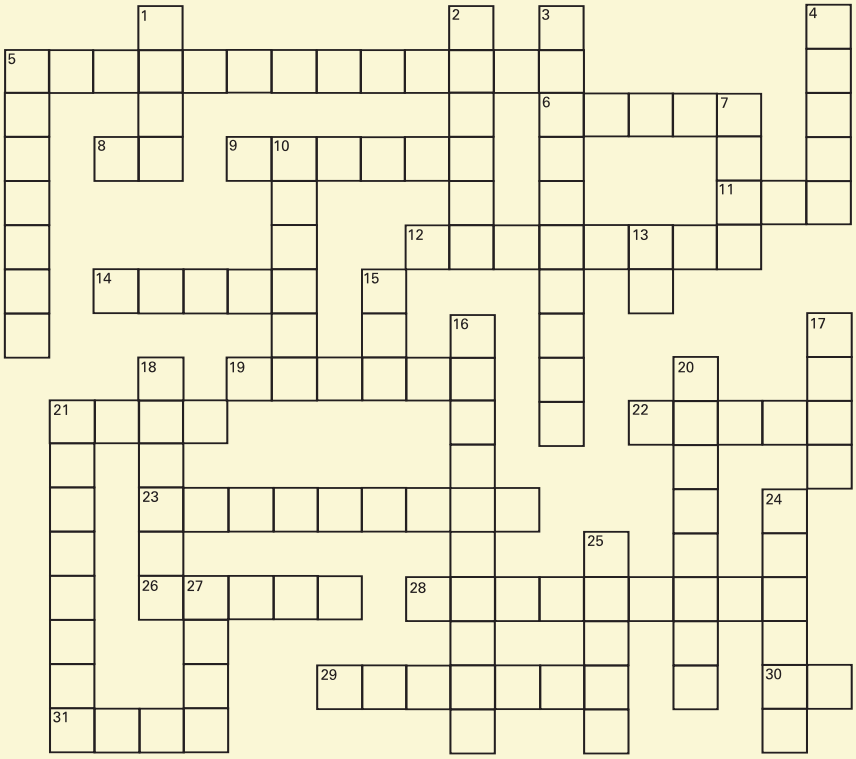
Hungry flies will battle over food—kicking, chasing, and boxing their peers in an effort to get their fair share. Some fight vigorously, whereas others are quite polite. The fact that different fly strains vary considerably in this behavior told Mackay that it might be at least partially inherited.

To learn more, she assembled three groups of flies of high, low, and average aggression. Mackay bred the groups of flies separately for 28 generations, choosing the most aggressive males in the "high" group and the least aggressive males in the "low" group to start each new generation. This step enriched the population for genetic variants that make flies more or less feisty.

Since the flies' behavior changed little over a period of about a year, Mackay deduced that only a small component (about 10 percent) of the variation in aggression could be attributed to variation in genes.

Although small, that 10 percent may hold significant clues toward understanding the biology of aggression. In follow-up experiments, Mackay found 15 fruit fly genes clearly linked to aggressive behavior. Several of the genes have counterparts in humans, which may help scientists understand such behavior in people.—*A.D.*

The Last Word



ACROSS

5. virus that infects bacteria
6. not here
8. gaseous substance and chemical messenger
9. leading cause of death
11. do, yesterday
12. database
14. funny teaching tool
19. what Endy builds
21. synthetic biology contest
22. lung, for example
23. made by humans
26. egg's partner
28. smallest blood vessel
29. oxygen lack
30. ambulance destination
31. pickle flavor

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

DOWN

1. research vet Cynthia
2. roof of the mouth
3. related to the care of animals
4. bronze medal place
5. take in air
7. synthetic biologist Drew
10. save from danger
13. one bacteriophage
15. also
16. breathing machine
17. air organ
18. life-threatening body-wide illness
20. AIDS drug target
21. not actual
24. component of air
25. dirt-free
27. swimming spot

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