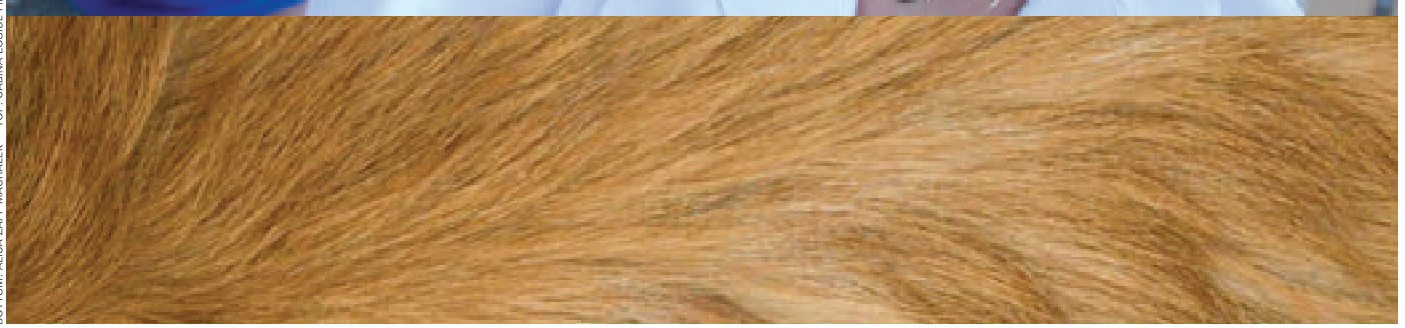
Dogging Sepsis



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.

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.

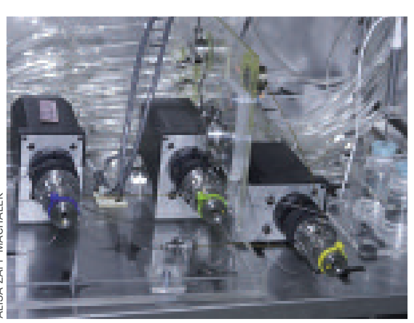
To begin investigating this idea, she tracked NO back to where it is produced—in macrophages. When these white blood cells encounter toxic bacterial products or when they are deprived of oxygen, both of which occur early in sepsis, they ramp up production of the enzyme that makes NO.

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



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.

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.

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.

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.

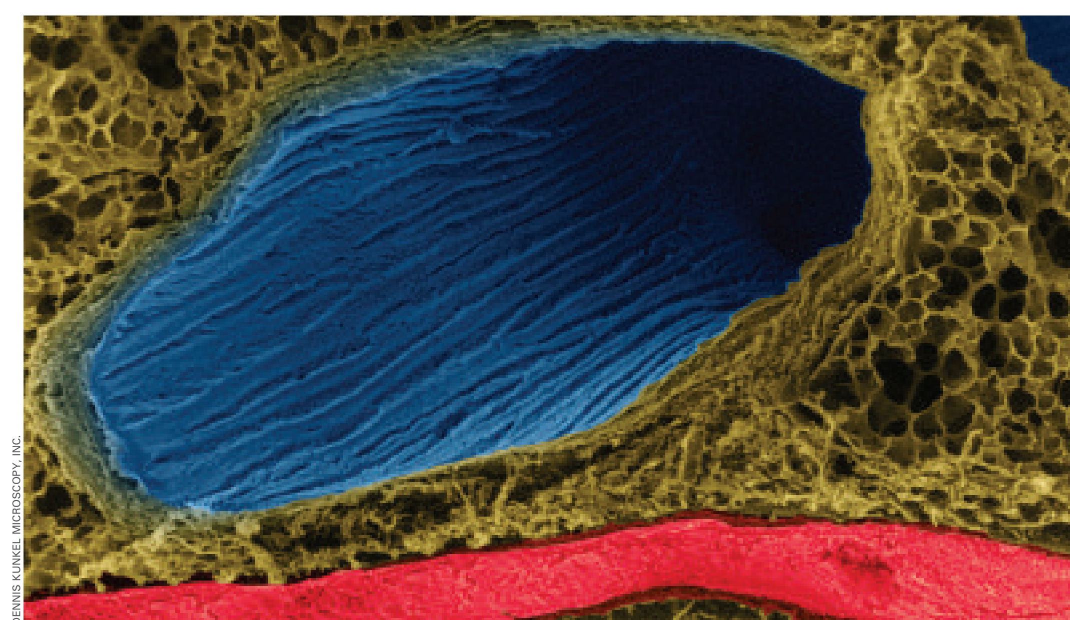
Dog Detectives

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.*