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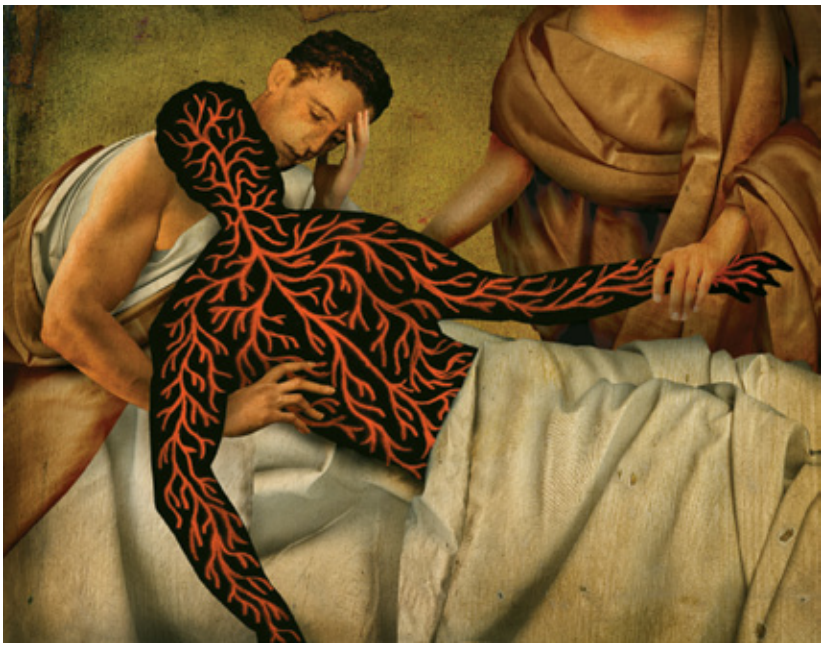

Shock to the System

During sepsis, the body attacks itself. Researchers are working on new ways to fight back

Sepsis is a serious and often deadly illness, yet it remains an unfamiliar threat to most of the general public, as well as one of the most difficult diseases for doctors to diagnose and treat. The condition, which begins with an aggressive immune system reaction to an infection, kills 18 million people around the world every year, including around 260,000 in the U.S. By many estimates, sepsis—and its most severe form, septic shock—is the leading cause of death for intensive care patients in the U.S. and the 10th most common cause of death for everyone else in the country. Yet only one in five Americans recognizes the term, according to a 2011 study commissioned by the nonprofit group Sepsis Alliance, and of those survey participants who had heard of sepsis, most could not define it.

Even physicians, who learn about sepsis in medical school, often miss its early signs because they mimic other disorders and because the illness progresses so rapidly from what looks like a mild infection to a life-threatening situation. As a result of these difficulties, doctors are often late to launch the necessary interventions, such as antibiotics to obliterate the infection, drugs to counteract a perilous drop in blood pressure, and a mechanical ventilator to raise dangerously low oxygen levels.

"The timing of antibiotics is a critical determinant for whether someone lives or dies," says James O'Brien, who is medical director of quality and patient safety at Riverside Methodist Hospital in Columbus, Ohio, and serves as an adviser to Sepsis Alliance. But some of the most compelling data out there, he says, shows that only 50 percent of patients with septic shock get appropriate antibiotics within six hours of first being seen by a health professional. "If we had a similar record with getting heart attack patients to the catheterization lab, there would be an uproar," he adds.

To further complicate the picture, better treatments have been slow in coming. Some are on the horizon—such as an experimental blood test and filtration therapy—but failure of four potential antisepsis drugs in the past two years has discouraged researchers and advocates alike. Carl Flatley, a retired dentist, founded Sepsis Alliance after his daughter died of the syndrome in 2002. "In the 10 years since, we have lost 2.5 million people to this [in the U.S.], and it could take another 10 years before we have something that works," he says. "We need to move faster."

CHEMICAL CASCADE

SEPSIS BEGINS INNOCUOUSLY ENOUGH when the immune system performs its usual task of recognizing invading bacteria, viruses or fungi. Immune cells release signaling proteins called cytokines to stimulate one another and overcome the invaders—but for poorly understood reasons, the immune cells release far more cytokines and other inflammatory molecules than is typical. All the extra immune molecules surging through the bloodstream have the inadvertent effect of making blood vessels slack and permeable, reducing blood pressure and allowing the fluid component of the blood to seep into surrounding tissues. The blood components left behind clot in the smallest vessels, preventing oxygen from reaching major organs. At this point, someone with sepsis has transitioned from the earliest stage of the disease, known as systemic inflammatory response syndrome, to the later stages of severe sepsis and septic shock. Confusion sets in, the heart's electrical activity becomes erratic, the kidneys and other organs fail, and blood pressure cannot be raised even with large amounts of intravenous fluids and drugs.

Because the immune system's reaction is responsible for

Illustration by Shannon Freshwater

the destructive progression of sepsis, researchers have tried using various drugs to interrupt the chemical cascade that triggers inflammation and clotting. Recent attempts have been disappointing.

In January 2011 the highly anticipated drug eritoran, made by Tokyo-based Eisai, was withdrawn after clinical trials showed no benefit in comparison with a placebo in preventing sepsis deaths. By October of that year the drug that eritoran had been intended to compete with—Xigris, made by Eli Lilly—was withdrawn from sale 10 years after being licensed by the U.S. Food and Drug Administration because mandatory postmarketing studies showed no benefit to patients. In February 2012 Agennix in Munich, Germany, halted studies that applied its existing cancer drug, talactoferrin, to sepsis after the number of deaths among patients receiving it in rigorous clinical trials turned out to be greater than the number of deaths among placebo recipients. Later that year, in August, research into the new drug CytoFab was canceled by partners AstraZeneca and BTG after an early trial showed no effect greater than a placebo.

All those drugs were predicted to be billion-dollar blockbusters if they had proved effective against sepsis, but instead they cost their creators millions in foregone research and canceled trials. As a result, "I think the big companies have given up," says Richard P. Wenzel of Virginia Commonwealth University, a longtime sepsis researcher.

How did such a diverse array of compounds, from so many different companies, fail? Investigators have suggested several reasons. A 10-year study published online in February revealed serious flaws in the animal research on which sepsis drug trials were based. Severe inflammatory responses in mice, it turns out, do not accurately mimic sepsis in people—so a drug that helps mice could make things worse for a person. In addition, patients in sepsis trials may have been too sick to respond well to any drug. Because sepsis patients are seldom diagnosed early, by the time they are enrolled in a trial they are likely to be more challenging to treat. Furthermore, people with sepsis may not all be sick in exactly the same way, so individuals may respond quite differently to the same compound.

"Where we are currently is similar to diagnosing people with 'cancer' without giving them any further information—not that they have leukemia, not what cell type, not what molecular abnormalities are present," O'Brien explains. "'Sepsis' is a bucket that contains different groups of patients. We have not done the groundwork of separating out their underlying pathophysiology."

NEW IDEAS

DESPITE THE MANY DISAPPOINTMENTS, researchers continue to search for treatments that could halt sepsis before it becomes deadly. Spectral Diagnostics in Toronto, for example, pairs a diagnostic blood test with a therapeutic device. The test looks for endotoxin, a molecule that is released from dying bacteria and can trigger the start of sepsis. About 50 percent of sepsis patients, often the most critically ill, have high levels of endotoxin in their blood. Blood is drawn from these patients and pumped over a filter infused with an antibiotic that binds to endotoxin, removing the molecule before the blood is returned to patients. The FDA has approved the test (the filter already existed, and Spectral has licensed it), and the combination of diagnostic and device is currently being tested in 14 U.S. states and in Canada in a large trial.

Spectral acknowledges that its treatment, even if successful, would not help patients who do not have high levels of endotoxin. But "if our trial turns out positive, we could potentially save 50,000 lives per year," says Paul Walker, Spectral's chief executive officer and a critical care specialist.

Richard Hotchkiss, who is a professor of anesthesiology, medicine and surgery at the Washington University School of Medicine in St. Louis, has proposed a very different approach—not just to treatment but to the whole way of thinking about sepsis as well. He sums up his view of the current research landscape as: "Just because you're traveling down a well-worn path doesn't mean you're heading in the right direction."

Although current dogma explains sepsis as a sustained, excessive inflammatory response, Hotchkiss bases his approach on evidence to the contrary. His studies, which include examination of cells extracted from patients soon after death, suggest that the symptoms of sepsis persist because during the course of the illness, the immune system shifts from an overreaction to a kind of collapse—instead of doing too much, it does too little. If that is correct, Hotchkiss says, then immune-stimulating compounds such as interleukin-7, which are already used in cancer treatment, could prevent deaths from sepsis—an idea that traditional sepsis researchers might view as adding fuel to a fire.

With no new drugs on the horizon, some investigators urge a shift in focus from discovering pharmaceutical treatments to the importance of critical care, improved long-term care and increased public awareness. They point out that while the death rate from sepsis remains high, it has decreased over time, not because of new treatments for sepsis but because doctors have in general become better at saving the lives of critically ill patients. Clinicians should pay more attention to the four fifths of sepsis patients who survive, some researchers argue. Many survivors have profound disabilities, such as amputated limbs, blindness and cognitive problems. O'Brien, the Sepsis Alliance adviser, emphasizes that public awareness encourages early recognition, which greatly enhances the chances of recovery. SA

Early Warning Signs

A diagnosis of sepsis requires at least two of these symptoms, as well as a suspected or confirmed infection of bacteria, viruses or fungi. The earliest symptoms of sepsis often mimic a mild infection, but the disease can worsen swiftly, ravaging the body.

- ✓ **Quickened breathing** (respiratory rate > 20 breaths/min)
- ✓ **Increased heart rate** (> 90 beats/min)
- ✓ **Unusually high or low core body temperature** (< 36° Celsius or > 38° C)
- ✓ **Unusually high or low numbers of white blood cells**

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