

Health & Medicine

Suspended Animation

Hibernation could be the key to surviving a trip to the ER.

by Alex Stone

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When 35-year-old Mitsutaka Uchikoshi was found last October lying in an ice-cold field on Japan's Rokko Mountain, a bucolic hiking spot north of Kobe, he was presumed dead. He had no detectable pulse or respiration, and his body temperature was 71 degrees Fahrenheit, 27 hatch marks shy of normal. While returning alone from a party on the mountain, Uchikoshi had stumbled and hit his head; he spent the next 24 days sprawled unconscious in the frigid air, without food or water. But when he arrived at Kobe City General Hospital, something remarkable occurred: [He woke up](#). To the astonishment of the doctors who treated him for severe hypothermia and blood loss, Uchikoshi made a full recovery without a trace of brain damage. "I was in a field, and I felt very comfortable. That's my last memory," he told reporters before walking out of the hospital.

Freak survival stories like Uchikoshi's pop up every so often in the news. In May 1999, a female Norwegian skier was submerged in icy water for over an hour and deemed clinically dead—no heartbeat, no respiration, and a core temperature of 57°F—only to snap back to life in the hospital. In February 2001, doctors revived a [Canadian toddler](#) whose heart had stopped beating for nearly two hours and whose body had cooled to 61°F after she wandered outside, unnoticed, on a freezing night. These strange tales hint at what was, until quite recently, an underappreciated facet of our nature. Humans, it seems, can hibernate.



By exposing mice to toxic hydrogen sulfide gas, molecular biologist Mark Roth triggers a latent hibernation response that seems to exist in all mammals.

Photo courtesy of Dean Forbes

These death cheaters survived by entering a state of suspended animation, in which the machinery of life temporarily comes to a grinding halt. Far more than a biological

curiosity, suspended animation has the makings of a powerful medical tool. In the past five years, labs around the country have begun artificially inducing this state by cooling animals to ultralow temperatures, pumping them full of fake blood, and plying them with toxic gases in order to reversibly arrest life's basic processes. Human tests are now just around the corner. If successful, they will pave the way for a revolution in trauma care that could save the lives of thousands of patients—suffering heart attacks, strokes, or near-fatal injuries—who would survive if only there were a way to shut down the body long enough to reach the operating room.

Two summers ago, anesthesiologist [Patrick Kochanek](#) of the Safar Center for Resuscitation Research at the University of Pittsburgh dramatically demonstrated the power of suspended animation. He and his team [revived dogs](#) that had been clinically dead for three hours—with no heartbeat, no breathing, and no brain activity. The researchers discovered they could preserve a dog in limbo for several hours by cooling the animal and flushing its veins with a chilled solution of salt, glucose, and dissolved oxygen. The dogs came back to life after they were given a blood transfusion and reheated, although a few of them experienced minor brain damage.

To [the horror of](#) the Safar scientists, the [tabloid press](#) responded to this work with morbid glee, publishing ghoulish stories about “[zombie dogs](#)” alongside images of werewolves. Such slavering was perhaps unsurprising, given that suspended animation has often been associated with sci-fi images of astronauts hibernating in pods en route to distant stars. In the late 1960s and 1970s, NASA even [funded research](#) on halting metabolic activity during long-duration space travel but abandoned the effort after it was deemed technologically unfeasible. These days it is the United States military and the National Institutes of Health that finance such research, with the Safar group—which now hides behind a cloak of silence—being one of the grantees.

Following a similar approach, an independent group of trauma surgeons at Massachusetts General Hospital, led by Hasan Alam, recently completed a successful series of experiments in human-size Yorkshire pigs. In the study, Alam anesthetized the pigs, removed 60 percent of their blood, and using scalpels, inflicted injuries that would ordinarily be fatal—lacerating solid organs and rupturing their aortas—to simulate wounds a person might suffer in a car accident or a shooting. The animals quickly went into shock. “In a human with this combination of injuries and blood loss, survival would be close to zero,” Alam says.

The animals would also have died had the surgeons not initiated a procedure similar to that used by the Safar Center. For 20 minutes, the pigs were cooled to 50°F and their veins pumped full of an icy organ-preservation fluid known as a plasma expander, a mélange of electrolytes and antioxidants that mimic fluids found naturally in cells. As a result, the animals entered a state of profound quiescence indistinguishable from death. “There was no heartbeat, no blood flowing, and no electrical activity in the brain,” Alam says. He then repaired the injuries and [revived the animals](#) by slowly raising their temperature back to normal. The pigs remained at the lip of death for nearly three hours, yet in repeated studies they emerged from their torpor without any cognitive impairments.



A mechanical ventilator at Massachusetts General Hospital is used by trauma surgeons to revive pigs from a state of suspended animation.

Photo courtesy of Alex Stone

Alam admits to being awed by his seemingly miraculous ability to resuscitate the animals. “There have been seven different studies, and they’ve all been successful,” he says. “In injuries that would ordinarily be fatal, I can save the animals over 90 percent of the time.” Yet the science underlying this miracle is rather straightforward. In essence, suspended animation is an exercise in basic economics at the biological level. Life demands oxygen, and without enough of it the body dies. In the case of severe trauma—from massive blood loss, say—oxygen supply falls while demand remains high. When deprived of oxygen, the average person will suffer brain damage within 5 minutes, and death follows in another 15 minutes.

Cooling the body is a way to restore the balance between oxygen supply and demand by slowing metabolic activity and thus curtailing oxygen needs until the supply can return to baseline. Low temperatures have long been known to depress the body’s metabolic rate. Organs intended for transplant are stored on ice during transport—a stopped heart can be preserved this way for up to four hours—and neurosurgeons routinely cool the brains of stroke patients during surgery to minimize damage. Alam’s team and the Safar group have shown how to extend this concept to the whole organism.

The crucial next step is to test suspended animation in humans, and Alam has teamed up with the Safar group to design a clinical trial that will bring the procedure to hospitals in the United States. Informed consent is by far the thorniest issue because the procedure can be tested only on people who are mortally wounded. “When a person is bleeding to death, it is not an appropriate time to get them to sign forms,” Alam says. To have a meaningful test sample, the researchers would therefore need to obtain pro forma compliance from all (or at least a substantial fraction) of the residents of a host city. That would require an extensive public education campaign—“a challenging undertaking,” Alam admits, but not an impossible one; other researchers have cleared similar hurdles. An alternate and even more outlandish approach to suspended animation involves not cooling the body but poisoning it, a tactic being pursued by molecular biologist [Mark Roth](#) and his colleagues at the Fred Hutchinson Cancer Research Center in Seattle. A tour of his lab—a space crammed with ventilated walk-in fume hoods, state-of-the-art security sensors, hoses, flasks of bubbling water, and a network of metal tubes—quickly reveals why so few scientists do this sort of research. His facility houses tanks containing some of the world’s most toxic gases—cyanide, phosphine, carbon monoxide, hydrogen sulfide—hermetically sealed inside computer-controlled glass cabinets. “These are very, very toxic to humans and would kill them immediately,” Roth warns.

Broadly speaking, Roth's work taps into the same biological tricks that the Safar and Alam teams exploit, though in a distinctly different way. For Roth, the key is not to induce hypothermia but to provoke a state resembling hibernation. Hibernating animals drastically reduce their metabolic rates and thus their need for oxygen. Conversely, by depriving his experimental subjects of oxygen, Roth reasoned he could put them into an artificial state of hibernation. Early results in the roundworm *Caenorhabditis elegans*, [reported by Roth](#) in 2004, bolstered this notion. He found that placing the worms in an atmosphere with an oxygen concentration of just .001 percent or less triggers a condition in which all of their biological activity shuts down for up to two days. By contrast, the worms normally suffocate at a far less austere oxygen concentration of .1 percent; ordinary room air is 21 percent oxygen.

At the heart of this paradox is a process called [oxidative phosphorylation](#), by which cells produce energy. Cells require oxygen to make molecules of adenosine triphosphate, or ATP, the primary fuel of life. When oxygen falls below an optimal level, energy production goes haywire, and destructive molecular fragments known as free radicals are released instead. Roth's term for this fatal middle zone is evil oxygen tension. But in a world almost completely devoid of oxygen, oxidative phosphorylation stops, and the animal simply rests. "This is something we hadn't expected," he says. "If you have some oxygen, you're dead. But if I take away that little bit of rope you're using to hang yourself, then you're alive again."

Roth set out to find a means to induce oxygen deprivation while bypassing evil oxygen tension. One day he recalled a documentary he had seen about a [Mexican cave system](#) with extremely high levels of hydrogen sulfide, a toxic gas that smells like rotten eggs. Without a respirator, anyone entering the cave would fall unconscious after one breath and die within a few minutes. But during those few minutes, he hypothesized, they would enter a trance similar to that of the roundworms. To test his theory, Roth tried hydrogen sulfide on brown lab mice and was stunned by the outcome. Under the influence of the gas, the animals experienced a precipitous drop in respiration—down to four breaths per minute—and consumed only one-tenth as much oxygen as usual. The mice could linger in this Zen-like stasis for hours before the air was turned back on and were normal in every respect when they finally woke up.

A video of one of the nine-hour-long experiments, sped up 30-fold, initially shows a brown mouse darting manically about its quarters, sniffing and munching its rations. Next comes the dose of hydrogen sulfide. The animal collapses, lying motionless in the straw without so much as a shudder or twitch. Finally, the air is turned back on, and—voilà—the mouse is back to sniffing and munching. Remarkably, while in the resting phase, the mouse's core temperature drops to match that of the environment, a cool 57°F in this case. "I'm cooling the body in order to slow down metabolic rate," Alam says. "Roth is slowing metabolic rate, and the temperature comes down as a by-product."

In the future, ambulances and trauma wards could routinely include equipment needed to maintain life in a state of suspension until surgeons can repair the damage.

Like oxygen deprivation, hydrogen sulfide retards metabolic activity by tweaking the body's main power-generating apparatus. Oxidative phosphorylation is mediated by an enzyme called cytochrome c oxidase, which binds to oxygen and shuffles its electrons around to produce molecules of ATP. But hydrogen sulfide, which is chemically similar to oxygen, attaches itself to cytochrome c oxidase with even greater affinity. In fact, the body naturally produces trace quantities of hydrogen sulfide to help regulate metabolism.

At higher concentrations—just beneath the toxic threshold—the gas induces a latent hibernation response that appears to reside in all mammals, including humans.

With this in mind, Roth figured he could keep animals alive in a severely oxygen-sparse environment by simply reducing their respiratory demand. Following this logic, he put mice in a vessel of 5 percent oxygen, a level at which the animals die in less than 15 minutes. But before locking the mice in the chamber, Roth gave them a 20-minute hit of hydrogen sulfide, to rein in their metabolism and reduce oxygen needs. The results were astounding: All the mice survived in experiments that ran for hours. “We have done this for six hours, and we don’t lose any of them,” he says. “We just stop the experiment because we get bored.” As in the previous study, the rodents are no worse for wear.

Based on this track record, Roth has cofounded [Ikaria](#), a company that will try to apply these techniques to humans. Ikaria has already shown that sulfide-induced hibernation works in pigs and dogs, animals physiologically similar to humans, and has a marked clinical benefit when used to treat injuries in these animals. “We’re developing a variety of formulations and testing them in appropriate large-animal models of human disease with an eye on taking one or two of them into the clinic in the near term,” says Steve Gillis, the company’s CEO.

It is difficult to overstate the impact these techniques could have on health care, particularly in the treatment of patients with severe injuries. Be they from car crashes, falls, exposure, or work-related incidents, [accidents are the fifth-leading cause of death](#) in America and the number one killer of people under age 44, [resulting in more than 49,000 deaths](#) a year. The Centers for Disease Control estimates that the 50 million new injuries seen annually cost up to \$406 billion to treat. In the vast majority of cases, terminally wounded patients die either on their way to the emergency room or soon after getting to the hospital because they bleed to death before receiving proper surgical care.

In the future, ambulances and trauma wards could routinely include equipment needed to maintain life in a state of suspension until surgeons can repair the damage. “If you get in a car accident today, what are they going to do? Call 911 and put you in an ambulance with a breathing tube and an IV and drive as fast as they can,” Alam says. “Once you get to the hospital, there are not many things we can’t fix anymore. The problem is that by the time most people get to the hospital, it’s too late.” Cooling equipment and portable sulfide gas masks could greatly improve survival rates among critically wounded patients by forestalling blood loss, cellular breakdown, and the buildup of toxins—ravages that trigger permanent disability and death. “If we can slow down life processes so that you don’t require oxygen and the entire body is preserved for a few hours, that buys us precious time to fix the injuries,” Roth says.

These methods would nonetheless entail a radical departure from conventional medical practice. Roth argues for a new philosophy to accompany a new standard of care. “Really, there is alive and there is dead, and then there is a third space which is neither alive nor dead,” he says. “We can call it potentially alive but at the moment not alive.” As medicine steadily encroaches on the dreams of science fiction, visits to this liminal space may one day seem no more unusual than a trip to the emergency room.