# Buying Time Through 'Hibernation on Demand'

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Scientists at Fred Hutchinson Cancer Research Center have, for the first time, induced a state of reversible metabolic hibernation in mice. This achievement, the first demonstration of "hibernation on demand" in a mammal, ultimately could lead to new ways to treat cancer and prevent injury and death from insufficient blood supply to organs and tissues. "We are, in essence, temporarily converting mice from warm-blooded to cold-blooded creatures, which is exactly the same thing that happens naturally when mammals hibernate," said lead investigator Mark Roth,

Ph.D., whose findings will be published in the April 22 issue of *Science*.

"We think this may be a latent ability that all mammals have — potentially even humans — and we're just harnessing it and turning it on and off, inducing a state of hibernation on demand," said Roth, a member of Fred Hutchinson's Basic Sciences Division.

During a hibernation-like state, cellular activity slows to a near standstill, which reduces dramatically an organism's need for oxygen. If such temporary metabolic inactivity — and subsequent freedom from oxygen dependence — could be replicated in humans, it could help buy time for critically ill patients on organ-transplant lists and in operating rooms, ERs and battlefields, Roth said.

"Manipulating this metabolic mechanism for clinical benefit potentially could revolutionize treatment for a host of human ills related to ischemia, or damage to living tissue from lack of oxygen," said Roth, also an affiliate professor of biochemistry at the University of Washington School of Medicine.

Collaborators on the research included first author Eric Blackstone, a graduate research assistant in Roth's laboratory and a member of the joint Fred Hutchinson/University of Washington Molecular and Cellular Biology Program; and co-author Mike Morrison, Ph.D., a staff scientist in Roth's lab.

Clinical applications of induced metabolic hibernation could include treating severe blood-loss injury, hypothermia, malignant fever, cardiac arrest and stroke.

The potential medical benefits also include improving cancer treatment by allowing patients to tolerate higher radiation doses without damaging healthy tissue. Cancer cells, Roth explained, aren't dependent on oxygen

to grow. As a result, they are more resistant to radiation than surrounding healthy cells, which need oxygen to live. Roth hypothesizes that temporarily eliminating oxygen dependence in healthy cells could make them a less-vulnerable target for radiation and chemotherapy and thus spare normal tissue during high-dose cancer therapy.

"Right now in most forms of cancer treatment we're killing off the normal cells long before we're killing off the tumor cells. By inducing metabolic hibernation in healthy tissue we'd at least level the playing field," he said. The delivery of such treatment could be as simple as an intravenous infusion of saline solution mixed with trace amounts of an agent that would interfere with the body's ability to use oxygen, Roth said.

Using oxygen deprivation to depress metabolic activity also might extend the amount of time that organs and tissues could be preserved outside the body prior to transplantation, Roth said. Yet another potential application of oxygen deprivation would include accelerating wound healing in patients, such as diabetics, whose ability to do so is compromised. This could reduce the number of amputations caused by irreparable tissue damage from wounds that won't heal. A wound to the skin allows the entry of oxygen, which initiates cell death. In healthy people, cell death subsides when a clot forms, which allows the healing process to begin. Exposing a diabetic's clot-resistant wound to an oxygen-free environment would speed the healing process.

While the notion of putting a human or a human organ into an oxygen-free state of biological limbo and then reversing the process at will with no ill effects may sound like science fiction, dozens of documented cases exist of humans surviving prolonged hibernation-like states with no lingering physical or neurological damage. For example:

-- In May 1999, a female Norwegian skier was rescued after submersion

in icy water for more than an hour. When rescued she was clinically dead with no heartbeat, no respiration, and her body temperature had fallen to 57 degrees Fahrenheit (normal is 98.6 F). She was resuscitated and since has made a good physical and mental recovery.

-- More recently, in February 2001, Canadian toddler Erika Nordby made headlines around the world — and a complete recovery — after she wandered outside at night and nearly froze to death. Before she was resuscitated her heart had stopped beating for two hours and her temperature had plunged to 61 F.

"Understanding the connections between random instances of seemingly miraculous, unexplained survival in so-called clinically dead humans and our ability to induce — and reverse — metabolic quiescence in model organisms could have dramatic implications for medical care," Roth said. "In the end I suspect there will be clinical benefits and it will change the way medicine is practiced, because we will, in short, be able to buy patients time."

In the Science paper, Roth and colleagues report inducing a state of clinical torpor in mice for up to six hours before restoring their normal metabolic function and activity.

They achieved this by placing the mice in a chamber filled with normal room air laced with 80 parts per million of hydrogen sulfide, a chemical normally produced in humans and animals that is believed to help regulate body temperature and metabolic activity.

Within minutes of breathing the hydrogen sulfide and room-air cocktail, the mice stopped moving and appeared to lose consciousness, their respiration dropped from the normal 120 breaths per minute to fewer than 10 breaths per minute, and their core temperature dropped from the normal 37 degrees Celsius to as low as 11 C, depending on the controlled

ambient temperature within the chamber.

"We have, on demand, reversibly demonstrated the widest range of metabolic flexibility that anyone has ever seen in a non-hibernating animal," Roth said.

"The cool thing about this gas we're using, hydrogen sulfide, is that it isn't something manufactured that we're taking down from a shelf — it isn't 'better living through chemistry' — it's simply an agent that all of us make in our bodies all the time to buffer our metabolic flexibility. It's what allows our core temperature to stay at 98.6 degrees, regardless of whether we're in Alaska or Tahiti," Roth said.

In addition to mice, Roth and colleagues in previously published work have demonstrated the ability to metabolically arrest — and subsequently re-animate — such model organisms as yeast and worms, as well as the embryos of fruit flies and zebrafish.

In each case they achieved metabolic suspension through oxygen deprivation caused by exposure to gases such as hydrogen sulfide and carbon monoxide. Known as oxygen mimetics, these chemicals are very similar to oxygen at the molecular level and so bind to many of the same receptor sites. As a result, they compete for and interfere with the body's ability to use oxygen for energy production - a process within the cell's power-generating machinery called oxidative phosphorylation. The inhibition of this function, in turn, is what the researchers believe causes the organism to shut down metabolically and enter a hibernation-like state. In each case, upon re-exposure to normal room air, the organisms quickly regained normal function and metabolic activity with no long-term negative effects.

If Roth and colleagues are able to replicate these findings in larger animal models, they foresee the first clinical use of this technology in

humans could involve treating people suffering from severe fevers of unknown origin. Currently, when a person comes to an ER with such a fever they run the risk of brain-damaging seizures during the crucial time it takes to diagnose the bacterial or viral cause and administer the proper antibiotic.

"Here's a patient group, quite commonly found in emergency rooms around the country, who would do well if they could just have their core body temperature taken down in order to buy them time until the pathology reports come back and they can get on the right course of treatment," Roth said. "Today, physicians have no way of dealing with uncontrolled fever other than literally putting people on ice. Well, we believe we know how to flip the breaker on the patient's furnace; if they have a fever, we believe we know how to stop it on a dime." Roth anticipates that such clinical trials in humans could be under way within about five years.

Source: Fred Hutchinson Cancer Research Center
(Thanks, ***DataHaunt***)