

## Science awakens to the possibilities of human hibernation

by Scott LaFee

In December, a 35-year-old Japanese man was found after he spent 24 days in the wild, reportedly without food or water. The man - Mitsutaka Uchikoshi - told rescuers he remembered falling asleep in a field, possibly losing consciousness after a fall. After that, nothing.

When searchers discovered him, Uchikoshi appeared to be beyond sleep. His pulse was almost undetectable. His body temperature had dropped to 71 degrees - 27 degrees below normal. His organs had mostly shut down.

**SLOW MOTION** - During winter, some cold-blooded reptiles and amphibians, such as the desert tortoise seen here, enter into a state of brumation, where their metabolic rate and food intake are dramatically reduced. CNS Photo courtesy of U.S. Fish & Wildlife. Uchikoshi was treated for hypothermia, multiple organ failure and blood loss from his fall. Remarkably, he recovered fully, with no lasting ill effects. His doctors speculate that he survived, essentially unscathed, because he slipped into some kind of hibernation.

Maybe, maybe not. In fact, there's little scientific evidence that humans are even capable of hibernating - at least not in the same way as some animals, such as Punxsutawney Phil, the celebrated groundhog who looks for his shadow on Gobbler's Knob in Punxsutawney, Pa., each February.

Potential, on the other hand, is a different matter. Increasingly, researchers think it may be possible to apply elements of hibernation to a host of human ailments and endeavors, from extending the utility of donor organs to permitting long-term human space travel.

"It may not be necessary to learn how to put humans into the very deep, profound hibernation states of some animals in nature," said Hannah V. Carey, a zoologist at the University of Wisconsin and a hibernation researcher. "It may be enough to learn how they do what they do and mimic some of those states."

Such knowledge would be useful in treating surgery and trauma patients, she said. "Some hibernating animals are masters of knowing when to eat and when to stop. If we understood those signals, like when the body knows it has enough fat and switches metabolisms, it could be very useful."

Practical success will not come easy. Hibernation isn't simply sleeping deeply. It isn't merely triggered by cold or the calendar. The fat-tailed dwarf lemur of tropical Madagascar, for example, hibernates during winter not because the weather is cold (the average temperature is 63 degrees) but because conditions are dry and food is scarce. Hibernation in its various forms and degrees boils down to survival, making it through hard times by doing less with less. Different animals do it in different ways, but humans can take lessons from all of them.

## ARCTIC GROUND SQUIRRELS

Arctic ground squirrels are hibernation champs and a preferred research subject. (For obvious reasons, they are a lot easier to work with than, say, bears.) When winter begins in northern Alaska, the indigenous squirrels burrow underground, curl into balls and, for all intents and purposes, play dead. Metabolic processes like heart rate, blood pressure and respiration virtually disappear. Body temperatures hover around freezing. The squirrels are utterly unresponsive to touch. And yet, come spring and warmer temperatures, they emerge unaffected from their slumber and burrows.

John Hallenbeck, a researcher at the National Institute of Neurological Disorders and Strokes, said part of the reason is the way the squirrels deal with fat. As any cook will tell you, fat is affected by temperature. When it's cold, some fats separate and congeal. The same thing happens inside cells.

Cold causes saturated and unsaturated fats in the membranes of cell components to differentiate. While unsaturated fats remain liquid, saturated fats turn into a kind of crystalline gel. Proteins - the cell's workhorses - can become stuck in the gel and stop functioning normally.

Hallenbeck and his colleagues discovered that squirrel cells get around this problem by changing their internal structure, clustering proteins in patches of liquid unsaturated fat so the proteins can continue to work regardless of how cold it is. When temperatures rise, the cells restructure again - usually within a couple of hours of the animal waking and warming up.

Something similar, albeit less effective, occurs inside chilled human cells, according to Hallenbeck. By figuring out how squirrel cells do it better, he believes scientists might apply the knowledge to human biology, leading to improved cryopreservation techniques and storage of transplanted organs.

## BLACK BEARS

Black bears are not true hibernators - not like squirrels and other small mammals. Because of a bear's size, its temperature does not drop as dramatically, nor does its metabolic rate. Indeed, bears frequently wake up during hibernation, leaving their den or "hibernaculum" for brief periods of time. Still, they spend as much as five months in hibernation. For humans, such a prolonged period of inactivity would be catastrophic, perhaps fatal.

"Bedridden patients lose 0.7 percent of their strength per day, resulting in problems such as severe atrophy," said Hank Harlow, a professor of zoology at the University of Wyoming. Bone and muscle loss can approach 80 percent to 90 percent.

But post-hibernation bears display comparatively little loss of either. Seth Donahue, an associate professor of biology at Michigan Technological University, said bone production in black bears remains constant throughout hibernation, even though the bears are not eating.

Donahue credits recycling. During hibernation, black bears rarely urinate or defecate. Virtually all metabolic waste is reused, including excess calcium, which is refashioned into new bone.

Similarly, black bears help keep their muscles full and fit by converting urea - a nitrogen-rich waste product found in urine - into new amino acids, thus preserving existing proteins and contributing to new muscle tissue.

They also exercise - in their sleep. Using electronic leg braces attached to the knees of hibernating bears, Harlow and colleagues showed that the animals undergo massive episodes of shivering about four times a day.

"It's almost like a human getting on an exercise bike," Harlow said. "We think these massive muscle contractions are helping the bears to maintain strength and muscle tone through the winter."

Work like Harlow's presents a wide array of potential applications, from treating muscle disorders to minimizing the negative effects of prolonged hospital confinement to exercising astronauts during lengthy space missions.

## LEARNING FROM EXAMPLES

Bears and squirrels are hardly the only animals to hibernate. It's a diverse evolutionary adaptation. Certain terrestrial frogs, for example, essentially freeze during winter. In most species, that would be fatal. Ice crystals forming inside the cells would puncture delicate membranes, killing the cells and, ultimately, the animal.

Ice crystals form inside hibernating frogs, too - in the body cavity, bladder, under the skin - but the frogs survive because their vital organs are flush with the sugar glucose, which acts like antifreeze.

Skeptics note that humans aren't like tree frogs or ground squirrels. We lack the ability to concentrate glucose in key organs or safely vary our metabolic processes. They question the practical value of animal hibernation models. But other researchers counter that humans may not be so completely different.

"It's hypothesized that hibernation represents an ancient trait in mammals that continues in selected lineages today, including possibly humans," said Brian Barnes, director of the Institute for Arctic Biology at the University of Alaska in Fairbanks.

Case in point: oxygen deprivation. In hibernation, many animals significantly reduce oxygen flow to their brains with no negative consequences. There are anecdotal examples of humans surviving under similar circumstances. In 1999, a female Norwegian skier was pulled from icy waters after being submerged for more than an hour. With no measurable heart rate, respiration and a body temperature of 57 degrees, she appeared to be dead. And yet, she was resuscitated and recovered fully.

In 2001, a Canadian toddler named Erika Nordby wandered outside at night in a diaper and T-shirt. The temperature was minus 11 degrees. When Erika was found two hours later, her heart had stopped and her body temperature was 61 degrees, but she, too, was revived with frostbite as the only lingering complication.

## SLEEP AIDS

Even if humans can't hibernate, Barnes and others say they are inching closer to reproducing hibernation's protective and beneficial effects through drugs and therapies. Already, researchers have discovered how to place lab mice into suspended animation, using a common gas produced by the body.

Hydrogen sulfide smells like rotten eggs, but scientists have found that in small doses (an 80 parts-per-million mixture with air), it puts mice into a hibernationlike state, substantially reducing their heart

rate, breathing and body temperature while keeping blood pressure normal. Exposed to normal air, the mice recover within minutes.

The phenomenon presents some interesting possibilities, said Mark Roth, of the University of Washington and Fred Hutchinson Cancer Research Center in Seattle. In safe doses (high concentrations of hydrogen sulfide are toxic), the gas could be used to slow oxygen-deprivation damage in people with critical injuries or during transplantation surgeries.

It might even lead to more effective cancer therapies. To wit: Some cancer treatments work by denying oxygen to malignant cells. But the approach can also harm nearby healthy cells. If the oxygen needs of healthy cells could be reduced through suspended animation, then cancer medicines could be used longer, with greater effect.

"Right now in most forms of cancer treatment, we're killing off the normal cells long before we're killing off the tumor cells," Roth said. "By inducing metabolic hibernation in healthy tissue, we would at least level the playing field."

"The cool thing about 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," he added. "It's what allows our core temperature to stay at 98.6 degrees, regardless of whether we're in Alaska or Tahiti."

Meanwhile, other scientists are investigating the potential of vitamin C. Humans and primates get most of their vitamin C from food, but many animals synthesize it in their livers. Margaret Rice at the New York University Medical Center and Kelly Drew at the University of Alaska note that hibernating squirrels and turtles accumulate massive amounts of vitamin C in their brains and central nervous systems.

The vitamin, they theorize, protects against damaging free radicals and acts as a buffer when the animals emerge from hibernation and expose their depleted brains to lots of oxygen, which can be just as damaging as

not enough oxygen. The findings could have direct significance for stroke victims, who frequently suffer additional brain damage when blood flow returns.

Chances are, humans will never be like Arctic ground squirrels. Space-faring astronauts aren't likely anytime soon to slip into hibernation pods for journeys to distant planets and stars.

"Human applications are years, if not decades away," said Steve Swoap, a hibernation researcher at Williams College in Massachusetts.

But prospects of hibernation science, say Swoap and others, are numerous and eye-opening.

*Science awakens to the possibilities of human hibernation by Scott LaFee*