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Life on hold

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Life on hold

There's a strange state between being dead and alive that could save your life, says **Bijal Trivedi**

HASAN ALAM gazes over the cold, motionless body of a pig lying on a stainless steel table before him. The animal has no pulse, no blood, no electrical activity in its brain, and its tissues consume no oxygen. It has been in this state for two-and-a-half hours. It looks dead. "You would think so," he says, "but you can bring it back."

He flicks a switch and warm blood starts pumping into the animal, gradually ramping up its body temperature. At about 25 °C the pig's heart starts beating of its own accord and the animal jolts back to life.

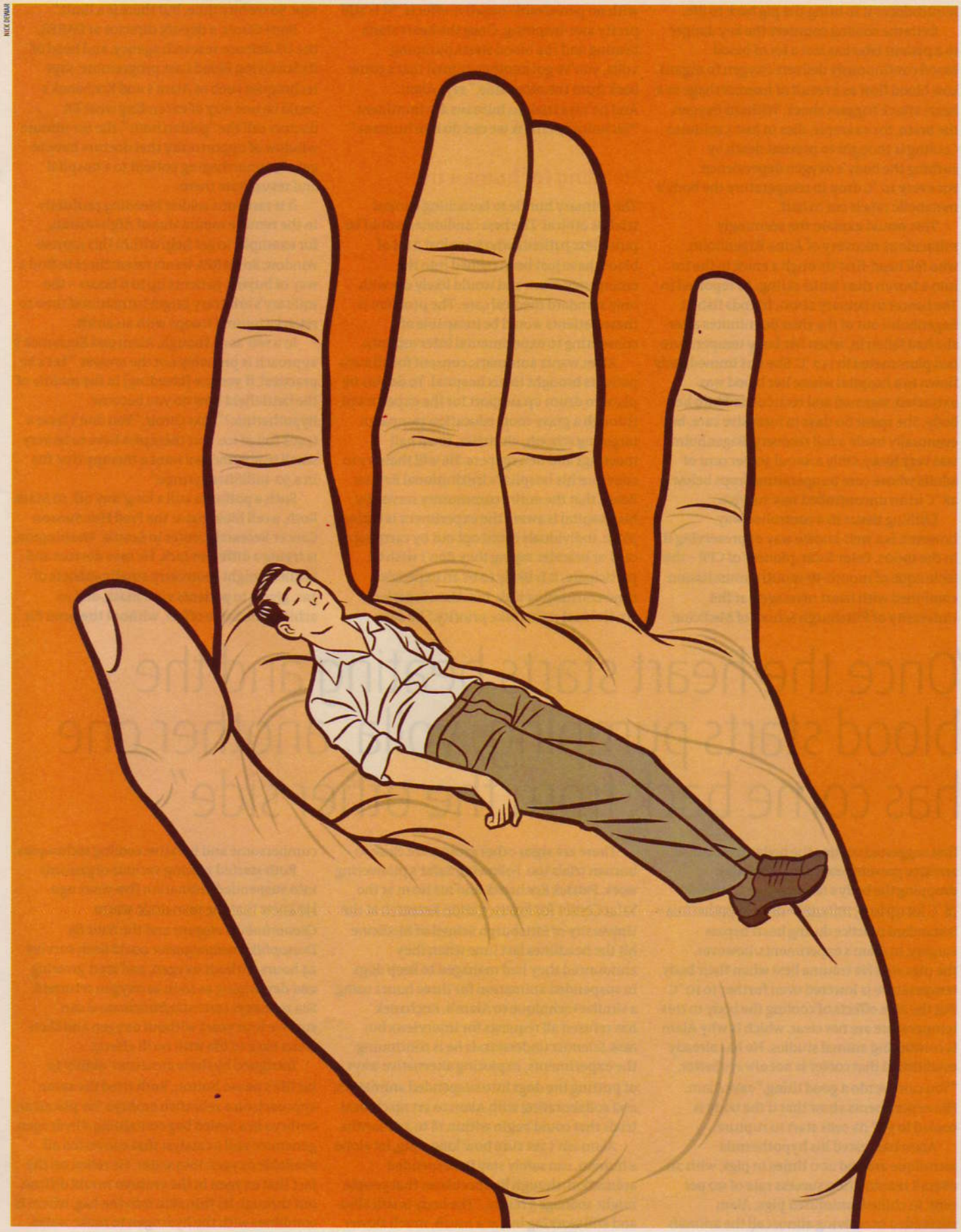
Alam, a trauma surgeon at Massachusetts General Hospital in Boston, is testing a new technique to grab patients at the brink of death and divert them into a state of suspended animation. Doctors could keep a body hovering in this twilight zone between life and death for hours while repairing wounds, and then revive it. The work could save the lives of gunshot and car accident victims, and patients suffering other life-threatening wounds that have caused severe blood loss.

Alam is one of several researchers experimenting with suspended animation. Strategies range from extracting all the oxygen from an organism to awakening what some scientists believe is our latent ability to hibernate. Though clinical techniques to induce comas already exist, these only suspend activity in the brain. Alam and others are studying ways to put the entire body on hold. They are still deciphering the precise mechanisms behind how and why life can so routinely be paused in vitro and in animals. But after countless experiments, they are increasingly sure of one thing: it can be done.

The pig experiment is brutal, but vital if Alam is to get the go-ahead to use the technique on humans. First he anaesthetises the pig to minimise the possibility of pain. Then he cuts into its abdomen and slices a major vein and artery. The cuts are designed to simulate multiple gunshots to a person's chest and abdomen. Blood loss is rapid and massive – about 50 per cent – and the animal's body quickly enters an advanced state of shock. He then drains the pig's blood and stores it. Finally, he pumps organ preservation fluid – a cocktail of nutrients and free-radical scavengers routinely used to store transplant organs – chilled to 2 °C, into its circulatory system to replace the blood and cool the animal from inside out. Over 20 minutes the pig's body temperature falls from 37 to a frigid 10 °C – what ER doctors call profound hypothermia.

Alam keeps the pig in suspended animation for 90 minutes, long enough to repair its damaged blood vessels. He then warms the pig's blood stored earlier and ▶

NICK DEHAN



reintroduces it to bring the pig back to life.

Extreme cooling counters the key danger to a patient who has lost a lot of blood. Blood continuously delivers oxygen to organs. Low blood flow as a result of haemorrhage or a heart attack triggers shock. Without oxygen, the brain, for example, dies in just 5 minutes. Cooling is thought to prevent death by curbing the body's oxygen dependence. For every 10 °C drop in temperature the body's metabolic rate is cut in half.

This would explain the seemingly miraculous recovery of Anna Bagenholm, who fell head-first through a crack in the ice into a frozen river while skiing. As reported in *The Lancet* in January 2000, friends fished Bagenholm out of the river 80 minutes after she had fallen in, when her body temperature had plummeted to 13.7 °C. She was immediately flown to a hospital where her blood was extracted, warmed and recirculated into her body. She spent 60 days in intensive care, but eventually made a full recovery. Bagenholm was very lucky. Only around 30 per cent of adults whose core temperature drops below 28 °C in an uncontrolled way survive.

Chilling tissue in a controlled way, however, is a well-known way of preserving it. In the 1960s, Peter Safar, pioneer of CPR – the technique of mouth-to-mouth resuscitation combined with heart massage – at the University of Pittsburgh School of Medicine, first suggested cooling the body after cardiac arrest to prevent brain damage. Today, dropping the body's temperature to around 18 °C for up to 45 minutes – deep hypothermia – is standard practice during heart bypass surgery. In Alam's experiments, however, the pigs survive trauma best when their body temperature is lowered even further to 10 °C. But the side effects of cooling the body to this temperature are not clear, which is why Alam is continuing animal studies. He has already established that cooler is not always better. "You can overdo a good thing," says Alam. His experiments show that if the body is cooled to 5 °C its cells start to rupture.

Alam has tested his hypothermia technique around 200 times in pigs, with an overall reanimation success rate of 90 per cent. In chilled, uninjured pigs, Alam succeeded in reviving almost all the animals with no perceivable negative effects. "It is still pretty awe-inspiring. Once the heart starts beating and the blood starts pumping, voila, you've got another animal that's come back from the other side," says Alam. And he says trials in humans are imminent. "Technically I think we can do it in humans."

Heading for human trials

The primary hurdle to launching clinical trials is ethical. The best candidates would be pulse-less patients who have lost a lot of blood, have just been rushed into the emergency room and would likely die with only standard medical care. The problem is these patients would be incapable of consenting to experimental interventions.

Alam wants automatic consent for all such patients brought to his hospital. To do this he plans to drum up support for the experiment through a grass-roots education campaign targeting schools, churches, town hall meetings and newspapers. He will then try to convince his hospital's Institutional Review Board that the entire community served by his hospital is aware the experiment is taking place. Individuals could opt out by carrying a card or bracelet saying they don't wish to participate. It is likely to be an expensive, time-consuming task, but Alam is patient. "Individual rights take priority," he says.

> "Once the heart starts beating and the blood starts pumping, voila, another one has come back from the other side"

There are signs other groups are close to human trials too. Following Safar's pioneering work, Patrick Kochanek and his team at the Safar Center for Resuscitation Research at the University of Pittsburgh School of Medicine hit the headlines last June when they announced they had managed to keep dogs in suspended animation for three hours using a similar technique to Alam's. Kochanek has refused all requests for interviews but *New Scientist* understands he is continuing the experiments, exploring alternative ways of putting the dogs into suspended animation, and collaborating with Alam to set up clinical trials that could begin within 18 to 24 months.

Alam isn't yet sure how long a pig, let alone a human, can safely stay in suspended animation, though he speculates that people might manage 3 hours. "The body is still alive and still working but at a much, much slower rate. So we buy time, but there is a limit."

Brett Giroir, a deputy director at DARPA, the US defence research agency, and head of its Surviving Blood Loss programme, says techniques such as Alam's and Kochanek's could be one way of extending what ER doctors call the "golden hour", the 60-minute window of opportunity that doctors have to get a haemorrhaging patient to a hospital and resuscitate them.

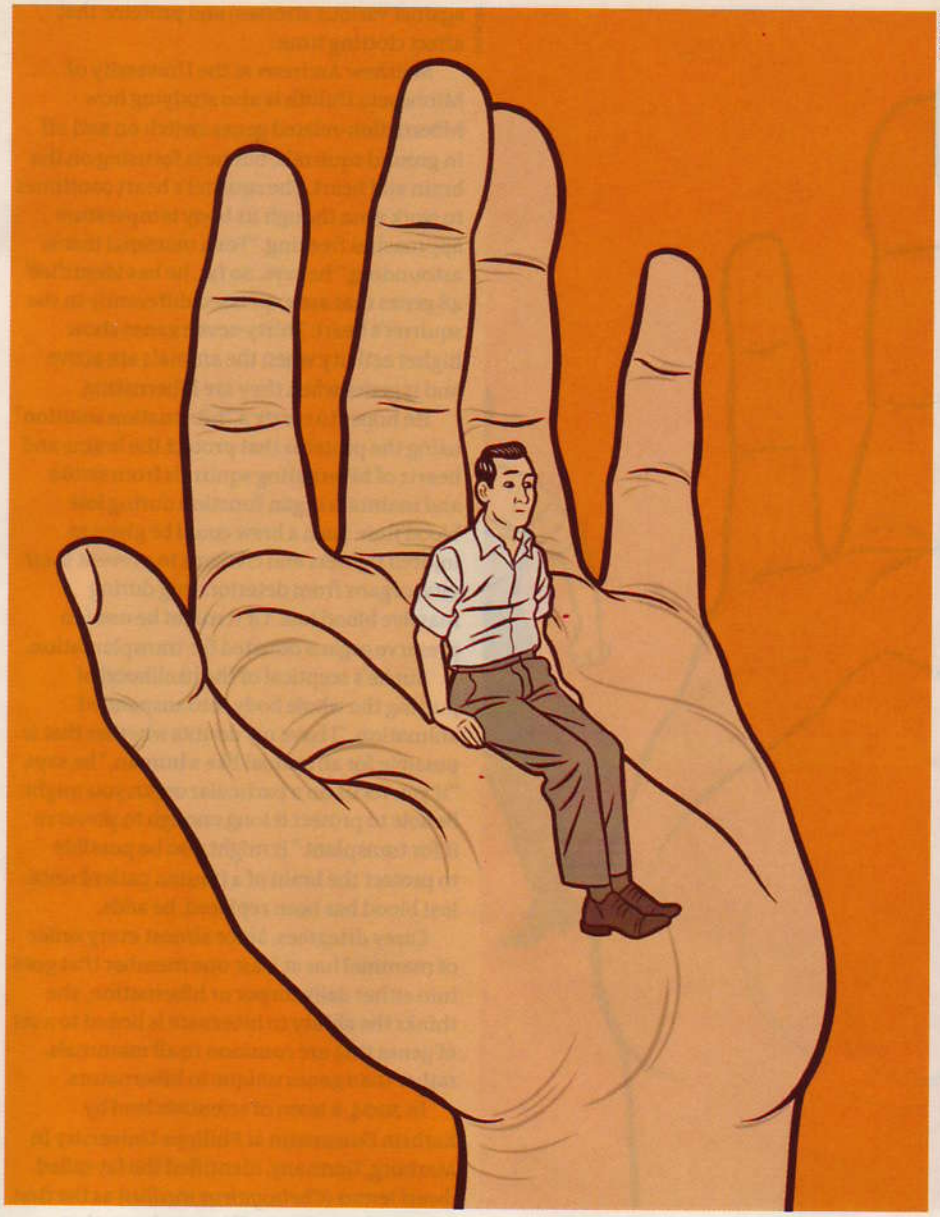
It is rare for a soldier bleeding profusely in the remote mountains of Afghanistan, for example, to get help within this narrow window. So DARPA wants researchers to find a way of buying patients up to 6 hours – the military's arbitrary target turnaround time to retrieve injured troops with an airlift.

In a war zone though, Alam and Kochanek's approach is probably not the answer. "Let's be practical, if you are [bleeding] in the middle of the battlefield how do you become hypothermic?" asks Giroir. "You don't have a truck full of ice. Our therapies have to be very small in volume: we want a therapy that fits in a 50-millilitre syringe."

Such a potion is still a long way off, so Mark Roth, a cell biologist at the Fred Hutchinson Cancer Research Center in Seattle, Washington, is trying a different tack. He says doctors and soldiers might soon carry small canisters of gas, give it to patients via a mask, and so achieve the same effect, without the need for cumbersome and invasive cooling techniques.

Roth started placing various organisms into suspended animation five years ago. He knew that the nematode worm *Caenorhabitis elegans* and the fruit fly *Drosophila melanogaster* could both survive 24 hours without oxygen, and start growing and developing as soon as oxygen returned. Sea monkeys (*Artemia franciscana*) can survive four years without oxygen and then come back to life with no ill effects.

Intrigued by these creatures' ability to hit life's pause button, Roth tried the same approach on a zebrafish embryo. He placed an embryo in a sealed bag containing a hydrogen generator and a catalyst that converted all available oxygen into water. He relied on the fact that oxygen in the embryo would diffuse out through its thin skin into the bag, where it combines with the hydrogen to make water.



NICK EDWARD

As the levels of oxygen in the embryo dropped, the cells stopped dividing, development froze, and its heart stopped beating. When he restored the oxygen supply 24 hours later, the zebrafish immediately continued developing, delayed by one day.

Such an approach would clearly be impractical for humans, given the sheer mass and thickness of our bodies. So rather than removing oxygen altogether, Roth decided to try blocking its uptake. He tested the idea in microscopic worms by exposing them to carbon monoxide, which prevents oxygen from binding to key sites in the cell. Without oxygen, cells cannot make adenosine triphosphate (ATP) – the energy source for muscle contraction and all sorts of bodily functions. This slows cellular metabolism and as a result the worm drifts into a state of suspended animation.

Carbon monoxide would not be a good choice for sending humans into suspended animation: it clings so tightly to haemoglobin, the molecule in the blood that transports oxygen, that awakening patients could be a problem. Hydrogen sulphide, on the other hand – the same poisonous gas produced by rotten eggs – also blocks oxygen but has a looser grip on haemoglobin and thus is easier to remove, making it a better choice.

To test it, Roth put a mouse in a glass chamber and exposed it to a cocktail of gases including hydrogen sulphide. Within just five minutes the mouse's metabolism plummeted: its oxygen demands dropped by 50 per cent and it produced 60 per cent less carbon dioxide. Over the next 6 hours the animal's metabolism dropped to 10 per cent of its original level, with less than 10 breaths per minute compared to the normal 120, and its temperature dived from 37 °C to 15 °C. The mouse slipped into a suspended animation-like state. The chamber was then flushed with fresh air, and 4 hours later the mouse was back to normal (*Science*, vol 308, p 518).

Suspended animation is not a natural state for a mouse, or a human, but Roth thinks it could become routine. He is now working on similar experiments in larger animals, and aims to scale up to human trials if successful.

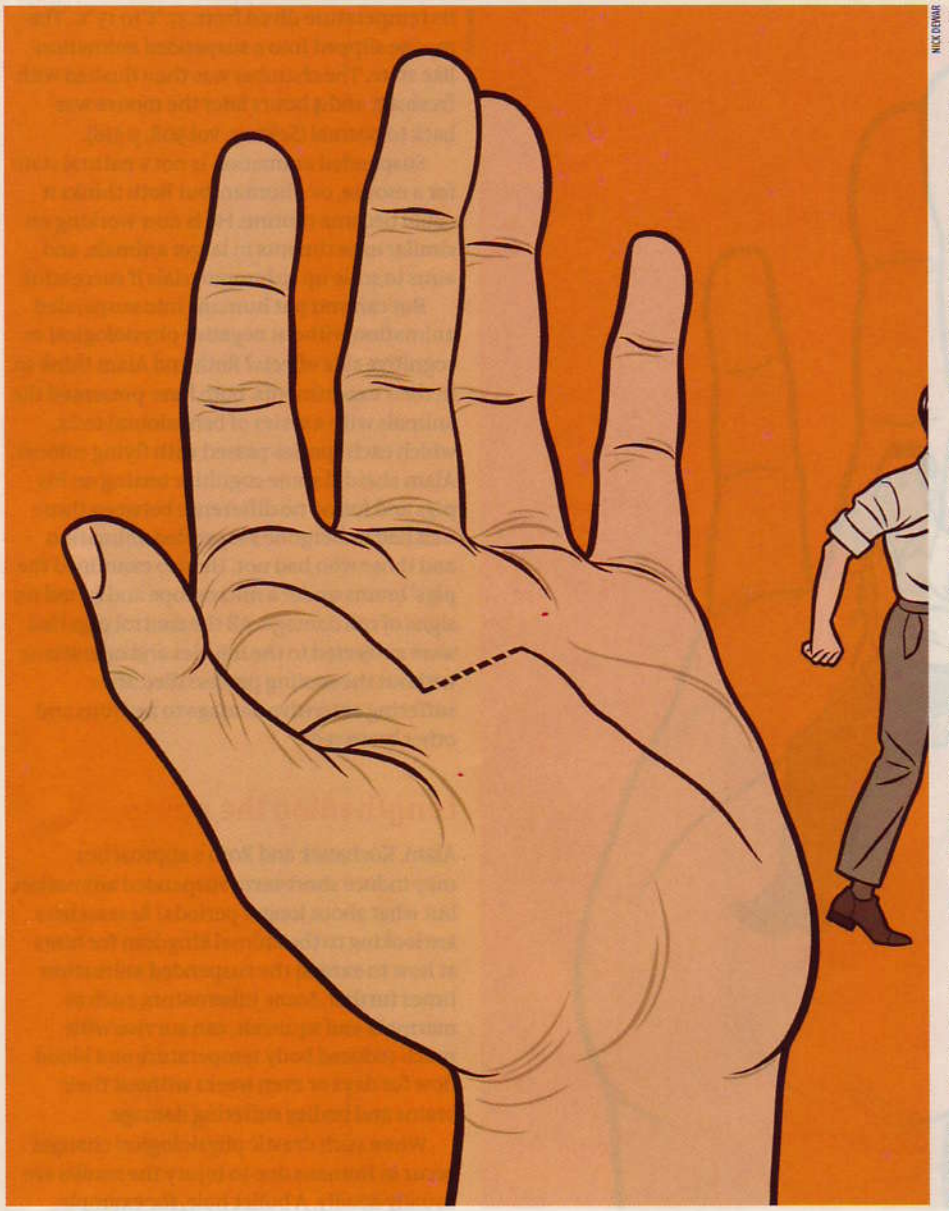
But can you put humans into suspended animation without negative physiological or cognitive side effects? Roth and Alam think so. In their experiments, both have presented the animals with a series of behavioural tests, which each species passed with flying colours. Alam also did some cognitive testing on his pigs and found no difference between those that had undergone suspended animation and those who had not. He also examined the pigs' brains under a microscope and found no signs of cell damage. All the control pigs that were subjected to the injuries and operations without the cooling process died after suffering extensive damage to neurons and other brain cells.

Lengthening the pause

Alam, Kochanek and Roth's approaches may induce short-term suspended animation, but what about longer periods? Researchers are looking to the animal kingdom for hints at how to extend the suspended animation times further. Some hibernators, such as marmots and squirrels, can survive with much reduced body temperature and blood flow for days or even weeks without their brains and bodies suffering damage.

When such drastic physiological changes occur in humans due to injury the results are usually deadly. A bullet hole, for example, rapidly reduces blood flow, and hence oxygen, to organs. But the body's cells continue functioning at a high metabolic rate, keeping oxygen demand high. This oxygen imbalance causes cells to increase production of free radicals, which damage cells. By contrast, hibernators quite deliberately decrease their metabolism and body temperature to match the drop in oxygen levels and blood flow, and so avoid this problem.

Understanding hibernation could help scientists develop drugs to put people into a similar state with the pop of a pill, or a simple injection. Hannah Carey, a physiologist at the School of Veterinary Medicine at the University of Wisconsin, Madison, is investigating how thirteen-lined ground squirrels (*Spermophilus tridecemlineatus*) swing from an active state into torpor in a matter of hours. Most hibernating animals don't fall asleep for the entire winter. Instead they spend the season ▶



NICK DEHAR

cycling though short active periods, often of just a few hours, and a special form of low-metabolism sleep called torpor – days or weeks of low body temperature, low oxygen requirements and low blood flow.

The secrets of squirrels

Carey's squirrels hibernate at 4 °C in a cold room near her lab. Their metabolic rate drops to between 2 and 4 per cent of normal; their heart beat plummets from 200 to 300 beats per minute to 3 to 5; and respiration falls from 100 to 200 breaths per minute to 4 to 6.

Carey thinks the squirrels' physiology, which has evolved to protect them during hibernation, ought to kick in if they suffer haemorrhagic shock. Some of her early studies support this idea. Five ground squirrels and six rats (which do not hibernate) were anaesthetised and then bled to remove 60 per cent of their blood, to imitate the most common form of death on the battlefield.

The rats' body temperature and blood pressure fell quickly and they died within the hour. By contrast, the squirrels stabilised their blood pressure and body temperature and lived for between 4 and 10 hours. "Trauma causes the squirrels to click into their torpor mode and they just go along like this for hours," says Carey.

She thinks the key to these abilities lies in their genes. If we can work out which genes are active during hibernation and which are not, says Carey, it will "give us clues how to induce that kind of a state on demand [in humans]".

Already there are intriguing candidates. Carey says that, during hibernation, there are changes in the levels of antioxidants, protein chaperones (molecules that guard proteins against various stresses) and proteins that affect clotting time.

Matthew Andrews at the University of Minnesota Duluth is also studying how hibernation-related genes switch on and off in ground squirrels, but he is focusing on the brain and heart. The squirrel's heart continues to work even though its body temperature approaches freezing. "For a mammal that is astounding," he says. So far, he has identified 48 genes that are expressed differently in the squirrel's heart. Thirty-seven genes show higher activity when the animals are active and 11 genes when they are hibernating.

He hopes to create a "hibernation solution" using the proteins that protect the brains and hearts of hibernating squirrels from stroke and maintain organ function during low blood flow. Such a brew could be given to injured fighters and civilians to prevent their vital organs from deteriorating during massive blood loss. Or it might be used to preserve organs donated for transplantation.

But he's sceptical of the likelihood of putting the whole body into suspended animation. "I have my doubts whether that is possible for an animal like a human," he says. "If you focus on a particular organ you might be able to protect it long enough to preserve it for transplant." It might also be possible to protect the brain of a trauma patient until lost blood has been replaced, he adds.

Carey disagrees. Since almost every order of mammal has at least one member that goes into either daily torpor or hibernation, she thinks the ability to hibernate is linked to a set of genes that are common to all mammals, rather than genes unique to hibernators.

In 2004, a team of scientists lead by Kathrin Dausmann at Philipps University in Marburg, Germany, identified the fat-tailed dwarf lemur (*Cheirogaleus medius*) as the first hibernating primate. "Now we know that lemurs hibernate. That is even closer to humans in terms of the genetic machinery," says Carey. "The genes are there for us but we aren't turning on the right pathways at the right time to actually do this. But I think it is in our blueprint. It has to be."

If Alam is successful, reanimation could be with us very soon. Once he has satisfied the funding agencies that there are enough animal studies to support human trials, and he gets the ethical go-ahead, it might not be long before a state between living and dying becomes the difference between whether you live or die. ●

Bijal Trivedi is a science writer based in Washington DC