RHYTHMS OF THE COSMOS

AN ASTRONAUT'S SLEEP DIFFICULTIES PARALLEL THOSE IN ELDERLY MEN | **BY ROBIN KRIEGER MEJIA**

Early this morning, while you were still asleep, your brain ramped up production of the hormone cortisol to raise blood sugar levels. At about the same time, your body temperature began to rise. These changes were part of a complex set of daily cycles controlled by your biological clock. They occur, explains Timothy Monk, professor of psychiatry, so that when you wake up, you "hit the ground all warmed up and ready to go."

A bundle of about 10,000 neurons, the biological clock, or endogenous circadian pacemaker, orchestrates the activity of the signals that make us sleepy at night, wake us up in the morning, and keep us alert during the day. To get a feel for the magnitude of the changes your body makes to get ready for a solid night's sleep, think about how you would deliberately prepare to forgo eating, drinking, or using the restroom for eight hours.

But what exactly affects the signals that drive circadian rhythms? It may help you rest easier just to know that scientists are looking at this question from a number of perspectives—including some that are way out there, in a manner of speaking.

In a study published in the December issue of *Psychosomatic Medicine*, Monk examined what happens to the biological clock under the extreme conditions found in outer space. On the space station Mir, which completed an orbit every 90 minutes, astronaut Jerry Linenger saw 16 sunrises and sunsets every 24-hour "day" (though he kept a regular daily schedule based on Moscow time in order to be in sync with his earth-bound counterparts). Monk wondered: How would the astronaut's body respond to the lack of regular scheduling cues such as day and night?

To answer this question, Linenger monitored his own temperature, alertness, and sleep for three two-week blocks during a nearly five-month stay on Mir in 1997. He recorded when he went to sleep, when he got up, and if he'd awakened during the night. Five times each day, he took his temperature and used a computer program to rate his alertness.

After about three months in space, Linenger's biological rhythms flattened. His normal flux in body temperature became less pronounced. He slept more fitfully. And by the end of the voyage, he felt less tired at night and less alert during the day. (Though, after three months in space, the astronaut scored about as well on the computer-based alertness assessment as at the beginning of the trip. Monk explains that Linenger's subjective baseline for alertness may have moved over the months, or he may have been able to focus for the 10-minute test even if he wasn't feeling his best throughout the day.)

On Mir, Jerry Linenger saw 16 sunrises and sunsets every 24 hours.

Finding a way to keep the biological clock working will be key to the future of extended space missions, be they on space stations or a trip to Mars. Accidents can quickly become emergencies in space. Staying alert can mean staying alive.

Bright light therapy might help keep the clock on track in the cosmos. We know that on earth, when people are removed from the influence of light and other daytime signals, the biological clock cycles over a slightly longer period, about 24.2 hours, and people sleep less effectively, with more bouts of lighter, interrupted sleep, instead of one solid chunk of shut-eye. Exercise might also help astronauts sleep better. In the weightless environment of space, they expend little energy performing regular duties.

Monk, who is affiliated with the University's Clinical Neuroscience Research Center, notes that this research may also offer benefits to those of us content to stay put on this planet.

"The flattening that I saw in Dr. Linenger towards the end of the mission is very similar to the flattening of the alertness mechanism that I've seen in older men, men in their 70s and 80s," he said. "If we found ways of tricking the circadian system into solving this problem, it might work for older people." ■

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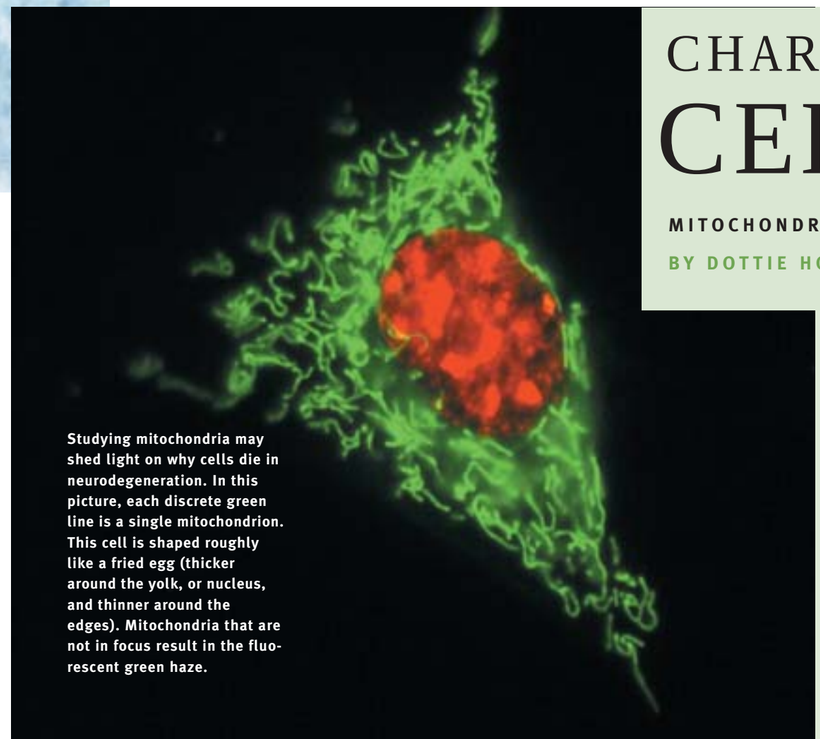


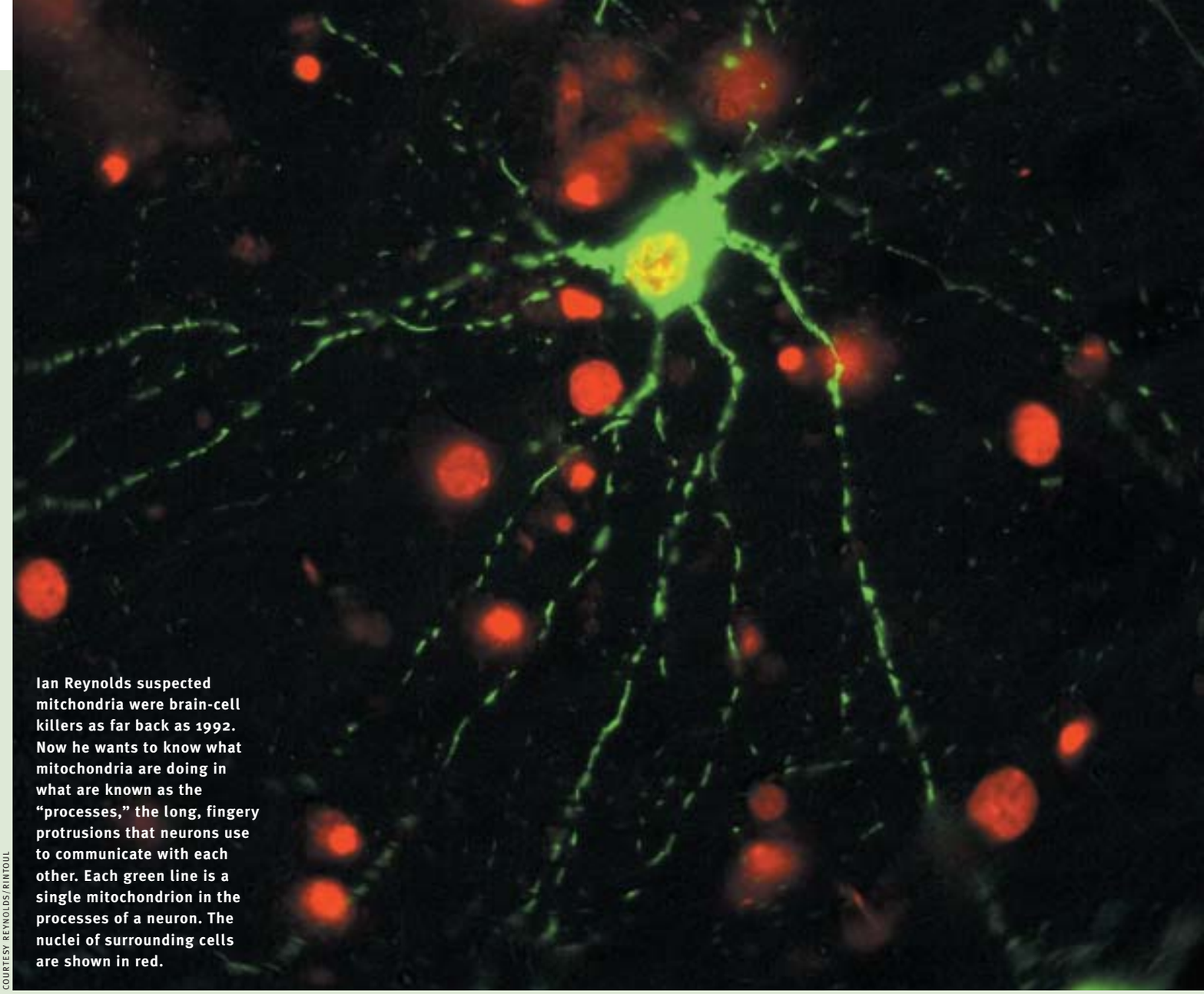
Studying mitochondria may shed light on why cells die in neurodegeneration. In this picture, each discrete green line is a single mitochondrion. This cell is shaped roughly like a fried egg (thicker around the yolk, or nucleus, and thinner around the edges). Mitochondria that are not in focus result in the fluorescent green haze.

CHARGED WITH CELLICIDE

MITOCHONDRIA SEEMED UNLIKELY CULPRITS

BY DOTTIE HORN

Inside brain cells, mitochondria wiggle and wend. One, looking like a short pencil, bends into a horseshoe, then straightens again. Sometimes, one will split in two; other times, two will fuse together. One mitochondrion, moving at a speedy clip, zips up one of the slender tendrils, called "processes," by which nerve cells communicate with each other. When the process splits into two divergent paths, the mitochondrion



Ian Reynolds suspected mitchondria were brain-cell killers as far back as 1992. Now he wants to know what mitochondria are doing in what are known as the "processes," the long, fingery protrusions that neurons use to communicate with each other. Each green line is a single mitochondrion in the processes of a neuron. The nuclei of surrounding cells are shown in red.

COURTESY REYNOLDS/RINTOUL

chooses one fork over the other as it rushes on its hurried way.

Ian Reynolds, professor of pharmacology, watches the antics of mitochondria on videos he makes using fluorescence microscopy. He points to one as it squirms: "It's almost like a worm trying to figure out which way it wants to crawl off to next." His videos have raised many questions for which, as of yet, he has no answers: Why do some mitochondria travel and how is their movement controlled? Why do they break into two and fuse? Why do some cells have lots of mitochondria, while neighboring cells may have only a few? The answers, Reynolds hopes, will reveal clues to why cells die in neurodegenerative diseases like Parkinson's and Huntington's. The organelles certainly appear to be a factor in those disorders as well as in cancer.

The raison d'être of mitochondria is not straightforward, however. Once scientists think they understand the importance of these organelles, another function seems to wiggle and wend into the picture.

Using microscopes early in the last century, scientists noticed parts moving inside cells. Later, during the 1950s and 1960s, they were able to observe these moving parts with new technologies—these were mitochondrial boom times. In 1961, the University of Edinburgh's Peter Mitchell published a paper delineating the mechanisms by which mitochondria use oxygen to convert sugar into ATP, the form of energy the cell uses. (Mitochondria's need for oxygen is why we have to breathe—they consume 95 percent of the oxygen we take into our bodies.) Mitchell's hypothesis was initially met with skepticism. By 1978, the year he won the Nobel Prize for Chemistry, it was accepted widely.

In the years that followed, many researchers abandoned mitochondria to study intercellular signaling, second messenger function, protein kinases. Then in 1997, mitochondria made an extraordinary comeback among investigators. Scientists, notably Xiaodong Wang, associate professor of biochemistry at the University of Texas Southwestern Medical Center in Dallas, realized that one kind of programmed cell death, or apoptosis, is triggered by the mitochondria's release of cytochrome c into the cytoplasm. The idea that an organelle so important for maintaining cell functioning could also routinely offer a protein that causes the cell to die—*that* seemed to come out of left field. It was, notes Reynolds, very unexpected.

The discovery has heralded a second wave of boom times for mitochondrial research. However, the organelles commanded

Reynolds' attention years before this second mito-boom.

In 1992, he was gathering evidence that mitochondria were killers. Reynolds was using a simplified model of stroke, in which he gave neurons in culture high doses of glutamate, an excitatory neurotransmitter, which killed a fair portion of them. He knew that the way glutamate caused damage was by stimulating excessive calcium to enter the cell. But where in the cell was the calcium going? He discovered the answer—into mitochondria.

Reynolds wondered what would happen if he put calcium into cells but prevented the element from entering mitochondria. When he did the experiment, he found that calcium had no detrimental effect on the cells, as long as it didn't enter the mitochondria.

From what Reynolds has gathered, mitochondria are killing brain cells, and not just through the process of apoptosis. They seem to take on the role of executioner in some other way as well—yet another function to be elucidated. ■

WHEN OUR OTHER DNA MUTATES

The woman had high cholesterol, but otherwise had always been healthy since a bout of irritable bowel syndrome 10 years earlier. She started taking medicine to control her cholesterol and, within a few months, developed weakness and muscle aches. Her grandson had some of the same symptoms and was dying from a rare inherited mitochondrial disease called MELAS. Her brother had died after showing similar symptoms years before. When the woman stopped taking the cholesterol medicine, her symptoms went away.

Carolyn Bay, assistant professor of pediatrics, has heard similar stories from other family members of children with inherited mitochondrial disease. The children become sick because in a large percentage of the cells in their bodies, there are mutations in the mitochondrial DNA. Bay suspects that apparently healthy family members on the maternal side (mitochondrial DNA, which is different from the nuclear DNA, is inherited from the mother only) may also have defects in their mitochondrial DNA, but at lower levels. The family members may develop symptoms of mitochondrial disease if they come down with a serious illness or take medications that affect mitochondrial function like statins and some HIV drugs.

"We are just at the beginning of our understanding of how mitochondrial diseases work," says Bay. "We know the glaringly obvious cases. As we get more sophisticated, we're going to learn the more subtle cases." —*DH*

DOUBLE TAKE

The scientific community did a double take five years ago when it learned that mitochondria, long understood as vital for converting oxygen into energy the cell needs, also play a role in apoptosis. As it turns out, the organelles set off a process of programmed cell death by releasing cytochrome c into the cytoplasm.

Hannah Rabinowich, a professor of pathology, says that since 1997, scientists have largely uncovered what happens in cells *after* mitochondria release cytochrome c. However, they have yet to understand what happens *inside* mitochondria *leading up to* the release of cytochrome c.

"Within the mitochondria, it's a black box," she says.

Rabinowich is determined to understand the mitochondrial events that trigger the release of cytochrome c and other apoptotic proteins. Her experiments utilize a cell line, cloned from leukemia cells, which is deficient in two mitochondrial proteins—Bak and Bax. A couple of years ago, she wondered: Are the proteins essential players in stimulating the release of cytochrome c? To get at the answer, she exposed the cells to chemotherapeutic drugs. (Like many common chemotherapeutic drugs, the ones she used kill cells by inducing apoptosis.) The cells were left unscathed by the drugs—suggesting that without these proteins, apoptosis cannot occur.

She's now working on further experiments using the deficient cell line. If she puts Bak into the cells, so that they are deficient only in Bax, will that deficiency alone protect them from apoptosis? What if she turns the tables so that there's a Bak deficiency instead? The answers, she believes, will give researchers more insight into how cells set in motion their own death. —*DH*

HOT FLASHES

When Ian Reynolds, professor of pharmacology, used a fluorescent dye to light up mitochondria in astrocytes (a type of brain cell), he didn't expect to see the mitochondria flashing—getting dimmer and brighter and dimmer and brighter again. Instead, he expected to see them steadily illuminated. The dye he uses, based on tests by former postdoc Jennifer Buckman, he explains, works because it is drawn to a negative charge. Mitochondria are negatively charged on the inside of their membrane and positively charged on the outside. This difference in charge, called the membrane potential, is what allows the mitochondria to do their job of converting sugar into ATP. When the mitochondria become dimmer, they are losing the negative charge on the inside of the membrane, and thus losing their membrane potential. "All these spontaneous changes in membrane potential—we had no idea they were occurring," says Reynolds. He believes that, as membrane potential is lost, mitochondria are unable to produce ATP. But he has no idea why the membrane potential changes. And he doesn't know why he has seen the flashing in astrocytes, but never in neurons.

"Every time you do one of these experiments," he says, "you bump into something different, some things you don't expect." —*DH*