

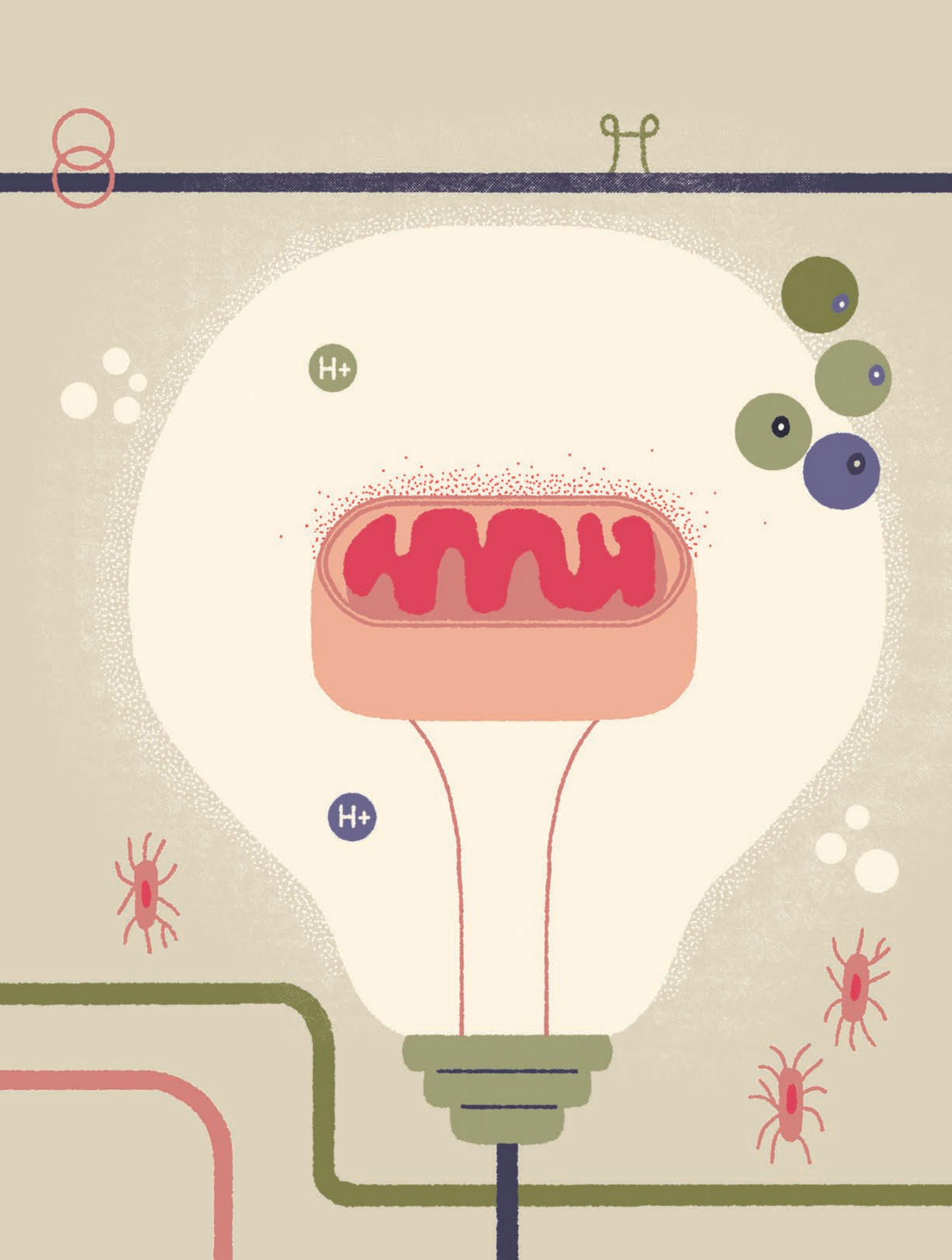
BIOLOGY

Power Play

Could a new theory of cellular energy help explain why we age and get sick?

BY ROWAN JACOBSEN

ILLUSTRATIONS BY NOEMI FABRA


H+
H+

AS DISEASES GO, TYPE 2 DIABETES AND EPILEPSY SEEM TO HAVE LITTLE in common. One is a metabolic disorder involving high blood glucose and failing insulin, the other a matter of neurons and electrical pulses. So it is odd that both often respond to fasting. Likewise, depression, obesity, Alzheimer's, heart disease—all are wildly different diseases, yet all are influenced by diet. This shared vulnerability points to metabolism—the way we harvest energy from the food we eat and use it to power our cells.

One of the leading proponents of an energy-centric view of disease is Martin Picard, a biologist who directs the Mitochondrial Psychobiology Group at Columbia University. "Once we see ourselves as energetic processes," he says, "many things make sense that didn't make sense from a molecular perspective."

Picard and a growing number of colleagues are making the big claim that many chronic diseases we treat as separate failures of separate organs may share one deeper problem: cells struggling to extract and use energy from food. If they are right, a common weakness runs beneath diseases now parceled out among different specialties, and medicine might have spent a century drawing boundaries in the wrong places.

At the heart of this argument lie mitochondria, the microscopic organelles that live in our cells and convert the energy stored in molecules of food into adenosine triphosphate, or ATP, the molecular power pack that drives virtually every reaction in the body, whether it's moving, thinking or healing. We produce our body weight in ATP every day, and we burn just as much.

Any meltdown in our mitochondria will lead to a shortage of ATP, leaving cells with less energy to do their jobs. Picard believes many states of poor health start there, and his once unusual research focus is now mainstream. "Everybody agrees that mitochondrial dysfunction is part of aging biology," says Matt Kaeberlein, former director of the Healthy Aging and Longevity Research Institute at the University of Washington. "It's one of the hallmarks of aging. And I think you can make a pretty reasoned argument that mitochondrial dysfunction can precede and potentially drive many of the other hallmarks of aging."

Certainly, Kaeberlein says, health is about more than mitochondria. "If you're going to argue that *everything* starts with mitochondrial dysfunction, I think most people would push back against that." But the idea doesn't need to explain all of aging to be worth chasing. "Mitochondrial dysfunction may contribute to the vast majority of common diseases," he says. "Almost any disease you look at, you find a mitochondrial connection."

That connection has gerontologists and biohackers alike racing to understand what makes mitochondria tick—and what we can do to keep them ticking as long as possible.

ALTHOUGH MITOCHONDRIA'S central role in our existence is often overlooked, scientists have understood their importance since the 1960s, when British biochemist Peter Mitchell proposed a then radical explanation for how mitochondria capture energy—work that earned him the Nobel Prize in Chemistry in 1978. The process, Mitchell showed, is fundamentally electrical. Electrons stripped from the atoms of our food are drawn toward atoms that will accept them. Among the elements biology has to work with, oxygen exerts the strongest pull.

Animals owe their existence to that attraction. We eat food, break it down into simpler molecules and send those to the mitochondria in our cells, which pry off electrons and let them flow through a string of molecules in their membranes known as the electron transport chain. At each step in this chain, a portion of the electrons' energy is siphoned off to pump protons across a membrane—Mitchell's great insight—and the pressure of those protons rushing back through a molecular turbine is what makes ATP. At the

Rowan Jacobsen is a journalist and author covering science, nature and the environment. His work has appeared in *The Atlantic, Harper's, The New York Times* and *MIT Technology Review.*

end of the chain, oxygen accepts the electrons and, together with protons, becomes water.

As many observers have noted, this flow of electrons through the body resembles the flow of electricity through the power grid. Power plants drive electricity through wires and into our homes, where our devices tap that energy to light our rooms and power our lives. The current has to meet the right amount of resistance in the right places. Too little, and the energy races past without doing any work, eventually damaging other components.

Something similar happens in our mitochondria. Under ideal conditions, electrons are slowed in their passage through the electron transport chain just enough that their energy can be transferred. But if the mitochondrial circuits are impaired or if there are simply more electrons from food pouring into the system than the mitochondria can handle, the flow can get bogged down. Electrons can then leak out of the chain, bonding with oxygen in the wrong parts of the mitochondria to form highly reactive free radicals that attack and deform neighboring molecules. These reactive oxygen species, or ROS, can do real damage to mitochondria, cells and organs.

No matter how smoothly electrons flow through mitochondria, a certain amount of ROS is unavoidable in everyday life. The classic free-radical theory of aging, first proposed in the 1950s, held that aging itself resulted from the relentless buildup of ROS in our cells, decade after decade, and the wear and tear this caused. Now we know the body is quite capable of repairing manageable amounts of ROS, which at lower levels can even act as signals, telling a cell to get to work. Only when the oxidative stress gets out of hand do mitochondria get dinged up, but when they do, they move electrons less efficiently, which leads to even more ROS and more damage. The brownouts spread. Eventually cells lose capacity, and the body follows.

Picard has written in this magazine about mitochondria's role in health. In November 2025 he and Nirosha Murugan, a biophysicist at Wilfrid Laurier University in Ontario, codified this concept in the journal *Cell Metabolism* as the energy resistance principle. If a major cause of chronic disease is simply too many food-derived electrons frying the mitochondrial wires, then a major goal of medicine should be to reduce that overload. "The secret to longevity," Picard says, "is to find ways to live at optimal energy resistance."

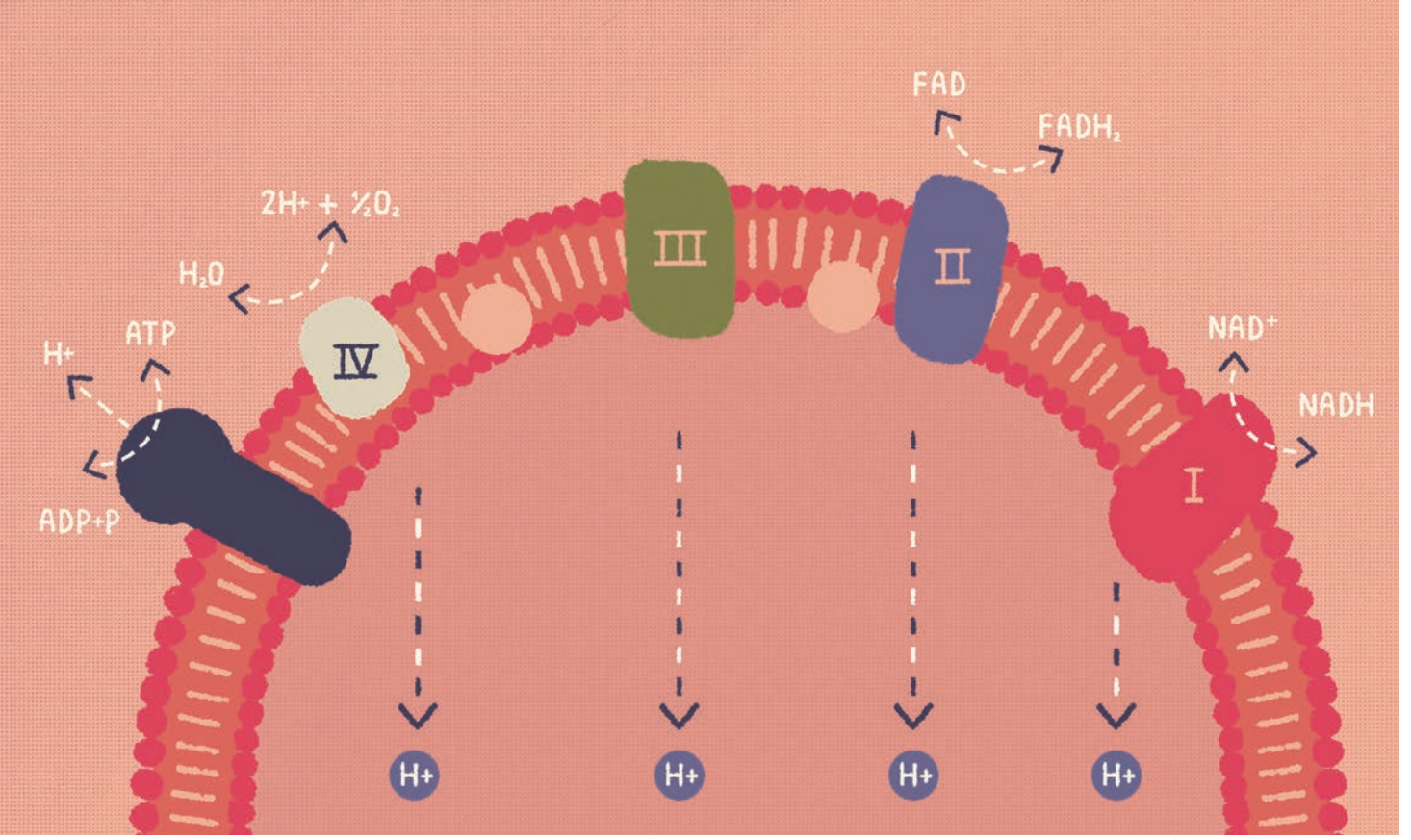
These disruptions in cellular energy can have very different consequences throughout the body. "The specific pathology depends on where the mitochondrial dysfunction is happening," Kaeberlein says. "If it's in the muscle, you get muscular degeneration, myopathies, things like that. If it's in the heart, you get different types of heart disease." The brain is no exception. "You get things like Parkinson's disease. Certainly mitochondrial dysfunction contributes to other types of dementia, including Alzheimer's." The Alzheimer's link is strong enough that Paula Moreira, who is co-editor in chief of the *Journal of Alzheimer's Disease* and specializes in brain mitochondria, has taken to calling the disease "diabetes of the brain."

The claim that mitochondrial dysfunction is a factor in mental health disorders as well as physical ones is surprising to many people. It's less intuitive to picture energy supply affecting our mind as it does our muscles, but the brain is the most energy-hungry organ in the body. Neurons are closer to Formula One race cars than to family sedans, burning fuel at a furious rate and threatening to blow up at any moment. If any cells are going to betray signs of energetic stress, it's them.

> "Mitochondrial dysfunction may contribute to the vast majority of common diseases."
>
> —MATT KAEBERLEIN *UNIVERSITY OF WASHINGTON*

AS MITOCHONDRIAL DYSFUNCTION has become a familiar suspect in disease and aging, efforts to tinker with it now range from a cottage industry of supplements, such as coenzyme Q10, that promise happier, healthier mitochondria, to experimental interventions involving gold nanoparticles. That worries Jonathan Jarry, a science communicator at McGill University's Office for Science and Society in Montreal. "My concern is that people start to believe that this has been successfully translated into the clinic when it hasn't," he says. "So it's one thing to say, 'Hey, here's what we know about this thing that's in our cells. It's really cool. People are studying this.' And it's another to say, 'Hey, we know the problems that this causes, and we know how to fix this, and we can sell you solutions.'"

Kaeberlein agrees that the hacks have thus far disappointed. "None of the data so far looks all that compelling," he says. Of all the supplements suspected to have mito-boosting powers, he says only one is convincing. "The one I would point to is creatine. There's a clear mitochondrial connection, and the biology is very plausible. I think it's a very



In mitochondria, the electron transport chain helps to convert energy from food into ATP, the molecule that powers our cells.

good supplement. It works in the context of also doing exercise, but there's emerging evidence on creatine and brain function, at least in situations like sleep deprivation or severe cognitive stress. You can buffer the ATP supply of the brain and muscle with creatine."

For now the boring advice has better evidence than the hacks: sleep, exercise and diet.

Sleep is extraordinarily important to mitochondrial health. That may be a big part of what drives our need for it. Neuroscientists at the University of Oxford have recently found direct links between oxidative stress in the brain and the need to sleep. As neurons fire furiously over the course of the day, ROS can accumulate. Specialized neurons track that buildup, and when a certain threshold is reached, they send a sleep signal to the brain at large. During sleep, neurons go quiet, ROS are cleared, and damaged mitochondria are repaired or recycled.

Exercise also improves the capacity of mitochondria to process energy, in part by stress-testing the system. Any kind of workout is a temporary emergency for the cells involved. Energy demand might rise to 100 times resting levels, which pushes mitochondria and their support systems to the limit, producing a burst of ROS and other stress signals. During recovery, though, the body responds to this challenge so it will be better prepared for the next one, fixing damaged tissue and building more blood vessels and mitochondria. The payoff is a system that can handle more energy without straining the rest of the time. The leg muscles of a marathoner can have twice as many mitochondria per cell as those of a couch potato, spreading the energetic load across much more capacity.

The system also gets better at repair, which may turn out to be a more important part of healthy aging than we've realized. Exercise triggers a process known as autophagy, the cell's salvage system for worn-out parts, including mitochondria. Damaged material gets dismantled; useful components go back into circulation.

Recycling also seems to help explain another old standby: calorie restriction. "Autophagy is an adaptive response to nutrient deprivation," Kaeberlein says. "When you're in nutrient shortage, you don't have the energy to produce a bunch of new complex machinery, so you break down the damaged machinery, and then you can reuse those components. And the most important time to recycle is when you don't have sufficient nutrients to build new machinery."

That efficient scavenging can also clear damaged components before they become a liability. At the same time, reducing the amount of energy entering the system eases the load on mitochondria and reduces oxidative stress. Calorie reduction reliably improves health and lifespan in many organisms, including yeast, worms, flies and rodents. In primates, the results aren't as clear, although long-running studies point to health benefits.

Diet-based interventions have shown promise for the brain as well as the body, a connection physicians made long ago when they noted that fasting

could often prevent seizures in people with epilepsy. "Hippocrates knew about it 2,000 years ago," says Christopher Palmer, a Harvard Medical School psychiatrist and author of the 2022 book *Brain Energy*. "In the 1920s physicians put it to the test. And to their shock, it actually worked."

We now know a lot about the mechanisms of action, Palmer says, including "changes in neurotransmitter function, changes in hormone signaling, changes in epigenetics, reduced brain inflammation and changes in mitochondrial function." Those changes seem to be linked to metabolic shifts, among them reductions in the load of glucose, the body's standard fuel, which is produced mostly from carbohydrates. A ketogenic diet can reproduce fasting's metabolic effects by strictly limiting carbohydrates and relying more on fat. When carb intake falls sharply, the liver turns fat into ketones, an alternative fuel for the brain and other tissues that may cause less metabolic stress. Whether this broader metabolic shift can improve psychiatric symptoms is now being put to the test.

In July a team led by researchers at the San Francisco VA Medical Center published the first randomized controlled trial of a ketogenic diet in people with bipolar I disorder and schizophrenia-spectrum disorders. After a month, the ketogenic group showed clear metabolic improvements; the more striking psychiatric and cognitive gains turned up at four months—by which point the diet had been offered to everyone, eliminating the control-group comparison. The clinical signal remains intriguing but preliminary.

"We've known for decades that a ketogenic diet is effective for antiseizure," Kaeberlein says. "It definitely has effects on brain metabolism that are potent. That's going to affect mitochondrial dysfunction. So it's reasonable to think a ketogenic diet will have broader-reaching effects on brain biology that could affect emotion, psychological state, cognitive abilities, all of those things."

Kaeberlein cautions that it is too early to assume that we understand how these incredibly complex systems work. "The arrows all point in the direction that repairing and preserving mitochondrial function during aging is important for the lifespan and health span benefits we see from these interventions. But because all of these things are multifactorial, it's hard to know how much is because of their effects on mitochondria versus other things that these interventions are doing." The wrinkle is that mitochondria live inside the cell and depend on it, so anything that improves their function will improve the cell, but anything that improves the cell will also improve them.

ON THEIR FACE, none of these interventions are revolutionary. The appeal of the energy-centric perspective is that it gives familiar advice—eat lightly, sleep well, get exercise—a common language. "The disease-centric point of view looks at a singular snapshot and then looks backward to see how that applies to health. The energy-resistance framework flips that," Murugan says. "It reframes health as a dynamic process, and it allows us to look at how different interventions can influence that process. It puts them into context."

A good example is type 2 diabetes. "From a molecular perspective," Picard says, "diabetes is excess blood sugar and insulin resistance. So you fix it with drugs. You give insulin to override the resistance." He reads insulin resistance differently. In some cases, he argues, cells may begin to resist glucose because their mitochondria are already struggling to process the fuel coming in. In that telling, they need a break, Picard says, not an override.

An energy-centric perspective may also offer early warning signs. Cells under stress release a signaling protein known as GDF15. "It's the way cells tell other cells, 'I'm not doing well,'" Picard says. High levels of GDF15, which also rise in pregnancy and illness, trigger feelings of malaise and nausea—a built-in brake on energetically costly activities such as movement and digestion. He thinks the body is then able to conserve energy while confronting the internal challenges. High levels are also among the best predictors of future disease and mortality, which he takes as strong evidence that energetic dysfunction within cells precedes later problems—and may offer us an early opportunity to head them off.

These disruptions in cellular energy can cause very different consequences throughout the body.

But beyond such practical applications, the biggest appeal of seeing health through the lens of energy may be the new light it shines on the very concept of disease. "Once we see ourselves energetically, it's going to change how we teach and practice medicine," Picard says. Rather than fixing parts piecemeal after they break down, we can ask what keeps us all happily humming along in the first place. In a sense, we are all energy benders, channeling an endless flow of what was once sunlight through the labyrinth of our molecules and gracefully shaping it into this thing we call life. ●