



# NOT SO FAST

**Scientists disagree**  
on how to eat for your  
best life. **DiETING** may  
never be the same.

by MARK BARNA  
photos by LUCAS ZAREBINSKI

# So much was happening, it was hard to take it all in.

Just over a year ago, Alex Allen moved across the country to San Francisco. He'd landed a job as a software engineer, achieving his dream of working in a city at the center of the tech industry. The 24-year-old loved the area's open culture and mild, consistent weather. He wanted to make the most of his adopted city.

But socializing inevitably posed a problem. Sometimes, dinner with new friends meant he sipped water as he watched them chow down.

In the last couple of years, he'd started a fasting diet — 16 hours of fasting and then eating within an eight-hour window each day. It had been a wake-up call for his body. In his late teens and early 20s, he lifted weights regularly, but he also packed on a lot of fat. He was over 200 pounds, and he was tired of it.

Research shows it's an effective weight-loss strategy and also has potential to improve health for people of normal weight. Regular practice may delay the onset of age-related diseases, such as cancer, Type 2 diabetes and neurodegenerative diseases, such as Alzheimer's. It also appears to enhance learning and memory, and can increase life span.

In addition, fasting is being explored as a supplemental treatment for brain injury, various cancers and metabolic syndrome. Most of these results are preliminary, and many of them are conclusions from animal studies.

Still, Valter Longo, a cell biologist and fasting researcher at the University of Southern California, says fasting is the body's built-in fixer. It holds the power to heal. "But now, because we eat all the time, that inner repair has been eliminated," he says. "We are not benefiting anymore from this ability."

Fasting is not the first dietary approach to excite researchers. Before fasting, there was caloric restriction, or CR. The methods have much in common. Overall, they both drastically reduce energy intake and bring about similar health benefits. They're like siblings in a way, especially since fasting studies emerged from work

Fasting began as a way for him to lose flab. It soon became a way of life.

So he tried a 16-hour fast, a popular method called 16:8. He experimented with another popular regimen, 20:4, eating within a four-hour window of a 24-hour day. Like a bodybuilder switching to heavier barbells, Allen eventually mixed in daylong fasts to his routine. His weight dropped to 166 pounds within four months.

He stuck to his diet in San Francisco but realized he'd have to just get through that part of sitting down to a meal with people. "It was a bit odd at first," says Allen. "But I don't mind doing it anymore. It starts a lot of conversations."

Fasting began as a way for him to lose flab. It soon became a way of life. "Nowadays, I do it for the other health benefits and just because it makes me feel great," says Allen. Those benefits are more energy, inner calm and mental clarity. "I can't imagine fasting not being part of my routine for the rest of my life."

Allen is part of a growing trend that started several years ago, when fasting caught the public's attention as a weight-loss strategy. Advocates say the practice is easier to stick to than other diet plans. But that alone doesn't account for its staying power. Fasting also has its share of clinical studies to back it up.

on CR. And now, many former CR researchers are exploring fasting, often setting the two against each other in the lab.

Although CR never caught on with the public like fasting has, it remains an important dietary experiment for scientists studying the biology of aging. To better understand today's fascination with fasting, we first need the skinny on CR.

## 120 OR BUST

Scientists have studied CR for 100 years. In that time, they have realized that lab animals whose daily energy intake was restricted by 20 to 40 percent lived longer and had a lower chance of chronic illness and disease. It was a baffling revelation: Eating less than the body apparently needs is a healthy strategy.

Up through the 1980s, researchers carried out the majority of CR experiments only on yeast, flies, mice and rats. An important question remained: Would CR work in humans?

That opportunity came by chance in 1991, when eight scientists entered Biosphere 2, an enclosed artificial ecological system near Tucson, Arizona.

Their mission was to live for two years on food grown within the domed habitat to glean information for future biosphere space colonies.

Physician Roy Walford was one of the scientists. He also happened to be a CR devotee and had recently written a book on living to the age of 120 by following the regimen. Soon after entering, the team realized the food they raised in the dome wouldn't be enough to sustain them. So Walford implemented an impromptu CR experiment. The four men and four women reduced their approximate calorie intake by up to 30 percent. It was essentially the first human study of CR and its effects.

In a paper published in 2002 on the pseudo-experiment, Walford and colleagues reported that the Biosphere staff had been in excellent health. Nearly all of them lowered their blood pressure, blood sugar, cholesterol and other health measures. Still, their skeletal appearance was shocking. "They were malnourished, and they didn't look healthy," says Eric Ravussin, a metabolic researcher at the Pennington Biomedical Research Center in Baton Rouge, Louisiana.

Biosphere 2 helped lay the groundwork for an unprecedented study. In 2008, Ravussin and collaborators put together the first rigorous clinical human trial of CR, called Calerie.

The trial, which aimed to investigate how food deprivation affects the aging process, involved 218 normal and slightly overweight men and women between the ages of 21 and 51. Of the group, 143 of them were tasked with

following CR, eating 25 percent fewer calories than usual — a decrease deemed feasible based on animal studies. They were to keep this regimen for two years with help from a behavioral intervention team and dietitians to make sure they were getting basic nutrition.

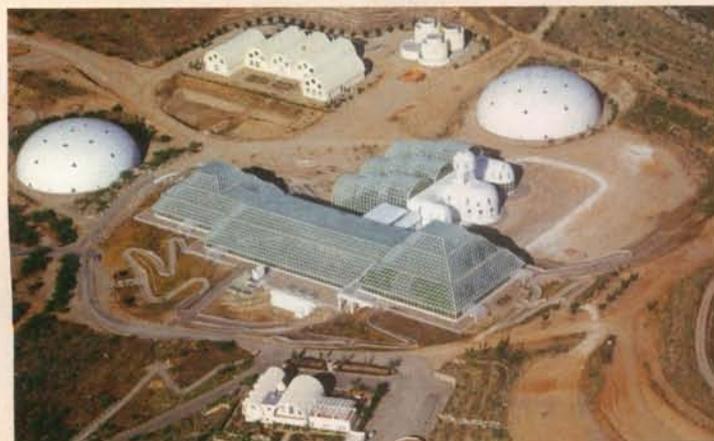
Most people in the CR group completed the trial, but their average drop in calories was just 12 percent. It didn't matter, though. Blood pressure, cholesterol, glucose, insulin and other biomarkers fell, possibly lowering their risk for heart disease, cancer and diabetes.

After the trial, another research group fed the Calerie biomarker data into age-estimation algorithms; they wanted to see whether CR might have had an effect on longevity. The conclusion was striking: During the study period, the people following CR had aged more slowly than those in the control group.

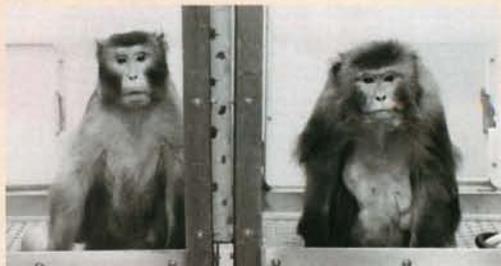
This mirrored some of what researchers were finding in non-human primates. Rhesus monkeys share 93 percent of their genetic makeup with humans and usually live to about 26 in captivity. In one study on 76 rhesus monkeys that's been running since 1989 at the Wisconsin National Primate Research Center, monkeys on a 30 percent calorie cut lived, on average, two to three years longer than control monkeys. Another ongoing study, started in 1987 by the National Institute on Aging on 121 rhesus monkeys, hasn't detected the same boost to longevity. But CR has worked remarkably well for the 10 males that started the diet later in life. At least four have lived past age 40, including one to 43 — a record for the species.

## Caloric Restriction Studies

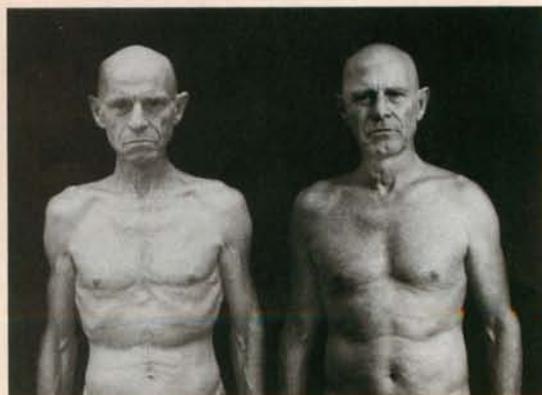
Researchers have been studying caloric restriction (CR) for decades. The dietary practice involves cutting calories by 20 to 40 percent for animals and around 25 percent for humans. There are impressive benefits, with followers reporting not just weight loss but improved health measures such as lower blood pressure and drops in cholesterol, glucose and insulin levels.



In 1991, eight scientists aimed to live for two years in Arizona's Biosphere 2, surviving off food grown in the domed facility. They soon realized supplies wouldn't last and cut their daily caloric intake by up to 30 percent, in the first impromptu CR quasi-experiment in humans. Roy Walford, one of the Biosphere residents, led the effort. His weight dropped from 150 (far right) to 119 (left).



Long-term studies of rhesus monkeys have found that those on CR (left) live longer than those on regular diets (right). In captivity, these monkeys typically live until about 26, but some on CR have lived beyond 40.



## AS OLD AS LIFE ITSELF

Despite the data from studies, scientists still aren't completely sure how and why CR works. It might be an adaptation that developed billions of years ago in microorganisms trying to survive when food was scarce. Studies on *E. coli* show that when switched from a nutrient-rich broth to zero nutrients, the bacteria live four times longer.

It appears that restricting calories activates genes that direct cells to preserve resources. Rather than grow and divide, cells in famine mode are, in effect, stalled. In this state, they are mostly resistant to disease and stress and enter into autophagy, a process of cleaning out dead or toxic cell matter and repairing and recycling damaged components.

On top of that, in mammals, production of a hormone that's key to cellular growth, called IGF-1, drops, according to several papers. The hormone helps youngsters grow tall and strong, but in adults, it increases cancer risk and accelerates aging when not suppressed.

Jeffrey Peipert wasn't necessarily after any potential anti-aging benefits when he enrolled in the Calerie trial. And he wasn't purely aiming to advance the research on cellular aging. He mostly wanted to lose weight.

Peipert was 48, stood at 5 feet, 5 inches, and weighed 174 pounds. During the trial, he cut his daily food intake from 3,300 to 2,475 calories, and his weight dropped to 147 pounds. His health biomarkers, especially his blood pressure, were excellent. "It was a remarkable drop in blood pressure. That taught me that, for our health, if we were just a little thinner, we'd be better off," says Peipert, a gynecologist and researcher at the Indiana University School of Medicine.

The big takeaway from Calerie, Longo says, is that the biomarkers of health are controllable through weight loss. "So if your doctor is telling you that you need drugs to control these things, that's not true," he says.

## NOT ALL MAGIC

Although CR might be metabolic magic, it's no magic bullet. Some mice bred to carry certain genes for lab research don't benefit from it, and it actually shortens life in other genetically modified mice. The deprivation can weaken the immune system of very young and very old animals, making them susceptible to disease. And although cutting calories by 25 percent has been standard, it's not clear if that's best for animals and humans.

As with mice, people react differently to food deprivation. In recent years, scientists have learned that genetics, diet composition (amount of carbs, protein and fats), regular exercise and other factors play a role in CR's effectiveness.

Peipert's experience in the Calerie trial points to these issues. Despite his banner biomarkers, he had trouble sleeping, a reduced libido, low energy and was hungry most of the time. "I used to love to garden," says Peipert, now 57. But during the trial, "I was wheeling a wheelbarrow around full of dirt, and I felt weak. I wasn't myself."

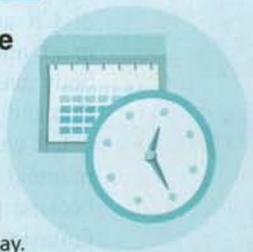
# FAST LANE

## Popular Water-Only or Low-Calorie (500-600) Fasting Plans

**1. Time-restricted feeding:** Eating within a specific window of time in a 24-hour period. The most popular is 18:6, eating only during a six-hour period of a 24-hour day. Other variations are 20:4, 22:2 and 23:1.

**2. Alternate-day fasting:** Fasting every other day.

**3. Intermittent fasting:** Fasting one day or several days a week. Most popular is 5:2 — eating normally five days a week, fasting two days a week.



## How Low Can Calories Go?

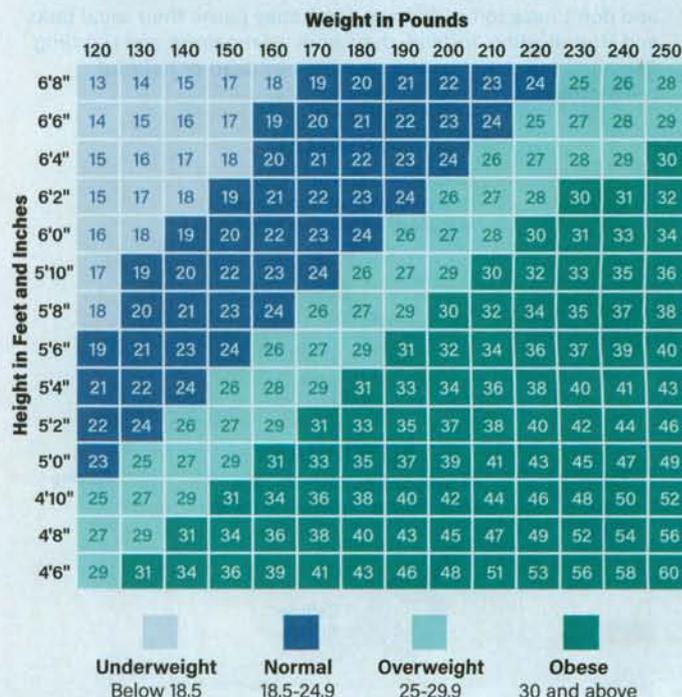
People can live days with no food and water, and weeks or several months consuming only water. In lab animals, when calorie intake is cut by more than 50 percent, they eventually die of complications from starvation. In the final stages of starvation, the body, depleted of glucose and fatty acids, turns to muscle protein for energy. Humans die when their body mass index (BMI) is around 12.

Gender	Average calorie requirements	Low but sustainable: 25% restriction	Danger zone: 40% restriction	Fatal BMI
Men	2,500	1,875	1,500	13
Women	2,000	1,500	1,200	11

## BMI Ranges for Adults

Body mass index, or BMI, uses height and weight to determine how healthy a person's weight is. Though it doesn't measure body fat, BMI has been shown to correlate closely with metabolic and disease risks. In general, health risks rise for people with BMIs of 30 and above or below 18.5.

$$\text{BMI} = \frac{\text{Weight (pounds)}}{\text{Height}^2 \text{ (inches)}} \times 703$$



Sources: CDC, NIH, British Nutrition Foundation

These types of side effects weren't more common in CR dieters overall, but several people had to pull out of the study because of safety concerns. Noted side effects of CR are chronic loss of bone density and lean body mass, and excessive weight loss. Some CR dieters have body mass indexes in the teens, which suggest malnutrition and frailty, Longo says.

CR can lead to psychological issues, too. These were minimal in the Calerie trial, but Ravussin says that's likely because people were screened for predispositions: food fantasies, irritability and social isolation, he says. Some of the Biosphere 2 scientists said they became prickly and obsessed about food during their 21-month deprivation.

to a significantly reduced calorie load every day was the hammer blow. At this point, fasting was CR's heir apparent: It seems eating nothing on occasion might be better than eating less all the time.

### FASTING REDUX

Fasting has deep roots in human culture. It's been a practice within various religions for millennia, and the ancient Greeks marveled at its impact on the body and mind. For centuries, doctors noticed it could reduce epileptic seizures. Paracelsus, a 16th-century German-Swiss physician, called it "the physician within."

But it wasn't until the 1940s that the first experiments

## It seems eating nothing on occasion might be better than eating less all the time.

Kelly Vitousek, a psychologist at the University of Hawaii who has written review papers on CR, says these problems make sense from an evolutionary perspective; food is one of our top priorities. "Don't waste your time on other stuff," she says. "Think food, not about socializing, not about sex. Be preoccupied with food. Obtain it."

During the Biosphere 2 experience and the Calerie trial, some researchers hoped CR would become a viable regimen. But the enthusiasm has significantly cooled. While side effects were an issue, people's inability to stick

began as an outgrowth of CR studies. Researchers started withholding food from lab animals on alternate days, says Michelle Harvie, a research dietitian in Manchester, England. And in 1946, *The Journal of Nutrition* published the first study on fasting, showing that rats deprived of food every third day lived longer and were less likely to develop tumors than control animals. Later work showed that fasting spurs metabolic changes similar to those of CR.

By the 2000s, some fasting studies were showing better results than CR. In a 2003 experiment, Mark Mattson, a neuroscientist at Johns Hopkins University and the National Institute on Aging, found that mice fed on alternate days were healthier than mice that were calorie-restricted by 40 percent.

In 2012, the idea of fasting was popularized when BBC commentator Michael Mosley aired a popular television documentary about the diet. A best-selling book, *The Fast Diet*, followed the next year.

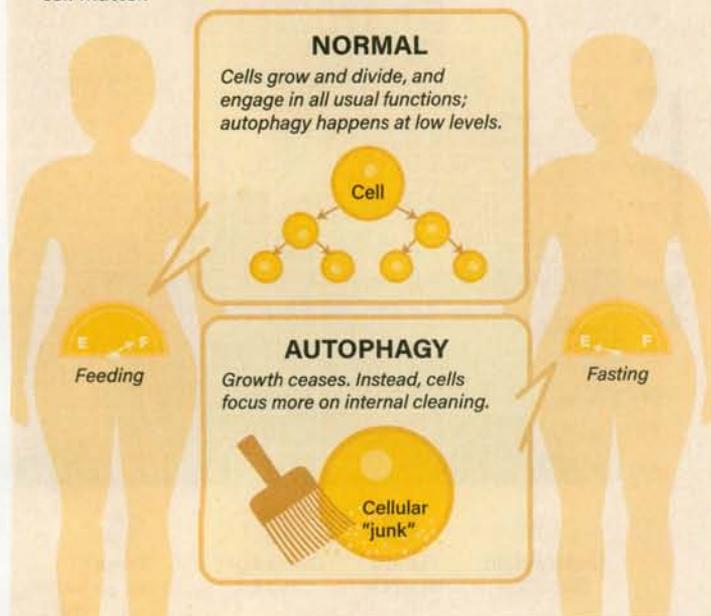
As fasting has grown in popularity, scientists and nutritionists have developed different methods of the practice. Some, such as Allen, practice time-restricted feeding, like the 20:4 regimen. Some push the approach to 23:1, cramming all their eating into one hour of a 24-hour day. Other approaches space out fasting days throughout the week, such as the 5:2 method — two days of fasting over seven days. Some enthusiasts supplement their practice with dayslong fasts.

Although people normally think of fasting as only consuming water, the most popular of these plans does allow for calories on "fast" days — just not enough to impede the practice's healthy physiological effects, says Mattson.

In 2012, Carolyn Corbin, who lives in the Channel Islands, got some firsthand experience with fasting's flexibility. At 5 feet, 2 inches tall and 159 pounds, Corbin was overweight, with a BMI of 29.1. After seeing Mosley's BBC show, she took up the 5:2 regimen, eating 500 calories two days a week and eating normally the rest of the

### Cellular Cleanup Crew

Fasting and caloric restriction both can ramp up autophagy, a kind of cellular housekeeping. When cells are in famine mode and don't have to break down food, they pause their usual tasks and stop dividing. Instead, they work on repairing and recycling damaged components, and cleaning out dead or harmful cell matter.





# FASTING SHORTCUTS

Even though fasting and caloric restriction can offer health benefits, both require eating less — something unappealing to most people. So scientists and nutritionists have experimented with ways to mimic the biochemical and physiological effects brought about by sustained periods of food deprivation.

## Keto Diets

Ketosis occurs when the body, deprived of food for 12 hours or more, switches its energy source from carbs and glucose to fatty acids. The process generates ketone bodies that may have healthy effects.

Keto diets, composed of low-carb, high-protein and high-fat foods, can also spark this metabolic switch. Since the 1920s, keto diets have been used in medicine to reduce epileptic seizures. More recently, the diets have supplemented standard treatments for Type 2 diabetes and cancer, with promising results.

Over the last few years, keto diets have gained mainstream popularity. Some celebrities and sports stars embrace them, and people who fast use the regimen to further push their body into ketosis.

But followers beware, says nutrition researcher Michelle Harvie. Dieters going keto tend to lose weight, but the diets are low in fiber and high in saturated fat, which is a risk for cardiovascular disease. “And there is increasing evidence that its effect on the gut microbiome is pretty adverse,” says Harvie. “The gut microbiome is a poorly understood but potentially important part of our metabolic health. And if you mess that up, you’re in trouble.”

## Fasting-Mimicking Diet

Valter Longo, a cell biologist at the University of Southern California, has developed ProLon, a five-day diet that mimics a five-day fast, but without loss of essential nutrients. It’s an all-vegan diet with high unsaturated fat (think almonds, avocados and peanut butter), low sugar and low protein.

In a 2017 study in *Science Translational Medicine*, 71 participants who completed the fasting-mimicking diet showed health benefits including weight loss, lower blood pressure and a drop in levels of the hormone IGF-1, which primarily stimulates growth but also plays a role in regulating blood glucose levels. And depending on how healthy you are, you may not need to stick to the diet too long. For instance, Longo says a healthy athlete may need to do it only twice a year, while someone who’s overweight may need to continue with it until they see the improvements they want.

## Pharmacology

Medicines that treat chronic medical conditions, like epilepsy and Type 2 diabetes, are being explored to mimic fasting. The major players are rapamycin, metformin, resveratrol and hydroxycitrate. The drugs show promise, but also have downsides.

Rapamycin, for example, tricks cells into thinking they’re nutrient-deprived, sparking the cellular rejuvenation seen in fasting, but it also suppresses the immune system. That’s helpful in medical scenarios, such as preventing organ rejection after a transplant or to treat autoimmune diseases, but not so great for the average dieter. —M.B.



time. She soon switched to water-only fasts two days a week. Since taking up the practice, the 65-year-old has lost 35 pounds and kept it off. “Forget calorie counting, diet food and diet drinks,” Corbin says. “Fasting for weight loss works.”

And there’s more than anecdotal experience like Corbin’s that fasting can help people lose weight. In a one-year study, 100 obese adults ages 18 to 64 were assigned to three groups. One group practiced alternate-day fasting, eating 75 percent fewer calories every other day; another group followed CR, with a 25 percent calorie restriction every day; the rest were in a control group. Compared with the control group, the fasters averaged 6 percent weight loss, and those assigned to CR averaged about 5 percent, according to the 2017 paper in *JAMA Internal Medicine*.

Even with these results, one of the concerns with fasting is that people will binge on non-fast days. But the results of two months-long trials, published in 2018 in the journal *Food Science & Nutrition*, showed that dieters, specifically those following 5:2, didn’t binge. “When you impose a two-day 70 percent calorie restriction, what they do on the natural days is eat about 25 percent less,” says Harvie, one of the authors of the study and a co-developer of the 5:2 diet. “And that is why the diet is so effective.”

## THE KETONE CONNECTION

Is fasting better at improving people’s health than CR? It’s far from clear. However, rodent experiments suggest it might be better at enhancing cognition.

For years, researchers have seen mice and rats perform well on cognitive tests when famished. While on alternate-day fasting, rodents improve their endurance, senses, memory and ability to learn.

So what accounts for this heightened mental state? It seems fasting triggers a dramatic switch in the body’s metabolism, according to a paper Mattson and colleagues published in February in the experimental biology journal *FASEB*. In humans, fasting for 12 hours or more drops the levels of glycogen, a form of the cellular fuel glucose. Like changing to a backup gas tank, the body switches from glucose to fatty acids, a more efficient fuel. The switch generates the production of ketones, which are energy molecules that are made in the liver. “When the fats are mobilized and used to produce ketones, we think that is a key factor in accruing the health benefits,” says Mattson.

One type of ketone flooding the brain is  $\beta$ -hydroxybutyrate, or BHB. According to a paper published in February in *Nature Reviews Neuroscience*, BHB stimulates memory, learning and the cellular housekeeping process of autophagy in mice. BHB also triggers neurons, including those in the hippocampus, a memory center in the brain, to release what’s called brain-derived neurotrophic factor, or BDNF, a protein that is important for learning, memory and improved mood. CR doesn’t generate these levels of ketones because glucose stores are never empty.

Mattson points out that, from an evolutionary perspective, the brain power that fasting generates makes sense. Mammals typically go days without food, often hunting on an empty belly. Semi-starved animals with enhanced smarts and energy would be more likely to obtain food and live another day. “If you are that wolf or lion, now a week with no food, you better be able to focus your mind and concentrate on what you need to do to get food,” he says.

Ketones might also help explain several mysteries surrounding brain injuries and disorders. For instance, fasting rodents recover more fully from brain trauma and spinal cord injury, according to several studies.

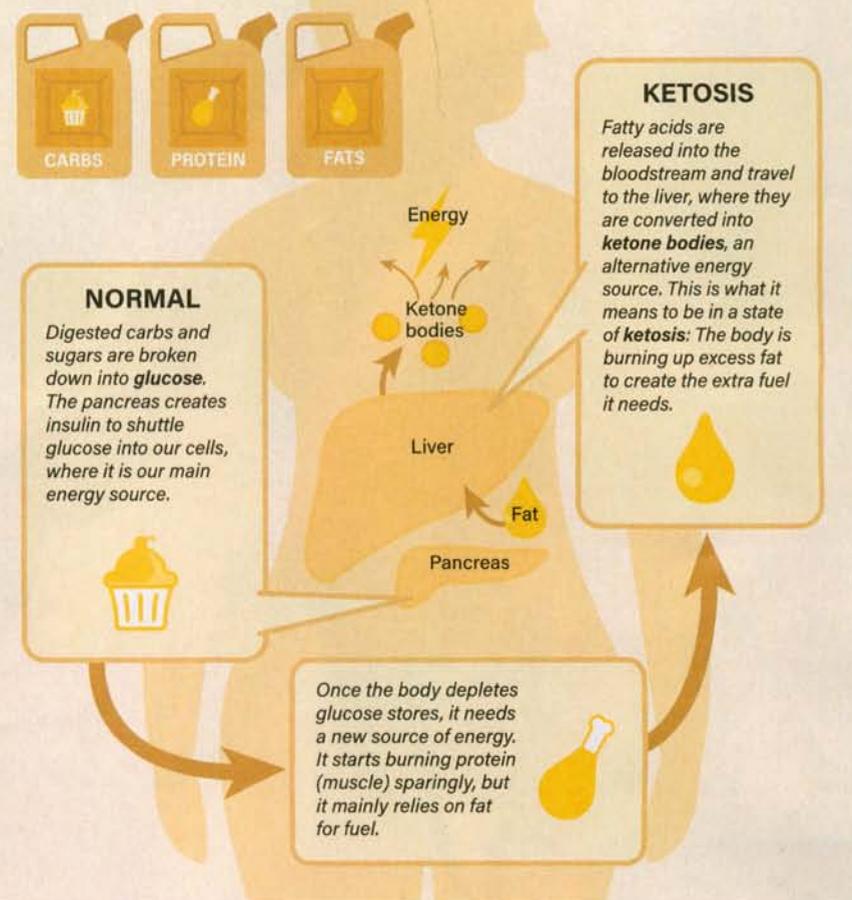
### FEAST OR FAD?

But fasting comes with its own caveats: a higher risk of binge eating, low blood pressure, irritability and headaches. The latter two tend to go away after a few weeks, as the body adjusts to fewer calories. Still, dayslong fasts can cause fainting spells. Doctors recommend it only under the guidance of a physician.

Ravussin, the CR researcher, isn't convinced fasting offers more benefits than CR, or that ketones are as powerful as Mattson and Longo say. “Ketones are a good thing to curb your appetite, but are they a good thing as far as

## Throwing a Metabolic Switch

The body can use three types of fuel: **carbohydrates, protein and fats.**



## Ketones might help explain several mysteries surrounding brain injuries and disorders.

cellular health?” he asks. “I have not seen convincing data that says yes.”

Harvie believes fasting might be here to stay, partly because it's flexible. People can choose a fasting practice and nutrient plan that fits their lifestyle, she says. “We twitter on about which diets are better. But at the end of the day, a diet is only as good as the person who follows it,” says Harvie. “For some people, the 5:2 will be perfect, and for others, it will be absolutely awful.”

Vitousek, the psychologist, has seen this kind of enthusiasm before — and it was for CR. Caloric restriction never reached fasting's popularity, but it had its share of lay followers in the 2000s, when she got a chance to talk with members of a group practicing it. Initially, they were excited and motivated. Then, like most dieters, the majority began to fall away. Some who had done CR for years simply couldn't do it anymore. “You can pretty

much take that to the bank,” Vitousek says of dieters' waning enthusiasm. “That's why we have these cyclical waves.”

For Peipert, it's been a seesaw journey. He's always struggled with his weight, and obesity runs in his family. A few years after the Calerie trial, he regained all the weight he'd lost, plus 6 pounds. “That kind of drastic calorie reduction for two years is probably not a sustainable or good plan for lifelong weight loss,” he says.

When fasting emerged as a diet, Peipert was skeptical. But in March, he started the 5:2 regimen. It was hard at first, he says, but by midsummer, he'd lost 9 pounds. He hopes to lose 10 to 15 more. “It has helped me control my hunger,” says Peipert. And with his experience of CR still on his mind, “No side effects.” **D**

**Mark Barna** is an associate editor at Discover.