**HELL, NO,**

Richard Isaacson bellows when asked whether some form of cognitive decline is inevitable with age, especially for those genetically tilted toward the disabling dementia of Alzheimer’s disease. Then, in the interest of science, an enterprise customarily cloaked in the conjectural, he restrains himself. Even of the 60 or so genes thought to influence the risk of Alzheimer’s disease after age 60, he says, none of them makes inexorable what surveys show is the most feared condition in a population living longer and longer. That fact, along with an earthquake of emerging evidence that cognitive impairment shows itself only after decades of decay in the processes that power our brain cells, has given Isaacson, a neurologist at Weill Cornell Medicine and New York-Presbyterian, enough of an edge to open the country’s first Alzheimer’s-prevention clinic.

The quick cascades of molecular events that enable you to toss a word off the tip of your tongue or remember where you parked the car begin at a basic level of body operations, and new methods of capturing their footprints have led to the recognition that cognitive decline is, in the words of science, modifiable. That such a tepid term cloaks a revolutionary possibility reflects the cautionary tale of recent history: Hundreds of trials of hundreds of agents to slow or stop cognitive decline in thousands of patients have been conducted over the past two decades, and every one has been a bust.

It may be that they all targeted the wrong mechanisms of disorder. Recent studies show that the plaques of amyloid proteins that accumulate between brain cells and the tangles of tau proteins that cluster within brain cells, both considered a signature of Alzheimer’s, also occur in many who have no memory loss—and are absent in 35 to 40 percent of those who, by neuropsychological testing, do. There’s no correlation between the presence of plaques and cognitive function. Rather than the trigger for disease, the plaques and tangles may be more peripheral phenomena or downstream effects of other processes.

Although no one can say for sure what causes the changes in the brains of those afflicted, that doesn’t mean those changes are not preventable. “In 2007, I used the term ‘treating prodromal Alzheimer’s disease,’ and no one paid attention to me,” says Isaacson. “Since 2014, when the clinic was founded, it’s been OK to say ‘Alzheimer’s disease’ and ‘prevention’ in the same sentence.”

And here’s the paradox of cutting-edge intervention—it may not entail anything exotic. No magic bullet, rather an array of mostly mundane choices accessible to almost anyone on the planet—primarily diet and moderate amounts of exercise. Much research suggests that at its core, Alzheimer’s disease—and garden variety cognitive decline—may be a metabolic disorder, a perturbation in fuel use by the brain, a process that loses efficiency with age and is inherently influenced by what we eat. After all, our bodies must run on the nutrients we consume, and the flora and fauna we harvest for the table are made from the same molecules that we are, their chemical constituents shuffled and reshuffled inside us—whether they arrive dressed up as duck à l’orange or unadorned as kale salad.

It matters hugely which nutrients we put on the table. In a preliminary study of 166 patients, Isaacson has found that as little as six months of a diet rich in fresh vegetables and light on carbohydrates can attenuate memory decline in those at risk, speed up mental processing, and boost executive function, including inhibitory control and attention. The diet includes fatty fish but no more than one serving of red meat a week—and then only grass-fed. When patients eat as important as what they eat; meals must leave room for at least a 12-hour carbohydrate fast overnight.

The diet is also a significant shift from standard American fare, which is so rich with red meat, fried foods, and denuded carbohydrates that ketchup was once proposed to constitute a vegetable serving. Even those who follow government-issued dietary guidelines are consuming only what is calculated to avert nutrient deficiencies, points out nutritional neuroscientist Lisa Mosconi, founder and director of the Nutrition and Brain Fitness Lab at New York University Medical Center. “We don’t know how to eat right for the brain,” she says.

**CIAO!**

**IF ANYONE KNOWS**, it’s people who live along the Mediterranean, as scientist Ancel Keys discovered nearly half a century ago. Regions where inhabitants build meals around fresh fruit and vegetables, eat substantial amounts of grain and legumes, and lavish olive oil on their food have the highest concentrations of healthy centenarians, Keys reported in 1970.

The Mediterranean way of eating is an unhurried event of several small courses accompanied by moderate amounts of wine. It features fish more than meat along with soups and sides of leafy vegetables, like Swiss chard and chicory in several variations, that do not win popularity contests at American supermarkets. Then, too, a major meal in Italy is typically followed by la passeggiata, a stroll around...
town that is as much an exercise of fashion as of musculature, and exercise is a proven brain protector.

Over the years, many trials of the Mediterranean diet have established that heart attacks are not an inevitable consequence of aging. And with gathering urgency over the past decade, trials of the diet—sometimes tweaked as new evidence rolls in—are demonstrating that cognitive aging isn’t either.

Because both the heart and the brain are exquisitely intolerant of disruptions in blood supply, what protects one also protects the other. “Vascular factors are as critical in cognitive function and the development of dementia as they are in cardiovascular disease,” says Irwin Rosenberg, head of the Human Nutrition Research Center on Aging at Tufts University. “Nutritional factors are similar for both.” The brain is only 2 percent of the body by weight, but it is metabolically active that it consumes 25 percent of the body’s fuel. Under ordinary conditions, that fuel is glucose. An array of nutrient-specific transport systems help nutrients cross the heavily guarded blood-brain barrier. Mess with the system and...well, that is exactly what hordes of researchers are desperately trying to figure out.

MIND CONTROL

HAD SHE NOT been born and raised in Italy, Mosconi would nonetheless be a champion of the Mediterranean approach. Her studies of clinically and cognitively normal men and women in their 40s and 50s show that even in middle age, the brain areas and functions most vulnerable to disruption by Alzheimer’s pathology are already being affected by diet, in ways that implicate typical American consumption patterns. Mosconi doesn’t view Alzheimer’s as a disease of old age: “It’s a lifelong process that starts young and reaches a tipping point only after age 50.”

In one study, Mosconi collected detailed information on food intake from 52 participants consuming their normal diet. She paid special attention to 35 nutrients linked one way or another to cognitive function. At the same time, she used magnetic resonance imaging to assess the volume of gray matter, which is a measure of brain atrophy—that is, cell death. Brain shrinkage—starting in the hippocampus, the seat of memory storage in the medial temporal cortex, and spreading to the frontal lobes, which control executive function—is a hallmark of Alzheimer’s disease. Mosconi also measured the amount of amyloid protein in the brain and glucose uptake by the brain.

Whether or not subjects had risk factors for Alzheimer’s disease, such as a family history of the disorder, Mosconi found a firm correlation: The higher the intake of vitamin B12, vitamin D, and omega-3 fatty acids, the lower the load of brain amyloid and the greater the brain volume and glucose metabolism. And consumption of foods rich in vitamin E, mono- and polyunsaturated fats, carotenoids, vitamins A and C, and fiber all positively affected glucose metabolism. Conversely, both brain volume and metabolism were lowest among those who consumed the most saturated fats, trans fats, cholesterol, and

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### Foods to Favor

<table>
<thead>
<tr>
<th>Foods to Favor</th>
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<tbody>
<tr>
<td>Sardines, herring</td>
<td>omega-3 fats, vitamin D</td>
</tr>
<tr>
<td>Leafy greens: Swiss chard, red-leaf lettuce, kale, spinach</td>
<td>B vitamins, vitamin E, fiber, vitamin C, antioxidants (carotenoids, flavonoids)</td>
</tr>
<tr>
<td>Cruciferous vegetables: cabbage, broccoli, cauliflower</td>
<td>B vitamins, vitamin C, fiber, antioxidants, glucosinolates</td>
</tr>
<tr>
<td>Yellow vegetables: carrots, squash</td>
<td>carotenoid antioxidants, B vitamins, fiber</td>
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<tr>
<td>Walnuts, almonds</td>
<td>vitamin E, antioxidants, omega-3 fats, vitamin B, fiber</td>
</tr>
<tr>
<td>Blueberries, strawberries</td>
<td>antioxidants, vitamin C</td>
</tr>
<tr>
<td>Legumes: lentils, chickpeas, beans</td>
<td>B vitamins, fiber</td>
</tr>
<tr>
<td>Extra-virgin olive oil</td>
<td>monounsaturated fats</td>
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sodium. Mosconi reported in *Journal of Nutrition, Health, and Aging*. The protective patterns were linked to a higher intake of vegetables, fruit, whole grains, fish, low-fat dairy food, and a lower intake of sweets, fried potatoes, processed meat, and high-fat dairy foods, including butter.

The same nutrients and their food sources turned out to be brain-protective in a separate study of cognitively normal individuals ages 25 to 72, all of whom were at risk for Alzheimer's: They either had a first-degree relative with the disease or carried a specific gene—the ApoE4 gene. Apolipoprotein E (ApoE) is one of several transporters of the fats, or lipids, the body deploys to move nutrients around, and it exists in three variant forms. The E4 variant, which is also implicated in heart disease, increases the risk of late-onset Alzheimer's disease, and it is present in about 20 percent of Americans. Those who have one copy of the ApoE4 variant have two to three times the average risk of Alzheimer's, while those with two ApoE4 alleles have 15 times the normal risk. But even they are not doomed to develop the disorder. The findings, Mosconi and her colleagues reported in *BMJ Open*, suggest that "nutritional interventions aimed at preserving brain activity might be particularly useful if instituted in young adulthood in normal individuals at risk for Alzheimer's disease, before irreversible neuronal loss."

Critically, Mosconi found strong effects of nutrients only when they came from actual foods, not from supplements. "The beauty of food is that it contains multiple forms of a nutrient. There are eight forms of vitamin E; one isolated form is less effective than all of them together." Only foods supply a broad array of antioxidants, and a motley army may be
needed to combat all the events underlying cognitive decline.

Few in the brain business doubt that the Mediterranean diet is good. But the MIND diet may be even better. Developed by Martha Clare Morris, a nutritional epidemiologist at Rush University Medical Center in Chicago, it bears the formal name Mediterranean-DASH Intervention for Neurodegenerative Delay and incorporates only those foods shown by "compelling scientific evidence" to be neuroprotective.

It prominently features green leafy vegetables and recommends at least one serving of them every day, along with two other vegetable servings. In year-long trials of the diet, Morris has conducted to deter decline among those at risk for Alzheimer's disease, green leafy veggies—good sources of carotenoids, the B vitamin folate, vitamin E, and polyphenols—had the highest positive correlation with brain function. "The rate of decline among those who consumed one to two servings per day was the equivalent of being 11 years younger in age, compared with those who rarely or never consumed green leafy vegetables," Morris found. Also high on the recommended list are berries (the only fruit to pass the evidence test); cruciferous vegetables; yellow veggies, rich in antioxidant-heavy carotenoids; along with nuts, beans, whole grains, poultry, extra-virgin olive oil, and wine.

Nearly a thousand Chicagoans ages 58 to 98 consumed the MIND diet and were rated based on their adherence to its brain-healthy food groups and avoidance of unhealthy food groups—red meats, butter and stick margarine, cheese, pastries, and sweets. The top scorers wound up testing 7.5 years "younger" in brain age than their nonadherent peers. The diet is powerful enough that even those who stick to it only moderately also benefit, with reduced rates of decline.

**ON-RAMPS TO OXIDATIVE STRESS**

ISAACSON DEPLOYS the MIND diet and adjusts it to the idiosyncrasies of individual biology—more omega-3-rich foods for those at cardiovascular risk because of high triglyceride levels, more vitamin D consumption for people with two copies of the ApoE4 gene.

But just as important as what people eat is when; for at least 12 hours overnight, five nights a week, no carbohydrates at all. Carbohydrate restriction shunts the brain onto its backup fuel, ketone. There is evidence that fasting resets the machinery of glucose utilization, starting with the elaborate system the body has for sensing the availability of nutrients. "The data suggest that the very earliest changes in Alzheimer's disease are those affecting glucose," says neuroscientist Gary Gibson, and they occur especially early—in young adulthood—in those who carry the ApoE4 gene. "Glucose changes are very highly correlated with cognitive changes."

In the brain, glucose powers all nerve cell activity, most intensively in the gray matter of the cortex, and for this key task it is converted, through several oxygen-needy steps, into adenosine triphosphate, or ATP, in the cell's mitochondria. But glucose also provides the precursors for synthesis of the brain's neurotransmitters, and it sets in motion processes to clear away waste products and cell debris, a necessary maintenance task for an organ that is a metabolic powerhouse.

As Gibson, who is a professor at Weill Cornell Medicine and its Brain and Mind Research Institute, sees it, the mitochondria are the first cause of Alzheimer's disease. With age, changes in the mitochondria impair oxidative metabolism and create oxidative stress, marked by excess levels of free radicals of oxygen—by themselves a potent agent of damage: to DNA, to fats, to proteins, and to vitro molecules. Oxidative damage is pervasive in the Alzheimer's brain, even more so than plaques and tangles, especially in the early stages of the disease, says Gibson. Oxidative stress, in turn, activates an enzyme that cleaves beta amyloid from its precursor protein, accelerating amyloid production and setting the stage for its accumulation.

But oxidative stress does much more, Gibson says. It impedes debris clearance, promoting the buildup of cell toxins, inflammatory processes, and cell death. And of particular interest to Gibson, it deactivates a mitochondrial enzyme called ketoglutarate dehydrogenase complex (KGDHC).

In animal studies, KGDHC deficiency leads to plaque formation, memory deficits, and diminished neurogenesis, which, Gibson says, suggests that increasing production of the enzyme could be therapeutic. KGDHC production hinges on the presence of vitamin B1, also called thiamine. Clinicians have long known that thiamine deficiency mimics Alzheimer's memory deficits and changes in cognition. Funded by the National Institutes of Health, Gibson is currently conducting a one-year clinical trial of a thiamine variant, benfotiamine, in 76 patients with mild cognitive impairment or mild Alzheimer's disease. Benfotiamine is a long-established treatment for neural complications of diabetes.

It may be that oxidative stress gets a pathologic push from the accumulation of iron in the brain. Studies have found high concentrations of the mineral in areas of the brain associated with neurodegeneration, and people at low risk for dementia have no such deposits. Diets rich in red meat may contribute to toxic levels—but so may government rules requiring iron-enrichment of refined grains. While the science sorts itself out, researchers believe
it is wise to keep blood hemoglobin levels at the low end of normal—yet another reason to limit consumption of red meat.

**TIME OUT: THE ROLE OF FASTING**

**GETTING GLUCOSE INTO** the brain in the first place is the job of a transport system that hinges on the hormone insulin. In the brain, the density of insulin receptors is highest in those parts of the organ with the toughest jobs, like the hippocampus and the prefrontal cortex, says Auriel Willette, assistant professor of food science and human nutrition at Iowa State University. The problem is that while insulin is essential for normal brain function, the body tends to become insulin resistant with age. What’s more, many foods in the American diet—refined carbohydrates, beef—promote insulin resistance, as do obesity and inactivity. The brain is so sensitive that even a small degree of insulin resistance (much less than it takes to set off diabetes) may have widespread downstream neural effects.

Willette’s work links insulin resistance with neurodegeneration and cognitive decline. In one study, he and colleagues looked at 150 cognitively normal middle-age adults at risk for Alzheimer’s and found that insulin resistance predicted diminished glucose metabolism—especially in the prefrontal and temporal cortices—as measured by PET scans, and it impaired memory on tests of cognitive function. “Insulin resistance confers a nontrivial risk for Alzheimer’s disease in midlife,” the team reported in *JAMA Neurology.* Willette contends that the way to interrupt “presymptomatic Alzheimer’s disease” is to target mechanisms involved in insulin signaling.

Enter fasting. Calorie restriction in general, and carbohydrate restriction more specifically, help overcome insulin resistance by forcing the brain off glucose and onto its backup fuel, ketone. Because brain function is so important, it is protected even under conditions of starvation; fat cells are directed to release their booty, and the liver converts free fatty acids into ketone bodies as a glucose replacement. Ketones are particularly efficient; the brain gets more ATP bang for its fuel buck from ketones than from glucose, and studies show that the increased energy boosts cognitive performance. Bypassing glucose helps restore insulin sensitivity.

Since the 1930s, scientists have known that calorie restriction can extend lifespan, and it does so by delaying or preventing age-related chronic conditions like diabetes, heart disease, neurodegenerative diseases, and many cancers. That such disparate disorders respond similarly suggests they are connected through some basic biological processes. The suspicion that there may be shared causes of the diseases of aging constitute what is now known as “geroscience,” and the hunt for those causes has become science’s latest gold rush. Targeting one may tackle them all, paying what has been called a “longevity dividend.” At least with the research that’s publicly funded, the work aims not so much to extend lifespan as to extend “healthspan,” to postpone chronic disease and compress decline into a fast endgame. Research focuses strongly on metabolism—because every cell needs energy and nutrients.

As effective as calorie restriction may be, it’s just too tough to maintain for long. Instead, researchers, working with creatures from single-cell yeast to worms, mice, and men, are exploring regimens that mimic the effects of calorie restriction and trying to figure out how they protect the body and brain. Cell biologist Valter Longo, a professor of gerontology at the University of Southern California and the director of its Longevity Institute, is one of them.

Periodic starvation is actually part of life, says Longo, a condition all organisms have faced from the beginning of existence. “We’ve forgotten that, because food is all around us. But fasting is a very carefully evolved process, and it revolutionizes metabolism in the brain. It changes the way the brain functions.” He calls it “a wide-action strategy” that works independently of the genetic hand anyone is dealt.

In humans, as in all other animals, Longo explains, biochemical mechanisms are built in for acquiring and storing food and then, during the lean times, calling on the stored energy for repair and resisting stress. Fasting triggers a host of intrinsic cell-renewal mechanisms, and studies in multiple organisms show that this fasting physiology is tied to the circadian cycle, as is our nutrient-sensing apparatus. At the dawn of life, both energizing and repair facets of metabolism were set in harmony with the day/night activity rest cycle. Whatever gains we’ve made with our full larders open 24/7 and artificial lighting, we’ve disrupted the activity/rest cycle: our metabolism was built on over millions of years of evolution, and we’ve inadvertently kick-started many chronic diseases. But fasting physiology, Longo finds, can be switched back on by intermittent and periodic fasting.

Restricting the timing of food intake to 12 hours daily, without any overt attempt to cut consumption, accomplishes the same thing calorie restriction does: It triggers cellular reprogramming, revitalizing glucose metabolism and signaling pathways, juicing up the complex cascades of molecular signals the body relies on to get nutrients to the brain. Middle-age mice placed on a fasting-mimicking diet for four days twice a month for seven months not only lived significantly longer and lost body fat, they outperformed standard-fed controls...
on tests of motor coordination and short- and long-term memory, Longo and the Salk Institute's Satchidananda Panda recently reported in *Cell Metabolism*. Studies show that the feeding strategy generates new and functional neurons.

**A METABOLIC MASTER**

**FASTING MAY NOT** be the only "wide-action" route to cognitive youth. Gerosciptists are keen on metformin, an antidiabetic drug in use for the last half century. Data collected on it over the years suggests it **curbs cancer risk and preserves cognitive function**, while laboratory studies show that it **aids glucose metabolism** by acting directly on mitochondria to slow oxygen consumption, thereby curbing oxidative stress as well as molecular damage, even to DNA. It's possible that it also exerts effects by favorably altering the composition of the gut microbiome. **A five-year, randomized, double-blind clinical trial of the drug that focuses on its antiaging effects (called TAME, or Targeting Aging with Metformin) has been approved and is awaiting adequate funding.**

**Rapamycin** is another drug already in use against one disease of aging—cancer—that may mitigate the other ills or, at the very least, provide insights into basic processes.

*BRAIN continued on page 88*
Fasting, Circadian Rhythms, and Time-Restricted Feeding in Healthy Lifespan

Valter D. Longo 1,2,* and Satchidananda Panda 3,4,*

1Longevity Institute and Davis School of Gerontology, University of Southern California, Los Angeles, CA 90089, USA
2IFOM, FIRC Institute of Molecular Oncology, Via Adanello, 16, 20139 Milano, Italy
3Regulatory Biology Laboratory, Salk Institute for Biological Studies, La Jolla, CA 92037, USA
*Correspondence: vlongo@usc.edu (V.D.L.), satchin@salk.edu (S.P.)
http://dx.doi.org/10.1016/j.cmet.2016.06.001

Most animals alternate periods of feeding with periods of fasting often coinciding with sleep. Upon >24 hr of fasting, humans, rodents, and other mammals enter alternative metabolic phases, which rely less on glucose and more on ketone body-like carbon sources. Both intermittent and periodic fasting result in benefits ranging from the prevention to the enhanced treatment of diseases. Similarly, time-restricted feeding (TRF), in which food consumption is restricted to certain hours of the day, allows the daily fasting period to last >12 hr, thus imparting pleiotropic benefits. Understanding the mechanistic link between nutrients and the fasting benefits is leading to the identification of fasting-mimicking diets (FMDs) that achieve changes similar to those caused by fasting. Given the pleiotropic and sustained benefits of TRF and FMDs, both basic science and translational research are warranted to develop fasting-associated interventions into feasible, effective, and inexpensive treatments with the potential to improve healthspan.

Introduction
Life forms on our planet have evolved under the strong influence of a daily light/dark cycle. With sunlight as the primary source of energy for photosynthesis, the daily production of photosynthetic biomass has a predictable diurnal rhythm. The daily cyclical production of photosynthesized chemical energy is at the base of the food chain. Daily changes in light and darkness result in diurnal rhythms in other environmental parameters such as temperature and humidity. Such a predictable and robust daily rhythm in food availability and environmental factors has led to the evolution of an ~24 hr internal timing mechanism or circadian rhythm to enable organisms to anticipate daily changes and to optimize fitness. Fundamental to this 24 hr rhythm is the ability to acquire food when it is available and to store a portion of these resources for utilization during the rest of the day (i.e., the fasting period) without compromising fitness and vitality. The fasting period also serves as a time for standby and repair so that the organism is fit and competent to harvest energy when light (for photosynthetic organisms) or food becomes available. While many non-photosynthetic lifeforms with short lifespan (< a few days) may not derive profound benefit from a circadian timing system, they share fundamental biochemical mechanisms for acquiring and storing food when it is available and then utilizing this stored energy during a quiescent period of fasting for repair, stress resistance, and vitality.

Inherent to this alternating cycle of feeding and fasting (irrespective of circadian rhythm-proficient or circadian rhythm-deficient organisms) is the theory that “fasting physiology” (biochemical processes associated with fasting) is triggered once stored energy is being utilized and therefore does not occur during the feeding period. This theory also highlights the notion that certain aspects of repair and rejuvenation that are integral to fasting-re-feeding physiology may be associated only with fasting. Hence, intermittent and periodic fasting may represent important factors in optimizing lifespan and healthspan. In circadian rhythm-deficient organisms, the optimal duration of fasting (i.e., one that avoids a low energy state that compromises viability) depends on the extent of stored nutrients and ambient conditions. These simple organisms have made tremendous contributions to the experimental dissection of molecules and mechanisms of cell-autonomous fasting physiology that is conserved across species. In circadian rhythm-proficient organisms, the inherent circadian oscillator has programmed a natural cycle of feeding and fasting that occurs with ~24 hr periodicity. However, even oscillator-proficient organisms have retained mechanisms to adapt to a few days of reduced or no energy intake without substantial loss of vitality. As a result, the oscillator-proficient organisms can benefit from sustained daily rhythms as well as from periodic fasting of several hours. Reducing energy intake on a daily basis, as in caloric restriction, may allow the fasting physiology to be triggered sooner and to be sustained for longer periods of time than when consuming standard or excessive amounts of calories. Similarly, restricting the timing of food intake to a few hours without an overt attempt to reduce caloric intake, as in time-restricted feeding (TRF), may trigger the fasting physiology after a few hours of feeding cessation on a daily basis. In summary, these arguments highlight the relevance of fasting physiology within the energy-restriction or time-restriction paradigms.

Modern humans face complex health challenges and solutions. While prevention, vaccination, and treatment for infectious diseases have prolonged lifespan, the presence of artificial light enables human activity throughout the 24 hr day. This disrupted activity-rest cycle indirectly disrupts the natural daily cycle of feeding and fasting, and facilitates excessive caloric intake. Such chronically disrupted temporal regulation contributes to metabolic diseases and may also accelerate the aging process. Treating for metabolic diseases has been challenging, as the traditional pharmacological approach to disease management may not be sufficient. Long-term chronic pharmacological
interventions have been particularly successful when the pharmacological molecule is a replacement of an essential biochemical agent, such as insulin (for type 1 diabetes), thyroid hormone, vitamins, or minerals, that is deficient. These replacement agents often have multiple modes of actions and exert pleiotropic effects. If daily, alternate daily, or periodic fasting can promote healthy lifespan by exerting pleiotropic effects, restoring a fasting period or switching to a diet that mimics fasting may be an effective treatment strategy for several chronic diseases.

**Historical and Evolutionary Arguments for the Safety and Potential Efficacy of Periodic Fasting in Health and Longevity**

The emergence at major university hospitals around the world of complementary and integrative medicine centers that utilize nutrition, exercise, yoga, and acupuncture to prevent and treat disease is evidence that the medical field is sampling traditional interventions to discover ways of improving and replacing FDA-approved therapies involving peptides, antibodies, and pharmaceuticals (Rakel, 2012). Many standard-of-care therapies are based on the discovery of enzymes, receptors, or other targets that mediate biological effects of interest, followed by the identification of specific drugs or biologics that interfere with or enhance the activity of specific targets. Although processes by which the drug target and drug are identified are highly sophisticated, resulting intervention (e.g., the inhibition of cholesterol synthesis by statins or the damage of DNA by chemotherapy drugs) can be viewed as rather unsophisticated strategies. In the case of statins, the inhibition of cholesterol synthesis does not take into account long-term effects of the accumulation of cholesterol precursors or counteracting mechanisms by which the human body is capable of synthesizing more cholesterol. In the case of chemotherapy drugs, the obvious collateral damage to non-cancerous cells is clear evidence of the lack of sophistication involved. It is therefore not surprising that years after a drug’s initial FDA approval, which is supposedly based on demonstrated efficacy, a wide range of side effects, as well as evidence for limited efficacy, often emerge. Undoubtedly, a more detailed understanding of the underlying causes of disease, and the undesirable short- and long-term consequences of standard therapies, could lead to more effective and safer drugs.

One promising alternative or complement to pharmaceutical interventions is to identify dietary and traditional remedies that have been safely utilized for hundreds of years to trigger sophisticated physiological responses resulting from billions of years of evolution. These evolutionary and historical arguments are scientifically meaningless, unless accompanied by (1) insights into their molecular mechanisms of action, (2) extensive and unbiased cellular and animal data, (3) epidemiological data, and (4) randomized clinical trials.

Among alternative interventions for the prevention and treatment of chronic metabolic diseases, different forms of fasting and fasting-mimicking diets (FMDs) have the greatest potential of being integrated into the standard medical care. These range from TRF, feeding every other day (alternate day fasting), adopting a reduced calorie regimen twice a week (5:2 fasting), or undergoing a periodic cycle of diets that provide a relatively high caloric content but are able to mimic many of the effects of fasting (FMDs).

Here we will review the evolutionary origins of fasting-related health benefits by examining the response of microorganisms to starvation and the mechanisms by which nutrients affect cellular protection and longevity. We will then describe how different forms of fasting affect the health and/or longevity of rodents and humans. The focus will be both on efficacy and safety.

**Model Organisms and Mechanisms: Chronic and Periodic Fasting**

The entry into fasting physiology that allows organisms to respond and adapt to starvation conditions first appeared in prokaryotes billions of years ago. This response represents one of the most potent examples of comprehensive cellular reprogramming and appears to be functioning in virtually all organisms (Longo and Mattson, 2014). Bacteria and baker’s yeast, switched from rich medium to NaCl or water, respectively, survive several fold longer, and the removal of bacteria from the worm’s medium causes a major lifespan extension (Fabricio and Longo, 2003; Kaebberlein et al., 2006; We et al., 2006). The network of genes and mechanisms responsible for these starvation responses are perhaps best understood in the unicellular *S. cerevisiae*, whose chronological lifespan is doubled when all nutrients are removed from the medium.

The two central dietary components that block the starvation response in yeast and whose removal results in lifespan extension and stress resistance are amino acids and glucose. In particular, serine activates Pkh/PDK signaling, and threonine and valine activate Tor signaling. Both of these pathways converge on the serine/threonine kinase Sch9, the yeast ortholog of mammalian S6 kinase (Figure 1) (Mirisola et al., 2014). Other amino acids, including methionine, have been implicated in the reduced protection and longevity of *S. cerevisiae* (Ruckenstein et al., 2014). Glucose, on the other hand, activates the Ras, adenylyl cyclase, PKA pathway. Subsequently, the glucose and amino acid pathways converge to inactivate the serine/threonine kinase Rim15, which, in turn, positively regulates at least three major stress-resistance transcription factors: Msn2, Msn4, and Gis1 (Figure 1). Therefore, when glucose and amino acids are removed from the medium as part of the switch from rich medium to water, these protective transcription factors are activated and regulate a wide range of stress-resistance and metabolic genes responsible for protecting DNA against oxidative damage, switching from a glucose- and mitochondria-dependent mode in which ethanol and acetic acid are accumulated to a mode in which acetic acid and ethanol are utilized for energy, and glycerol plus trehalose are produced (Hu et al., 2014). This starvation-dependent reprogramming of the yeast metabolic pathways is reminiscent of the fasting-dependent switch from a glucose-driven oxidative phosphorylation to a ketone bodies and fatty acid-dependent metabolism in mammals, which is also associated with the generation of glycerol. The mechanisms of starvation-dependent lifespan extension in yeast are still not fully understood, but because they largely depend on the activity of transcription factors Msn2, Msn4, and Gis1, they are likely to be, in part, dependent on the increased expression of genes involved in the heat-shock response as well as antioxidant genes SOD1 and SOD2, but also on the reduced generation and/or concentration of superoxide and other toxic molecules. One of the consequences of the inhibition
human studies in which FMDs are combined with standard cancer therapies. Because they require a more in-depth understanding of what they do, how they can be combined, and the type of condition or disease they can prevent or treat, it will be necessary to involve and train medical doctors, registered dietitians, and other healthcare professionals on how to safely and effectively implement their use.

ACKNOWLEDGMENTS

This work was supported, in part, by the NIH grants AG20642 and AG031906 to V.D.L. and EYO16807 to S.P. We thank Dr. Min Wei for the careful reading of the manuscript. V.D.L. has equity interest in L-Nutra, a company that develops medical food.

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