FOCUS ON: URIC ACID

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FROM THE DESK OF DR. PERLMUTTER

A Note Before Reading

What do obesity, insulin resistance, diabetes, fatty liver disease, hypertension, cardiovascular disease, stroke, neurological disorders, and premature death have in common? All can be stoked by high uric acid levels.

Yes, that's right, uric acid.

For years I've talked to you about gluten, carbohydrates, and healthy fats. None of what I'm about to tell you in the following pages runs counter to the recommendations I've made in my recent works. What this will do though, is shed light on an until now undiscussed and critically important area of health: our relationship to fructose and its by-product, uric acid.

Until recently, uric acid was only considered to be worrisome in the context of either kidney stones or gout. Now, we know that elevated of uric acid actually predicts having high blood pressure, obesity, type-2 diabetes and raises the risk of developing any number of chronic health conditions.

But the empowering part of our message focuses on the impressive effectiveness of simple changes in diet and other lifestyle parameters in bringing uric acid under control. On the pages that follow, you'll discover exactly how.

When you've finished reading, do visit my website to learn and discover even more. I'll continue to scour medical journals for the latest research, and help you understand what that means for your health.

In good health,

David Perlmutter, MD

Uric Acid, Blood Sugar, and Body Fat

AMPK is an enzyme of central importance in human metabolism. Yes, this post is a bit steeped in science, nonetheless, the information is really important as you soon will see.

AMPK plays such an important role in regulating human metabolism that it has been called metabolism's "guardian." It basically serves to inform our metabolism as to the energy status of our bodies, allowing changes to occur when energy (food) is abundant or when we are in a state of calorie scarcity. As such, AMPK lets the body know whether it should be producing glucose and storing fat or focus on using fat for energy while not adding glucose when it is already abundant. AMPK, in this role, helps dictate whether we are in a state of *autophagy* whereby we are activating processes to break down cellular components that are defective and can be recycled, or building tissue.

Understanding how AMPK functions has provided researchers the opportunity to target this enzyme for treating, for example, type 2 diabetes. Obviously, in type 2 diabetes we wouldn't want to turn on the production of glucose, a process called *gluconeogenesis*. And activating AMPK helps reduce this activity. This is exactly the mechanism whereby the diabetes drug *metformin* is able to help control blood sugar. Stimulating AMPK basically tells the body that food is plentiful so there's no need to make sugar. And because there is an abundance of food, the body doesn't need to store fat. Instead, fat is oxidized for fuel—a true example of fat burning.

Context is everything. And there is a context in which we would *want* to shut down AMPK and increase the production of glucose. That is essentially what happens to our bodies when we are in starvation mode—when we aren't finding food and need to power our brains to help us through this time of food scarcity. What I am describing is how shutting down AMPK was a terrific survival mechanism for our hunter-gatherer ancestors. Creating glucose to power the brain while at the same time slowing down how the body burns fat, and thus conserving energy, allowed our ancestors the ability to make it through the tough times when food was scarce.

In the context of our world, where for many food is abundant, we need to keep AMPK active. This helps with keeping glucose under control and tells our bodies that there is no need to keep packing on the fat. And one of the best and most direct things we can do to activate AMPK is really straightforward. All it takes is exercise. Exercise, like metformin, is a potent AMPK activator that helps control blood glucose while stimulating fat oxidation.

On the other hand, it's now been revealed that a central mechanism that actually *reduces* the activity of AMPK, paving the way for fat retention and elevated glucose is *uric acid*.

Uric acid, the end product of fructose metabolism, has been described as a "danger signal" that alerts the body to get ready for winter, a time when food will be scarce. And it does so by shutting down AMPK. This would have been really handy back in the day, but frankly these days, the winter of food scarcity never really comes. But we pack on the fat nevertheless and watch as blood sugar rises and rates of diabetes reach epidemic proportions.

So the actionable point here is to get to know your uric acid level, and keep it below 5.5 mg/dl. It's a lab test any healthcare provider can perform and it can even be checked at home using a monitor much like those people use to check their blood sugar. Strategies that you will learn in Drop Acid that can help bring uric acid under control include reducing fructose, alcohol, and purine consumption as well as the benefits of supplements including quercetin and vitamin C.

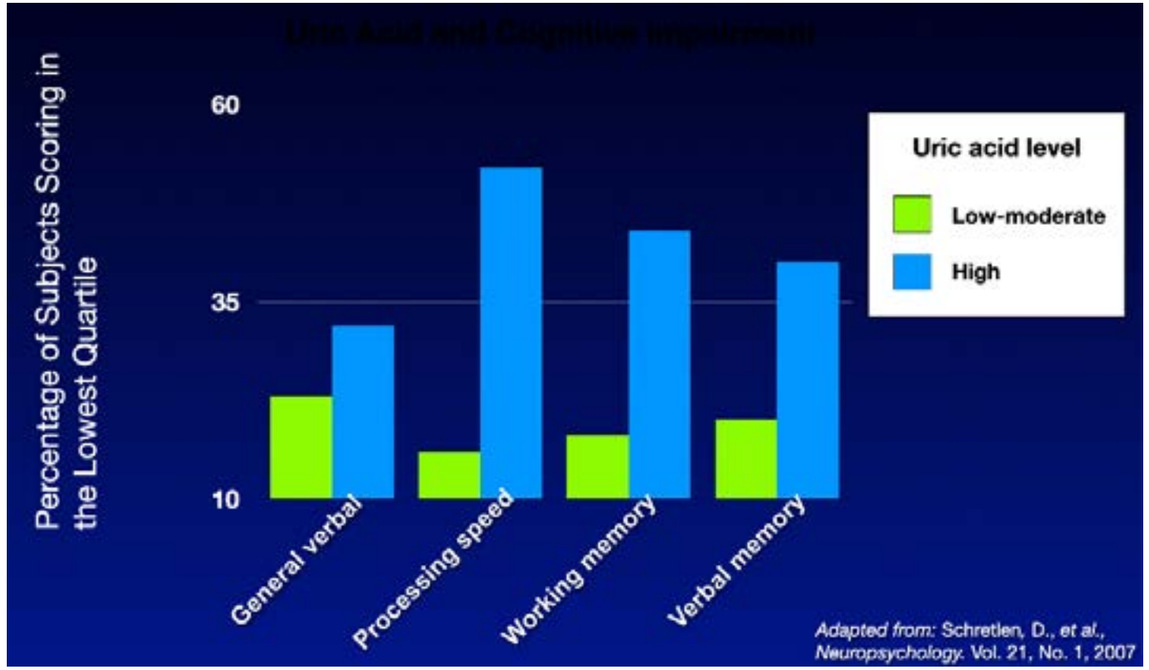
Uric Acid and Cognitive Decline

There are several key mechanisms that are directly involved in what causes our most pervasive degenerative conditions like coronary heart disease, type 2 diabetes, overweight and obesity, hypertension, and dementia of the Alzheimer's type. These mechanisms include inflammation, metabolic issues that involve insulin resistance, and even poor blood supply. We now recognize that uric acid elevation contributes quite dramatically to these mechanisms and as such, can serve as a potential target in terms of getting to the root cause of these and other problems. Inflammation, blood supply issues, and metabolic factors like insulin resistance are involved as primary mechanisms that lead to brain degeneration. And with the now recognized central role of uric acid in amplifying these damaging mechanisms, it seems reasonable to expect to see some correlation between uric acid levels and cognitive decline.

This relationship was evaluated by researchers at Johns Hopkins University School of Medicine and published in their report entitled Serum Uric Acid and Cognitive Function in Community-Dwelling Older Adults. The study involved 96 elderly adults and was designed to investigate the relationship between uric acid level and cognitive function. The participants were age 65 or older and each underwent a physical as well as neurological examination, a psychiatric interview, laboratory blood studies, an MRI scan of the brain, and a battery of neuropsychological tests to determine cognitive function. Specifically, the neurocognitive evaluation looked at general verbal skills, processing speed, working memory, and verbal memory, and compared how these individuals fared in terms of their performance in these domains versus their blood levels of uric acid.

The findings of the study were quite dramatic. Based on their neurocognitive testing, the subjects were ranked in four categories based upon their performance, from worst to best. These four categories are called quartiles. In the graph below, across all four domains of cognitive function, having a high serum uric acid (blue) was related to a much greater likelihood of scoring in the lowest quartile in comparison to those with a low or moderate uric acid level (green).

What this study shows is there is a very powerful correlation between high levels of uric acid and poor cognitive performance. It doesn't necessarily prove that poor cognitive performance is caused by the elevation of uric acid. But when we circle back to what uric acid does, when elevated, in terms of inflammation, insulin resistance, and blood supply compromise, these results, looked at in this context, are all the more understandable.



Indeed, as the authors of this study concluded:

> *These findings suggest that high normal concentrations of serum UA should be added to the growing list of cardiovascular and metabolic biomarkers of mild cognitive impairment among elderly adults.*

Cognitive dysfunction joins a long list of other maladies that have now been related to elevation of uric acid like type 2 diabetes, hypertension, obesity, and dyslipidemia. While there is no hard, set value of uric acid that will take away the risk of all of these situations, it seems reasonable to try to keep your uric acid level below 5.5 mg/dl. Fortunately, we now understand how dietary choices directly influence uric acid levels. The big players in terms of increasing uric acid are fructose, alcohol, and the breakdown products of DNA and RNA called purines. In my new book Drop Acid, you will learn about specific nutritional supplements like quercetin and vitamin C and dietary and other lifestyle interventions that are designed to normalize uric acid levels as well as how uric acid can be easily tested at home.

Uric Acid – How We Got Here

As scientific research begins to more fully understand the incredible depth of the relationship between elevation of *uric acid* and some of our most aggressive metabolic problems including diabetes, insulin resistance, obesity, hypertension, and dyslipidemia, it's important to take a step back and ask, how did uric acid become the central player, mechanistically, in these issues?

To understand the how and why of uric acid, we have to go back to a place in time when our primate ancestors did not manifest the biological mechanisms for uric acid accumulation. And indeed, we need to go back a long way. Somewhere between 15 and 17 million years ago, during the Miocene period, the earth's temperature experienced a progressive decline, and this played out as a threat to food availability for these early primates. Over several million years, adaptations took place that allowed our ancestors to make fat, store fat, and increase their endogenous production of blood sugar, *glucose*. Our primate ancestors that experienced genetic changes permitting these metabolic shifts to take place were the ones who survived.

We are now beginning to understand exactly what those genetic changes involved. Mammals typically deal with accumulation of uric acid by utilizing an enzyme called *uricase*. Uricase breaks down uric acid so it can be excreted as allantoin. The series of mutations in our primate ancestors that took place millions of years ago ultimately shut down the uricase enzyme which set the stage for accumulation of uric acid. So, all of the great ape descendants of these early primates, including chimpanzees, orangutans and bonobos, as well as we humans carry this lack of uricase enzyme. So, unlike most other mammals, we accumulate uric acid to the extent that our uric acid blood concentrations and those found in great apes are at least 10 times higher than in other mammals. And it is this genetic change or adaptation that allowed these primates the ability to make fat, store fat, and create glucose when needed. This allowed their survival in the face of an environmental stress, lack of food availability. Essentially, this was a situation of "survival of the fattest."

The pathway then and now causes uric acid to be increased in the presence of dietary fructose and *purines* (breakdown products from DNA and RNA in various foods). And what proved to be a powerful survival mechanism for our ancestors, now, in the face of food abundance, is fundamentally relevant in terms of our most challenging issues from a health perspective. This survival mechanism, in one environment, is a powerful threat to human health in our modern world.

This is a classic example of an "evolutionary/environmental mismatch." No doubt this mutation, or series of mutations, served our more recent ancestors, like hunter-gatherers, who may also have been challenged by food scarcity.

One of the most threatening aspects of elevated uric acid is how it enhances insulin resistance. These days, combating insulin resistance is certainly front and center as it relates to our goal of keeping blood sugar levels normalized. But in the context of our distant ancestors, becoming insulin resistant was actually another survival mechanism as it led to higher levels of insulin, again favoring fat storage and increased appetite. In our modern world, these are things we can certainly do without, for the most part.

With our understanding that uric acid is the end product of fructose metabolism, it's no wonder that in the past 100 years, uric acid levels have skyrocketed in lockstep with our increased consumption of sugar. Table sugar is 50% fructose, and as such, its increased consumption has led to a dramatic elevation of uric acid, which translates to increased risk for the very situations we don't want to find ourselves in, like being hypertensive, overweight, diabetic, or having issues with dyslipidemia like elevated cholesterol.

As we move forward and learn more about the metabolic effects of uric acid and its relationship to various disease states, as well as what we can do from a lifestyle perspective to bring uric acid under control, it's important to recall the history of how we got here in the first place. Again, it's not that uric acid is necessarily bad, nor is fat storage or insulin resistance for that matter. It's really all about the context. What once proved favorable and advantageous now threatens us in terms of chronic degenerative conditions, the number one causes of death on our planet.

Uric Acid and Cardiovascular Disease Risk

Why is uric acid included on the typical comprehensive blood panel that many people get as part of their annual physical examination? This certainly would be a good question to ask your doctor. Quite likely the answer you will receive will center on the role of uric acid in terms of either kidney stones or gout. But if you don't have kidney stones and don't suffer from gout, why would you need to know your uric acid level? As it turns out, this is an incredibly important metric to follow and understand as it relates to far more than simply risk for gout or kidney stones. We now understand that elevation of uric acid strongly correlates with so many disease issues including type 2 diabetes, obesity, dyslipidemia, hypertension, kidney disease, and many other conditions.

Over the past 20 years there has been an ever-increasing body of research that has explored the relationship between elevation of uric acid and cardiovascular disease. But while this relationship may seem like a new discovery, it was actually suggested in the late 19th century.

British physician Dr. Alexander Haig was the first to call attention to the importance of uric acid far beyond its relationship to gout. In his 1894 book, *Uric Acid as a Factor in the Causation of Disease – A Contribution to the Pathology of High Arterial Tension, Headache, Epilepsy, Mental Depression, Gout, Rheumatism, Diabetes, Bright's Disease, and Other Disorders*, Haig painstakingly explored the relationship of uric acid to blood pressure, and blood flow, stating:

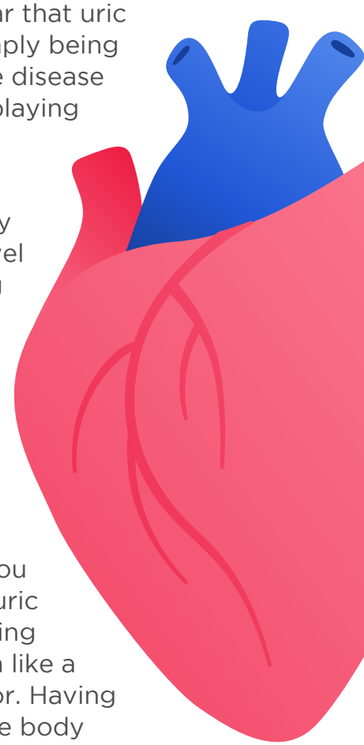
> *But not only is the pulse affected in this way by the uric acid, but it in turn affects the circulation in, and the function of, several important organs in a way, and to an extent which leads little doubt as to the real existence of the cause-and-effect of which I have been speaking.*

Unfortunately, his prescient observations and publications were almost completely ignored until the early part of the 21st century. Now, we are seeing a virtual explosion in the number of research publications from around the world linking elevation of this seemingly meaningless metabolic waste product to some of our most challenging health issues.

A significant relationship between uric acid levels and coronary heart disease or mortality has been described in two large Asian studies looking at tens of thousands of men and women. This research has shown that having a serum uric acid level greater than 7 mg/dL was associated with a 16% increase risk of all-cause mortality, meaning death from any cause, a 39% increase risk for cardiovascular disease, and a 35% increased risk for stroke.

Uric acid elevation was correlated with an increased risk for mortality from stroke by an astonishing 59% in a large study of Australian men encompassing more than 83,000 individuals followed over a 13.6-year period of time. The increased risk for death from stroke was found when comparing the highest quartile of uric acid to the lowest. In another important study evaluating 1017 patients who had coronary stenosis or narrowing of the coronary arteries as proven by angiogram with greater than 30% narrowing of the artery, a five-fold increase in deaths was seen in patients who had the highest level of uric acid in comparison to those who had the lowest level over a 2.2-year follow up. This was noted in both sexes. Finally, in looking at the well-known *Framingham Offspring Cohort Study*, the association between uric acid and risk of developing congestive heart failure was evaluated in close to 5000 participants equally balanced between men and women and followed over an average of 29 years. Again, these researchers compared those in the highest quartile of uric acid defined as greater than 6.3 mg/dL with those in the lowest quartile, defined as less than 3.4 mg/dL. The comparison was quite revealing. The risk of developing congestive heart failure was an astonishing *six-fold higher* in the group with the highest level of uric acid in comparison to those in the lowest quartile. Other research has confirmed not only increased risk of congestive heart failure but also increased risk of death from congestive heart failure when uric acid is elevated. These reports and many others are summarized in a comprehensive review entitled Uric Acid and Cardiovascular Disease, published in 2018.

These studies are correlative studies. That means they have demonstrated a correlation or a relationship between elevation of uric acid and the various outcomes described. These studies do not necessarily prove causation, but moving forward, we will be exploring the incredible number of mechanisms by which elevation of uric acid threatens how our blood vessels are able to function. Thereafter, I think it will become very clear that uric acid, well beyond simply being associated with these disease outcomes, is clearly playing a central role in their genesis.



You may have already had your uric acid level evaluated. So, finding out how your values relate to the levels described above may simply require a phone call to your doctor's office. If your uric acid level hasn't been checked, there's good news. You can now check your uric acid level at home using a simple device much like a home glucose monitor. Having reviewed an extensive body of research on this topic, we have elucidated the goal for uric acid level is keeping it below 5.5 mg/dl. And achieving that goal may well require a reassessment of your fructose consumption, as well as a reduction in purine-rich foods like sardines and organ meats. We will soon post a much more extensive compendium of uric acid lowering strategies associated with my new book Drop Acid, so stay tuned!

Fructose – Bad For Your Brain

Nearly 70% of the food items sold at your local grocery store have an added sweetener and, more often than not, that sweetener is fructose delivered from high fructose corn syrup (HFCS). We know that fructose consumption is associated with things like insulin resistance, weight gain, and an increase in blood pressure, but we're also seeing research that links it to neurological issues like pre-clinical Alzheimer's Disease.

In a study published in the journal Alzheimer's and Dementia, researchers looked at the sugary beverage consumption of around 5,000 people using a food frequency questionnaire. These individuals underwent neuropsychological examination to evaluate their brain function, with nearly 3,800 also having an MRI scan. The results showed that those who consumed two or more sweetened drinks per day had a brain age score equivalent to nearly 2 years greater than those who did not. MRI scans of those individuals also some pretty dramatic shrinking of the hippocampus.

When we look at function, it's really quite dramatic that having one or two sugary drinks per day was associated with a decline of logical memory and a delayed recall score of almost 5.8 years greater than those who did not. If they had more than two sugary beverages per day, that increased to nearly **11 years**. And when we look at brain volume, consuming three or more sweetened soft drinks per week, not per day, was associated with a nearly 2.6 year decline and a declining logical memory immediate score of about 13 years. The truly striking part of this study is that these findings were evident in middle-aged people, and were observed even after they made corrections for various confounding factors.

We really need to think about our sugar consumption, and especially anything that is sweetened by fructose and HFCS. Fructose is a precursor to diabetes, it contributes to weight gain and obesity, and increases the production of uric acid.

David Perlmutter, MD & Dr. Richard Johnson

DP How did this all start with you?

RJ I was studying kidney disease, and one of the things about the kidneys is that they play an important role in blood pressure, probably because of their effects on salt excretion. So I was interested in why that was.

We realized that people with high blood pressure don't have normal kidneys, but have kidneys that have low-grade inflammation. A study in the 60s found that kidney disease was present in something like 95% or higher of people who suffered from gout. So I started thinking about it and thought to myself, could uric acid - the substance that causes gout - be causing subtle kidney damage that might lead to higher blood pressure?

Now, at the time, uric acid was not considered very important. It was thought to be a waste product basically, but it wasn't thought to be important in kidney disease or that although it's associated with kidney disease, it probably doesn't have a causal role. But we thought to ourselves, maybe in patients who have gout or patients with high uric acid, small amounts of crystals could deposit in the kidney that could cause low-grade inflammation, and that might make the kid you wanna hold on to salt.

So we started doing some experiments where we raised uric acid in animals. And so it turns out that humans have higher uric acid than other animals because we lack an enzyme called uricase, which is an enzyme in the liver that degrades uric acid. So to raise uric acid in a laboratory rat, we gave it this uricase inhibitor, thinking that we were going to get low-grade inflammation in the kidney and crystals and that that might cause high blood pressure.

What we found was that we did get high blood pressure. The animals became hypertensive when we raised uric acid. But when we looked in the kidneys, we didn't see any crystals at all.

DP What are some positive effects of having lower uric acid levels?

RJ What we found is that, when we lowered the uric acid in the rats, their blood pressure improved, their triglycerides were less, their insulin levels came down, their glucose was less, they had less fat in their livers, and even their weight gain was affected!

Click here to watch full interview

DP Why would a species evolve with this feature if it's so detrimental?

RJ Humans have higher uric acid levels because we lack the enzyme uricase, which helps break down the uric acid. Having higher uric acid levels means that you're able to make and store more fat and glucose.

Around 17 million years ago, during the Miocene epoch, the world was going through some intense changes. The Earth was getting a lot colder, and our prehistoric ancestors that had migrated from Africa and into Europe and Asia had to deal with a far more limited food supply because of it. The loss of the uricase enzyme was a way for our ancestors to survive on fewer resources.

SCIENCE

> Serum Uric Acid Concentrations and Risk of Adverse Outcomes in Patients With COVID-19 - *Frontiers in Endocrinology, 2021* [LINK]

> Involvement of inflammasome activation via elevation of uric acid level in nociception in a mouse model of muscle pain - *Molecular Pain, 2019* [LINK]

> Uric acid and cardiovascular disease - *Clinica Chimica Acta, 2018* [LINK]

> Natural Products Improving Hyperuricemia with Hepatorenal Dual Effects - *Evidence-Based Complementary and Alternative Medicine, 2016* [LINK]

> Uric acid in metabolic syndrome: From an innocent bystander to a central player - *European Journal of Internal Medicine, 2016* [LINK]

> Review of Hyperuricemia as New Marker for Metabolic Syndrome - *ISRN Rheumatology, 2014* [LINK]

> Uric Acid Level and Erectile Dysfunction In Patients With Coronary Artery Disease - *The Journal of Sexual Medicine, 2014* [LINK]

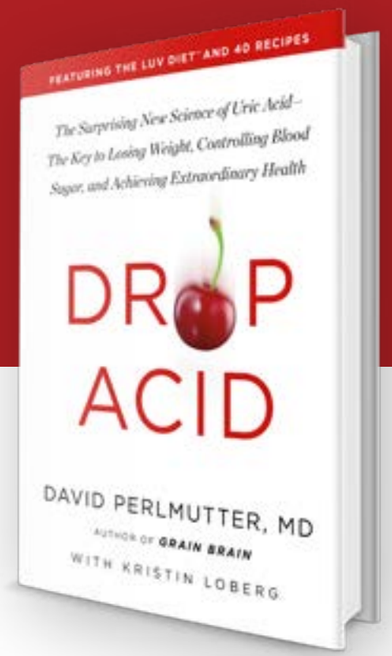
> Sugar, Uric Acid, and the Etiology of Diabetes and Obesity - *Diabetes, 2013* [LINK]

> The Epidemiology of Uric Acid and Fructose - *Seminars in Nephrology, 2011* [LINK]

> Prevalence of Gout and Hyperuricemia in the US General Population - *Arthritis & Rheumatism, 2011* [LINK]

> Prevalence and Determinants of Hyperuricemia in Middle-Aged, Urban Chinese Men - *Metabolic Syndrome and Related Disorders, 2010* [LINK]

> Serum uric acid and cognitive function in community-dwelling older adults - *Neuropsychology, 2006* [LINK]



About Drop Acid

Scientific literature is bursting with evidence that elevated uric acid levels lie at the root of many pervasive health conditions, but mainstream medicine for the most part remains unaware of this connection. This is especially alarming because a large number of Americans don't know they are suffering from increased levels, putting them at risk for developing or exacerbating potentially life-threatening illnesses.

Offering an engaging blend of science and practical advice, *Drop Acid* exposes the deadly truth about uric acid and teaches invaluable strategies to manage its levels. Featuring the groundbreaking "LUV" (Lower Uric Values) diet, 35 delicious recipes, self-assessment quizzes, and a 21-day program for dropping levels, *Drop Acid* empowers readers with the information they need to address this hidden danger and live longer, leaner, and healthier lives.

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