THE FAT GENE

A genetic mutation in prehistoric apes may underlie today's pandemic of obesity and diabetes

By Richard J. Johnson and Peter Andrews

IN 1962 A HUMAN GENETICIST NAMED JAMES NEEL PROPOSED A HYPOTHESIS TO SOLVE A VEXING EVOLUTIONARY puzzle. What is now called type 2 diabetes—which he thought was caused by a single variant of some unidentified gene—can cause debilitating symptoms, including blindness, heart disease and kidney failure. It can also affect people in their reproductive years. In ancient humans, when no treatments were available, those features could have kept afflicted individuals from finding a mate, having children and passing the disease-causing gene down to future generations. In other words, natural selection should have eliminated the gene and, thus, the disease.

Yet the disorder was common and growing more so. How could people with such a debilitating gene have survived, Neel wondered, and why was diabetes, which is defined by the presence of abnormally high levels of the sugar glucose in the blood, becoming more prevalent?

Neel spent much of his time studying indigenous populations such as the Yanomami in the Amazon, who presumably had the same diabetes-related gene variant in their gene pool as other modern humans yet were almost never diabetic or fat. (Obesity increases risk for type 2 diabetes.) The contrast between native people and those in developed societies gave him an idea. In the distant past, he argued, there were most likely times when food was in short supply, causing hunger or even widespread famine. People with a gene variant that made their body particularly

Illustration by Tim Bower

"efficient in the intake and/or utilization of food," Neel wrote, would have socked away more of the scarce calories as fat. That extra fat would have given individuals with this so-called thrifty gene a survival edge in times of famine. In times of plenty, though, such as today, the same trait would lead to excessive weight gain and diabetes.

The thrifty gene hypothesis has drawn criticism, but it has endured in one form or another for half a century. The idea that our body can be genetically programmed to store fat and that our rich modern diet and sedentary ways can send this program into overdrive has prompted a good deal of research into possible thrifty genes at the root of diabetes and other obesity-linked diseases: hypertension (high blood pressure), nonalcoholic fatty liver disease and heart disease. But critics of the hypothesis have argued that starvation in ancient humans happened too rarely and was over too quickly to select for genes that favor fat storage and that no definitive thrifty genes have been found.

Recently, though, the two of us have looked deeper into our evolutionary past and found solid evidence confirming the essence of Neel's hypothesis—that a mutation in a single gene made modern humans thrifty with calories. This mutation arose in ancient apes millions of years ago and in so doing, we think, enabled them to survive long periods of hunger. If we are correct, our hypothesis could also help reveal how those apes evolved into the earliest human ancestors, and it may pinpoint a gene that is behind many of the major diseases of modernity.

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Peter Andrews is an emeritus research scientist at the Natural History Museum in London and a professor in the department of anthropology at University College London. He has described many new genera and species of fossil apes and was among the first to propose that the ancestors of today's great apes and humans evolved outside of Africa.

BACK TO AFRICA

AT FIRST NEEL AND OTHER SCIENTISTS assumed that a thrifty gene appeared when ancestral humans were roaming the plains of East Africa. But our story starts much earlier, when apes were relatively new to the planet. It's a tale of global climate change, famine and a struggle for survival.

The earliest apes evolved from a common ancestor with monkeys, probably in East Africa around 26 million years ago. Those apes, the best known of which is *Proconsul,* walked on all fours and lived in trees like monkeys but had a big body, no tail, and a larger skull and brain. At the time, Africa was a tropical Eden, full of deciduous woodlands and rain forests, where the apes feasted primarily on fruit. The apes living there thrived and diversified, with as many as 14 ape species identified from the fossil record.

The world, though, was gradually cooling. The polar ice caps expanded, and sea levels fell. By 21 million years ago Africa, which had been an island continent like Australia and Antarctica today, became connected to Eurasia by the first of a series of land bridges. Giraffes, elephants, antelope and even aardvarks migrated from Africa to Eurasia, according to fossil digs by one of us (Andrews) and others in Turkey, Germany and Spain. Apes were among the emigrants. By 16.5 million years ago apes such as *Griphopithecus* and *Kenyapithecus* were living at a site near the modern-day Turkish village of Paşalar.

In Europe the newly arrived apes flourished at first in subtropical evergreen forests and moist, broadleaf woodlands, in part because fruit was plentiful. They diversified into at least eight species in five genera, including *Dryopithecus* and *Ankarapithecus.* Andrews and his colleagues concluded from 16.5-million-year-old deposits near Paşalar that seasonal climate resembled that of northern India now, with summer monsoon rains followed by long, dry periods and cool, frost-free winters.

As global cooling continued and the climate got drier, forest gave way to savanna, and fruit became scarce in the winter months. Through fossil digs conducted in the 1980s and 1990s, Andrews found evidence that the fossil apes were living on the ground rather than in trees, which would have helped them range farther and forage more effectively. Studies of the wear on fossil teeth and thickening of their enamel suggested to him that the hungry apes had turned to fallback foods such as tubers and roots.

Eventually the European apes began starving during the winter. In Paşalar, Andrews and Jay Kelley, now at Arizona State University, found young adult *Kenyapithecus kizili* fossils whose incisors displayed telltale striations that reveal intermittent dietary stress or starvation. Other paleontologists discovered that *Dryopithecus* apes, which lived 12 million to nine million years ago in the Vallès-Penedès basin in Spain, also had striations on their teeth. All the time, it kept getting cooler, and by about seven million years ago the European apes had disappeared.

Or so it seemed. Fossil evidence now suggests that some European apes journeyed to Asia and became the ancestors of gibbons and orangutans, whereas others returned to Africa and evolved into African apes and humans. One likely candidate for the move from Eurasia to Africa is *K. kizili,* which had similar teeth and jaws to those of *Kenyapithecus wickeri,* an ape that lived in East Africa two million years later.

Genetic evidence confirms the fossil evidence of hard times in Europe, and together the two lines of evidence led us to revive the

IN BRIEF

Fossil evidence shows that apes thrived beginning around 16 million years ago in then subtropical Europe. Global cooling subsequently changed the forest, making the fruit they ate scarce.

A mutation in a gene called uricase helps to convert fruit sugar (fructose) into fat, which enabled the European apes to survive famines.

Persistence of the same mutation in all modern great apes and all modern humans, along with the fossil evidence, implies that the now extinct European apes evolved into today's great apes and the earliest hominids.

The uricase mutation predisposes humans to obesity and diabetes today. The results suggest a need to eat and drink much less fructose to fight obesity and prevent its dangerous complications.

thrifty gene hypothesis in its new form. Our hypothesis centers on a gene that in many animals gives rise to an enzyme called uricase. In all modern great apes (gorillas, orangutans, chimpanzees and bonobos) and all modern humans, however, the gene is mutated, blocking uricase production. In addition, both groups possess the same mutant form of the gene, which is a sign that humans inherited the gene from a common ancestor we share with the great apes. By analyzing changes that occurred in the uricase gene over evolutionary time employing a method known as the molecular clock, Naoyuki Takahata of the Graduate University for Advanced Studies in Hayama, Japan, and his colleagues and, independently, Eric Gaucher of the Georgia Institute of Technology determined that the common ancestor of great apes and humans lived between 17 million and 13 million years ago—the same tumultuous time period when European apes were struggling to survive seasonal famines.

A different mutation separately silenced the uricase gene in the ancestors of lesser apes (gibbons), which probably lived in Europe at about the same time. Together these finds suggested to us that disabling uricase helped ancient European apes to survive famine. The question was, How exactly did it help?

GOOD TIMES, BAD TIMES

A CLUE TO HOW THE URICASE MUTATION might prevent starvation in times of famine ultimately came from a separate line of research into the roots of high blood pressure and heart disease. In most animals, uricase breaks down a substance called uric acid, which is a waste product produced when some foods are metabolized—that is, converted to fuel and raw materials needed by cells. The ancient mutation in the apes would have crippled the enzyme and thus would have caused uric acid to build up in the blood.

At first blush, this buildup would seem harmful rather than helpful because excess uric acid can precipitate as crystals in the joints to cause gout or in the kidneys to produce stones. Under normal conditions, however, humans and apes can excrete uric acid in urine quickly enough that the mutation would have elevated uric acid levels only moderately. Indeed, modern African apes do in fact have slightly higher uric acid levels than other animals, as do indigenous humans who have retained their ancient way of life, such as the Yanomami.

In societies with Western diets and sedentary habits, however, average uric acid levels are soaring. Physicians also know that obese people and patients with heart disease have higher uric acid levels in their blood than lean, fit people, just as they often have elevated cholesterol and triglycerides.

The authors of the influential Framingham Heart Study had monitored patients for decades and used statistics to identify which of these substances truly caused heart disease. In 1999 they reported that elevated uric acid did not by itself cause the disease. Instead, they argued, high blood pressure elevated the risk of heart disease, and it also happened to raise uric acid levels.

This conclusion, however, bothered the other of us (Johnson) because the authors had violated a basic tenet in biological science: they had drawn their conclusion without testing their hypothesis on laboratory animals. Marilda Mazzali, a doctor working with Johnson, proceeded to do such a study. Johnson's team had reported a few years before that subtle kidney injuries in rats could cause high blood pressure. Mazzali checked whether raising uric acid levels with a drug that blocked uricase would elevate blood pressure or harm kidney function. In earlier experiments we had found that raising uric acid did not cause any obvious kidney damage, so we predicted that the rise was unlikely to affect either blood pressure or the kidneys. But Mazzali shocked us all when she reported that the rats developed high blood pressure.

Johnson and his colleagues then conducted a series of studies showing that elevated uric acid levels in rats cause high blood pressure via two mechanisms. At first uric acid acts quickly, causing a series of biochemical reactions collectively called oxidative stress that constrict blood vessels, which forces the heart to pump harder to circulate blood and elevates blood pressure. Lowering uric acid reverses this effect. An ongoing excess of uric acid, however, causes lasting low-grade injury and inflammation in the kidneys, which make them less able to excrete salt. This, in turn, causes high blood pressure that can be reversed with a low-salt diet but not by lowering uric acid.

To see if humans respond the same way to elevated uric acid, Johnson and Dan Feig, a pediatric nephrologist then at the Baylor College of Medicine, measured uric acid in obese adolescents with newly diagnosed hypertension, finding to their amazement that it was elevated in 90 percent of them. Then, in a clinical trial, they treated 30 of these patients with a uric acid–lowering drug called allopurinol. The drug restored blood pressure to normal in 85 percent of the patients whose uric acid levels went down significantly. Other pilot studies have replicated the results, which Johnson and Feig reported in 2008 in the *Journal of the American Medical Association*. We will need a large clinical trial, however, before we can trust that lowering uric acid with a drug can ease newly diagnosed high blood pressure.

THE ENDLESS FEAST

BECAUSE HIGH BLOOD PRESSURE tends to follow from obesity and inactivity, Johnson wondered if uric acid was triggering not only high blood pressure but obesity itself. In thinking through this problem, Johnson took the long view. He considered how our evolutionary predecessors, from rodents to apes, adjusted their metabolism as they careened from feast to famine.

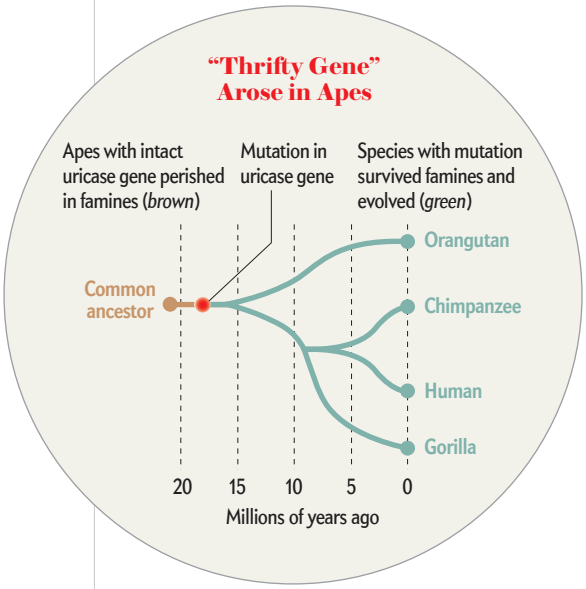
During prolonged food shortages in nature, the rule of thumb is survival of the fattest. Mammals increase their fat reserves to increase their odds of surviving hibernation, birds fatten up to survive a long migration and the Emperor penguin puts on pounds to nest during a tough winter. And when these animals sense hard times approaching, they are driven to forage, gorge and fatten themselves.

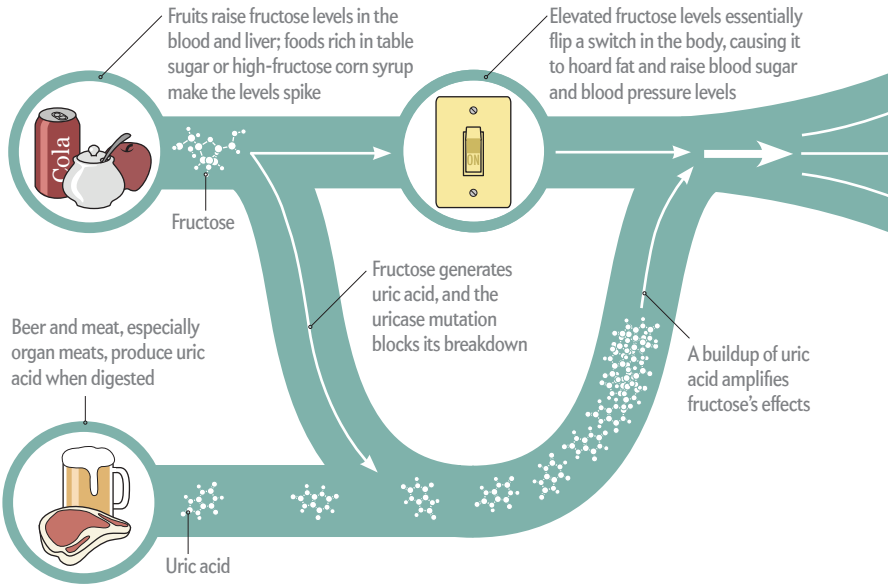
Birds and mammals also switch naturally at these times into a prediabetic state. Normally when the body digests carbohydrates, it produces glucose, which accumulates in the bloodstream. The pancreas responds by releasing insulin, which signals the liver and muscles to convert glucose into a starchlike energy-storage molecule called glycogen. When food is scarce, though, animals must persist in their foraging to survive, and their brain requires a steady supply of glucose to do so. For this reason, hungry animals from squirrels to warblers undergo a metabolic change that makes the body's cells start ignoring insulin's prompts. This "insulin resistance" keeps scarce glucose in their blood to supply their brain.

Johnson and others realized that there must be a kind of switch that alerted the animal's body to both get fat and become prediabetic, and he took to calling it "the fat switch." Because

A Jekyll-and-Hyde Mutation

The authors propose that a gene mutation in an ape species millions of years ago helped the animals to survive food shortages that felled other apes. The survivors then passed the mutation to later species that diverged from them, ultimately including humans (*lineage below*). The mutation, in a gene that encodes the enzyme uricase, favored survival during food shortages because, among other effects, it made the body "thrifty" with food—causing it to store calories as fat rather than burning them for energy on the spot. Today, though, when food is plentiful, the mutation may well contribute to obesity and disease (*diagram*).





birds, bears and orangutans gorge on fruit to store fat for lean times, he suspected that fruit sugar (fructose) might flip that switch. Experiments on mice by Takuji Ishimoto and Miguel Lanaspa, both then in Johnson's lab, showed that it did. Mice on a high-fructose diet eat more and move less than mice with a healthier diet, and they tend to accumulate fat. This buildup happens in part because fructose blunts the effect of the hormone leptin, which tells the brain it is time to stop eating.

Fructose, unlike other sugars, produces uric acid when it is broken down inside cells, and Johnson wondered whether the uric acid might mediate some of fructose's effects. To find out, Takahiko Nakagawa, then in Johnson's group, fed rats a high-fructose diet and gave half of them allopurinol to lower uric acid. The drug lowered the rats' blood pressure, confirming earlier results from the group. At the same time, it blocked many of the features of metabolic syndrome, a cluster of conditions that include low blood levels of HDL (the "good" cholesterol), high blood glucose, elevated triglycerides, excess belly fat and high blood pressure. And in a separate study on lab-grown human liver cells, the researchers found that lowering uric acid could prevent cells from turning fructose into fat.

A clear picture was emerging. A diet high in fructose flips the fat switch, and the lack of a working uricase in great apes and humans leads to elevated uric acid levels, which amplifies fructose's effects. This combination helps to steer people down the path toward metabolic syndrome, which raises the risk of heart disease, stroke and diabetes.

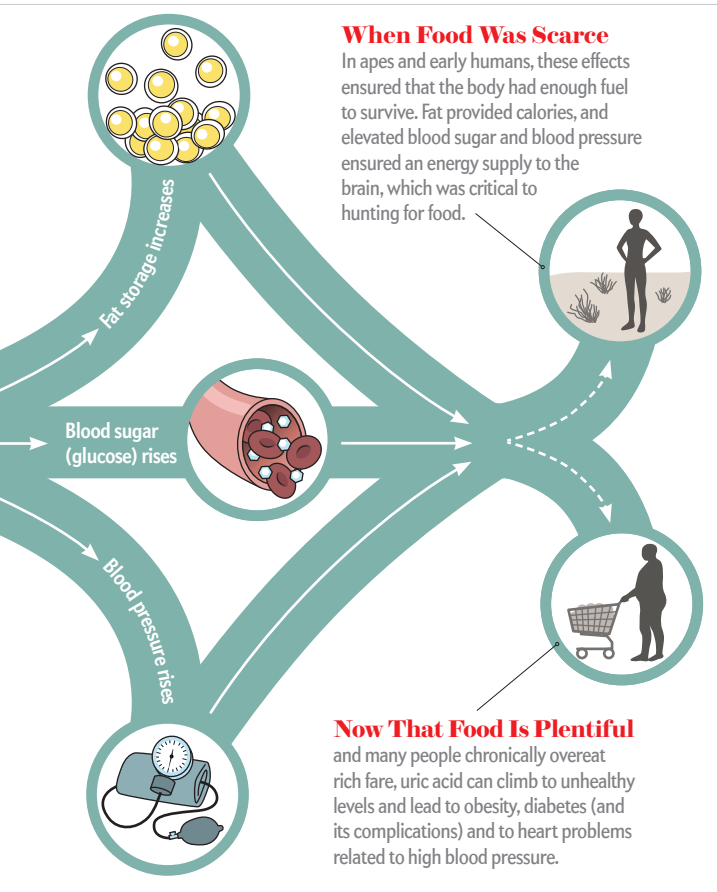
A LASTING CHANGE

IN JUNE 2008, AS THAT PICTURE was emerging, Johnson visited Andrews at the Natural History Museum in London, where Andrews was leading research efforts on ape and human evolution. For hours, we imagined ways that a mutated uricase gene, leading to an absence of uricase, could have helped now extinct apes to survive as global climate cooled. Johnson suggested that this lack of a working uricase and the resulting elevated uric acid levels would have helped apes turn fruit into fat and given them a survival advantage as winters became cool and dry beginning 15 million years ago, in the mid-Miocene. Andrews then provided an important insight. Although Africa was cooling, it was still hot enough to support tropical fig trees that were widespread and produced fruit throughout the year. African apes would thus have been able to eat fruit, especially figs, year-round, as chimps, gorillas and orangutans do now. But as Europe cooled from subtropical to temperate, fig trees grew scarce and stopped fruiting in winter. As a result, European apes regularly went hungry.

We hypothesized that a mutation that disabled uricase would have enabled the European apes to convert fructose into fat for lean times. The descendants of those apes would have carried that mutation to Africa a few million years later, better equipped to survive famine than whatever African apes remained. If those ancient European apes then outcompeted African apes of the era, they are the most likely ancestors of today's African apes—and of humans. And the mutated gene that produces uricase is James Neel's long-sought thrifty gene.

SOURCE: "EVOLUTIONARY HISTORY AND METABOLIC INSIGHTS OF ANCIENT MAMMALIAN URICASES" BY JAMES T. KRATZER ET AL., IN *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES USA*, VOL. 111, NO. 10; MARCH 11, 2014 (*timeline*)

SCIENTIFIC AMERICAN ONLINE Hear an interview with Johnson at ScientificAmerican.com/oct2015/obesity



OPEN QUESTIONS

DESPITE THE EXTENSIVE EVIDENCE we and others have gathered, our hypothesis that the silenced uricase gene is a thrifty gene is not yet proved. Some researchers have searched extensively for thrifty genes by seeking human genetic polymorphisms (variants of genes) that explain the epidemic of obesity and diabetes. They have found some that predispose people to these conditions but none that can explain the epidemic. A hunt for polymorphisms, though, would miss the silenced uricase gene because it does not vary; all humans have it. Skeptics have also argued that a thrifty gene would have evolved only if being fat offered ancient humans an advantage. But the silenced uricase evolved millions of years ago to help prevent the ape ancestors of humans from starving, not to make them fat.

Still others say that if we all had a thrifty gene, then obesity would be much more common in humans today. On its own, though, a silenced uricase only mildly increases blood uric acid levels, according to Johnson's studies on great apes and the Yanomami on their native diets. Instead, we propose, the gene enables uric acid levels to spike in response to two types of foods in the Western diet: those, like beer, that produce uric acid, and those that contain or produce a lot of fructose. The latter include honey and processed foods that are high in table sugar or high-fructose corn syrup (which each contain glucose and fructose). And when uric acid levels spike, we become far more susceptible to obesity and diabetes.

In 2014 Gaucher, James T. Kratzer, then on Gaucher's team, and Lanaspa on Johnson's team reported some of the strongest lab evidence yet fingering the mutant uricase as a thrifty gene. After deducing the DNA sequence of uricase genes from long-gone primates, mammals such as pigs, rats and dogs, and their common ancestors, they engineered human liver cells to produce the corresponding enzymes. The ancient uricases became less and less active as ancestral apes evolved until they were crippled entirely in the common ancestor of humans and great apes, they reported in 2014 in the *Proceedings of the National Academy of Sciences USA*. This loss would have made apes and humans better at storing fat and at releasing glucose to supply the brain, and it would have given them a survival edge when food was scarce.

The ultimate test of our hypothesis, however, will come from trials that lower uric acid levels in humans. Pilot trials so far have shown that reducing uric acid with an antigout drug can lower blood pressure, reduce insulin resistance, slow kidney disease and prevent weight gain. But larger trials are still needed to prove that the mutant uricase is in fact a thrifty gene.

SLASHING SUGAR

IF CRIPPLED URICASE IS THE THRIFTY GENE, then preventing obesity, diabetes and heart disease might require treating elevated uric acid as well as treating high cholesterol or elevated triglycerides. Down the line, it might even be possible to use new gene-editing methods to reclaim human uricase so we can break down uric acid more effectively rather than simply excreting it.

Until then, however, we can keep weight off and prevent diseases by exercising and adopting a healthier diet. Honey and table sugar both supply fructose, and for thousands of years, wherever wealthy people ate them, they became fat and often developed gout. In recent decades, as we have added more and more table sugar and high-fructose corn syrup to packaged foods, obesity and diabetes have skyrocketed and average uric acid levels in our blood have increased. By cutting way back on our fructose intake—and getting most of it from fresh fruit, which has substances such as vitamin C and antioxidants that can neutralize the effects of fructose and uric acid, we should be able to protect ourselves from multiple diseases. For such reasons, the American Heart Association, after weighing the science, has recommended slashing sugar intake to six teaspoons a day in women and nine teaspoons a day in men. Even less would be healthier.

Five decades after Neel's pioneering work, we may now know the identity of at least one of his thrifty genes, and it could well have had a large hand in today's twin epidemics of obesity and diabetes. Thrift is indeed a virtue, but when it comes to metabolism, there can be too much of a good thing. SA

MORE TO EXPLORE

Fructose, Uricase, and the Back-to-Africa Hypothesis. Richard J. Johnson and Peter Andrews in *Evolutionary Anthropology*, Vol. 19, No. 6, pages 250–257; November/December 2010.

The Fat Switch. Richard J. Johnson. Mercola.com, 2012.

Evolutionary History and Metabolic Insights of Ancient Mammalian Uricases. James T. Kratzer et al. in *Proceedings of the National Academy of the Sciences USA*, Vol. 111, No. 10, pages 3763–3768; March 11, 2014.

FROM OUR ARCHIVES

Gaining on Fat. W. Wayt Gibbs; August 1996.

scientificamerican.com/magazine/sa

Illustration by Amanda Montañez