

Discovering why so many people on a small island in Micronesia are overweight could help explain the genetics of obesity.

By David Ewing Duncan

Wired to Eat

MADISON “MAD” NENA nibbles on a tangerine picked from his garden on Kosrae, a tiny volcanic island in the Pacific Ocean some 4,670 kilometers southwest of Hawaii. The 53-year-old Nena is a rarity here. He’s thin in a place where fatty, sugary foods imported from the United States have caused an alarming number of people to inflate like dirigibles; obesity-related diseases such as diabetes and heart disease have struck the island’s 7,600 residents hard. Why Nena has stayed thin, and others have not, has drawn American researchers from Rockefeller University in New York City to this 109-square-kilometer patch of jungles, white beaches, mangrove swamps, and quiet villages for more than a decade, in a quest to tease out the genetic and molecular mechanisms of why humans are compelled to eat. And sometimes to eat and eat, far beyond what is healthy.

The Rockefeller team suspects that the proclivity of a person’s body to approach a certain weight is determined far more by genes than was previously thought—specifically, genes that control the impulse to eat. Growing evidence indicates that an indi-





vidual's weight is 40 to 70 percent decided by genes, which makes it about as heritable as height. (Height, however, is determined during infancy and childhood, whereas weight can continue to fluctuate throughout life.) Some people appear to be hardwired to be particularly ravenous. When access to food is unlimited, say hunger-gene experts, these people can will themselves to eat less, but their efforts will almost inevitably be overridden by the far more powerful force of genetics.

If true, this is not good news for many Kosraeans, or for anyone else unlucky enough to have the genes that compel him to gobble a second baked potato. "We have to realize that obesity is a disease, like cancer, that people have less control over than most of us think," says Jeffrey Friedman, an obesity researcher and leader of the Rockefeller team.

Not everyone buys this, of course. Those in the diet industry and many nutritionists make their living on the contention that people can readily choose to reduce calories and to stay thin. "There are too many cases where people have willed themselves to lose substantial amounts of weight and keep it off," says nutrition expert Marion Nestle of New York University.

Teasing out which perspective is right—or whether, as seems likely, obesity is a complex interaction of both genetics and lifestyle—will help determine our attitudes not only toward fat people but toward the effectiveness of dieting. Globally, more than one billion people are overweight, and that number is growing fast. Between 1991 and 2000, the average weight of Americans swelled by 10 pounds. The 1999–2000 U.S. National Health and Nutrition Examination Survey found that 64 percent of American adults are overweight or obese. Britain, Germany, and other Western countries are not far behind. Neither are developing countries that are rapidly modernizing, where diseases associated with obesity are increasing.

On Kosrae, more than 80 percent of adults are overweight or obese, and diabetes afflicts one in eight adults. Until the United States took control of Kosrae and the rest of Micronesia after World War II and began shipping in canned and processed foods, the people were predominately lean, eating fish, bananas, coconuts, and taro. For centuries before the arrival of the first European ship in 1824, the elites ate well. But most islanders lived a near-subsistence life, suffering through frequent droughts and stormy seasons that decimated crops. And they stayed thin.

The exact molecular mechanisms behind the rapid onset of obesity among island residents in this new dietary environment are still uncertain—and are the mystery that the Rockefeller researchers are intent on solving. Are many of the islanders genetically predisposed to large appetites, which, once food was plentiful, they were suddenly able to satisfy? Or as NYU's Nestle and Kosrae health officials maintain, is it simply a case of a population's sudden shift to an unhealthy lifestyle, which might be corrected by cutting down on frosted flakes and Spam? Kosrae's genetically isolated population and its abrupt changes in eating habits make it almost the perfect place to examine such issues.

"The local food is high in fiber and balanced in minerals," says Vita Skilling, who runs the public-health outreach program on the island. "But now it's so easy to get refined flour and refined sugar. It's also how we [now] prepare food. We take fresh bananas and we fry them with sugar." Skilling says that cars and a



Christina and Madison Nena

newly paved road ringing most of the island mean that few people walk as much as they used to. "We have plenty of food all the time," she says. "We don't exercise, because it wasn't the thing to exercise—that was work."

On Kosrae, crates full of goods and canned and processed foods arrive regularly in a container ship from overseas. The supplies are paid for mostly by the salaries and assistance that a large U.S. grant to Micronesia—part of a compact agreed to as part of Micronesian independence in 1986—provides each year.

I see this Western bounty in Thurston's, a general store in the town of Lelu. Cooled by a massive fan, the cavernous store displays rows of canned and packaged foods familiar to Americans: pork and beans, canned peas, soft drinks, and Spam. Tails of turkey and chicken—the fatty portion at the rump—are also popular. The store sells a smaller stock of homegrown produce in a stall in front: bananas, taro, limes, and tangerines.

Skilling takes me on a tour of the island's 40-bed hospital, built in 1978 on a hill below a jagged volcano. Dozens of people wait in the dark, humid halls to have their blood pressure taken and their blood tested for glucose and other indicators of diabetes and hypertension. Others wait in line at the small air-conditioned pharmacy for insulin and other medications. "Most of the admissions for adults, other than day-to-day minor trauma, are really to do with complications from diabetes and hypertension," says Skilling. She says the hospital might perform several amputations a month and treats patients with heart disease, eye problems, kidney failure, and other diseases associated with diabetes and obesity. "I was told that 70 percent of the admissions to the surgical unit are due to complications from diabetes," she says.

The Gene Hunters Arrive

In the summer of 1994, Rockefeller biomedical researchers first arrived on Kosrae, led by Friedman, director of the university's Starr Center for Human Genetics. The group set out to measure islanders' weight, height, and waist size; to collect information on the history of family diseases; and to perform a battery of tests, including measurements of cholesterol levels, blood sugar levels, and blood pressure.

In addition to finding that more than half of Kosraean adults were obese and 88 percent were overweight, the Rockefeller study also found that about 12 percent of the adult population had diabetes, compared with 8 percent in the United States. About 17 percent had hypertension, and 20 percent had high cholesterol. These rates are lower than those found in the United States, but they represent health problems that until recently were rare in Kosrae and the rest of the developing world. In a second round of tests, in 2001, the researchers also drew blood to be frozen and shipped back to New York, where they could extract the islanders' DNA to search for genes for obesity, heart disease, and diabetes.



The Rockefeller team chose Kosrae for its isolation, and because most of its people are descended from just a few families. The first Polynesians arrived 2,000 years ago. In the mid-19th century, European diseases and abuse reduced the islanders' numbers from several thousand to about 300. Having just a few genetic lineages on the island means that each person's genomic makeup is far more similar to his or her compatriots' than, say, an American's would be. "Looking for a gene is like searching for a needle in a haystack," says Friedman. "On Kosrae, the small gene pool makes the haystack smaller."

Friedman believes the Kosraeans' ballooning weight is a manifestation of what geneticist James Neel in 1962 dubbed the "thrifty gene" theory. Neel posited that in an environment prone to famine, hunter-gatherers gained a selective advantage if their genes predisposed them to storing fat when food was available. Those with such "thrifty genes" were more likely to survive famines and pass on their genes. But in modern times, the thrifty gene has proved a liability. The theory also posits that people who lived in early agricultural societies, such as those in the Fertile Crescent in the Middle East, had a steady supply of food from plants and domesticated animals and thus didn't need to store fat. So in our world today, people with lean genes are protected from obesity, and those with fat genes are at the mercy of DNA.

Friedman's search through the Kosraeans' genes recently became more precise with the use of a gene chip from Affymetrix, a Santa Clara, CA-based company. Researchers can use chips like

Affymetrix's to scan genomes for differences in individual base pairs at specific locations—variations known as single-nucleotide polymorphisms (SNPs)—which can then be associated with differences in susceptibility to diseases such as obesity or diabetes. Friedman's team has joined with Affymetrix to run one of the first large-scale, genome-wide association studies, using the company's new 100,000-SNP chip to begin to analyze genetic differences among Kosraeans. This is a vast improvement over earlier chips that scanned 6,500 SNPs, according to Greg Yap, vice president of marketing at Affymetrix. "With the 100K chip, we get a much higher resolution across phenotypes," he says. "It's like GPS. Before, we could only see select parts of the world in a general way; now, you get great resolution in lots of places."

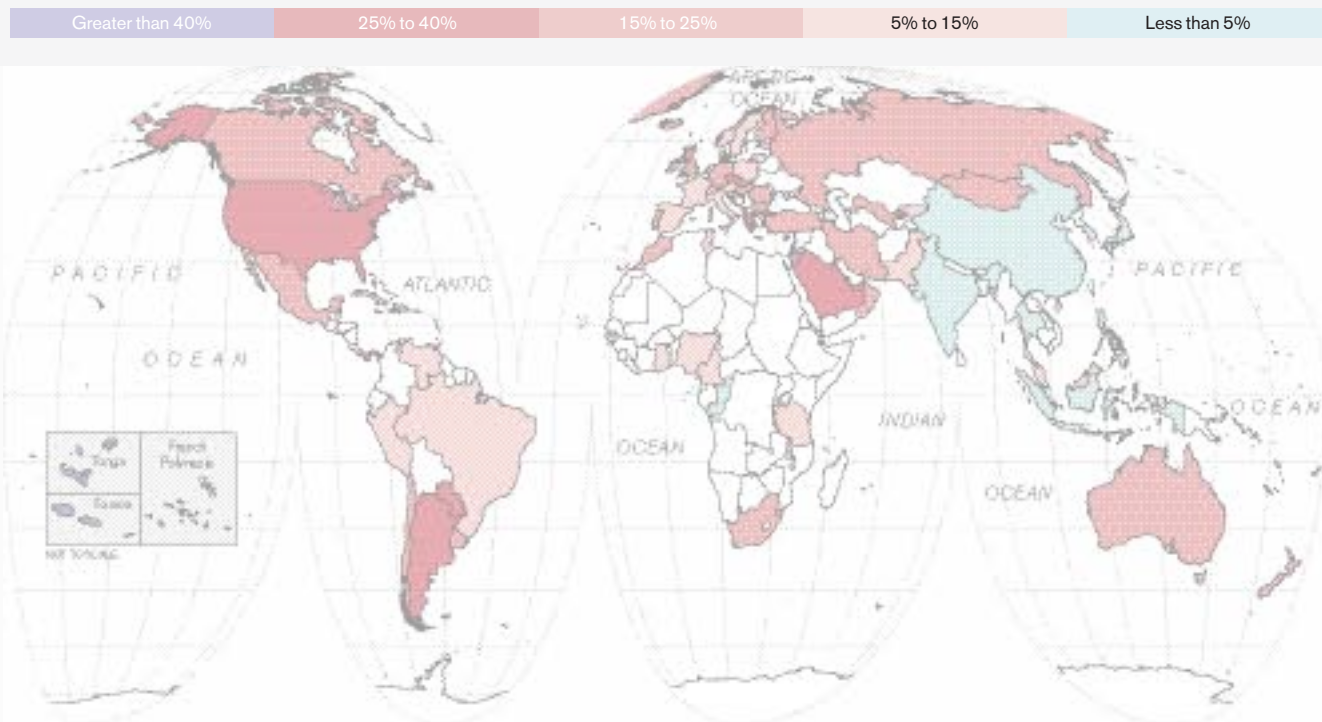
The gene-hunting effort is conducted in collaboration with a team at the Broad Institute, MIT and Harvard University's jointly operated center for genomic medicine. Led by David Altshuler, Broad's director of medical and population genetics, the researchers are about halfway through the SNP scanning process for the 2,000 Kosraean adults. The goal is to identify a library of SNPs that seem to correlate with the islanders' dispositions to be fat or lean. The researchers also hope to pinpoint patterns in the SNPs that will help support or refute the thrifty-gene theory.

Already, says Friedman, the preliminary data are pointing away from one of his theories—that the lean people on Kosrae are descendants of Caucasians with Fertile Crescent genes who mated with locals who had thrifty genes. "Early evidence sug-

A Growing Globe

Several Pacific Island nations, as well as some Middle Eastern countries and the United States, are among the most obese nations in the world.

Percentage of population classified as obese (according to body mass index)



DATA IS UNAVAILABLE FOR COUNTRIES COLORED WHITE. MOST DATA IS FROM 2000 OR LATER; A FEW COUNTRIES HAVE DATA FROM 1994-1999. BODY MASS INDEX (BMI) IS WEIGHT IN KILOGRAMS DIVIDED BY THE SQUARE OF HEIGHT IN METERS; OBESITY IS DEFINED AS HAVING A BMI OF 30 OR HIGHER. SOURCE: INTERNATIONAL OBESITY TASK FORCE

gests that there are fewer Caucasian genes than we thought,” explains Friedman. One possible explanation is that the genetics of something as important as appetite and eating would exhibit a great deal of diversity; that would guarantee that a population could adapt readily to different environmental conditions. In other words, the thrifty-gene theory might hold true even within a small, isolated population. “We’ll be studying this more thoroughly in the coming months, looking for an explanation,” says Friedman.



Vita Skilling (left), a health-care worker on Kosrae, regularly treats health problems caused by diabetes.

A Hunger ‘Set Point’

Dishes of jelly beans and peanuts sit in the office reception room of Friedman’s lab at Rockefeller University in New York. I try not to take a yellow jelly bean, my favorite, making myself grab a handful of peanuts instead. Tall and lanky with a graying beard and glasses, wearing gray-green corduroys and a flannel shirt, Friedman takes a couple of red jelly beans, which his assistant buys by the bagful. As we talk, my eyes keep wandering to the jelly beans. Later, I can’t help myself: I grab a few as we leave for lunch. I ask Friedman if the candy and peanut bowls are a test. He says no, though this is the core of his quest: determining how a person decides to eat or not to eat at a given moment in time. “Eating is binary,” he says. “We either do it, or we don’t. But where in the brain is this decision made, and what is the input that makes the decision?”

Several areas of the brain feed into this decision—behavioral and decision-making centers in the cerebral cortex, for instance, and the regions that process sensory input. But all of these, says Friedman, are trumped by the mechanism that drives organisms to eat. It is centered in the hypothalamus at the base of the brain, where two types of neurons appear to be the chief regulators of appetite. They tell us when we’re hungry and when we’re not. The so-called NPY neuron stimulates hunger, and the POMC inhibits it, each neuron turned up or down by chemicals that wash over them. “A dominant factor in controlling weight is this basic neural circuit,” says Friedman. The chief chemical is leptin, a hormone produced by fat cells in the belly. As people put on the pounds, fat cells increase the levels of leptin, which tells the POMC neuron to suppress appetite. In times of privation—or dieting—body fat is reduced, which decreases the levels of leptin. Less leptin means the POMC turns down and the NPY neuron predominates, which ramps up hunger in people. Other chemicals—fats, sugars, and neural transmitters—also influence the actions of these neurons, but leptin seems to be the key.

“Looking for a gene is like searching for a needle in a haystack.... On Kosrae, the small gene pool makes the haystack smaller.”

Friedman is famous for his 1994 discovery of the gene that codes for leptin. For a brief moment in the mid-1990s, leptin seemed to be a potential wonder cure for obesity, when Friedman and others showed that a mutation affecting the leptin gene caused morbid obesity in mice and humans. But leptin injections work for only a small percentage of the obese. It turns out that the majority do produce leptin, though their bodies actually resist the effects of the hormone by blocking its ability to turn up the hunger-suppressing action of the POMC neuron. So their appetites remain large, and they keep eating—and gaining weight—until they reach the point at which the resistance stops. Where that point lies, Friedman believes, is determined by genetic makeup.

Why leptin resistance occurs in some people is poorly understood, Friedman says. It may be a relic of the thrifty-gene response, ramping up appetite in those whose ancestors lacked adequate food. The Rockefeller team measured leptin levels in the Kosraean population; Friedman is using that data to help correlate leptin resistance with genes that might be responsible for it. According to Friedman, each of us has a “set point” of hunger and satiation, which we inherited from our individual forebears. We are born with this setting, and we are driven to keep eating until we reach it.

Friedman’s “blame the genes” hypothesis flies in the face of arguments mounted by nutritionists and the diet industry, and of the popular belief that eating habits—grabbing a handful of jelly beans, for instance—can be controlled through willpower. “We have some control over eating from our reasoning centers of our brain,” says Friedman, “but this seldom overrides our basic instinct to eat when we’re hungry.” Friedman advocates an entirely new way of thinking about fat, saying it’s pointless to tell most obese people that they can lose dramatic amounts of weight by force of will. “Obesity is a disease,” he insists, comparing current attitudes to those once associated with ulcers and cancer. “Because it’s largely genetic, and the drive to eat largely beyond our control, we should be sympathetic, not judgmental.”

When I ask him whether more Big Macs are at least partly to blame, Friedman says, “Diets are important for heart disease and overall health, but there is no evidence that types of food affect obesity.” Some people are just programmed to eat more, he says, and high-calorie fast foods simply allow them to do so quickly—and therefore cause a faster weight gain.

10,000-Step Program

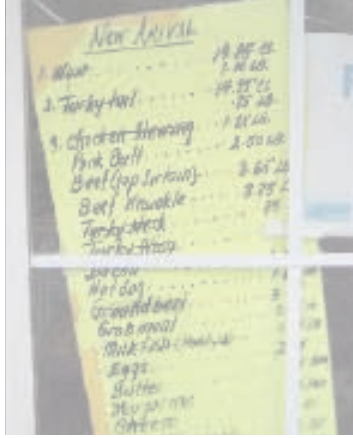
On Kosrae, Skilling is skeptical that people have so little control over their weight. The Rockefeller study, she says, was an eye-opener for islanders, who didn't realize what was happening to them. The islanders were also subjected to something quite unexpected when results of the 1994 study were published in 2000: a mini media blitz that portrayed Kosrae as a land of fatties. The *Atlantic* published an article called "New World Syndrome," whose introductory blurb declared, "Spam and turkey tails have turned Micronesians into Macronesians."

"It is unfair," says Skilling. "You really have to come out and see. If you are just looking at the study files, you might think these people are really unhealthy, but you come out here and you see it's not so bad." But media scrutiny has also spurred many islanders to improve their diets and exercise more. "Ironically, this media attention may save us," says Skilling.

Nena has adopted a back-to-nature gambit to improve the diet of his family. "I have banned turkey tails from my house," he says, walking through his garden of breadfruit, tangerines, limes, and taro root. "We eat almost nothing from cans." Some years ago he learned that his wife, Christina, who was overweight, was an early-stage diabetic. "This was shocking to us. We had not thought of eating or what we ate as something bad." Soon after, he and his sons began expanding their garden, creating arable land from a patch of jungle above a mangrove swamp and a beach on a shore that even on this remote island is isolated. Christina emerges from the house, a short, typically stocky Polynesian woman wearing one of the ubiquitous loose-fitting dresses in colorful floral patterns introduced by the missionaries in the 19th century. Nena and Christina tell me that since changing their diet and exercising more, they feel better. "I wake up at dawn and walk and work in my garden," says Nena. "Before, I got tired more easily." Christina has slimmed down, too, he says, but she still has a mild form of diabetes. They show me a shrub that Nena says is a local remedy for diabetes: noni, or the Indian mulberry, whose fruit works better than Western drugs, they say.

Skilling says the island has launched a campaign to promote exercise. It has issued bumper stickers that ask, "Have you walked 10,000 steps today?" The Kosraean government, with grants from the U.S. government and money from Rockefeller University, has launched a public-health project at the island's main hospital and in village clinics to improve awareness of healthy diets and treatment of weight-related maladies.

"I don't force my patients to lose lots of weight," says Skilling. "I try to work with them to lose 20 percent of their excess weight rather than try for the ideal body weight. Even those that want to lose lots of weight on this island have not been able to get to their ideal weight. Is it obtainable to get to an ideal weight? I think it's more attainable to lose 20 percent of their excess fat." The campaign, says Skilling, is beginning to work. "People talk about eat-



Kosraean stores sell high-fat meats.

ing sugar and eating fat and needing to exercise. Now we need a means to implement what we've learned."

Indeed, as I walk and drive around the island, I don't see an unusually high number of fat people, and I see more thin people than I expected. Does this mean that people have slimmed down since the original study in 1994? "We see people are eating more fish," says Skilling. "Many gatherings are now serving local foods, especially church groups. One hundred percent of the island dwellers are churchgoers, so much of the social life is church centered, and the churches are very influential, so this is a real plus." Each of the island's five villages has launched exercise groups. "The last time I counted the registries in three of the villages, we had over 300 people sign up for some sort of exercise," Skilling says. "This is mostly walking. They walk three times a week, in the morning, because it's cooler."

Friedman contends that exercise and better eating will make Kosraeans healthier but probably will not solve the obesity problem. Studies that measure the amount of calories burned during sessions of modest exercise indicate that hungry genes counter even the effects of physical activity. This contradicts a wealth of anecdotal evidence that exercising more slims waistlines, and Friedman concedes that more work is needed to understand the role of exercise in weight gain. But he does believe that the weight increases of the past 20 years in the United States represent a steady progression of people eating enough food to reach their set points, rather than a sudden spike in bad eating habits or more sitting around. What really intrigues Friedman is why everyone doesn't get chubby when there is plenty to eat. Analyses show that the number of lean people has remained steady for the past 30 years, he says. "One's size is not an environmental effect. Nor is it a matter of willpower."

Friedman acknowledges that what he suggests is counterintuitive, since people can resist jelly beans up to a point. But he insists that, for the majority of the obese, free will in weight control is an illusion. "This is a way of thinking that needs to change," he says, suggesting that for the overweight, drugs that modify weight-gain set points may be the only remedy. He says pharmaceutical companies are developing obesity drugs that work by influencing the NYP and POMC neurons or by tweaking chemicals such as leptin that might reduce the hunger impulse.

So who is right? Friedman? Or Nestle and, on Kosrae, Skilling, who believe the island is slimming down through a combination of attitude, change of diet, and exercise? Undoubtedly, both genetics and lifestyle play a role.

But once again, Kosrae could provide valuable clues. "Hopefully, there will be a follow-up," says Skilling of the Rockefeller study, which might reveal if the islanders have really willed themselves to slim down, or if their set points have prevailed. We'll have to wait and see if the fat habit can truly be shaken. If it can't, we need to radically rethink how we view a condition that may be a genetically determined disease that few can control. And we will need to stop treating it as a personal failing—a malady that we can fundamentally fix without pills and other medical interventions, in concert with improved diets and exercise. ■

David Ewing Duncan is a San Francisco-based biotech writer. In March, he wrote about brain chips for Technology Review.