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**W**HY DO SO MANY OF US GET SO FAT? THE ANSWER appears obvious. “The fundamental cause of obesity and overweight,” the World Health Organization says, “is an energy imbalance between calories consumed and calories expended.” Put simply, we

either eat too much or are too sedentary, or both. By this logic, any excess of calories—whether from protein, carbohydrate or fat (the three main components, or “macronutrients,” in food)—will inevitably pack on the pounds. So the solution is also obvious: eat less, exercise more.

The reason to question this conventional thinking is equally self-evident. The eat less/move more prescription has been widely disseminated for 40 years, and yet the prevalence of obesity, or the accumulation of unhealthy amounts of body fat, has climbed to unprecedented levels. Today more than a third of Americans are considered obese—more than twice the proportion of 40 years ago. Worldwide, more than half a billion people are now obese.

Besides getting fatter, we are also developing more metabolic disorders, such as type 2 diabetes, which is marked by hormonal abnormalities in the processing and storage of nutrients and is far more common in obese individuals than in lean ones.

The dissonance of an ever worsening problem despite a seemingly well-accepted solution suggests two possibilities. One, our understanding of why people get fat is correct, but those who are obese—for genetic, environmental or behavioral reasons—are unable or unwilling to heal themselves. Two, our understanding is wrong and hence so is the ubiquitous advice about how to make things better.

If the second option is true, then maybe what makes us fat is not an energy imbalance but something more akin to a hormonal defect, an idea embraced by European researchers prior to World War II. If so, the prime suspect or environmental trigger of this defect would be the quantity and quality of the carbohydrates we consume. Under this scenario, one fundamental error we have made in our thinking about obesity is to assume

that the energy content of foods—whether avocado, steak, bread or soda—is what makes them fattening, not the effects that these foods, carbohydrates in particular, have on the hormones that regulate fat accumulation.

Given how often researchers refer to obesity as a disorder of the energy balance, one might assume that the concept had been rigorously tested decades ago. But a proper scientific vetting never actually happened. The experiments were too difficult, if not too expensive, to do correctly. And investigators typically thought the answer was obvious—we eat too much—and so the experiments were not worth the effort. As a result, the scientific under-

IN BRIEF

**Which is the more important** cause of obesity: Eating too much food or eating the wrong kinds of food, especially easily digested carbohydrates? **Although nutrition researchers** think they know

the answer, investigators have never actually put the question to a rigorous, scientific test—until now. **Researchers sponsored** by the Nutrition Science Initiative will soon address the question by precisely

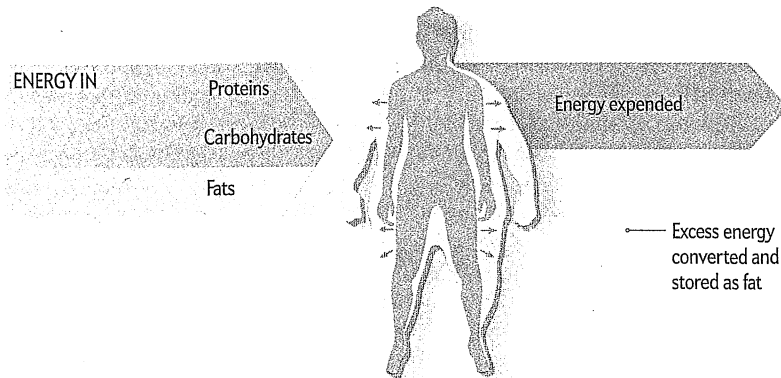
controlling food consumption by volunteers living in a test facility and then rigorously measuring energy expenditure and how it changes with differences in diet composition.

# Calories vs. Carbohydrates

In the next couple of years, investigators funded by NuSI plan to test two competing hypotheses about the dietary causes of obesity under scientifically rigorous conditions that are designed to force one of the possibilities to emerge as the clear winner.

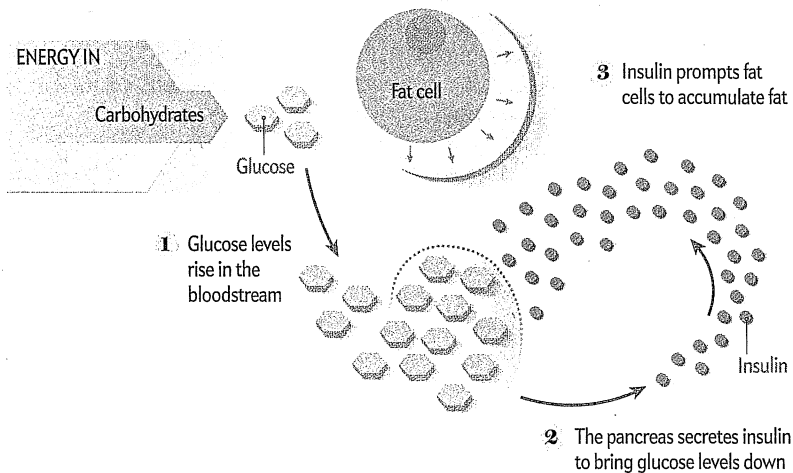
## Energy Imbalance

The conventional explanation focuses on how the body regulates the intake and expenditure of energy (measured in calories). Consuming too much of anything—whether fats, carbohydrates or proteins—increases body fat. The only way to lose weight is to eat fewer calories or to expend more calories.



## Hormone Imbalance

The alternative hypothesis focuses on the complex physiological regulation of fat cells. Consuming carbohydrates raises levels of sugar (glucose) in the blood, which in turn activates the release of the hormone insulin. Fat cells respond to insulin by holding on to their fat stores and even adding to them. Weight gain occurs when insulin levels—triggered by eating carbohydrates—remain elevated for long periods.



pinning of the most critical health issue of our era—the burgeoning rates of obesity and diabetes and their complications—remains very much an open question.

After a decade of studying the science and its history, I am convinced that meaningful progress against obesity will come only if we rethink and rigorously test our understanding of its cause. Last year, with Peter Attia, a former surgeon and cancer researcher, I co-founded a nonprofit organization, the Nutrition Science Initiative (NuSI), to address this lack of definitive evidence. With support from the Laura and John Arnold Foundation in Houston, Tex., we have recruited independent scientists to design and carry out the experiments that will meticulously test the competing hypotheses of obesity (and by extension, weight gain). The Arnold Foundation has committed to fund up to 60 percent of NuSI's current research budget and three years of operating expenses for a total of \$40 million. The investigators will follow the evidence wherever it leads. If all works out as planned, we could have unambiguous evidence about the biological cause of obesity in the next half a dozen years.

## THE HORMONE HYPOTHESIS

TO UNDERSTAND WHAT MAKES THE hormone hypothesis of obesity so intriguing, it helps to grasp where the energy-balance hypothesis falls short. The idea that obesity is caused by consuming more calories than we expend supposedly stems from the first law of thermodynamics, which merely states that energy can neither be created nor destroyed. As applied to biology, it means that energy consumed by an organism has to be either converted to a useful form (metabolized), excreted or stored. Thus, if we take in more calories than we expend or excrete, the excess has to be stored, which means that we get fatter and heavier. So far, so obvious. But this law tells us nothing about why we take in more calories than we expend, nor does it tell us why the excess gets stored as fat. And it is these “why” questions that need to be answered.

Specifically, why do fat cells accumulate fat molecules to excess? This is a biological question, not a physics one. Why are those fat molecules not metabolized instead to generate energy or heat? And why do fat cells take up excessive fat in some

areas of the body but not others? Saying that they do so because excess calories are consumed is not a meaningful answer.

Answering these questions leads to consideration of the role that hormones—insulin, in particular—play in stimulating fat accumulation in different cells. Insulin is secreted in response to a type of carbohydrate called glucose. When the amount of glucose rises in the blood—as happens after eating a carbohydrate-rich meal—the pancreas secretes more insulin, which works to keep the blood glucose level from getting dangerously high. Insulin tells muscle, organ and even fat cells to take up the glucose and use it for fuel. It also tells fat cells to store fat—including fat from the meal—for later use. As long as insulin levels remain high, fat cells retain fat, and the other cells preferentially burn glucose (and not fat) for energy.

The main dietary sources of glucose are starches, grains and sugars. (In the absence of carbohydrates, the liver will synthesize glucose from protein.) The more easily digestible the carbohydrates, the greater and quicker the rise in blood glucose. (Fiber and fat in foods slow the process.) Thus, a diet rich in refined grains and starches will prompt greater insulin secretion than a diet that is not. Sugars—such as sucrose and high-fructose corn syrup—may play a key role because they also contain significant amounts of a carbohydrate called fructose, which is metabolized mostly by liver cells. Though not definitive, research suggests that high amounts of fructose may be an important cause of “insulin resistance.” When cells are insulin-resistant, more insulin is required to control blood glucose. The result, according to the hormone hypothesis, is an ever greater proportion of the day that insulin in the blood is elevated, causing fat to accumulate in fat cells rather than being used to fuel the body. As little as 10 or 20 calories stored as excess fat each day can lead over decades to obesity.

The hormone hypothesis suggests that the *only* way to prevent this downward spiral from happening, and to reverse it when it does, is to avoid the sugars and carbohydrates that work to raise insulin levels. Then the body will naturally tap its store of fat to burn for fuel. The switch from carbohydrate burning to fat burning, so the logic goes, might occur even if the total number of calories consumed remains unchanged. Cells burn the fat because hormones are effectively telling them to do so; the body’s energy expenditure increases as a result. To lose excess body fat, according to this view, carbohydrates must be restricted and replaced, ideally with fat, which does not stimulate insulin secretion.

This alternative hypothesis of obesity implies that the ongoing worldwide epidemics of obesity and type 2 diabetes (which stems to great extent from insulin resistance) are largely driven

by the grains and sugars in our diets. It also implies that the first step in solving these crises is to avoid sugars and limit consumption of starchy vegetables and grains, not worrying about how much we are eating and exercising.

#### FORGOTTEN HISTORY

CONVENTIONAL WISDOM did not always favor the energy-imbalance hypothesis that prevails today. Until World War II, the leading authorities on obesity (and most medical disciplines)

## Land of the Supersized

More than  
**72**  
MILLION  
adults in the  
U.S. are obese

Colorado has  
the fewest  
proportion  
of obese adults  
in the U.S.

**20.7%**

Annual medical  
costs average  
**\$1,429**  
higher for obese  
persons than those  
of normal weight

Mississippi  
has the highest  
proportion  
**34.9%**

worked in Europe and had concluded that obesity was, like any other growth disorder, caused by a hormonal and regulatory defect. Something was amiss, they believed, with the hormones and enzymes that influence the storage of fat in fat cells.

Gustav von Bergmann, a German internist, developed the original hypothesis more than a century ago. (Today the highest honor bestowed by the German Society of Internal Medicine is the Gustav von Bergmann Medal.) Bergmann evoked the term “lipophilia”—love of fat—to describe the affinity of different body tissues for amassing fat. Just as we grow hair in some places and not others, we store fat in some places and not oth-

ers, and this “lipophilic tendency,” he assumed, must be regulated by physiological factors.

The lipophilia concept vanished after World War II with the replacement of German with English as the scientific lingua franca. Meanwhile the technologies needed to understand the regulation of fat accumulation in fat cells and thus the biological basis of obesity—specifically, techniques to accurately measure fatty acids and hormone levels in the blood—were not invented until the late 1950s.

By the mid-1960s it was clear that insulin was the primary hormone regulating fat accumulation, but by then obesity was effectively considered an eating disorder to be treated by inducing or coercing obese subjects to eat fewer calories. Once studies linked the amount of cholesterol in the blood to the risk of heart disease and nutritionists targeted saturated fat as the primary dietary evil, authorities began recommending low-fat, high-carbohydrate diets. The idea that carbohydrates could cause obesity (or diabetes or heart disease) was swept aside.

Still, a few working physicians embraced the carbohydrate/insulin hypothesis and wrote diet books claiming that fat people could lose weight eating as much as they wanted, so long as they avoided carbohydrates. Because the most influential experts believed that people got fat to begin with *precisely* because they ate as much as they wanted, these diet books were perceived as con jobs. The most famous of these authors, Robert C. Atkins, did not help the cause by contending that saturated fat could be eaten to the heart's delight—lobster Newburg, double cheeseburgers—so long as carbohydrates were avoided—a suggestion that many considered tantamount to medical malpractice.

### RIGOROUS EXPERIMENTS

IN THE PAST 20 YEARS significant evidence has accumulated to suggest that these diet doctors may have been right, that the hormone hypothesis is a viable explanation for why we get fat and that insulin resistance, driven perhaps by the sugars in the diet, is a fundamental defect not just in type 2 diabetes but in heart disease and even cancer. This makes rigorous testing of the roles of carbohydrates and insulin critically important. Because the ultimate goal is to identify the environmental triggers of obesity, experiments should, ideally, be directed at elucidating the processes that lead to the accumulation of excess fat. But obesity can take decades to develop, so any month-to-month fat gains may be too small to detect. Thus, the first step that NuSI-funded researchers will take is to test the competing hypotheses on weight loss, which can happen relatively quickly. These first results will then help determine what future experiments are needed to further clarify the mechanisms at work and which of these hypotheses is correct.

A key initial experiment will be carried out jointly by researchers at Columbia University, the National Institutes of Health, the Florida Hospital–Sanford-Burnham Translational Research Institute in Orlando, and the Pennington Biomedical Research Center in Baton Rouge, La. In this pilot study, 16 overweight and obese participants will be housed throughout the experiment in research facilities to ensure accurate assessments of calorie consumption and energy expenditure. In stage one, the participants will be fed a diet similar to that of the average American—50 percent carbohydrates (15 percent sugar), 35 percent fat and 15 percent protein. Researchers will carefully manipulate the calories

consumed until it is clear the participants are neither gaining nor losing fat. In other words, the calories they take in will match the calories they expend, as measured in a device called a metabolic chamber. For stage two, the subjects will be fed a diet of precisely the same number of calories they had been consuming—distributed over the same number of meals and snacks—but the composition will change dramatically.

The total carbohydrate content of the new diet will be exceedingly low—on the order of 5 percent, which translates to only the carbohydrates that occur naturally in meat, fish, fowl, eggs, cheese, animal fat and vegetable oil, along with servings of green leafy vegetables. The protein content of this diet will match that of the diet the subjects ate initially—15 percent of calories. The remainder—80 percent of calories—will consist of fat from these real food sources. The idea is not to test whether this diet is healthy or sustainable for a lifetime but to use it to lower insulin levels by the greatest amount in the shortest time.

Meaningful scientific experiments ideally set up a situation in which competing hypotheses make different predictions about what will happen. In this case, if fat accumulation is primarily driven by an energy imbalance, these subjects should neither lose nor gain weight because they will be eating precisely as many calories as they are expending. Such a result would support the conventional wisdom—that a calorie is a calorie whether it comes from fat, carbohydrate or protein. If, on the other hand, the macronutrient composition affects fat accumulation, then these subjects should lose both weight and fat on the carbohydrate-restricted regime and their energy expenditure should increase, supporting the idea that a calorie of carbohydrate is more fattening than one from protein or fat, presumably because of the effect on insulin.

One drawback to this rigorous scientific approach is that it cannot be rushed without making unacceptable compromises. Even this pilot study will take the better part of a year. The more ambitious follow-up trials will probably take another three years. As we raise more funds, we hope to support more testing—including a closer look at the role that particular sugars and macronutrients have on other disorders, such as diabetes, cancer and neurological conditions. None of these experiments will be easy, but they are doable.

One ultimate goal is to assure the general public that whatever dietary advice it receives—for weight loss, overall health and prevention of obesity—is based on rigorous science, not preconceptions or blind consensus. Obesity and type 2 diabetes are not only serious burdens to afflicted individuals but are overwhelming our health care system and likely our economy as well. We desperately need the kind of unambiguous evidence that the NuSI experiments are designed to generate if we are going to combat and prevent these disorders. ■

#### MORE TO EXPLORE

Insulin and Insulin Resistance. Gisela Wilcox in *Clinical Biochemist Reviews*, Vol. 26, No. 2, pages 19–39; May 2005. [www.ncbi.nlm.nih.gov/pmc/articles/PMC1204764](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1204764)

Obesity and Energy Balance: Is the Tail Wagging the Dog? J.C.K. Wells and M. Siervo in *European Journal of Clinical Nutrition*, Vol. 65, No. 11, pages 1173–1189; November 2011.

#### SCIENTIFIC AMERICAN ONLINE

For a video of Gary Taubes discussing some of his ideas with Stanford University nutrition expert Christopher Gardner, visit [ScientificAmerican.com/sep2013/taubes-video](http://ScientificAmerican.com/sep2013/taubes-video)