

# “Fat Chance”

*Doesn't “everyone know” that serving supersize meals to a young couch potato with plus-size parents is a sure recipe for an obese child? So why is the current epidemic of childhood obesity such a mystery to science?*

By Susan Okie

Rudolph L. Leibel's genes may have predisposed him to become a scientist, but his decision to spend his life trying to discover the causes of obesity was environmental happenstance, the result of a chance encounter. In the spring of 1977, Randall, a severely overweight child, and Randall's mother showed up at the pediatric clinic of Cambridge Hospital in Massachusetts, where Leibel was a specialist in hormone disorders. Leibel could find no evidence that hormone deficiency or, indeed, any other known medical condition, was the cause of Randall's obesity. But what struck the young doctor was the response of Randall's mother when Leibel told her there was little he or anyone else could do for her son: “Let's get out of here, Randall,” she snapped. “This doctor doesn't know s--t.”

Chastened by her words, Leibel soon traded his hospital post for the low-paying toil of a rookie laboratory scientist. At the Rockefeller University laboratory of Jules Hirsch, a leading figure in research on obesity, Leibel and Hirsch conducted extensive studies of weight homeostasis: how the body responds both to weight gain and weight loss by fighting to restore the status quo ante. In one of the studies, volunteers were induced to overeat to gain weight—a task that proved remarkably difficult. Whether they were fat or lean at the outset, the volunteers' bodies responded by turning up the metabolic rate, boosting the levels of certain hormones, reducing hunger, and burning up more calories as heat—all in a coordinated effort by the autonomic nervous system to restore the body's original weight. By contrast, when volunteers' food intake was restricted in order to promote weight loss, their bodies fought back even more fiercely: metabolisms slowed; the volunteers moved around less often and, even when they were exercising, their muscles burned fewer calories; and everyone felt constantly and uncomfortably hungry. A host of physiological defense mechanisms had swung into play, all aimed at regaining the lost pounds.

Such tight physiological regulation of body weight persuaded Leibel that a chemical signal from the body's stores of fat was being sent to the brain. Leibel's hypothesis led to the discovery of a gene that coded for the hormone leptin, which is produced by fat cells. Animal studies soon proved that leptin does indeed pass through the circulatory system to the brain. Could leptin be the key player in the signaling system Leibel had envisioned? If the brain detected enough leptin, would it decide that enough fat cells were storing energy, and so conclude that it was safe to stop

eating? Sure enough, mice that could not produce leptin ate nonstop and grew enormously obese. Treating such mice with leptin normalized their body weight.

The gene for leptin was identified and sequenced as the result of an intensive collaborative effort between Leibel and his Rockefeller colleague Jeffrey M. Friedman. When the announcement was made in 1994, it was greeted with much fanfare. Many people (along with some drug companies) predicted that the newly identified gene would enable the hormone to become a miracle cure for obesity. It has not turned out that way.

*Some evidence suggests body weight reaches a “set point” during puberty. So untreated childhood obesity can lead to the medical risks of adult obesity.*

Today, instead, the United States and many other countries are faced with an epidemic. Most people tend to think of an epidemic as an outbreak of a contagious illness. But to public health officials, obesity rates since the mid 1980s have exploded dramatically and unexpectedly, just as if they reflected the outbreak of a new infectious disease. Noting that obesity and physical inactivity, along with tobacco smoking, are the major causes of “noncommunicable diseases,” the World Health Organization estimated that 60 percent of the 56 million deaths worldwide in 2001 were caused by such obesity-related illnesses as heart disease and type 2 diabetes. Among children, obesity can have adverse effects that persist for life, just as surely as a virus can. For example, there is evidence suggesting that a person’s general body weight reaches a “set point” sometime during puberty, and so extreme obesity in childhood, left untreated, carries with it all the health risks of obesity for the rest of one’s life: substantial increases in the risks of diabetes, heart disease, and other adverse medical consequences. Some officials have even begun to respond with the kind of alarm that might greet the global resurgence of polio. As David L. Katz of the Yale School of Public Health puts it:

Children growing up in the United States today will suffer more chronic disease and premature death because of the way they eat and [because of] their lack of physical activity than [they will] from exposure to tobacco, drugs, and alcohol combined.

Even though the discovery of leptin has not led to a cure for childhood obesity, it has helped to show that the condition is largely biological, and not simply the result of faulty parenting or lack of willpower. And the years since the discovery have been hailed as a golden age for obesity research. In little more than a decade, investigators have sketched, in broad outlines, the biological system that regulates body weight. They have also learned a great deal about genetic vulnerability to obesity.

The control centers for tracking energy balance and regulating body weight are situated primarily in the hypothalamus, a small part of the brain that specializes in integrating messages from many parts of the body and orchestrating the organism’s response to its environment [see illustration on opposite page]. The hypothalamus communicates via nerve pathways and chemical signals with many other areas of the brain, as well as with the organs of the cardiovascular, digestive,

reproductive, and endocrine systems (the latter encompasses the glands that secrete the hormones circulating in the blood).

The output of the hypothalamus can fine-tune a number of unconscious processes that affect a person's weight, such as the rate at which the body burns calories in carrying out certain cellular processes or through spontaneous muscle activity, such as fidgeting. Conceptually, at least, understanding how the body controls such unconscious processes is fairly straightforward. What is surprising for some people is that signals from the hypothalamus also affect the cerebral cortex, the "thinking" part of the brain. The hypothalamus can modify such conscious, purposeful behaviors as food-seeking, simply by increasing or decreasing the appetite. As Leibel puts it, those unconscious signals contribute to such conscious actions as ordering a pizza or having a second piece of pie. Just because a behavior is conscious, he adds, doesn't mean that all aspects of it are voluntary.

To exert its control, the hypothalamus needs reliable, relevant information about the body's current need for food. But where does that information come from? Leptin and, to a lesser extent, insulin carry information about long-term energy depots. The level of leptin in the blood reflects how much fat is stored in the body. Its chief function seems to be to protect energy stores and prevent starvation. When a human or other mammal's food intake is severely restricted, leptin levels drop within twenty-four hours—well before fat stores have been materially depleted by being burned for energy. The fall in leptin immediately prompts the hypothalamus to lower the metabolic rate, increase the appetite, and, to some extent, suppress the reproductive and immune systems so as to focus the body's resources on gaining food.

Insulin, the hormone produced by the beta cells of the pancreas, is released into the bloodstream in response to glucose from food. It helps the body maintain a balance between storing glucose and fat and burning them. Insulin also serves as another signal to certain nerve cells in the brain, informing them about the body's overall nutritional status. The brain also receives messages from the digestive tract. Constant updates about food availability and the timing of meals are relayed to the hypothalamus by various messenger molecules released by cells in the stomach and intestinal tract.

What about the genetics? If Randall were Leibel's young patient today, the boy might undergo testing for a genetic cause of his obesity. A few unlucky people are born with a single genetic mutation that stacks the deck against them so overwhelmingly that they become severely overweight almost no matter what the environment. At least five distinct "obesity genes" have been identified so far. Each of them is so critical to the regulation of appetite and food intake that certain mutations in any of them can lead to extreme obesity.

The mutations that cause such "monogenic," or single-gene, obesity are quite rare. Moreover, even if a physician can diagnose such a condition, there is still no guarantee that it can be treated successfully. Nevertheless, monogenic cases of severe obesity have helped investigators understand how the body regulates food intake and fat stores in people without such debilitating mutations. And even though monogenic obesity is rare, Leibel notes, it does reinforce the idea that specific molecules are highly potent in determining energy balance and body weight in humans.

What about the vast majority of overweight children and adults, whose obesity is not the result of a single defective gene? The scientific consensus is that such people may have multiple genes whose net effect predisposes them to eat a few extra calories, burn up a bit less energy than they take in, or store the excess as fat. Like the members of a band, the genes in each person's personal collection play together, along with various factors in the environment, to determine the person's specific vulnerability to becoming overweight.

How many genes might be at play? Investigators don't yet know. At first, just after leptin was discovered, many people thought there must be a single obesity gene, and some believed it had been found. Now at least sixty genes are being investigated, and some workers fear that as many as a hundred genes could be contributing to the obesity risk.

Leibel's own suspicion, after examining patterns of obesity inheritance in families drawn from various populations and ethnic groups, is that the number of important players is much smaller. He suggests that each person may have as many as a dozen genes that combine to determine the individual risk of obesity. Some genes—perhaps six or seven of them—are probably major players that help determine the likelihood of obesity in people all over the planet. The rest of the dozen or so genes may have arisen from gene variants more common in one ethnic population than in another. That, says Leibel, is what makes the genetics so complicated. No one knows which genes are major players, and which genes are minor ones. And so the geneticists have no way of knowing how to apportion their efforts.

Most people, of course, do not become severely obese, even in today's calorie-rich environment. The average person consumes between 7.5 million and 10 million calories per decade, yet Americans and people in other developed countries typically gain only half a pound to a pound a year throughout their adult lives. To gain any weight at all, they must eat more calories than they burn—but the amount needed to account for the typical weight gain is only about ten to twenty calories a day. That's about the equivalent of one Ritz cracker, or less than 1 percent of the average adult's daily intake.

A calorie imbalance that small can't be reliably measured by studying people in their normal habitat. To study how weight gain and loss quantitatively affect people's appetite and metabolism, Leibel and his associates had to confine volunteers to hospital research wards and measure every mouthful. They found, surprisingly, that obese people do not eat more than lean people in proportion to their body size. Nor do obese people have slower metabolisms than lean ones, as long as they remain at what is their own "normal" weight. They still balance their calorie intake and output very precisely to maintain a constant weight, just as lean people do. It's just that the weight they maintain is higher.

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Yet the laws of thermodynamics dictate that people who are overweight must, at some point, have taken in more energy than they spent in order to gain the extra pounds. “There’s no way around it,” Leibel says. “You cannot eat like a canary and become the size of a pterodactyl.” But in most cases, once obese people have reached a personal set point determined by their own physiology, their weight stabilizes. Their food intake and their metabolic rates, when adjusted for their body size, are similar to those of lean people.

When a person loses weight, however, the circumstances shift dramatically. Whether people start out lean or obese, when they lose 10 to 20 percent of their body weight, their bodies respond by becoming more efficient and using less energy, in an effort to conserve calories and replenish lost reserves of fat. The reduction in energy expenditure is about 15 percent larger than would be expected for the amount of weight lost. That almost certainly accounts for some of the tremendous recidivism among dieters, Leibel says. Studies suggest that some 95 percent of people who lose weight by dieting gain it back within five years.

So though genes determine individual vulnerability to weight gain, environmental factors help dictate the outcome—the weight that a person reaches during childhood or adulthood. Imagine, Leibel says, that you can rank a hundred people, on the basis of their genetic endowment, from 1 to 100 according to their tendency to store excess calories as body fat. Then that same genetic ranking will tell you how they’ll line up relative to one another in most environments. What it won’t tell you, though, is what those hundred people will look like in any particular environment. For example, if a hundred people were exposed to famine and had to subsist on a starvation diet, they would all become thin—but some would lose less weight than others, according to their genetic endowments.

In spite of the scientific progress made in disentangling the body’s complex systems for regulating food intake, energy use, and energy storage, no one really knows how to treat most cases of obesity. Meanwhile, most of the developed world is facing an expanding public health crisis that clearly has not arisen because of newly mutated genes. Obesity is increasing at an unprecedented rate in the United States, and in many other countries as well. For example: in a study conducted in Europe between 1983 and 1986, more than half of the adults between the ages of thirty-five and sixty-five were either overweight or obese; and even in Japan and China, and throughout Southeast Asia, obesity rates have risen sharply during the past two decades. Recent shifts in the modern environment are undoubtedly at the root of the epidemic. People eat more and move around less. Most of us in the developed world enjoy an abundance of cheap, tasty, high-calorie foods, rely on cars, elevators, and other forms of motorized transportation, and lead sedentary lifestyles, in part because of the difficulty of incorporating walking and other kinds of activity into our daily routines.

Such a “toxic environment,” in the words of Kelly D. Brownell, a health psychologist at Yale University, is playing on individual genetic vulnerability, thereby causing unhealthy weight gain in increasing numbers of people. And if environmental factors are at fault, then by changing the environment—or by learning ways whereby we can consciously change our responses to it—it may be possible to slow down or even reverse the trend. Nevertheless, one must sound a cautionary note on what may be too sanguine an assessment: obesity experts who are studying

the epidemic think that a comprehensive solution to the rise in obesity will require broad environmental and social changes—a daunting task.

Leibel is proud that his genetic research has helped put a stop to “blaming the victim,” shifting the blame for fatness away from the people who suffer from it. The continuing discovery of obesity genes is proof that biological variation in vulnerability to weight gain is the main reason some people are fat and others are lean. That’s why Leibel views much of the current national debate about measures to prevent obesity with some concern. He points out that no one yet knows precisely what actions will be most effective. “On some level this is a disease that everybody thinks they understand, and yet in fact nobody understands,” he says. “We really don’t know what has happened, other than on a very macro, thermodynamic level. Food intake is greater than energy expenditure. Period.”

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This version of Susan Okie’s article on obesity was originally published in the February issue of Natural History magazine. The full version appears in Okie’s book, *Fed Up: Winning the War Against Childhood Obesity*, copyright 2005, Susan Okie.

