

# DECODING DIABETES

New discoveries about a growing disease threat

>BY ELIZABETH GUDRAIS

AS YOU READ THESE WORDS, conditions in your body may feel peaceful. Savor that feeling, because it is a Herculean achievement on nature's part. We owe this ability to sit reading quietly to a state of internal equilibrium—the technical term is *homeostasis*. This deceptive mantle of calm relies on an intricate choreography beneath the surface: picture air-traffic control at LaGuardia on a Friday evening. Under the skin, blood pulses, hormones circulate, microscopic proteins dart between cells. An incredibly complex web of signals transmits feelings of hunger and fullness, energy and fatigue, cuing the body to store energy or release it. We are oblivious to the hubbub within.

But in our bodies, as in the air-traffic control center, things can go wrong. A chronically overloaded flight schedule leads to chaos and, eventually, collapse. So, too, turning food into energy takes a toll. The body can metabolize a wide range of substances—fat, carbohydrate, protein—but this system begins to break down if chronically overloaded with excess calories that provide little nourishment. Our bodies' equilibrium is remarkably resilient—but not endlessly so.

Public-health statistics reveal the repercussions of pushing the limits of this resilience with poor diet, too little exercise, and otherwise unhealthy lifestyles. Two-thirds of American adults are now overweight, according to the Centers for Disease Control (CDC); half of these are clinically obese. In the past 30 years, the prevalence of obesity has more than doubled. In 1985, there were only eight states where more than 10 percent of adult residents were obese; by 2001, there was not a single state with obesity prevalence below 15 percent (see the map opposite). "Collectively," says Iacocca professor of medicine C. Ronald Kahn,

"American adults gained two billion pounds during the 1990s." (That's roughly 10 pounds for each American adult, but an arresting figure nonetheless.)

Obesity, in turn, brings vulnerability to another debilitating metabolic dysfunction: diabetes. Someone with a body mass index above 40 (240 pounds for a person 5 feet, 5 inches tall; 295 pounds for a person 6 feet tall) is *seven times* as likely to develop the disease as someone of normal weight.

The CDC estimates that 18 million Americans have been diagnosed with diabetes, and almost 6 million more have it but have not been diagnosed. The cost of caring for diabetes and its complications accounts for one in every 12 dollars of healthcare spending in the United States. In fact, the health-related costs of obesity have surpassed those of smoking, notes Kahn, who from 2000 to 2007 directed the Harvard-affiliated Joslin Diabetes Center, which has 44 principal investigators and a research budget of \$42 million this year. And, says Kahn, "the real impact of this hasn't even been felt yet." The CDC estimates that yet another 57 million Americans have prediabetes—elevated blood-sugar levels indicating the beginning of a breakdown in the body's mechanisms for reining in blood sugar after a meal and for getting energy from food.

In the face of this looming public-health crisis, science is a source of hope. New discoveries—driven by research in genetics, cell metabolism, and the study of small molecules—are creating a vastly more nuanced understanding of the risk factors that underlie obesity and diabetes, and of how those factors operate in the body to bring about disease. With such knowledge comes the promise of new therapies, preventive measures, and perhaps even a cure.

## >DIABETES BASICS

**Diabetes has two main variants:** type 1 and type 2. Both result from a defect in the body's insulin-producing mechanism, but the way they develop is quite different.

Insulin, the hormone that signals the body to take up circulating glucose from the blood, is produced by beta cells in the pancreas. That organ, lodged beneath the stomach, is roughly the size and shape of a banana; in a healthy person, the all-important beta cells, taken together, have the volume of the first joint of a pinkie finger.

Type 1 diabetes is an autoimmune disease: a person's own immune system attacks the beta cells, for reasons that are not well understood. Type 2 diabetes, the form associated with obesity, delivers

a double whammy: cells in muscles, fat, and the liver become resistant to insulin's effects, and the beta cells compensate by pumping it out in ever higher amounts. Although medications and lifestyle changes—such as weight loss and exercise—to increase insulin sensitivity are a first line of defense, many patients ultimately need injected insulin to balance their blood glucose after their beta cells fail altogether.

This article deals mainly with type 2 diabetes, the form that is linked to the obesity epidemic and modern lifestyle factors. (This is the variant that has commonly been called adult-onset diabetes, but it is increasingly affecting children, too.) To read about recent advances in the treatment of type 1 diabetes, often called juvenile diabetes, see "Stem-Cell Progress," page 63.

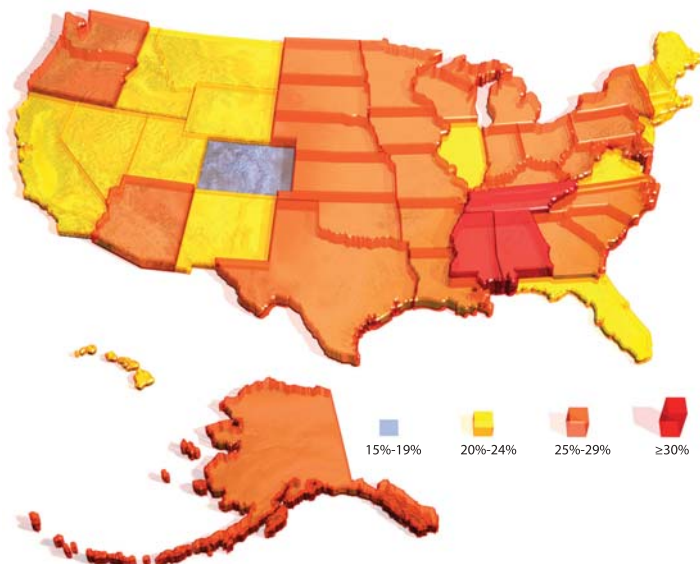


Gökhan Hotamisligil

## >BEYOND BLOOD SUGAR

DIABETES IS A COMPLEX DISEASE, but its medical definition is simple. In a healthy person, the body maintains blood glucose within a very tight range. (Commonly known as blood sugar, glucose is the body's primary circulating energy source, produced by metabolism of ingested food or synthesis from energy stores.) To keep glucose in check, beta cells in the pancreas secrete insulin. This, in turn, signals cells in the fat tissue, muscles, and liver to take up excess glucose from the blood and reserve it for use later.

## AMERICA, THE (INCREASINGLY) OBESE



MAP DATA COURTESY OF U.S. CENTERS FOR DISEASE CONTROL

But in diabetics, both the ability to produce and the ability to respond to insulin are impaired, so blood sugar remains elevated. The diagnosis of diabetes rests entirely on glucose level, but the reasons the disease is dangerous lie downstream. Experts agree that with perfect control of blood sugar, it would be possible to prevent most or all of the disease's complications. But monitoring blood sugar and injecting insulin, while life-saving, does not begin to approach the precision of the body's own control. Over a period of years, repeated glucose spikes after meals damage the blood vessels, contributing to a host of complications: heart disease, hypertension, nerve damage, kidney failure. Diabetes is a leading cause of blindness as blood vessels in the retina are damaged; poor circulation in the feet leads to sores that won't heal and, in a sadly high number of cases, amputation.

Some argue that developing better ways to monitor and manage blood sugar is the key to stemming the tide of diabetes-related healthcare costs, and certainly this is critical in the absence of a cure. But in the last decade, with the help of new research methods, scientists have been able to delve one layer deeper, fleshing out the insulin-glucose dichotomy to include contributions from other hormones, genes, organelles, and small molecules.

Consider the discovery of leptin, a hormone produced by adipose tissue, or fat. The hormone's identification in 1994 by Rockefeller University molecular geneticist Jeffrey Friedman

**OBEISY, THE MOST POWERFUL RISK FACTOR** for type 2 diabetes, is on the rise in the United States—at a dramatic pace. The map at left shows the prevalence of obesity among adults in each state in 2007. In 1985, there were only eight states where more than 10 percent of adults were obese; by 2001, not a single state had obesity prevalence below 15 percent. In some states, the prevalence now exceeds 30 percent.

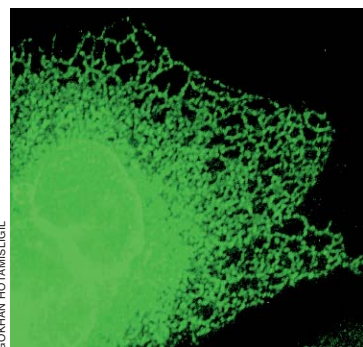




shook up existing notions of appetite, metabolism, and obesity. Up to that point, the scientific community had viewed fat as mere energy storage, excess calories socked away for later. Gradually, it came to view fat as an endocrine organ in its own right, secreting hormones and other molecular signals into the body. The discovery by Simmons professor of genetics and metabolism Gökhan Hotamisligil that fat emits inflammatory signals also informed this newly robust understanding of fat.

Leptin has potent effects on hunger and physical activity. Mice

that lack leptin due to genetic mutations weigh three times the normal amount



**PROTEIN STAINING** turns a cell's endoplasmic reticulum green. These organelles, responsible for folding newly made proteins, show up as a mesh-like network inside each cell. Endoplasmic reticulum stress, a state that results from caloric overload, is critical in the progression to diabetes.

GÖKHAN HOTAMISLIGIL

**MICE FROM Gökhan Hotamisligil's lab:** left, an ordinary mouse; center, a leptin-deficient mouse; and right, a mouse that lacks both leptin and adiponectin. Although hormone deficiencies and a high-fat diet have caused the latter mice to become obese, they appear to be immune to diabetes because of another genetic mutation. The next question is whether this discovery might translate to humans.

and are lethargic; injected with the hormone (named after the Greek word *leptos*, meaning "thin"), the mice become more active, eat less, and lose weight.

Nor are these its only effects. Associate professor of medicine Christos Mantzoros has shown that in female athletes who are so lean they stop menstruating, leptin therapy will restore menstrual periods absent any weight gain or changes in diet—a finding that also has implications for the study and treatment of anorexia nervosa. Walker professor of medicine Jeffrey S. Flier, who is dean of Harvard Medical School (and in whose lab Mantzoros trained), discovered that although some obese humans have low leptin levels—and lose weight when given synthetic leptin—most obese people have abnormally high levels of the hormone. Flier soon realized that leptin resistance commonly accompanies obesity, akin to the insulin resistance that characterizes, and precedes, type 2 diabetes. In these people, evidently, leptin does not have its normal effect of inducing feelings of satisfaction and energy, so their bodies produce more and more, but to little effect, because the signals are scrambled.

This finding prompted questions about why and how leptin resistance arises. Flier was among those to note a structural similarity between leptin and cytokines, proteins used in intercellular communication. He suspected that a category of proteins known as SOCS—suppressors of cytokine signaling—acted on the cellular receptor system that handles leptin signaling. His findings confirmed the hypothesis: a protein called SOCS3 interferes with leptin action. Increase the SOCS3 level and mice show decreased response to leptin and don't stop eating as

## >DIET, EXERCISE, AND YOU

**Plain and simple,** humans are becoming more obese and more diabetic. Although genetic factors undoubtedly contribute, the pace of change is so fast that the explanation cannot possibly lie in changes in our DNA.

But the recognition that environmental factors are vitally important to the obesity and diabetes epidemic is roughly where the consensus ends. Most scientists working in the area agree that some variation of too much food and too little activity is to blame. But others say the real problem is the wrong type of food—and even here there is disagreement about whether the chief culprit is too much sugar, too many carbohydrates in general, too many refined (as opposed to complex) carbohydrates, too little fiber, or too much animal fat.

And food and exercise are not the only environmental factors that matter. Some experiments have shown that sleep deprivation causes hormonal changes that ramp up hunger; a study published this year found that poor sleep quality impairs the body's ability to regulate blood sugar. One recent paper linked increased diabetes risk to chronic, low levels of arsenic in drinking water; another linked obesity to high levels of monosodium glutamate (MSG) consumption. But teasing out the relative importance of each influence is, in some sense, an academic exercise.

Diet and exercise are still the most powerful ways to protect against diabetes (see "The Way We Eat Now," May-June 2004, page

50, and "The Deadliest Sin," March-April 2004, page 36). But getting people to follow this advice is difficult—particularly when the cheapest and most convenient foods are often the least healthful, and government policies contribute to the problem by subsidizing the production of high-fructose corn syrup and livestock feed, making fresh produce relatively more expensive.

Professor of genetics and of medicine David M. Altshuler cites an experiment that reduced the progression to diabetes by two-thirds in a prediabetic population. That study provided people with exercise coaches and dietitians—the kind of one-on-one attention and monitoring that keep celebrities lean and fit, but are expensive and, says Altshuler, "unrealistic to apply in a broad-based way across the country." Even with that intensive intervention, he notes, some of the subjects still developed diabetes. "The rate in the control group was 10 percent per year," he says. "Slowing that by two-thirds was really great—but people were still getting diabetes." Other than bariatric surgery (which reduces the size of the stomach), says Altshuler, "the available treatments are just not very effective."

Even as scientists acknowledge the importance of behavior, they recognize that we are human and prone to falling off the wagon. A diet that succeeds fabulously in mice may be impossible to replicate in people, short of locking subjects in a lab and physically preventing them from eating more than a certain amount.

The notion of thinness as a badge of superior will power rankles some researchers. "Even today, at least 30 percent of people maintain normal body weight without thinking about it very much," says



David M. Altshuler

soon; take away SOCS3, and mice are *more* sensitive to leptin.

But this signaling pathway, once identified, did not translate easily into a new therapy. Removing one substance from the

body can leave receptors more sensitized to some other molecule that uses the same pathway; conversely, blocking the receptor may affect bodily processes far outside the intended conse-

associate professor of medicine Eleftheria Maratos-Flier, an endocrinologist who treats obese patients at the Harvard-affiliated Beth Israel Deaconess Medical Center and researches the hormonal signals and neural pathways that regulate energy balance. Although many people stay lean only through vigilant eating and exercise, others can eat vast amounts of food day after day without becoming obese. Some studies have found people who fail to lose weight despite very low caloric intake. Learning more about genetic variation can help explain why some people stay thin without trying. This, in turn, points to therapies that may help bridge the physiological gap between those who are prone to obesity and those who are not.

The study of individual variation also points to lifestyle-change strategies that don't set people up for failure. Research by associate professor of pediatrics David S. Ludwig, who directs the Optimal Weight for Life program ([www.optimalweightforlife.com](http://www.optimalweightforlife.com)) at the Harvard-affiliated Children's Hospital Boston, has revealed an apparent biological explanation for individuals' varied responses to the same weight-loss regimen. Ludwig has found that the population falls into two groups—rapid insulin secreters and slow insulin secreters. When given an oral glucose solution, the ultimate simple carbohydrate and the common test for diabetes, people in the first group show a pronounced spike in insulin secretion; such spikes can lead in turn to *low* blood sugar and hunger. The latter group, with more gradual insulin release, avoids this roller-coaster effect.

In an 18-month randomized controlled trial of obese young adults, slow insulin secreters lost the same amount of weight on a

low-fat diet as on a low-glycemic-load diet (rich in fat, protein, and slow-digesting carbohydrates such as vegetables and whole grains). The rapid insulin secreters, in contrast, lost *five times more* weight on the low-glycemic diet than on the low-fat diet. Probing individuals' distinct biology this way can help explain why some dieters find the pounds melting off, while others find weight loss stubbornly elusive, says Ludwig: "The individuals who do well on a low-carb diet may not be the same individuals who do well on a low-fat diet."

Take another example: eating seafood regularly and consuming one alcoholic drink per day are generally considered ingredients of a healthy diet. But professor of nutrition and epidemiology Frank B. Hu has found that for people with a condition called hyperuricemia—excess uric acid in the blood, a condition genetic in origin and more common among Asians than in the general population—these same dietary choices further heighten uric acid levels and, consequently, diabetes risk. Hu and others have also published findings of increased diabetes risk for people with an elevated level of iron in the blood: for certain people whose bodies are genetically primed to absorb iron with particular efficiency, iron supplements may harm, not help.

Such knowledge may one day produce personalized prescriptions for losing weight and avoiding diabetes. For now, they point to one conclusion, says Walker professor of medicine Jeffrey S. Flier, an obesity researcher who is dean of Harvard Medical School (and Maratos-Flier's husband): "It isn't as simple as eating less and exercising more."





Mary-Elizabeth Patti

quences. In this case, it would seem desirable to design a drug that somehow immobilizes SOCS3 in the body and therefore pumps up leptin's effects, were it not for another of the protein's functions: limiting inflammation. Mice with SOCS3 genetically deleted die when injected with inflammatory cytokines. SOCS3, says Flier, is "one way the body protects itself from going into shock every five minutes."

Even well-known biological mechanisms are often more complex, and more interconnected, than we ever imagined. Earlier diabetologists believed insulin's relevant action was on the liver, signaling the organ to synthesize or store glucose. Then a series of experiments in mice, some of them in Ronald Kahn's lab, showed that insulin also affects the brain, muscles, fat tissue, beta cells, and the endothelial cells of the blood-vessel walls. "It turns out," says Kahn, "that all tissue has insulin receptors." Such discoveries underscore the difficulty in devising a cure.

A newer line of research by Kahn illustrates that not all fat is created equal. Previous studies found an association between copious visceral fat, which accumulates around the internal organs, and health problems including insulin resistance and type 2 diabetes; subcutaneous fat, which resides just underneath the skin, is associated with *improved* insulin sensitivity and *lower* diabetes risk, particularly when that fat is located in the gluteofemoral region—the hips, thighs, and buttocks.

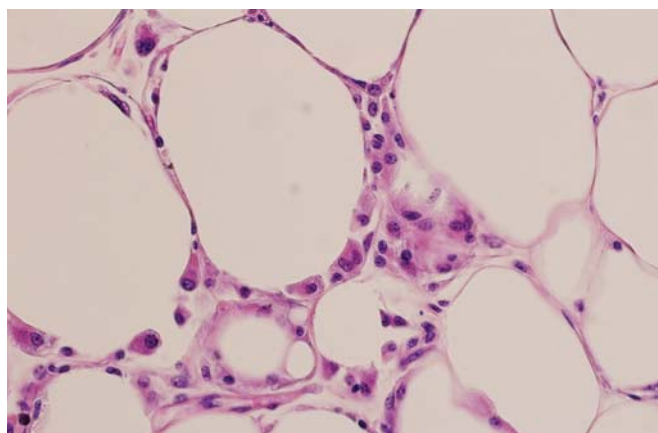
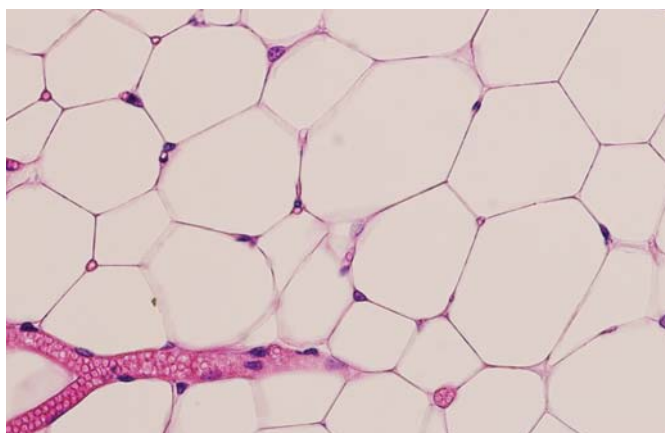
Kahn and colleagues used a fat-transplantation experiment in mice to test whether the operative factor was the fat's location or, rather, some properties inherent in the fat. Their results, published in *Cell Metabolism* in May, imply that visceral fat and subcutaneous fat are fundamentally different: mice that had subcutaneous fat added to their abdominal cavities scored better on

metabolic tests, while mice that had visceral fat added under their skin scored worse, indicating that the two types of fat tissue retained their original effects in a new location. The next challenge is to determine what makes subcutaneous fat salubrious and visceral fat harmful, and what factors—genetic or environmental—lead people to develop one type or the other.

Even if we narrow the focus to consider only hormones (chemical messengers that travel the relatively long distance from one organ or type of tissue to another), the contributors to weight gain and diabetes go beyond insulin and leptin. Also involved are adiponectin, which acts similarly to leptin and is also secreted by fat; ghrelin, secreted by the stomach and pancreas to stimulate appetite; glucagon, secreted by the pancreas to tell the liver to release stored glucose for immediate use; and melanin concentrating hormone, which stimulates appetite and is generated in the brain.

At the same time that scientists are trying to understand the functions of known hormones, they are discovering entirely new ones. Just this year, researchers at the Harvard School of Public Health announced the discovery of a new class of hormones: lipokines. Unlike previously identified hormones, which are steroid- or protein-based, lipokines are made of lipids, or fats. Hotamisligil, postdoctoral fellow Haiming Cao, and colleagues used a novel technique to identify hundreds of fatty acids and pinpoint one that carried a message from mice's fat cells to their muscles and livers, improving insulin sensitivity and blocking fat accumulation. Their work, published in *Cell* in September, also showed that obesity compromises the body's ability to make this marvelous molecule.

Mapping these small-scale processes can seem like a game of whack-a-mole: understanding one small constituent part leads



GÖKHAN HOTAMISLIGİL

**COMPARING THE ADIPOSE TISSUE** of fat and thin individuals reveals major differences in structure and function, as shown in these slides of mouse tissue. Fat cells from a lean mouse (above left) are tightly packed and relatively uniform in shape and size; fat cells in an obese mouse (above right) have swollen up with stored lipids and become much larger. The purple dots between the cells are inflammatory cells and macrophages that cluster around dead and degenerated cells to engulf and digest them.

only to the realization of how much else *isn't* understood. But the approach has already led to new therapies: several popular diabetes drugs act on signaling pathways—for instance, to stimulate insulin production, decrease glucose synthesis in the liver, and discourage fat storage. And teasing out each step has importance beyond finding drug targets; it helps distinguish primary changes from mere side effects in the progression to diabetes.

### >FROM HEALTH TO DISEASE

OBSESITY ALMOST ALWAYS PRECEDES type 2 diabetes, but not everyone who becomes obese will go on to develop the disease. Does obesity *cause* diabetes, or is there some underlying factor that causes *both* conditions? So far, the answer appears to be “some of each.” Assistant professor of medicine Mary-Elizabeth Patti is among the researchers who are working on the road map that leads from health to disease, trying to figure out where the balance lies.

“By the time people get diabetes, there are many, many things that have changed,” says Patti, a researcher and endocrinologist at the Joslin. “Their glucose levels are high. Their insulin levels are lower than they should be, given the high glucose. Their lipids—circulating fats in their blood—are high.” Using medical imaging, scientists (the Joslin’s Alan M. Jacobson and Gail Musen among them) have revealed changes in both brain structure and brain function in diabetic patients, compared to those without the disease. The challenge is distinguishing cause from effect. Says Patti, “There are a lot of things that are already abnormal. Each of these things clouds the picture, so it’s hard to tell which are the primary changes.”

Setting out to learn what people with diabetes had in common from a genomic standpoint, Patti found impaired function in the expression of genes regulating mitochondria, the cellular powerhouses that convert glucose, lipids, and amino acids into ATP, the form of chemical energy that powers the body. This defect in one of the body’s most fundamental cellular components made sense. “If you don’t have as many mitochondria, or you don’t have normal function of mitochondria, you wouldn’t be able to oxidize or burn fuel, and that fuel would reside in cells and not be utilized well,” she says. But among people with high risk of developing diabetes because of obesity or family history, Patti *did not* find higher incidence of mitochondrial dysfunction, indicating that it is probably not the medium by which these risk factors coalesce

into disease. Rather, she says, the results “suggest that mitochondrial dysfunction is an end result of everything that’s happened.”

Gökhan Hotamisligil believes he has a candidate for the culprit that tips a healthy human into a state of illness. He has zeroed in on a phenomenon called endoplasmic reticulum stress: a sort of energy overload, like an assembly line moving just slightly too fast for a worker to keep up. As the products move by, the worker can speed up a bit, but she tires faster, falls behind, and eventually gives up completely—at which point the products move by unattended and the whole operation collapses.

Like mitochondria, the endoplasmic reticula are organelles housed within cells, and they perform a function fundamental to life: folding newly made proteins and transporting them to the proper destinations. But the endoplasmic reticulum does not have an infinite capacity for increasing the rate at which it works: it “is highly sensitive to the energy and glucose level inside the cell,” says Hotamisligil, “and if demand is very high, it starts having trouble.” It emits an “SOS signal” in the form of enzymes called JNK, discovered by Hotamisligil’s lab in 2002, and IKK, identified around the same time by professor of medicine Steven E. Shoelson’s lab at the Joslin.

The medical world had long recognized that protein-folding problems played a critical part in cystic fibrosis and some neurodegenerative diseases, such as ALS (Lou Gehrig’s disease) and some forms of Alzheimer’s. But the idea of a link to diabetes was new. Now, Hotamisligil’s lab is working on “chemical chaperones,” compounds that they have already shown (in mice) to assist in protein folding and shore up the capacity of the endoplasmic reticulum, resulting in a reversal of diabetes. Pharmaceutical companies are hot on the trail of drugs that incorporate this technique, and also of JNK inhibitors that cancel the SOS signal and its effects downstream in the body.

### >THE INFLAMMATION CONNECTION

ELUCIDATING THE VERY SPECIFIC ROLES of tiny proteins points to large-scale synergies in the body. Obesity typically accompanies a whole host of health problems: not just diabetes but often heart disease, hypertension, cirrhosis, impaired fertility, and even cancer. New research is revealing the ways in which whole systems and processes are interwoven—elegantly so in health, and vexatiously so in disease. Efforts to understand what exactly ties isolated health problems together into multifaceted disease



have led scientists to focus on inflammation, a familiar physiological mechanism whose true import is only now becoming clear.

Many molecules implicated in type 2 diabetes—JNK, IKK, and SOCS3 among them—are components of the inflammatory signaling system, part of the body's immune response. And these signals are activated by food intake.

Whenever we eat a meal, the body responds as if to an infection. In healthy people, this reaction, which accompanies the release of insulin in response to food, dies down after a time. The trouble seems to come when meals are so close together, or so inordinately large, that the body never gets a chance to recover from its inflamed state. "This ancient capacity of fat cells to produce an immune-like response is activated when they're exposed to large amounts of energy," says Hotamisligil. "The body starts perceiving excess amounts of energy as a foreign invader."

While working in Hotamisligil's lab, Kathryn Wellen, Ph.D. '06, identified a new group of molecules called STAMPs that help fat cells cope with the onslaught of energy. Mice without these molecules developed metabolic problems (high blood sugar and lipids, insulin resistance, fatty liver, abdominal fat accumulation) when fed a normal diet; the hope is to harness STAMPs' effects for use against the hazards of overeating in humans. Foods such as fruits and vegetables, herbs and spices, oily fish, and some

nuts have natural anti-inflammatory properties, so a diet high in these foods also helps to mitigate this response.

Adipose tissue itself secretes pro-inflammatory molecules that are highly correlated with diabetes risk, independent of other factors. Professor of nutrition and epidemiology Frank B. Hu has found that obese people with high levels of interleukin-6—a potent inflammatory cytokine secreted by fat tissue—are more likely to develop diabetes than those with lower levels. On the other hand, people with high levels of adiponectin, an anti-inflammatory hormone also secreted by fat, enjoy a strong protective effect: people in the highest quintile for circulating adiponectin have a 90 percent reduced risk of getting diabetes. This effect held true in lean and obese subjects, whether active or sedentary, across all age groups. Because circulating levels of these substances are determined in part by genes, such findings help explain why some people are very resistant to developing diabetes, despite having multiple risk factors.

Particularly in obese individuals, adipose tissue contains clusters of macrophages, the immune-system cells that destroy and then digest invading pathogens. There are two types of macrophages: one that attacks viciously and kills alien microbes, and another that swoops in to repair the damage afterward, bringing about healing and tissue repair. The latter type is more plentiful in the fat tissue of lean people; obese people tend to have more

## > GENETIC PROTECTIONS

**Diabetes does not have** a simple, single genetic basis in the Mendelian sense (tall plants or short, blue eyes or brown, diabetic or not). Rather, it is a complex, *polygenic* disease. That is to say, in almost everybody who develops diabetes, several genes act together, with input from environmental factors, to bring it about.

New tools are enabling the systematic study of the genes that underlie the disease, and producing surprising findings. Comparing the genomes of people with and without diabetes, scientists at the Harvard-affiliated Massachusetts General Hospital and the Broad Institute of Harvard and MIT have identified 17 specific genetic variants associated with type 2 diabetes, says professor of genetics and of medicine David M. Altshuler, an endocrinologist and human geneticist who heads the Broad's program in medical and population genetics. Before conducting the analysis, researchers at the Broad and other prominent programs that study the disease made a list of more than 500 "suspect" parts of the genome where they expected to find a correlation with diabetes based on earlier research. Not a single one came back positive. "What this tells me," says Altshuler, "is there's a lot of the biology of the disease that we don't yet understand."

The fact that type 2 diabetes has a far stronger genetic concordance in identical twins than type 1 does is not widely recognized. Someone whose twin has type 1 diabetes has a 30 percent chance of developing it himself; for someone whose twin has type 2 diabetes, the probability is "upwards of 80 percent," says Altshuler.

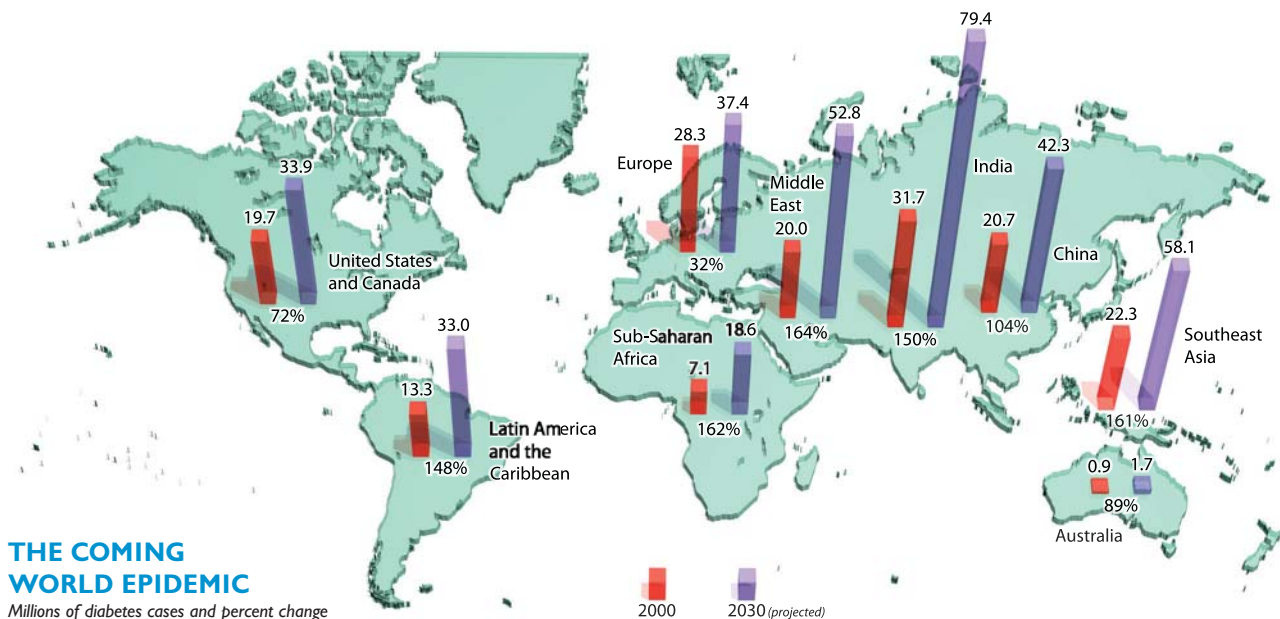
He hopes genetic analysis will ultimately lead to therapies. It has already yielded intriguing hints about how the disease might work. Of the 17 diabetes "hot spots" identified, 11 were associated with decreases in insulin secretion—and not one was associated with insulin resistance. Type 2 diabetics have both insulin resistance and impaired insulin secretion; this finding implies that the latter plays a stronger role than the former in the progression to disease. In other words,

the people who get diabetes are those whose beta cells cannot compensate by pumping out immense doses of insulin to compensate for insulin resistance—and individual genetic makeup strongly influences the body's capacity to generate more insulin. This, too, indicates a closer similarity between type 1 and type 2 diabetes than previously recognized, since type 1 diabetes is characterized by complete breakdown of insulin production when pancreatic beta cells are destroyed.

Another group of researchers is looking beyond the genome to epigenetics: changes in the expression of genes independent of changes in the underlying DNA. Changes in the way DNA is packaged encourage or discourage gene expression, and here the intrauterine environment has powerful influence. Assistant professor of medicine Mary-Elizabeth Patti studies low-birthweight mice as a way to understand the strong correlation between low birthweight and obesity later in life, in both humans and mice. Patti was surprised to find that the *offspring* of the low-birthweight mice—that is, the grandchildren of the mice that were underfed during pregnancy—were also predisposed to diabetes, even though nutrition during their gestation, and their entire lifetime, had been normal.

Although this study brought about low birthweight through gestational caloric restriction, low birthweight can result when the mother's health suffers in other ways—including hypertension and diabetes. So Patti's findings mean that the current epidemic of metabolic disease could result, at least in part, from our grandparents' life experiences. More unsettling is the potential impact on future generations.

But Patti's research has yielded one bit of happy news. Restricting food intake for the low-birthweight mice, so that they eat no more than the baby mice whose weight at birth was normal, keeps the former from gaining weight as rapidly—and from becoming obese and diabetic later in life. "There is a period of plasticity when the organism is still sensitive to manipulation," says Patti. "That's the key point." This research may have revealed a strategy for breaking this metabolic vicious cycle. But, she says, "We clearly need to test this in humans."



## THE COMING WORLD EPIDEMIC

Millions of diabetes cases and percent change

**THE UNITED STATES'S CAR-CENTRIC CULTURE** and labor-saving appliances have saved Americans from having to walk anyplace or get even the minimal amount of physical activity involved in washing dishes by hand or wringing out laundry. Combined with the easy availability of cheap, highly processed, calorie-dense foods, the American lifestyle represents the “perfect storm” for diabetes. As this lifestyle continues to spread, it is a fair assumption that so will the American pattern of health problems. In rural China, for instance, diabetes incidence is less than 2 percent; in Hong Kong—with a genetically similar, but urbanized, population—the rate exceeds 10 percent.

Although diabetes incidence in the United States, Canada, and Europe is still relatively high, it is not because people of non-European descent have some sort of genetic protection. In fact, with similar lifestyles they are more likely to develop the disease. Diabetes incidence among non-Hispanic white American adults is 6.6 percent; among Asian Americans, it is 7.5 percent; among Hispanics, 10.4 percent; and among blacks, 11.8 percent.

Disparities persist even after controlling for factors such as diet and exercise. One factor: the threshold for developing diabetes varies among racial groups. For example, researchers with the Asian American Diabetes Initiative (<http://aadi.joslin.harvard.edu>) have found that for people of Asian ancestry, heightened diabetes risk begins at a body mass index of 23—well within the range the Centers for Disease Control considers normal. And this group is doubly vulnerable: people of Asian descent have higher genetic susceptibility to the disease's complications, such as atherosclerosis.

If obesity and diabetes are a ticking time bomb in the United States, they pose an even larger threat in the developing world, where in many places the number of people with the disease is expected to double during the next two decades.

of the former. Assistant professor of genetics and complex diseases Chih-Hao Lee is trying to parse cause and effect, and has found evidence for causality in both directions, in mouse models that presumably would translate to humans: inflammation makes an individual more prone to gaining weight, which makes the body's baseline state more inflamed—a vicious cycle.

In a way, it makes perfect sense that inflammation and the immune response would be intimately linked to metabolism. Although the recognition of postprandial systemic inflammation is relatively recent, scientists have known for many years about another physiological state that triggers coordinated action. During acute infection, as the immune system fends off an invader, the body induces a temporary state of full-body insulin resistance, apparently because macrophages demand huge amounts of glucose. In a state of insulin resistance, the muscles, fat, and liver leave glucose circulating in the bloodstream instead of taking it up, and even release stored glucose to further bolster the immune response. Thus, the body gets the necessary power supply to counter the crisis of infection.

This phenomenon was taken for granted, perhaps because the articles documenting it were published so long ago, says Lee, that “when you do a PubMed search, you can't even find them.” But recognition of connections between insulin action and metabolism on the one hand, and inflammation and the immune system



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on the other, has spurred renewed interest.

It has also spurred a rethinking of the medical dogma that type 1 and type 2 diabetes are entirely distinct. Type 1 has been—and still is—characterized as an autoimmune disease, while type 2 was considered altogether different. Although a type 2 patient's body does not attack the beta cells in the pattern that defines type 1, scientists are beginning to recognize that the immune system plays a part in the development of type 2. And assistant professor of medicine Rohit Kulkarni, a researcher at the Joslin, has found that type 1's pathogenesis is also not as simple as previously thought. Studying mice genetically predisposed to get type 1 diabetes, Kulkarni found that in those animals that eventually developed the disease, there was a breakdown of insulin signaling—the hallmark of type 2 diabetes—even before beta cells began to die off. It is also not lost on those who study the disease that the onset of type 1 diabetes sometimes follows an acute infection—that is, it follows the aforementioned full-body insulin resistance.

As the gap between the disease's two variants shrinks, there is hope for new findings that shed light on both—and for therapies with dual applicability. “They are not the same,” says Hotamisligil. “But they are much more similar than we thought even five or six years ago.”

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Elizabeth Gudrais '01 is associate editor of this magazine.