The Covert Plague

Researchers call it insulin resistance, and it could bring down an entire health system. Yet most people could easily save themselves.

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Jerry Silva's body was not designed for life in the early 21st century. A 44-year-old financial analyst from Sherborn, Massachusetts, Silva spends most of his time behind a desk tracking high-tech stocks. It's a life far removed from that of his Mexican forebears, who spent their days hoeing maize fields and fishing near Guadalajara. Silva has more than enough to eat, whereas his ancestors often went hungry. The significance of that difference in lifestyle became painfully apparent last January, when he was diagnosed with diabetes. The disease, closely linked with not eating the right foods and sitting around too much, is beginning to look something like a pandemic as millions of people around the world confront a central irony of the modern world: A lifestyle of abundance can be deadly.

BIOCHEMICAL IMBALANCE: Type 2 diabetes develops slowly and relentlessly as insulin-producing cells in the pancreas malfunction, causing insulin levels to drop. Without insulin, the body cannot process all the glucose from the carbohydrates and other sugars in food. Nearly one out of five type 2 diabetics needs daily injections. That amounts to 3 million Americans, a number that is steadily rising.

On this planet 194 million people have diabetes, double the number of 25 years ago. In another 25 years the number is expected to double again. But those numbers represent only people who reach such high blood-sugar levels that diagnosis is clear and certain. Recent research suggests that the plague may be many times worse, affecting a much larger group of people who are slowly but surely developing a resistance to insulin in their bodies and who could be categorized as prediabetic. Long before such people are officially diagnosed, their eyesight, their hearts, and other organs come under attack. In this country, there are 41 million known prediabetics and 18 million diabetics, about one in every five Americans.

The tangible consequences of this growing epidemic are staggering. Each year in the United States 40,000 diabetics get kidney disease, up to 24,000 go blind, and 82,000 have amputations—a toe, foot, or leg—because of vascular failure. Recently, researchers have found alarming links between diabetes and neurodegenerative afflictions such as Alzheimer's disease. Diabetes and insulin resistance may cause depression, decreased cognitive function, and harmful alterations in brain structure. Diabetes can cut up to 20 years off the human life span and costs the United States at least $130 billion annually.

Globally, the number of diabetics and prediabetics is in the hundreds of millions and skyrocketing as nations in Asia, Latin America, and Africa modernize. In Africa today, overweight and obese children outnumber the hungry three to one. Those most at risk are people whose recent ancestors led subsistence lives. "We're sitting on a time bomb here," says Francine Kaufman, a physician-researcher at Children's Hospital in Los Angeles and a past president of the American Diabetes Association. "The problem is spreading around the globe, and it's getting worse."

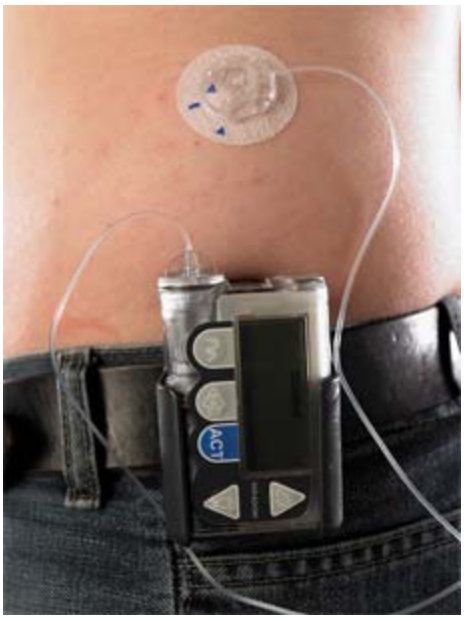
Why this is happening and the molecular mechanics of how it is happening are among the most intensively studied areas in medical research, and definitive answers have yet to emerge. "We have theories and ideas, but nothing concrete about the exact genetics of insulin resistance," says Gerald Reaven of Stanford, a pioneer researcher of type 2 diabetes,

which afflicts 95 percent of all people with diabetes. Type 2 usually appears later in life, but in the last two decades type 2 diabetes has quadrupled in children and adolescents, in lockstep with increasing weight gain. Type 1, which typically occurs when the pancreas shuts down and no longer makes insulin, strikes relatively early in life.

The frequency and growth of diabetes has not gone unnoticed by pharmaceutical companies—at least 20 firms are feverishly searching for remedies, and at least 40 new drugs are being tested. Yet none of those drugs will become a cure. "And many will fail," says Reaven.

Like diabetes, prediabetes is diagnosed when fasting blood-glucose levels rise above normal—100 to 126 milligrams per deciliter. The rise usually comes with weight gain, but not always. Too many french fries, servings of mashed potatoes, sugary sodas, and loaves of white-flour bread can result in insulin resistance, the underlying defect in both pre- and full-blown diabetics. It crops up when cells begin to resist absorbing glucose. Every type 2 diabetic and prediabetic is insulin resistant, which stimulates the pancreas to churn out even more insulin. This stresses pancreatic cells until they eventually shut down partially or completely, forcing patients to inject insulin.

Resistance to insulin can arise by simply eating too much and by not exercising enough. When a patient's blood-sugar levels rise, a physician may offer amazingly effective advice: "Lose five percent of your body weight and keep it off." Even in the half or so of all diabetes cases that seem to be related to genes that have programmed a person's cells to need less fuel, exercise and moderate diet changes can work wonders if the progress of insulin resistance is noticed soon enough during regular checkups.



AROUND-THE-CLOCK INSULIN: A portable pump is the most advanced means for delivering insulin. Typically, a pump can be programmed to release a low, steady dose of insulin throughout the day as well as a high dose before a meal. Spikes in blood-glucose levels exacerbate the health complications from diabetes, which can be fatal. Adults with diabetes are two to four times more likely to die of heart disease or stroke than adults without diabetes.

Prediabetes happens slowly and insidiously. Cells gradually become resistant to insulin, which is produced in the body to process glucose levels that rise in the blood after a meal. Insulin can open up a cell's outer membrane like a key in a door lock and set in motion the machinery that feeds the cell glucose, which is converted to energy. The human body works best when the supply of fuel equals the exact energy needs of its cells.

Nonetheless, our bodies are designed to compensate for times when food is scarce by taking advantage of times when it is abundant. One method is to turn excess glucose into fat, which can be stored for leaner times. On the ancient savannas, this manifested itself when hunters killed a wildebeest, and everyone gorged for a few days, storing the excess food in fat cells. Another method is for cells to throttle back the processing of glucose during lean times by becoming insulin resistant, which blocks insulin from entering the cell and in essence rations the supply of glucose to last longer while also creating a powerful hunger impulse to drive people to find food. Researchers in the 1960s theorized that modern people prone to obesity and diabetes might have inherited these two ancient methods of coping with feast and famine.

In 1962 James Neel suggested that early hunter-gatherers possessed a "thrifty gene" that helped them survive by speeding up the accumulation of fat when food was available. The closer a person is to the time when his or her ancestors were hunter-gatherers, says Allison

Goldfine, a physician and investigator at the Joslin Diabetes Center at Harvard University, "the higher the rates of weight gain." In 1966 George Cahill offered a different scenario for the thrifty gene, conjecturing that this gene is actually for insulin resistance. This notion is supported by the high numbers of diabetics and prediabetics who have insulin resistance running in their families. Moreover, while all diabetics are insulin resistant, not all of them are fat. Both theories may help explain the explosion of diabetes in our time.

Evolutionists suggest that some people are less prone to diabetes, even if they grow fat, because their ancestors had steady and abundant supplies of food. This allowed them to evolve away from needing a thrifty gene. Called the fertile crescent theory after a part of the world where agriculture appeared early, the notion is supported by lower instances of diabetes in people whose ancestors came from the Middle East and Europe. Still, Goldfine points out that there is much variability among people with and without the disease—some are skinny and diabetic, and some are grossly obese but not diabetic. No theory yet accounts for all possibilities.

Exercise and a careful dietary regime can help prevent the onset of type 2 diabetes. But in its advanced stages, the disease requires constant and expensive treatment. The average annual medical expenditure for a person with diabetes is $13,243, which is 5.2 times greater than the cost for a person without diabetes. Each month that includes the grab bag of personal medical supplies pictured below.

A: Most type 2 diabetics need to check their blood glucose twice a day using a test strip. B: Roughly 80 percent of type 2 diabetics manage fluctuations in blood-glucose levels with a prescription drug such as metformin, which is taken twice a day. C: Type 2 diabetics requiring insulin to control their blood glucose typically need one injection a day. D: The type of insulin diabetics use to control fluctuations in blood-glucose levels varies according to their needs. Lantus is a slow-acting form of insulin. Humalog is more fast acting and is commonly used to provide extra insulin before a meal.

Even without a comprehensive theory to explain the variability of diabetes, researchers are making headway in discovering how the disease works. Scientists have so far identified about 250 genes related to appetite, insulin resistance, metabolism, and fat storage. The number is growing as researchers apply ultrafast microarray technology (gene chips that scan for mutations for diseases) to search for relevant DNA. Efforts include the National Institutes of Health Diabetes Genome Anatomy Project and another NIH-sponsored venture, the International HapMap Project, which is creating a map of regions in the human genome called haplotypes, where the underlying DNA influences common diseases like diabetes.

For one out of 30 people with diabetes, genes are known to play a decisive role, particularly in a grouping of DNA known as maturity-onset diabetes of the young, which includes a mutation that causes the pancreas to produce less insulin. For everyone else, the genetic link is weak. No definitive diabetes gene has been found. At Joslin, researcher Andrzej Krolewski studied 140 families rife with diabetes and found mutations on two chromosomes. Only 40 percent of the 140 families had it. The others had no genes that could account for the disease. That suggests no primary gene for diabetes exists. But many genes could have a moderate impact on whether a person gets diabetes, and many others could have a minor impact.

The results of various gene combinations can be confusing: Some people can eat themselves into full-blown diabetes with nary a known gene to blame. Others are insulin resistant and

crank out huge levels of insulin to compensate, yet they never develop diabetes. A few diabetics are not fat, eat healthfully, and exercise. "These people have a very strong genetic basis for the disease," Reaven says.

Laboratories trying to tease out molecular answers have made some progress. Last summer, Gerald Shulman of Yale University and the Howard Hughes Medical Institute implicated mitochondria—the parts of the cell that burn fat and glucose to produce energy. He suspects that the mitochondria in people predisposed to developing type 2 diabetes produce less energy, causing cells to demand less fuel, which triggers insulin resistance. Shulman used a magnetic resonance spectrometer to test older adults for mitochondrial output. He found that as people age, their cellular energy production declines, which may explain why diabetes is related to aging. Shulman more recently tested young, healthy, lean 20-year-olds whose parents have diabetes and discovered that they, too, have mitochondria that produce less energy and are somewhat insulin resistant—strong indicators they will get diabetes when they're older.

Researchers are also trying to tease out the role of fat in diabetes. "All the problems start with fat," says Osama Hamdy, director of Joslin's obesity clinical program. "It is such an irony that in the modern era we are finally feeding huge numbers of people," he says, "but our bodies were not designed to be satiated with so much food." Clinical studies reveal that all that extra sugar gets stuffed into the fat cells our ancestors used to store energy for times of hunger. But crammed with too much, the cells start to die at the center, causing a cascade of harmful reactions, including chronic inflammation as the immune system tries to deal with the rot and a buildup of toxins that further injure cells and add to insulin resistance.

GRIM PHYSICAL TOLL: Higher-than-normal levels of glucose gradually cause irreparable damage to blood vessels and nerve cells throughout the body. Every year more than 82,000 diabetics in America have their toes, feet, or legs amputated. That's more than 60 percent of the nontraumatic lower-limb amputations nationwide. Diabetes is also the leading cause of new cases of blindness among adults 20 to 74 years old, accounting for as many as 24,000 cases each year.

"Imagine if you buy some food and you store it on a shelf, and then you go and buy more food," says Hamdy. "You need more space, so you expand the shelf space, but the food you originally bought doesn't get eaten, so it rots. That's essentially what happens to fat cells." As fat cells bulge, the body tries to store glucose in other tissues, including the liver, kidney, heart, muscles, and blood vessels, where the rotting process takes hold.

Medicines used to treat diabetes fall into four groups: those that stimulate the pancreas to put out more insulin; those that lower insulin resistance in cells; those that help the body use insulin; and those that slow down or block the breakdown of starches, which in turn keeps blood-glucose levels lower. Taken separately or in combination, these drugs work somewhat in some patients and not in others. They can only be taken in concert with a strict diet and require frequent blood tests to monitor glucose levels. None of the drugs cures anything. "They merely slow down the progression of the disease," says Paul Herrling, head of corporate research for Novartis, maker of Starlix, an insulin-cell booster.

Novartis is one of many drug companies with new medicines being tested in humans, according to Pharmaceutical Research and Manufacturers of America. Most of the new wave of drugs in development act to block the actions of specific proteins that bring on symptoms of diabetes, or they work to reduce obesity by dissolving fat or controlling appetite. Other companies offer ramped-up versions of drugs already on the market or ways either to increase the potency of insulin or ease its delivery. Several not on the list have failed in human tests, usually because of unacceptable side effects.

A recent contender in the drug wars is a chemical long known to reduce blood sugar—a relative of aspirin in the chemical family of salicylates. It is a version of aspirin that does not cause internal bleeding when taken in high doses. In 2002 Joslin researcher Steven Shoelson knew that salicylates block the action of a protein called NFkB, a genetic master switch in the liver that helps launch a cascade of genes that cause the chronic, low-grade inflammation associated with diabetes. Shoelson had already determined that weight gain and a Western diet trigger an increase in NFkB, long a culprit in the more severe inflammation and pain of rheumatoid arthritis. He thought of salicylates for diabetes after reading a study demonstrating that they block NFkB in arthritis patients. He reasoned that if high blood sugar activates NFkB, which causes inflammation, then blocking NFkB might not only reduce inflammation but also reduce blood-sugar levels. Amazingly, he found that another researcher had the idea more than 100 years ago. Searching the literature, he found a paper written by Wilhelm Ebstein, a German physician, in 1876.

DO YOU HAVE TYPE 2 DIABETES?

Five million Americans have diabetes but don't know it. An estimated 41 million are prediabetic—their cells are resisting insulin, and they cannot process all the sugars in their blood. The major risks of becoming diabetic or prediabetic are eating too much and being sedentary. In some cases, genetics plays a role. Hispanics, Native Americans, Africans, African Americans, Pacific Islanders, and South and East Asians have a higher risk of becoming diabetic than other groups.

SYMPTOMS: Excessive thirst, frequent urination, blurred vision, increased hunger, irritability, tingling or numbness in the hands or feet, and fatigue. If you have any of these symptoms, see your doctor.

WHAT TO DO: Diabetes can be reversed or dramatically improved by exercise and changes in diet. Several medications can help control blood-sugar levels. The most common is metformin, an inexpensive generic drug. Prediabetics can almost always prevent the disease by exercising and losing weight.

RISK FACTORS: People who are older than 45, overweight, sedentary, have a family history of diabetes, are members of certain groups prone to diabetes, and have elevated blood pressure and unhealthy levels of cholesterol and triglycerides are more likely to become diabetic.

Ebstein reported that he gave a patient large amounts of an extract of willow bark, or sodium salicylate, the primary component in aspirin. (Adding acetic acid, or common vinegar, to sodium salicylate produces aspirin.) The amount of sugar in the urine of the 58-year-old man with "diabetes mellitus," now known as diabetes, was significantly reduced. Ebstein gave him 10 grams of salicylate a day, more than 10 times the normal dose for a headache. Shoelson says his team is using about half that dosage. He and Allison Goldfine have tested salicylates on 36 patients at Joslin—including Jerry Silva. The results have not been tabulated, but earlier trials proved that salicylates not only lower blood glucose but also triglycerides. Silva does not yet know his results, but he suspects he was in the control group that got a placebo because he didn't notice a reaction. The downside for salicylates is the large dosage, says Goldfine, the equivalent of 20 aspirins a day. "We don't know if using these large doses is safe over a long time."

No medicine is as effective for treating diabetes as exercising seven days a week and following a healthy diet. Osama Hamdy likes to talk about the Diabetes Prevention Program, a national study at Joslin and elsewhere that tested the impact of exercise and diet versus that of drugs. The study split prediabetics into a control group and two experimental groups—one in which subjects exercised and watched their weight and another in which people took metformin, a drug that improves insulin sensitivity in the liver. People in the first group lost 7 percent of their body weight on average and reduced their risk by 58 percent. Those on metformin lost about four pounds and reduced their risk by 31 percent. "Losing even this small amount of weight," Hamdy says, "5 to 7 percent, substantially reduces the risk of getting diabetes."

Silva is counting on that being true. When his diabetes was diagnosed last winter, his doctor gave him glyburide. But the drug made him hypoglycemic—too little blood sugar. He felt woozy, so he opted for taking long strolls on a home treadmill and bicycling. On a recent Sunday, he watched his favorite football team, the Patriots. But he didn't sit on a couch "drinking beer like I used to." He walked seven miles on a treadmill, simulating the more active way of life of his ancestors. So far, Silva has lost 25 pounds, and his blood sugar has tumbled by 65 percent, to just above normal. He is still at risk, but he hopes that keeping the weight off will ease possible complications from his disease. "I have a 7-year-old daughter," he says, "and I want to live to see her grow up."