Prosperity’s Plague

Researchers have linked a growing number of chronic diseases to the metabolic disorder known as insulin resistance; two general theories have emerged about its mechanism.

Welcome to the age of insulin resistance. This condition is the thread that runs through many chronic afflictions of modern times—obesity, heart disease, and, most conspicuously, type 2 diabetes. All are entangled with diet, and all are linked causally to a dysfunctional response to insulin, the hormone that orchestrates the body's use and storage of nutrients.

Insulin resistance is the fundamental defect in type 2 diabetes, a disease that afflicts 6% of adult Americans, up from 3% in the early 1970s. Most type 2 diabetics are obese, a condition that’s so closely associated with insulin resistance that many researchers assume that it is a cause. The prevalence of obesity has increased in the United States almost 2.5-fold since the early 1970s, from 14% to 34%, according to the most recent national surveys.

Metabolic syndrome is another insulin-resistant condition. By some estimates, it affects 50 million Americans. It’s defined by a cluster of abnormalities—including abdominal obesity, hypertension, and high blood sugar—that precede both coronary heart disease and type 2 diabetes. Stroke, nonalcoholic fatty liver disease, polycystic ovary syndrome, asthma, some cancers, and even Alzheimer’s disease have also been associated with insulin resistance.

Once it takes hold, insulin resistance sets up a vicious cycle: As tissues become unresponsive to insulin, the pancreas compensates by secreting ever more insulin, and gradually the tissues grow more resistant.

Elucidating the causes of this destructive cycle is one of the most critical endeavors in modern medicine. Researchers have made progress identifying events that lead to type 2 diabetes and other insulin-involved diseases. But working back up the chain of causality has been a challenge. Unambiguous evidence on the initial stages of disease is missing, making it an excruciatingly difficult task to pin down the causes at the cellular and molecular level.

“The field is in a funny stage right now,” says Mitchell Lazar, director of the Institute for Diabetes, Obesity and Metabolism at the University of Pennsylvania. “It’s gone from having too few candidate explanations [for insulin resistance] to having too many.” Now when someone comes along with yet another possibility, Lazar says, “you go, ‘Okay, get in line, buddy.’ There are a lot of things that have to be figured out.”

Several candidate mechanisms have emerged in the past decade, and two competing theories have gained wide support. One is that cells essentially become poisoned by fat. This lipotoxicity or lipid overload hypothesis holds that normal processes break down when fat (adipose) tissue cannot store excess fat, and fat accumulates inappropriately in muscle and liver cells.

The main rival to this idea, the inflammation hypothesis, is that as fat cells increase in size with the accumulation of fat, they release inflammatory cytokines and molecules known as adipokines. It’s these molecules, so this theory goes, that cause insulin resistance elsewhere in the body. Researchers are now confident that these inflammatory mechanisms play some role in insulin resistance. But they still can’t say for sure whether those roles are causal.

Tangled pathways

What makes insulin resistance such an extraordinarily difficult problem to study is that it constitutes “the ultimate systems biology question,” says endocrinologist C. Ronald Kahn of the Joslin Diabetes Center in Boston, which is affiliated with Harvard Medical School.

Insulin is the primary regulator of fat, carbohydrate, and protein metabolism; it regulates the synthesis of glycogen, the form in which glucose is stored in muscle tissue and the liver, and it inhibits the synthesis of glucose by the liver. It stimulates the synthesis and storage of fats in fat depots and in the liver, and it inhibits the release of that fat. Insulin also stimulates...
Among insulin’s many functions is as a partner in the regulation of glucose metabolism and thus involved in the prevention of type 2 diabetes, a disorder of insulin resistance. Reaven says, “clearly, the more obese you are, the more insulin resistant you are.” The operative word, though, is how sensitive the liver is to insulin. It tells you very little about how sensitive the skeletal muscle or the adipocyte is.”

Fat overload
In the mid-1970s, endocrinologists focused on the insulin receptor itself as a likely key to the puzzle. They assumed that resistance was caused either by down-regulation of the insulin receptor—a normal desensitization process—or by a defect in the receptor itself or the binding of insulin to the receptor. By the mid-1980s, Jerrold Olefsky, now at the University of California, San Diego, had demonstrated that the primary defect was downstream in the signaling pathway, not in the receptor itself.

Since the early 1990s, the observation that insulin resistance is associated with elevated levels of free fatty acids in the bloodstream has led researchers to focus on lipid overload as the precipitating event. Several observations support the hypothesis. The single best predictor for the presence of insulin resistance in young, lean offspring of type 2 diabetics, according to Gerald Shulman, an endocrinologist at Yale University, is the accumulation of fat inside muscle cells. Shulman and his colleagues have also studied sedentary populations of lean, healthy, elderly subjects and obese, insulin-resistant adults and children. In all those cases, he says, “the more fat inside the muscle cells, the more insulin resistant they are.”

Using nuclear magnetic resonance spectroscopy to do noninvasive measurements of metabolic fluxes—what Shulman calls “basically real-time biochemistry in humans”—Shulman and his colleagues have established that when fat accumulates inside muscle cells, it blocks an intracellular chain of events that normally triggers glucose transport into the cell. The specific culprit, according to Shulman, is the buildup of diacylglycerols (DAGs)—an intermediate product in the formation of triglycerides, the form in which fat is stored in cells. When DAGs accumulate inside muscle cells or liver cells, Shulman has found, they shut down the insulin-signaling pathway. In the muscle cells, they do so by inhibiting the translocation of a protein, GLUT4, to the cell membrane, where it would normally work to pump glucose into the cell. Insulin-stimulated glucose transport...
no longer works efficiently, and the cell is insulin resistant.

“Over the last decade,” says Shulman, “we’ve been able to test this hypothesis using the power of mouse genetics. In more than a dozen transgenic gene knockout models, any time we raise intracellular diacylglycerols, the mice get insulin resistance in the target tissues; any time we lower it, we prevent insulin resistance.” In March, Shulman and his colleagues reported in the journal Cell Metabolism that DAG accumulation can also account for insulin resistance in the liver caused by the consumption of high-fructose diets.

The way to think about this, says Shulman, is that the concentration of DAG in a cell is balanced between the delivery of fat to the cells (in the form of fatty acids), the oxidation of fat, and the storage of the fat as triglycerides. “Any time you alter that balance to get a net accumulation of DAGs, through more delivery or decreased oxidation, you get insulin resistance. Anything that flips the balance the other way”—by blocking entry of fatty acids into the cell, for instance, promoting fatty acid oxidation, or even promoting the conversion of DAGs into triglycerides—“prevents insulin resistance.” In that sense, the DAGs work as both an intermediate form of a storage molecule and a signaling molecule that tells the cell whether fatty acids are accumulating and whether it’s necessary or beneficial to continue pumping in glucose.

Inflammation Competing with the lipid overload hypothesis is the theory that inflammation is to blame. The idea was sparked in the mid-1990s, when Gökhan Hotamisligil of the Harvard School of Public Health and Bruce Spiegelman of Harvard Medical School reported that the inflammatory cytokine TNF-α was overexpressed in animal models of obesity. They demonstrated that they could induce insulin resistance in fat cells in vitro by exposing them to TNF-α. They also showed that they could protect obese strains of mice from insulin resistance by knocking out the genes either for TNF-α or for TNF-α receptors.

The hypothesis began to gain wide acceptance after Steven Shoelson of the Joslin Diabetes Center reported in 2001 that he could make cells insulin resistant by overexpressing IKK-β, a molecule that works in signaling pathways to activate the inflammatory mediator NF-κB. Among the compounds that inhibit IKK-β are salicylates, aspirin-like compounds that are used at high doses to treat rheumatoid arthritis and rheumatic fever, both inflammatory conditions. “That struck a chord with me,” says Shoelson, because “among the list of things that can cause low blood sugar are salicylates.” One obvious implication, he says, is that “inflammation is a potential pathogenic mediator of both insulin resistance and type 2 diabetes.”

Fat as they come Researchers made a mouse that can accumulate huge amounts of fat, as the one on the left does by overexpressing adiponectin. The result: This mouse was insulin sensitive.

Since then, Shoelson has demonstrated in a series of studies through 2005 that insulin resistance can be induced in lean strains of mice by overexpressing NF-κB in their fat or liver cells and that obese mice can be protected from insulin resistance by inhibiting NF-κB expression. Last year, Shoelson and his colleagues published the results of a pilot study in Diabetes Care demonstrating that salicylate therapy could indeed both control blood sugar and reduce inflammatory mediators in obese subjects. Meanwhile, Hotamisligil has linked yet another molecule involved in inflammation, JNK, to obesity and insulin resistance. JNK plays a “predominant role” in the regulation of insulin sensitivity, Hotamisligil wrote on 5 September 2008 in PloS ONE. It is overexpressed in animal models of obesity, and knocking it out in these animals both decreases their adiposity and protects them from insulin resistance.

Hotamisligil now believes that the primary cause of JNK activation is stress in the cell’s endoplasmic reticulum, which functions to synthesize and fold proteins. In fat tissue, it works to package complex lipids such as cholesterol and triglycerides. Stress in the endoplasmic reticulum will activate JNK, says Hotamisligil, and it’s easy to imagine that the demands put on the endoplasmic reticulum by an expanding fat cell are the source of the stress.

The picture that’s coming together is that obesity is a low-grade inflammatory state. Excess fat or at least large, overstuffed fat cells activate the immune system, prompting “elevated levels of inflammatory cytokines—IL6, TNF-α, JNK, all kinds of stuff,” says Guenther Boden of Temple University in Philadelphia.

A primary source of these inflammatory signals is now believed to be macrophages trapped in the adipose tissue, a discovery first made in 2002 by Anthony Ferrante and his colleagues at Columbia University and, independently, by Hong Chen and colleagues at Millennium Pharmaceuticals. In lean humans or animals, says Ferrante, 5% of the cells in adipose tissue will be macrophages, compared with upward of 50% in obese humans or animals. What recruits the macrophages into the adipose...
tissue is still an open question. Nonetheless, says Hotamisligil, “it’s pretty clear that if there are inflammatory cytokines or stress signals around, the insulin receptor does not function very well.”

**Focusing on fat tissue**

When researchers discuss their favored hypotheses of insulin resistance, the metaphor that often comes to mind is a Russian nesting doll. Elucidate one mechanism of causation, and it immediately implies the existence of yet another mechanism further down the causal pathway that might be still more fundamental. The end point in this progression, however, invariably seems to be the fat tissue itself.

This has been a consistent theme in insulin-resistance research going back to the early days. Consider, for instance, that impaired glucose uptake by skeletal muscle has traditionally been perceived as the major contributor to insulin resistance. But one reason blood sugar is elevated in type 2 diabetes after a meal, and the primary reason it remains elevated during fasting conditions, is because the liver continues to synthesize glucose and pump it out into the bloodstream even when that glucose is no longer needed.

Insulin was always thought to suppress this process directly, and researchers believed that its failure to do so was a direct manifestation of insulin resistance by liver cells. But Richard Bergman of the University of Southern California in Los Angeles and his colleagues demonstrated in the mid-1990s that this failure to inhibit glucose production in the liver is actually an indirect effect of insulin resistance, and that the real location of the insulin resistance is at the fat tissue. What happens, says Bergman, is that the fat cells become resistant to insulin, which then fails to efficiently suppress, as it should, the release of fatty acids from these cells. It’s those liberated fatty acids that in turn stimulate the inappropriate production of glucose by the liver. “We believe most of the effect of insulin on the liver is indirect,” Bergman says, “and it’s mediated by free fatty acids” released from the fat tissue. (Complicating matters further, some of the apparent failure of insulin to suppress glucose production in the liver, as Rossetti and collaborators have demonstrated, also appears to be mediated by insulin resistance in the brain.)

Most researchers now believe that both inflammation and DAG accumulation are causal factors in insulin resistance, but this raises the obvious question of what causes the inflammation, and what causes the DAGs to accumulate in muscle and liver cells in the first place. One likely possibility, says Shulman, is that people simply eat too much for their level of physical activity. The excess nutrients, in this scenario, then overwhelm the fat tissue, causing the fat cells to expand and secrete inflammatory molecules, or they spill out of the fat tissue and into the bloodstream.
instead accumulate where they don’t belong. But that doesn’t explain why some obese individuals—often very obese—remain resolutely insulin sensitive. This suggests that something about the fat tissue itself, and maybe its ability to absorb and retain fatty acids and do so in a manner that doesn’t induce inflammation, is the fundamental defect, the critical factor determining whether fatty acids will accumulate as triglycerides in healthy fat depots or as DAGs in liver and muscle cells.

A telling piece of evidence, suggests Shulman, is that insulin resistance is also common in rare genetic disorders known as lipodystrophies, which are characterized by a deficiency or complete absence of fat cells. Lipodystrophic individuals have little or no place to temporarily store the calories they consume before they use them for fuel, and they are extremely insulin resistant. Researchers have also created lipodystrophic mouse models, genetically manipulated to have no fat cells, and these are also extremely insulin resistant. The fact that insulin resistance occurs in mice and humans lacking the fat cells necessary to store excess nutrients, says Shulman, “suggests that if you can’t store fat properly, it’s going to build up in liver and muscle and cause insulin resistance.”

So what does it mean to store fat properly? The key, some researchers say, is the ability to expand adipose tissue in a specific way. When fat tissue can generate new adipocytes, these researchers believe, it creates fresh storage capacity instead of shunting excess fat into existing, overstuffed fat cells. According to this hypothesis, insulin resistance develops when fat cells are overstuffed, stressing the endoplasmic reticulum and attracting macrophages, releasing inflammatory mediators, or leaking fatty acids out into the circulation—or any combination of these.

Among the evidence supporting this hypothesis is a transgenic mouse created by Philipp Scherer of the University of Texas Southwestern Medical Center at Dallas and his colleagues in 2007. It happens to be, as Scherer says, “probably the fattest mouse ever made.” It’s also extremely insulin sensitive. This particular mouse overexpresses a molecule called adiponectin, discovered by Scherer in 1995, that appears to stimulate the formation of new fat cells. Scherer says his transgenic mouse continues to generate new fat cells which can “deposit all these calories taken in into an expandable healthy fat pad.” The liver stays in pristine shape, he says: “There’s no lipid accumulation [even in muscle cells], … and there’s improved insulin sensitivity.”

Another line of evidence supporting this hypothesis comes from experience with insulin-sensitizing drugs, known as thiazolidinediones, used to treat type 2 diabetics. These drugs target a receptor on cells, called PPARγ, that also works in the subcutaneous fat tissue to differentiate new adipocytes. The diabetic patient gets fatter, but the excess is stored in new small fat cells rather than in overstuffed old ones. The patient gains insulin sensitivity as a tradeoff for the extra fat. “You redistribute fat out of the muscle, liver, and beta cells into subcutaneous fat,” says Ralph DeFronzo, chief of the diabetes division at the University of Texas Health Science Center at San Antonio. “As long as the fat is in subcutaneous adipocytes, it can’t hurt you.”

Good and bad fat cells?
While researchers have made considerable progress elucidating these mechanistic connections, every insight seems to come with unanswered questions or observations that remain stubbornly controversial.

Take the critical observation that fatty acid levels are elevated in obesity, and the idea that this leads to DAG accumulation in liver and muscle cells. At least some researchers—Keith Frayn, for instance, who studies adipose tissue metabolism at the University of Oxford in the United Kingdom—question whether this is true. “Every review of insulin resistance talks about an increase in free fatty acids” with obesity, Frayn says. “We have been looking at a collection of 1200 normal healthy individuals, and we see no correlation in that collection between body mass index and free fatty acids in plasma.”

The evidence that large, overstuffed fat cells are the problem has also recently been challenged. Reaven and Sam Cushman, a fat metabolism researcher at the U.S. National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Maryland, reported in August 2007 that when they look at subjects with the same level of moderate obesity but different degrees of insulin sensitivity, they find that the insulin-resistant subjects actually have fat cells that tend to be smaller, rather than larger.

“The conventional wisdom has been that the obese have these very big fat cells, and these secrete all these terrible things [inflammatory cytokines in particular], and these terrible things make you insulin resistant,” says Reaven. “What we found is that if you looked at the ratio of small fat cells to large, insulin-resistant people had the higher proportion of small cells.” To Reaven, this suggests that the underlying problem in insulin resistance isn’t the large fat cells themselves but a relative inability to expand smaller fat cells into larger ones as needed. “If you can’t make good fat cells to store fat,” he says, “then the fat may end up in ectopic places where it does more harm than good.”

One observation that seems indisputable is that when individuals lose weight, they become more insulin sensitive. If nothing else, this has given researchers the confidence to assume that excess body fat—particularly in the abdomen and around the internal organs—is a fundamental cause of insulin resistance. But that still avoids the question of what causes insulin resistance in lean individuals. This is something few researchers will even address, although one possibility is that they, too, simply can’t store fat safely in subcutaneous pads.

“The biggest question in the whole field of insulin resistance is still this direction of causality,” says O’Rahilly. “Does obesity make you insulin resistant? Or does underlying factor x cause both obesity and insulin resistance?”

—GARY TAUBES