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

17 JULY 2009 VOL 325 **SCIENCE**

www.sciencemag.org

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 afflicts 50million 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.

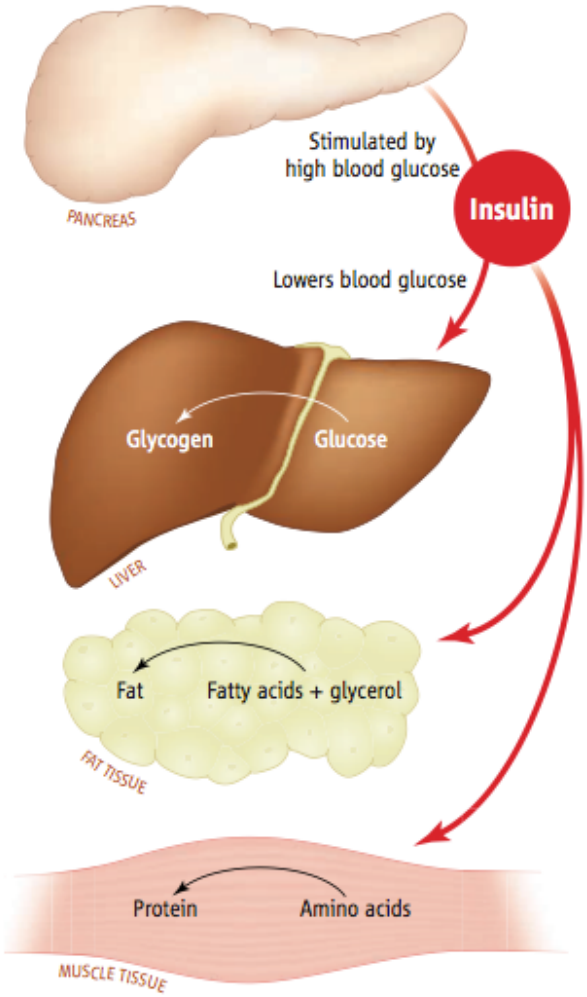
Once it takes hold, insulin resistance sets up a vicious cycle: As tissues become unresponsive to insulin, the pancreas compensates by secreting ever more insulin, and gradually the tissues grow more resistant.

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 the synthesis of proteins and of molecules involved in the function, repair, and growth of cells, and it functions as a signaling molecule conveying information on fuel availability from the periphery to the brain and central nervous system.

"Compared with other hormones," the late J. Denis McGarry of the University of Texas Southwestern Medical Center wrote in *Science* in 1992 (30 October 1992, p. 766), "insulin elicits a bewildering array of metabolic responses in target cells. Deciding which of these are dependent or independent events continues to pose a major challenge." Sixteen years later, that assessment still holds true.

A fundamental role of insulin is to orchestrate the use of fuels in the body, partitioning them to oxidation or storage. When blood sugar is elevated—during and immediately after a meal, for example— insulin works to store excess calories as fat in the fat tissue and transport glucose into muscle tissue. It also signals the mitochondria to use glucose as the primary fuel source. As insulin and blood sugar levels drop in the hours after a meal, they allow fatty acids to be mobilized from stored fat and signal the mitochondria to oxidize these fatty acids for conversion into energy. This "metabolic flexibility," or the capacity to switch easily between glucose and fat for fuel, is a key feature of healthy individuals, as endocrinologist David Kelley, now at Merck Research Laboratories in Rahway, New Jersey, has pointed out.

In insulin resistance, these natural responses break down and become pathological. A "natural system of feedback loops," as Merck's Luciano Rossetti says, is overwhelmed or degraded and disease is often the response. The operative word, though, is "often."

Even among healthy individuals, measurements of insulin-stimulated glucose uptake, insulin sensitivity, and insulin resistance will vary by 600% to 800%. “There’s an enormous range,” says endocrinologist Gerald Reaven of Stanford University in Palo Alto, California, who deserves much of the credit for persuading the medical research community to take insulin resistance seriously as a causal factor in heart disease and type 2 diabetes. A quarter of this variation in sensitivity can be explained by variations in physical fitness, and another quarter by weight, a relationship that Reaven says has held up in studies of populations as diverse as the Pima Indians of Southwest Arizona and descendants of Europeans living in Palo Alto. “Clearly, the more obese you are, the more insulin resistant you are,” Reaven says, but the same variation can be found in obese subjects, a third of whom are relatively insulin sensitive.

Without being able to pinpoint the tissue, organ, and cell type in which insulin resistance first manifests itself, says Stephen O’Rahilly, co-director of the Institute of Metabolic Science at the University of Cambridge in the United Kingdom, it’s virtually impossible “to unpick the causal chain.”

What researchers almost invariably measure, though, is how the entire body responds to insulin, not how the individual tissues and organs do. And how the body responds also changes dramatically over the course of a day, and from day to day, in response to food intake or physical activity. “We’re studying a phenomenon that is happening differentially over a 24-hour period,” says O’Rahilly. “But most studies are done when the subject or patient is fasting. Those are essentially looking at insulin’s dialog with the liver and how sensitive the liver is to insulin. It tells you very little about how sensitive the skeletal muscle or the adipocyte is.”

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?”