This mechanism enables companies and countries to offset their own carbon emissions by paying another for an ecosystem service. In this case, Brazil might receive payments for agreeing to preserve trees that would otherwise be burned and release carbon dioxide, a potent greenhouse gas, into the air. At the next meeting of the Conference of the Parties on the Climate Convention in November, delegates will decide whether this mechanism can be applied to protecting standing forests.

Nepstad estimates that the Amazon stores 70 billion tons of carbon. The World Bank has estimated that Indonesia's fires in 1997 alone contributed more carbon to the atmosphere than did all humanmade sources in North America—about 30% of all anthropogenic global carbon emissions. Curran is in the process of calculating the amount of carbon stored in the dipterocarp forests in Borneo, which she suspects is substantial. In addition to the carbon contained in their wood, dipterocarps form unique symbiosis between their roots and fungi, and as a result potentially store tons of carbon in roots below ground. Says Curran: "The challenge is to show local and regional governments that these forests are worth something standing, that they're worth more alive than dead."

But the outcome of the November debate is far from certain. Nepstad points out that the Brazilian governmental delegation itself opposes including standing forests as part of the Clean Development equation. One thing is for certain: While the debate smolders, so do fires in the rainforest.

—BERNICE WUETHRICH

Bernice Wuethrich writes from Washington, D.C.

BIOMEDICINE

New Insights Into Type 2 Diabetes

After discarding the old dogma, researchers are converging on a new hypothesis to explain this prevalent metabolic disorder

After 30 years of chasing leads down one blind alley after another, researchers studying type 2 diabetes are optimistic that they are closing in on the elusive causes of the world's most prevalent metabolic disorder—although no one is willing to bet the bank on it. Using both biochemical and genetic approaches, diabetes researchers have identified multiple intracellular signaling pathways that appear to lie at the heart of this condition, which affects some 250 million people worldwide and is the leading cause of blindness, kidney failure, and amputation among adults.

And in the process, they have thrown out much of the dogma of the past 10 years. The hallmark of type 2 diabetes is insulin resistance, a defect in the body's ability to remove glucose from the bloodstream despite the presence of normal or even elevated levels of insulin. For years, researchers thought a simple explanation, such as a malfunction in the insulin receptor, might lie behind this puzzling defect. But a decade of research has failed to turn up a direct link between insulin receptor malfunction and the disease, except for the rare mutation that accounts for less than 5% of cases. Indeed, "nearly every major feature of this disease that we thought was true 10 years ago turned out to be wrong," says Morris White, a molecular biologist at the Joslin Diabetes Center in Boston. "We used to think type 2 diabetes was an insulin receptor problem, and it's not. We used to think it was solely a problem of insulin resistance, and it's not. We used to think that muscle and fat were the primary tissues involved, and they are not."

Now researchers are converging on a more complex explanation. Work from several groups, published over the past few months, suggests that the disease is triggered when the delicate balance between insulin production and insulin responsiveness goes awry. First, cells in muscle, fat, and liver lose some of their ability to respond fully to insulin, a hormone released by the pancreas after a meal. At the heart of this insulin resistance lie at least two related pathways that normally respond to insulin by signaling cells in these tissues to remove glucose from circulation and convert it into chemical energy stores. In response to growing insulin resistance, pancreatic cells temporarily ratchet up their production of the hormone. But in some people, that's when the second malfunction occurs: The insulin-producing cells give out, and insulin production falls. Researchers are only now gaining insight into the molecular mechanisms involved in this failure, says White. "It's only then, when the body loses the fine-tuned balance between insulin action and insulin secretion, that type 2 diabetes results."

> **"Nearly every major feature of this disease that we thought was true 10 years ago turned out to be wrong."**
>
> —Morris White

If this picture proves correct, the results could be significant for the growing number of people with this disorder. "If we're right about the pathways that we think are involved, then the treatment of type 2 diabetes should be completely different in 5 years," says Domenico Accili, a geneticist and head of the diabetes research unit at Columbia University.

But not everyone is convinced. The most intriguing support for this new view has come largely from studies in knockout mice. Unfortunately, research into the human genetics of type 2 diabetes doesn't necessarily mesh with those animal data. Graeme Bell, for one, a University of Chicago geneticist who has spent over a decade searching for human genes related to type 2 diabetes, is skeptical. Bell believes that there will prove to be just a few biochemical pathways involved, but he's not sure that the ones now under scrutiny are the true culprits: "We still have work to do to pin down the causes of this disorder."

Even supporters of the new view caution that it's premature to declare victory. "I do think we've identified many of the major biochemical pathways involved in this disorder, but we still don't know why these pathways are not working properly, and that's a critical piece of the puzzle we're missing," concedes Steven Shoelson, a senior researcher at Joslin.

The shift in thinking began in the mid-1990s, when, after the insulin receptor proved to be a dead end, investigators turned to probing the intracellular signaling apparatus that responds when insulin binds to and activates its receptor. Some of the first leads came from White and members of his lab, who were studying mice with inherited defects in glucose metabolism. In the process they discovered two related proteins that are activated inside a cell when insulin binds to the insulin receptor. Named IRS-1 and IRS-2, these two proteins serve as docking stations for numerous other intracellular proteins. When assembled, the resulting molecular complex turns on a multistep signaling pathway that activates the glu-

cose transporter, which in turn ferries glucose into the cell. The IRS-bound complex also activates a second pathway, called the Ras complex, that triggers gene expression in the cell, although the role of the Ras complex pathway in type 2 diabetes has been little studied to date.

White says that although there is some overlap in the function of these two proteins, studies with knockout mice done over the past 2 years in his laboratory, as well as those of Accili and C. Ronald Kahn, a cell biologist and president of the Joslin Diabetes Center, have shown that IRS-1 plays a more prominent role in stimulating glucose uptake by muscle and fat, while IRS-2 is the major player in liver; IRS-2 also boosts insulin production by the pancreas.

This tissue specificity may prove to be a critical insight for deciphering the mysteries of type 2 diabetes. Using tissue-specific knockouts of either IRS-1 or IRS-2 or both, Kahn, White, and Accili turned up some surprising results. The most notable one, published this past January in the *Journal of Clinical Investigation*, was that the liver plays a key role in the development of type 2 diabetes. "Most of us believed that glucose uptake by muscle alone was critical for the development of type 2 diabetes," explains Kahn. Now, it appears that insulin resistance must occur in both muscle and liver for type 2 diabetes to develop, prompting the researchers to conclude that the insulin regulating system must fail at multiple points for the disease to arise.

Experiments with knockout mice also highlight the importance of insulin production by the pancreas in the genesis of type 2 diabetes. In mice that developed the disorder, White found that the pancreas responded to the initial insulin resistance by overproducing the hormone. But the insulin-producing cells, known as β cells, eventually died, leading to full-blown diabetes. The insulin shutdown may result from a defect in the signaling pathway linked to IRS-2. Data from White's lab, published in *Nature Genetics* last September, suggest that insulin somehow turns on its own production by the β cells, and that this feedback stimulation only occurs when IRS-2 is present. White says that there may be some factor, still unknown, that eventually interferes with this IRS-2–mediated boost in insulin production and leads to insulin shutdown instead. "That's a very interesting result, because it could provide a biochemical mechanism linking insulin resistance and insulin production," explains Accili.

These same signaling pathways may also affect fat metabolism, explaining the association of type 2 diabetes with obesity. Patients with type 2 diabetes often have elevated serum levels of fatty acids. Gerald Shulman, a clinical physiologist at Yale University, has been using in vivo nuclear magnetic resonance to study glucose metabolism in both human and mouse muscle. In studies just submitted for publication, his group at Yale has shown that elevated plasma levels of free fatty acids suppress glucose uptake by interfering with the IRS-1 signaling pathway. "It may be that any perturbation that results in accumulation of intracellular fatty acids or their metabolites in muscle and liver sets off a cascade that leads to reduced IRS-1 and IRS-2 activity, leading to insulin resistance in these tissues," explains Shulman. Such a decrease in IRS-2 activity could prove to be one of the factors that causes insulin production to drop as well, a possibility that Shulman is now investigating.

What still confounds researchers is that, despite much searching, geneticists have failed to uncover any mutations in IRS genes in diabetics or even much variation in the genes among the human population as a whole, suggesting that defects in the insulin signaling pathway leading to human disease must be subtle, says Chicago's Bell. He believes that finding such mutations will be difficult. "I don't think that we're going to find mutations that knock out some protein completely, but that these will be mutations that cause a subtle decrement in the function of a protein," he posits. "But I also think that insulin's regulation of sugar metabolism is so finely tuned that one or two such mutations will be enough to upset the entire system when combined with the proper environmental insults," such as eating the typical high-fat American diet.

Although numerous questions remain, Shoelson, among others, thinks the new findings can already be used to design more effective and badly needed drugs for type 2 diabetes. Such efforts are already under way, with pharmaceutical companies searching for compounds that stimulate the insulin signaling pathways and overcome insulin resistance. For example, researchers at both Merck and American Home Products are focusing on an enzyme that modifies the insulin receptor and enables it to turn on the IRS pathways more efficiently (*Science*, 5 March 1999, p. 1544). In addition, says Accili, both genetic and biochemical studies should eventually provide the means to distinguish between different subtypes of type 2 diabetes based on which points in the pathway are deficient in a given patient, enabling researchers to "better target specific drugs to specific patients."

—JOE ALPER

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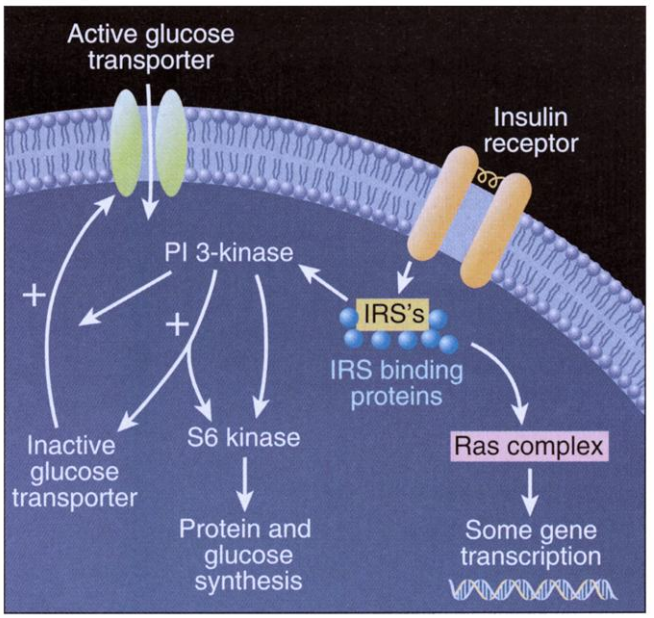

Pathways of Insulin Control

The insulin receptor is a tyrosine kinase that adds phosphate groups to two insulin receptor substrates, proteins named IRS-1 and IRS-2, that are located just inside the cell membrane. Once phosphorylated, these two proteins serve as docking sites for other intracellular signaling proteins that link insulin stimulation to two major intracellular pathways. One pathway, the so-called Ras transcription activation complex, produces a selective increase in gene expression that researchers have yet to characterize in any detail. The other pathway turns on the enzyme phosphatidylinositol 3-kinase (PI 3-kinase), which in turn phosphorylates a host of proteins, one of which is the glucose transporter that can then transport glucose into the cell.

ILLUSTRATION: C. CAIN