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## A New Path to Diabetes

Diabetes researchers have debated for years whether errant genes or faulty biology are responsible for the disease. Some scientists believe that the production of insulin by the pancreas is genetically flawed in persons with diabetes. Others think that diabetics may have a faulty cellular response to insulin.

Now Hughes investigators at the Joslin Diabetes Center/Harvard Medical School and at Yale University School of Medicine suggest that diabetes may be caused by a combination of errant genes and faulty biology.

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— **Morris F. White**

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Hughes investigators Morris White at Joslin and Gerald Shulman at Yale report in the February 26 issue of *Nature* that mice born without the protein IRS-2 develop a disease that mimics type 2 diabetes, the most common form of diabetes in humans. IRS-2 is a protein that translates the insulin signal into molecular events that regulate cellular metabolism and growth.

"We were surprised to find that IRS-2 plays such an important role in insulin resistance and is defective in cells that secrete insulin," White said. "This suggests that a single pathway is responsible for the disease, which may simplify how we look at this complex disease."

"For researchers trying to understand diabetes, this is an intriguing observation," said Graeme Bell, a Hughes investigator at the University of Chicago, who has identified several candidate genes involved in diabetes. If these findings can be replicated in humans, Bell said, "they may eventually offer new ways of treating diabetes."

Diabetes is a metabolic disorder. After food is digested, one of the components left is the simple sugar, glucose, which cells use for fuel. Insulin secreted by the pancreatic beta cells provides that source of fuel by secreting

insulin, which moves glucose into cells and enables the use of glucose.

People with type 2 diabetes have a high level of glucose in their blood because their cells respond poorly to insulin. The majority of people with type 2 diabetes have defective beta cells that don't properly secrete insulin in response to elevated blood glucose. Their muscle, liver and fat cells also do not increase glucose transport in response to the higher levels of insulin.

White and Shulman began their studies seeking a better explanation for how insulin signals cells to increase glucose uptake. The researchers developed a knockout mouse with defective copies of one of four genes that code for insulin receptor substrate (IRS) proteins. Mice without the IRS-2 protein showed insulin resistance that is, skeletal muscle and liver cells did not respond as they should to insulin - and they had a smaller number of insulin-producing beta cells.

White believes that IRS-2 plays a role in the effective functioning of these beta islet cells. Without IRS-2, beta cells cannot increase production of insulin to a level that compensates for the inability of peripheral cells to use glucose.

Although White and others have not found a genetic mutation in the IRS-2 gene in humans with diabetes, he suspects that the genetic basis of diabetes will be found somewhere in the insulin signaling pathway. "If the primary problem is a genetic mutation, we may not be able to fix it," White says. "With a normal gene, we may be able to treat diabetes by finding ways to increase the production of IRS-2, a much easier task than genetically altering the IRS-2 gene in millions of people."