Researcher ready to test new diabetes treatment in humans

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A longtime diabetes researcher at University of Texas Southwestern Medical School is setting up human tests for a new treatment he says might have fewer side effects than standard insulin therapy.

Dr. Roger Unger, chairman of diabetes research at the school, is quick to warn a novel method that worked in mice with Type 1 diabetes may not help people.

"You can't make any claims until the tests have been done," he said.

The tests using leptin, a natural hormone produced by fat cells, would build on results of experiments performed by Unger's research team and published Monday in a major scientific journal, Proceedings of the National Academy of Sciences.

The paper, titled "Leptin monotherapy in insulin dependent type 1 diabetes," describes studies done on diabetic mice. The journal cites the new paper as "reporting findings of exceptional interest."

The new work is a follow-up to a paper published in 2008 by Unger's team that reported about diabetic mice and rats that were genetically modified to produce extra leptin and thrived without insulin. The 2008 paper was the research equivalent of a talking dog -- startling even to experts, whether or not it said anything practical.

Genetic modification is not an option for humans, so Unger's team next

tried treating mice using a technique well-known to people with diabetes: leptin injections delivered by a pump. Not only did the leptin-treated mice thrive, Unger said, but they did so without some of the side effects familiar to people using insulin.

"I think (this) paper is much bigger, because the last one was just academic," said Unger, 85, who has been researching diabetes for more than 50 years. "This is a translatable paper into something that might be useful for people. The other was not."

Unger's team has been ready to start testing leptin on people for almost a year, he said. The hospital is prepared, they have an ample supply of potential volunteers, and they've lined up funding. What's holding the process up, Unger said, is getting the manufacturers of leptin to set up the logistics to guarantee the supply.

"We thought it would happen six months ago," he said. "And it hasn't happened yet."

Why is his claim about leptin such a surprise? Since 1921, when researchers first linked what is now known as Type 1 diabetes to a lack of insulin, doctors have assumed the only successful treatment replaced insulin, usually through multiple daily injections. Insulin is used by more than a million Type 1 diabetics in the United States.

Insulin is normally produced by specialized "beta" cells in the pancreas that respond to the level of sugar in the bloodstream. The hormone has at least two functions:

• It acts like a key to a locking gas cap, letting many kinds of cells absorb sugar from the blood to use for fuel.

• Insulin also sits on the opposite side of a biochemical teeter-totter from

a hormone called glucagon. Glucagon tells liver cells to dump storage supplies of sugar into the bloodstream, providing more fuel as needed. At higher levels, it signals cells to convert amino acids and fats into fuel -- basically telling the body to "burn" muscle and fat.

In Type 1 diabetes, which affects about a million people in the United States, the body's immune system mistakenly kills the beta cells -- and the ability of the body to produce insulin.

Without insulin on the other side of the teeter-totter, excess glucagon over-triggers the consumption of muscle and fat, which produces the wasting and rapidly fatal symptoms associated with untreated Type 1 diabetes, Dr. Unger said.

But Unger said the dosage of insulin needed to treat Type 1 diabetes is much higher than what is normally produced, and therefore causes unwanted side effects -- including hard-to-avoid large swings in blood sugar levels and possible increases in the effects of bad cholesterol on blood vessels in the heart. Those problems seem to be reduced in the leptin-injected mice, Unger said, even when a small amount of insulin was added to the treatment.

Leptin, discovered in 1994, has been tied to a wide range of body functions that range from appetitive control to regulation of menstrual cycles. Several prior studies hinted at its ability to affect blood sugar, but Unger's team was the first to see if it worked without insulin.

Dr. Jeffrey Friedman, the researcher who first identified leptin, was the editor for the paper published Monday. For him, the most surprising part of the new paper is an indication relatively low doses of leptin might be enough for treatment.

"It's an interesting result," he said.

Unger's research was funded by the Veterans Administration, the National Institute of Diabetes and Digestive and Kidney Diseases, and several private donors.

But he and other diabetes experts agree leptin is a long way from becoming a practical treatment. Dr. Barbara Kahn, a diabetes expert at Harvard Medical School and chief of endocrinology at Beth Israel Deaconess Medical Center, was asked to co-author a commentary to run with Unger's new paper.

Among the challenges Kahn says leptin therapy might face:

• Mice snack frequently on slow-digesting food. People eat meals a few times a day. Leptin levels that kept blood sugar stable in mice may not be able to handle the rapid ups and downs in blood sugar created by the human eating pattern.

• The mice used in the tests had a shortage of leptin. Most Type 1 diabetics have normal leptin levels. The amount of additional leptin needed to control blood sugar in people may induce significant side effects that are more damaging than those associated with insulin.

• Extra leptin could make it harder for a Type 1 diabetic to be aware of the dangerous condition of low blood sugar -- and make it harder to return low blood sugar to normal levels.

And Kahn said Unger's claim leptin might reduce the risk of coronary artery disease rests on assumptions and a chain of reasoning that has not been proven in humans.

Despite all that, Kahn says there could be value in leptin treatment for diabetics if Unger's results prove out in people, perhaps used in addition to insulin. Maybe it could lower appetite or reduce the amount of insulin

diabetics now need to take, she said.

But the only way to find out is to test it.

"I would say it should be tried, but very cautiously," she said.

She and other experts agree leptin is not likely to help people with the much more common Type 2 diabetes, a condition that mostly affects people who are overweight and have developed a resistance to both leptin and insulin.

Those issues aside, Unger's paper doesn't explain why leptin (or something else in those leptin-treated mice) works to handle one of insulin's key tasks: Getting sugar from the bloodstream into muscle and fat cells.

"We don't know the answer to that," Unger admitted.

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WHAT IS DIABETES?

Diabetes is actually several diseases that affect more than 23 million people in the United States, all involving the hormone insulin and problems with the body's ability to use sugar as fuel. The most common forms of diabetes:

• Type 1 affects 5 to 10 percent of those with diabetes and happens when the body's immune system mistakenly kills cells in the pancreas that manufacture insulin. While it usually appears in children, and once was known as juvenile diabetes, it can show up in adults. If untreated, Type 1 diabetes is rapidly fatal. It can't be prevented, and the loss of the body's ability to produce insulin has nothing to do with diet. The only successful treatments are insulin injections or pancreas transplants.

• Type 2 diabetes is much more common, accounting for 90 to 95 percent of all cases. It usually appears in overweight adults but has been found in children. In Type 2 diabetes, either the body is not producing enough insulin or the extra fat somehow reduces the ability of the body to use insulin. If untreated, Type 2 diabetes can eventually lead to serious circulation problems that can lead to organ failure, limb amputation and death. Type 2 diabetes often can be treated successfully with diet, exercise and oral medication.