BIOMEDICINE

Pig Transplants Offer Hope in Diabetes

In the United States, half a million diabetics depend on daily insulin injections to prevent them from drifting into a diabetic coma—and even death. This solution is far from ideal. Not only are daily injections painful, but blood sugar levels may still fluctuate enough to damage blood vessels, leading to blindness, kidney failure, and amputations. To overcome these disastrous side effects, researchers are working on a technique for replacing damaged insulin-producing cells, called islet cells, in the pancreas with healthy ones from another human. However, that technique will always have one major limitation: Human pancreases are in very short supply.

But the results of a pilot study published in last week's issue of *The Lancet* suggest an alternative: islet cells from pigs. According to the report by a Swedish group led by Carl-Gustuv Groth of the Karolinska Institute in Stockholm and Claes Hellerströem of the University of Uppsala, the human body can sometimes accept transplanted pig cells, even in the absence of extreme measures to prevent immune rejection. The investigators are now aiming to increase the yield of insulin from these cells, which did not produce enough to have an impact on the patient's diabetes.

"It's surprising that it works; it's very interesting," says Scott Chappel, senior vice president of research at Diacrin Inc., a Massachusetts biotechnology company that is developing a technique to mask certain distinctive proteins, called MHC-1 antigens, on the pig islet cells in an attempt to help the human immune system accept the foreign cells. Chappel adds, however, that the Swedish group gets "survival, and that's good, but they also need some function."

To achieve its results, the Swedish team used two methods. In eight patients, islet cells from fetal pigs were injected directly into the portal vein that feeds the liver; in two others, the injections were made under the capsule that surrounds the kidney. All the patients had undergone kidney transplants because of kidney failure, and all were receiving standard immunosuppressive drugs. Following the transplants, all patients received some additional immunosuppressants.

Even with these preparations, says Groth, "according to dogma, with the very strong immunological barrier, pig cells placed in the human body would be expected to be rejected within days." Indeed, that happened in six patients. But in the remaining four, pig cells survived for up to 14 months, secreting a protein called porcine C-peptide, indicating that they were manufacturing insulin, although only at very low levels, says Groth. The team also took a biopsy from one patient that confirmed that the pig islet cells contained insulin.

To explain these unexpected data, Groth argues that the pig cells were accepted by the host because they lack any of the pig blood vessels that trigger a violent rejection reaction when an entire pig organ is transplanted (*Science*, 18 November, p. 1148). But, he admits, it's not clear why some patients accepted the cells and others did not. For the next step of their research, the Swedish team is developing a technique for producing adult islet cells—more difficult than producing fetal ones—in the hope that when they are transplanted they will secrete sufficient insulin to make injections unnecessary.

–Rachel Nowak

PHARMACEUTICALS

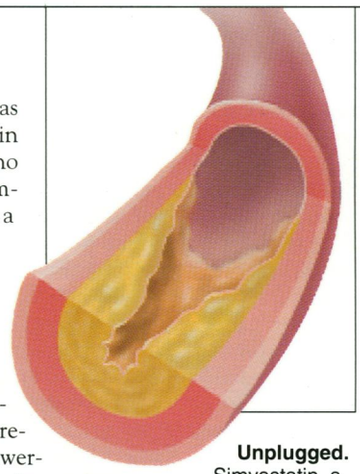
Dropping Cholesterol—Safely

Reducing cholesterol has become the mantra of doctors and patients alike. Over the last decade clinical trials have shown that a drop in cholesterol levels slows the growth of arterial blockages and reduces heart attacks among patients with a high risk of heart disease. But orchestrating that drop with drugs has been controversial: Several studies suggest that such drugs increase the risk of death from cancer and suicide, even as they lower the death rate from heart attacks.

Now a study by a team of Scandinavian researchers shows that a member of a new class of cholesterol-lowering drugs has the benefits without the drawbacks. The treatment reduces the number of fatal heart attacks by more than 40% without raising the death rate due to other factors.

The researchers, led by Terje Pedersen, who heads the coronary care unit at Oslo University's Aker Hospital in Norway, studied the effect of a drug called simvastatin on more than 4400 patients in Denmark, Finland, Iceland, Norway, and Sweden who were monitored for a median of 5.4 years. The researchers reported in the 19 November issue of *The Lancet* that treatment with the drug reduced hospitalizations due to nonfatal heart attacks by 30% and lowered the need for bypass surgeries by 37%. Most importantly, says University of California, San Diego, professor of medicine Daniel Steinberg, there was an overall 30% reduction in mortality among patients who received simvastatin compared to those who received a placebo.

"This is an excellent study with a superb outcome," says Basil Rifkind, a senior science adviser for the National Heart, Lung, and Blood Institute in Bethesda, Maryland. "This trial resoundingly confirms that lowering cholesterol is very effective [for people with a history of heart disease], and it should have widespread significance." Simvastatin is one member of a new family of drugs that block the action of enzymes essential for the synthesis of cholesterol. The drug interferes with an enzyme in the liver known as HMGCoA reductase. When this enzyme is blocked, the liver produces additional cholesterol receptors that pull cholesterol out of the bloodstream, thereby lowering serum cholesterol levels. Other cholesterol-lowering drugs have different mechanisms and appear to cause a wider range of side effects. One study by Michael Oliver, now with the National Heart and Lung Institute in London, indicated that patients who received the drug clofibrate had a higher risk of dying from cancer. While the risk was not statistically significant, "nevertheless it was there," says Steinberg. "With simvastatin we saw no such effects," says Pedersen. Four such enzyme-inhibiting drugs are currently on the market in the United States.



K. SUTLIFF

Unplugged. Simvastatin, a member of a new class of cholesterol-lowering drugs, may halt the buildup of arterial plaques.

Some researchers caution that the new study doesn't provide evidence that cholesterol reduction will prolong the lives of healthy people. Thomas Chalmers, a clinical epidemiologist with MetaWorks Inc. in Boston and an adjunct professor of medicine at both Dartmouth and Tufts University medical schools, says that "We don't have evidence that normal people should be on low cholesterol diets." Others, such as Rifkind, emphatically disagree, saying there is abundant evidence that such diets do help.

–Robert F. Service

With additional reporting by Elizabeth Gardner in Stockholm.