

# Researchers explore curing diabetes with animal transplants

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The descendents of Abraham are ready. They were born inside a cinderblock bubble in an anonymous building surrounded by fields in western Wisconsin.

Raised on sterilized food and filtered air, they have never seen the sun, felt the rain, or been exposed to the germs known to make swine or people sick.

This dynasty of pigs, which began with a boar named Abraham, has the same little eyes and floppy ears as those that become bacon and pork chops. But these are destined for a different service to humanity -- to provide insulin-producing cells for people who have diabetes.

All they need are the humans.

After decades of research and debate about the ethics and safety of putting living animal tissue into people, the first of such clinical research trials are within sight.

Researchers at the Mayo Clinic and at the University of Minnesota have been studying the problem for a decade or more, and say now they will be among the first to propose transplanting living pig tissue into humans.

Minnesota, as a result, has become the global epicenter for a unique type of medical-grade pig -- animals raised in biosecure environments that insulate them from the infectious agents that have thwarted such

transplants in the past.

"We have a lot of pig wisdom and expertise" in Minnesota, said Bernhard Hering, a university diabetes researcher who has been studying animal-to-human transplantation for a decade. "You don't find that at Rockefeller University."

In Rochester, the FIOS company, owned by the Mayo Clinic, houses genetically modified pigs that promise to provide a future supply of hearts and perhaps other organs for people. In New Richmond Wis., the nonprofit Spring Point Project facility houses pigs bred to generate an unusually large number of insulin-producing "islet" cells that Hering hopes to use to treat diabetics.

The first pig-to-human heart transplant could be just three to five years away, said Dr. Christopher McGregor, a transplant researcher at Mayo. The first pig-to-human islet cell transplant could happen within one to three years, Hering said. In December he accepted a \$40 million gift from the family of Best Buy founder Richard Schulze that he said will greatly accelerate the diabetes research.

If successful, islet cells and new hearts would be just the beginning.

"The market is huge," said Dr. Steven Miles, a professor and bioethicist at the university who studies the issues surrounding animal-to-human transplantation, called xenotransplantation. "Everybody would love to find a way to use xenotransplantation for blood," he said.

The 120 pigs at Spring Point's facility in New Richmond have no idea how special they are. When visitors call, a few of them stare back intently at the faces peering through a thick glass window. They squeal and jostle for feed just like any other herd of pigs.

But what extraordinary feed they are served. Without any animal fat or proteins, it's a vegetarian's dream. It's been irradiated to sterilize it.

The water used to power wash the concrete pens everyday has been exposed to ultraviolet light to kill any germs before it comes out of the sprayer.

Humans are not allowed inside, except the handful of workers who must shower with microbial soap each time they enter what they call "the barrier" -- the seven rooms that house the pigs. They don not one but two layers of sanitized suits. When they clean the floor of pig feces, they wear the same kind of caps and face masks used in hospital operating rooms.

Two or more times a month, one of the pigs is killed and tested for 40 or 50 of the infectious agents that could be transmitted to humans and other pigs. So far, after two years and two generations of pigs born and raised entirely within the barrier, none has been found.

"These are not your everyday 'other white meat' type of product," said Miles.

The extreme precautions are required to convince the Food and Drug Administration that transplanting tissue from pigs will be safe for humans. Surgeons have used treated porcine heart valves to repair human hearts for years, but islet cells and entire hearts are different -- they constitute living tissue from pigs and cannot be purified before transplant.

The potential for disease is terrifying. Regulators aren't just worried about the known infections or pathogens that pigs and humans share -- swine flu and toxoplasmosis among them. They also fear the epidemic that could occur if a virus or bacteria exclusive to pigs jumped to

humans and evolved into something altogether new and lethal. Think bird flu, and all the global efforts to prevent its spread.

The reward, however, could be enormous, the researchers say.

People with diabetes, for example, often face a life of insulin injections, to say nothing of the many health risks that result from their disease. Their islet cells can be replaced by transplants from deceased human donors \_ either more islet cells or entire pancreases. But there aren't nearly enough donated organs to go around, considering that 18 million people in the United States have been diagnosed with Type 1 and Type 2 diabetes. The same kind of hopeless ratios exist for patients needing transplanted hearts, livers and kidneys.

The pathogen-free descendants of Abraham could solve the problem of supply. Pig products, including insulin, have been used in humans before, but transplanting the very islet cells could give human patients an almost limitless supply.

Yet significant barriers remain.

In 1996, researchers discovered that viruses called retroviruses, which live inside of cells, could be transmitted from pig cells to human cells. Though all animals and humans carry retroviruses, the discovery "created a shiver in the community," McGregor said. It nearly brought the field of xenotransplantation to a halt.

AIDS, which originated with monkeys, is a retrovirus.

There is no way to eliminate those viruses because they are embedded in cells, and the risk of retrovirus transfer remains today. But the danger is not as great as was feared in 1996, McGregor said. Additional studies have shown that the pig retroviruses cannot live in as many human cells

as researchers once feared. As a result, "people are becoming much more interested" in xenotransplantation, he said.

That leaves the biggest problem of all: the human body's own defense mechanism, the immune system. Most tissue transplanted into a human from another species would be rejected in minutes, McGregor said. Anti-rejection drugs that have been developed for human-to-human transplants could not stop it.

To solve this problem, McGregor and his colleagues at Mayo have turned to genetic engineering. Their pigs at the FIOS facility have been genetically altered to eliminate the molecule on cell surfaces that triggers the human immune system to recognize transplanted tissue as foreign and to attack. They've also added genes to the pig that help minimize the immune response after transplantation.

So far, monkeys receiving genetically altered pig hearts have survived for two months. "That's huge," McGregor said.

Hering, too, must overcome the immune challenge. But pig islet cells may be much easier to transplant into humans because they trigger a much milder immune response, he said. That's why he thinks his first human clinical trials might happen within a year or two. He has already successfully treated diabetic monkeys, which lived for six months after pig islet cells were implanted in their livers.

Hering's ultimate goal, however, is the holy grail of diabetes research: a limitless supply of insulin-producing cells that require no anti-rejection drugs at all.

To accomplish that goal, Hering is attempting a kind of biological camouflage: a bioengineered scaffolding that can be seeded with pig islet cells and transplanted into a human patient's abdomen. The combination

of technologies would mask the foreign tissue from the human immune system in what he describes as biological "sanctuaries."

Hering is years away from that yet. But the promise is immense: a whole new field of medicine that could replace the failed organs of humans and cure diseases that have no cure today.

If and when that time comes, the pigs in their biosecure bunker in New Richmond will be ready and waiting -- a whole new twist on pig farming.

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