Surgeons transplant a pig kidney into 62-year-old Richard Slayman, who died this month.

WHAT THREE HUMANS GIVEN PIG ORGANS HAVE TAUGHT SCIENTISTS

Researchers mark the loss of the first living recipient of a pig kidney and share what they've learnt.

By Max Kozlov

This month, the first living person to receive a kidney from a pig died, just under two months after his transplant — sooner than his doctors had expected. But the timing is in keeping with that of the first people to receive pig hearts, both of whom died around two months after their transplants.

The relatively short survival time for all three recipients demonstrates that these pioneering cross-species transplants "have not had as great success as would have been predicted from the primate studies", says Robert Montgomery, a transplant surgeon at New York University (NYU) in New York City.

But the three procedures offered hope to desperately ill people who had run out of options. And researchers say that they have learnt valuable lessons from the first pig-organ transplants into humans, on topics ranging from the types of medication that recipients need to the amount of testing that pig organs must undergo. "This is not an insolvable problem," Montgomery says. "I'm encouraged that we're as far along as we are."

Nature spoke to xenotransplant surgeons about what they've learnt so far, and how they see the field moving forwards.

The use of organs from other species in humans, called xenotransplantation, has long been a dream of surgeons because of the chronic shortage of suitable human organs. Researchers have homed in on pigs as a donor species, in part because their organs' size and anatomy resemble those of humans.

Data from non-human primates that have received pig organs are promising: a study[1] published in 2023 reported that five monkeys each survived for more than one year after receiving transplanted pig kidneys.

The first xenotransplant into a living person was in 2022, when 57-year-old David Bennett received a pig heart and survived for 60 days after the procedure. A second man, Lawrence Faucette, received a pig heart in 2023 and survived for 40 days.

Infection complications

Muhammad Mohiuddin, a surgeon at the University of Maryland School of Medicine in Baltimore who was on the care team for both pig-heart transplants, cites several possible reasons for Bennett's death. In the weeks before he died, Bennett had an infection, so doctors gave him an immune-boosting therapy made up of pooled antibodies from many donors. Scientists later found that some of the antibodies had reacted to the pig organ[2], meaning that the treatment could have exacerbated Bennett's condition. Mohiuddin has since worked with local blood banks to develop ways to screen for reactive antibodies.

Another possible explanation for Bennett's limited survival is a latent infection of the transplanted heart with a pathogen called porcine cytomegalovirus, which might have been activated and then harmed the heart. The virus was found in the organ after Bennett's death but was missed by tests before the transplant, signalling that more sensitive tests must be used to screen organs, Mohiuddin says.

Compassionate use

All the xenotransplants into living people have received 'compassionate use' approval from the US Food and Drug Administration (FDA), granted in rare cases in which a person's life is at risk and no other treatments are available. People treated on such grounds tend to be much sicker than the average person on the transplant waiting list, making it difficult to work out whether an unfavourable outcome is the result of the procedure itself, Mohiuddin says. That's why some researchers have been pushing for the FDA to begin clinical trials of the procedure, which would allow systematic evaluation of its performance.

It's possible, for example, that poor underlying health contributed to the death on 7 May of Richard Slayman, the first living recipient of a pig kidney. Tatsuo Kawai, one of the surgeons who conducted the transplant at Massachusetts General Hospital in Boston, tells *Nature* that Slayman's kidney was functioning well the day before his death and that he died for reasons unrelated to his transplant. In the year before the procedure, Slayman had developed congestive heart failure.

Researchers are also experimenting with what can be done before the transplant to best prevent organ rejection. One technique is genetically modifying the donor pigs, but the number of genetic edits necessary to stave off rejection is far from settled, Montgomery says.

eGenesis, a biotechnology firm in Cambridge, Massachusetts, that bred the pig used in Slayman's surgery, has produced pigs with a record 69 edits, both to avoid rejection and to reduce the risk that a virus lurking in the organ could infect the recipient. Meanwhile, Revivicor, a firm in Blacksburg, Virginia, has opted for about ten genetic edits.

In the fourth and latest xenotransplant in a live person, Montgomery and his team tried a new approach using the thymus, an immune-related organ that could help to teach the recipient's immune system to recognize the pig organ. They grafted the source pig's thymus to the kidney and then transplanted both into 54-year-old Lisa Pisano on 12 April. They used a pig with only one genetic modification, which could make producing pig organs easier, Montgomery says. Pisano is in stable condition in hospital, he adds.

There is still much more to be learnt, he says. In a forthcoming study and in one published this month in *Nature Medicine*[3], Montgomery and his colleagues analysed tissue samples from two people who had been declared legally dead before receiving a pig heart and found that at the cellular level, rejection of xenotransplanted organs looks “very different” from that of organs transplanted from a human donor, Montgomery says. He adds that these findings could help researchers to anticipate rejection and develop tailored immunosuppressant regimens for future surgery.

1. Anand, R. P. *et al. Nature* **622**, 393–401 (2023).
2. Mohiuddin, M. M. *et al. Lancet* **402**, 397–410 (2023).
3. Schmauch, E. *et al. Nature Med.* https://doi.org/10.1038/s41591-024-02972-1 (2024).

‘BILINGUAL’ BRAIN IMPLANT DECODES SPANISH AND ENGLISH

Artificial-intelligence system allows a man who cannot speak clearly to converse in the language of his choice.

By Amanda Heidt

For the first time, a brain implant has helped a bilingual person who is unable to articulate words to communicate in both of his languages. An artificial-intelligence (AI) system linked to the brain implant decodes, in real time, what the individual is trying to say in either Spanish or English.

The findings[1], published on 20 May in *Nature Biomedical Engineering*, provide insights into how our brains process language, and could one day lead to long-lasting devices capable of restoring multilingual speech to people who can’t communicate verbally.

“This new study is an important contribution for the emerging field of speech-restoration neuroprostheses,” says Sergey Stavisky, a neuroscientist at the University of California, Davis, who was not involved in the study. Although the study included only one participant, “there’s every reason to think that this strategy will work with higher accuracy in the future when combined with other recent advances”, Stavisky says.

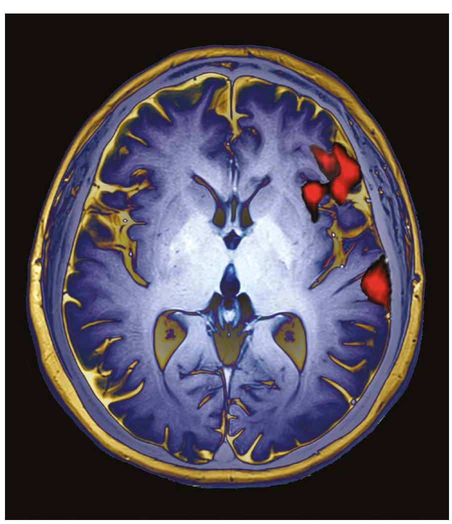
Speech-restoring implant

The person at the heart of the study, who was nicknamed Pancho, had a stroke at age 20 that paralysed much of his body. As a result, he can moan but he can’t speak clearly. In his thirties, Pancho partnered with Edward Chang, a neurosurgeon at the University of California, San Francisco, to investigate the effects that the stroke had on his brain. Chang’s team surgically implanted electrodes on Pancho’s cortex to record neural activity, which was translated into words on a screen[2].

Pancho’s first sentence — ‘My family is outside’ — was interpreted in English. But Pancho is a native Spanish speaker who learnt English only after his stroke. It’s Spanish that still evokes in him feelings of familiarity and belonging. “What languages someone speaks are actually very linked to their identity,” Chang says. “And so our long-term goal has never been just about replacing words, but about restoring connection for people.”

To achieve this goal, the team developed an AI system to decipher Pancho’s bilingual speech. This effort, led by Chang’s PhD student Alexander Silva, involved training the system as Pancho tried to say nearly 200 words. His efforts to form a word created a distinct neural pattern that was recorded by the electrodes.

The authors then applied their AI system, which has both a Spanish and English module, to phrases as Pancho tried to say them aloud. For the first word in a phrase, the Spanish module chooses the Spanish word that matches the neural pattern best. The English component does the same, but chooses from the English vocabulary instead. For example, the English module might choose ‘she’ as the most likely first word and assess its probability of being correct to be 70%; the Spanish one might choose ‘estar’ (to be) and measure its probability of being correct at 40%.



Brain activity during speech production.

ZEPHYR/SPL

Word for word

From there, both modules attempt to build a phrase. They each choose the second word on the basis of not only the neural-pattern match but also whether it is likely to follow the first one. So ‘I am’ would get a higher probability score than ‘I not’. The final output produces two sentences — one in English and one in Spanish — but the display screen that Pancho faces shows only the version with the highest total probability score.

The modules distinguished between English and Spanish on the basis of the first word with 88% accuracy. Pancho could eventually have candid, unscripted conversations with the research team. “After the first time we did one of these sentences, there were a few minutes where we were just smiling,” Silva says.

Two languages, one brain area

The findings revealed unexpected aspects of language processing in the brain. Some previous experiments using non-invasive tools have suggested that different languages activate distinct parts of the brain[3]. But the authors’ examination of the signals recorded directly in the cortex found that “a lot of the activity for both Spanish and English was actually from the same area”, Silva says.

Furthermore, Pancho’s neurological responses didn’t seem to differ much from those of children who grew up bilingual, even though he was in his thirties when he learnt English — in contrast to the results of previous studies. Together, these findings suggest to Silva that different languages share at least some neurological features, and that they might be generalizable to other people.

Kenji Kansaku, a neurophysiologist at Dokkyo Medical University in Mibu, Japan, who was not involved in the study, says that in addition to adding participants, a next step will be to study languages “with very different articulatory properties” to English, such as Mandarin or Japanese. This, Silva says, is something he’s already looking into, along with ‘code-switching’, or the shifting from one language to another in a single sentence. “Ideally, we’d like to give people the ability to communicate as naturally as possible.”

1. Silva, A. B. *et al. Nature Biomed. Eng.* https://doi.org/10.1038/s41551-024-01207-5 (2024).
2. Moses, D. A. *et al. N. Engl. J. Med.* **385**, 217–227 (2021).
3. Kim, K. H. S., Relkin, N. R., Lee, K.-M. & Hirsch, J. *Nature* **388**, 171–174 (1997).