This little

In January, as the world reacted to news that the first pig-human heart transplant had taken place in the US, scientists at one German facility were less surprised than most of us. The work happening inside their labs suggests unsuspecting swine could soon be saving lives around the globe

piggy...

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Above
DR BARBARA KESSLER

A small, windowless room within a nondescript laboratory complex just north of Munich. I am gazing at what may turn out to be the future of transplant medicine. And standing on hind legs, propped up against a knee-high metal fence, what may turn out to be the future of transplant medicine is gazing right back. I think it wants to eat my shoes.

'It' is, in fact, a she, with large almond eyes, enviable lashes, a quivering snout and a polka-dot complexion. Around her, siblings and friends mingle. I pat her hairy head for a moment, then notice a name tag hanging from her ear: '12428,' it reads. Probably for the best. 'Susan' might have made her destiny harder to stomach.

She and her comrades are month-old Auckland Island piglets, and it is not far beyond the realms of science or possibility to say that 12428, or more likely a pig not dissimilar to her, might one day save your life. Cloned from embryos shipped from New Zealand, she is one of about 350 kept here, at the Center for Innovative Medicine Models, part of the Ludwig Maximilian University of Munich (LMU), so scientists can look into 'the generation, characterisation and implementation of large animal models in biological and biomedical research'.

The lab's 40-odd staff use animals to look into everything from genetic diseases to reproduction, but a chief concern is xenotransplantation: moving living cells, tissues or organs from one species to another – usually humans. In this developing scientific field, leading the pack is the prospect of genetically modified (GM) pigs like 12428 being cut open, their hearts (or possibly kidneys, lungs and livers) removed and carefully but hastily given to a desperately ill human.

It is difficult to fathom, watching the piglets play in their pen, but the science is more than encouraging. Currently, about 6,000 people await an organ transplant in the UK, including hundreds needing hearts – the latter a number the NHS says has increased by 85 per cent in the past decade. In the US, the figures are much higher: about 106,000 people are waiting for a transplant, and roughly 17 people die each day before a suitable organ can be found. These pigs may soon be the answer.

'Well, we hope so,' says Professor Dr Eckhard Wolf, as he scratches the ear of 12428's playmate. If anything, he's playing it down. On 7 January, in a world first, surgeons at the University of Maryland School of Medicine in Baltimore successfully replaced the waning heart of a 57-year-old man, David Bennett, with a modified pig heart supplied by a facility in Alabama not dissimilar to the Munich lab.

Almost two months on, Bennett is continuing his recovery with no reported signs of rejection – yet. On 13 February, he was photographed watching the Super Bowl from his hospital bed, and while he didn't exactly radiate wellness, the very fact he was still alive bettered many expectations. One of the surgeons involved compared the transplant to 'putting a new Ferrari engine in [a] 1960s Ford', a comment meant both to impress and instil caution. 'Apparently,' Wolf tells me, eyes widening, 'he is working even better than before!'

The Center for Innovative Medicine Models is found off a winding country lane, between two suburban towns. Once a farm belonging to the German government, for the past three decades this small collection of dull-looking buildings has been transformed into a state-of-the-art blend of agriculture and science.

Pigs, whose size and physiology are remarkably similar to ours, are the most suitable donors for human transplants in the animal kingdom. Their presence here is unavoidable. The environment is both clinical – spotless lab equipment worth hundreds of thousands of pounds apiece, PhD students scurrying around with furious concentration – and oddly rural. It is a collision most jarring in the pig compound: as scientists in scrubs look through microscopes, the soundtrack is of raucous squealing from the next-door rooms.

Wolf, a suave, jovial 58-year-old with a gentle eminence and a remarkably smooth brow, has worked with large animals in Munich since 1995, and with GM pigs since 2002 – just six years after Dolly the sheep, the first mammal cloned from an adult somatic cell, was born at The Roslin Institute in Scotland. At the time, the field of xenotransplantation was not quite the stuff of science fiction, but certainly under-recognised and scarcely funded. Nobody was quite sure where it would lead.

'We never imagined how straightforward the techniques could get, like they are now,' Wolf says. Advances in gene editing, not least Crispr technology, mean strides have been taken in the past decade. Now, since Bennett's operation, people are starting to believe the start of clinical trials is possible within the next two or three years, potentially leading to pig-human heart transplants becoming a viable option some time over the next decade.

'Oh, we were very excited when we heard about [Bennett]. It gave a boost to the whole field, and came after a series of developments,' Wolf says of that procedure. His lab is the leading one of its kind in Europe, and has an even simpler model, using half as many genetic modifications, than was used for Bennett.

A sow awaits impregnation with an edited embryo

106,000 people await an organ transplant in the US alone

Though not directly involved in the US operation, Wolf's team did donate a pig heart to a 2016 study that saw it attached to a baboon (which kept its own heart too). Transfused with baboon blood, it kept working, without rejection, for more than 900 days. Another, more advanced study saw pig hearts transplanted into 14 baboons, two of which survived for six months. That in turn helped convince regulators the Baltimore operation was worthwhile. Experts had predicted 2022 might be 'the year' – and it was.

According to Wolf, all 'xeno' labs are in competition, but they are also frequent collaborators, share data, and are working towards a common goal. Baboons are the largest primates xeno scientists can gain ethical approval to experiment on ('Of course, we would love to work on chimpanzees, because they are so close to humans, but we would never be allowed to'), and LMU Munich keeps a group of about four at a time in a facility on the other side of the city. They are not receiving visitors.

Is Wolf, like many sceptics, surprised Bennett is still alive? 'I am not, no,' he says. 'I'm no cardiac surgeon, but I can imagine it must be easier to do this on a human than a baboon, because you do not get cardiac surgeons for baboons so you need specialists. And besides, it is much easier to say to a human, "Take this medication, take that medication," than a baboon.'

Good point, I say. I can imagine it's not easy to convince a monkey to pop a pill. Wolf's eyes crinkle behind his face mask. 'No, not if you want to keep your fingers.'

The pigs are kept in a set of buildings away from the main research laboratories and offices. To get there, we cleave a path between some lawns, which are surrounded – as is the entire compound – by a severe-looking fence. It is not designed to keep the pigs in (they don't even go

Auckland Island piglets at the Center for Innovative Medicine Models – the breed is especially suitable for xenotransplantation

outside, so there's never been an escapee), but to keep local, Bavarian wild swine out.

'Cross-contamination is the absolute main concern,' Wolf says, beetling along in his jeans, tweed blazer and loafers. 'There has been African swine fever, which means all pigs in a 5km area need to be culled, but because of this extremely expensive fence, we are OK.'

He pauses. 'So, first things are first, have you touched any pigs in the past five or eight days?' Neither, I say. 'Then let's go and meet them.'

Given the risks to the animals, everybody in the building must completely disrobe, disinfect themselves, shower (including hair washing) and re-dress in scrubs or a plain polo shirt, loose black trousers and Crocs before they get pig-side. 'It is important you get the right size to fit for you,' Wolf says, having reappeared in fairly tight plum scrubs. That could be a motto in xeno labs.

I am immediately confronted by three seven-month-old sows, penned in an anteroom next to a stark operating theatre. Ferreting around them is Dr Barbara Kessler, a lean veterinarian who seems to be in perpetual motion.

What are their names, I ask? 'Oh, we do not give them names,' she says. 'As soon as you give an animal a name, you have a personal connection to it. And I have to kill all these poor guys one day… It's a lot easier to kill… "10250" than a real name. This is to protect myself.'

Wolf strokes the head of one of the sows, a landrace breed that hasn't been chosen with xeno specifically in mind. 'They have a great, great life here. Most pigs for slaughter only live a few months. But they can live for 20 years.'

Kessler shrugs. 'Well, until they meet me.'

Some of the pigs, like these three, are here simply to produce young. GM embryos are conceived in a lab dish, implanted in the 'mothers' in a procedure I'm about to see, then delivered by safe caesarean section about 120 days later. Others, like the Auckland Island piglets (a breed that is particularly pathogen-free and genetically clean, meaning it has become the favourite of xeno labs, supplied by a Kiwi company that specialises in medical pigs) are the product themselves. It is their organs that may be harvested.

In a moment, the sows, each of which is about the size of a St Bernard, will be anaesthetised, placed in a hoist, then winched into the operating theatre, where Kessler will make three small incisions and implant them with the edited embryos. It is an extraordinary thing to watch, in pure silence, as a 19-stone pink beast, legs akimbo on an operating slab, is poked and prodded so effortlessly by Kessler, who does this every Friday in a pain-free procedure that is successful 60 or 70 per cent of the time.

'Have you ever seen this happen before?' a staff member whispers to me as we watch. I rack my brains: have I ever seen a hog upside down on a gurney, getting impregnated with modified embryos that might one day grow organs that could save the life of someone I love? 'No, I can't say I have.' We make way for somebody shuffling past with a sack of hay.

The procedure is over in minutes. Within 20, Kessler has done all three. Within 25, the sows are awake again, groggy but piggy once more.

> 'We do not give the pigs names… I have to kill these poor guys'

Cryotubes containing frozen stocks of pig cells

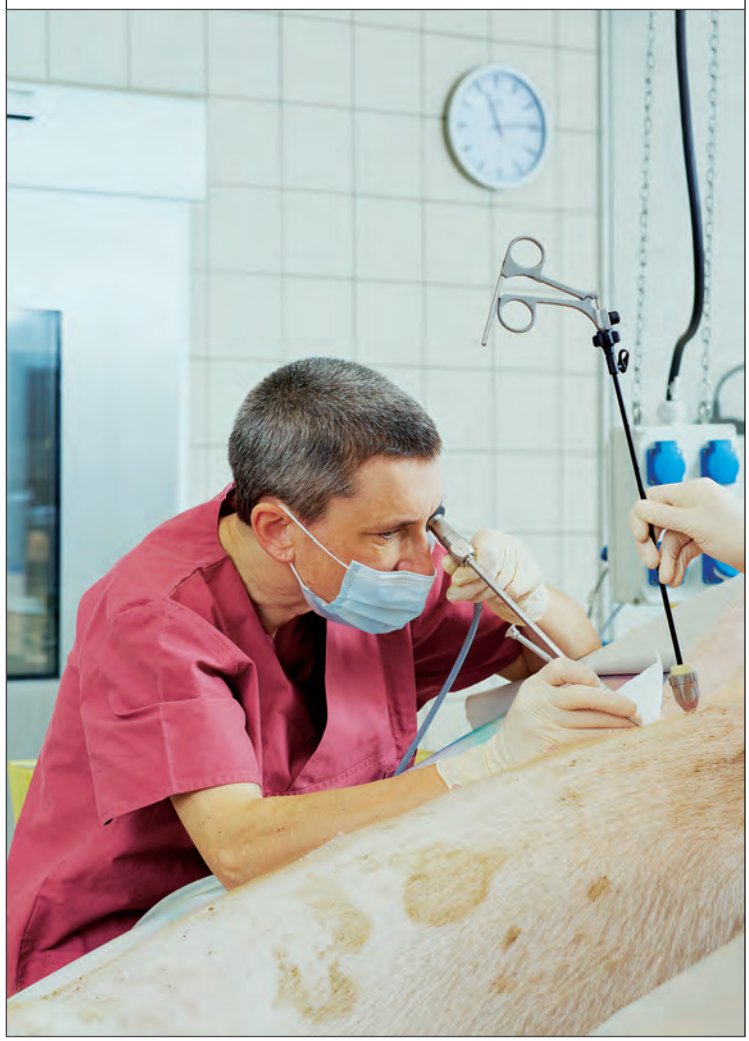
Since the first man popped open a sheep and thought, 'Hey, this all looks familiar,' humans have been curious about the prospect of moving animal organs into sick people. Some of the earliest proper xenotransplants are cited as having happened in the 17th century, when Louis XIV's personal physician, Jean-Baptiste Denis, decided that animal blood had fewer 'impurities than that of men because debauchery and irregularity in eating and drinking are not so common in them as in us'.

He obviously hadn't seen a dog on heat eat its own faeces. A subsequent lamb-human blood transfusion didn't end well. In the 19th century, skin grafts were sought after, to cover ulcers and burns. Frogs, chickens, monkeys, rabbits, chihuahuas – they were all tried, but never lasted.

By the early 1900s, parts of other primate testicles were implanted into humans, an attempt to boost virility. One legendary American quack, John Brinkley, offered patients goat testicle transplants, claiming they gave 'an astonishing sexual vigour'. Brinkley became world-famous but was later discovered to have no proper medical qualifications, was sued for wrongful death multiple times, and allegedly signed the death certificates of 42 people; most weren't ill when they met him.

It wasn't until the 1950s, when human-to-human organ transplants started, that people began taking xenotransplantation seriously again. Chimp kidney and heart transplants were unsuccessful in the 1960s, the organs failing, but in 1984 'Baby Fae',

Dr Barbara Kessler implants an edited embryo



a 12-day-old American baby, received a baboon heart, for lack of available infant hearts. She lived for 21 days, two weeks longer than expected. It was declared 'an adventure in medical ethics' and sparked global debate.

Primate hearts are the right size, but they take years to develop, and the public are uncomfortable with harvesting the organs of monkeys and apes. We eat pigs, though, and one sow can have eight piglets in a litter, which within half a year can be ready – if modified – for organ transplantation.

At the Center for Innovative Medical Models, Wolf's team look into using pigs for all possible transplants. Hearts show the most promise. Kidneys are more in demand, and one company plans to start clinical trials of genetically engineered pig-to-human kidney transplants this year, though given dialysis exists as a backup, gaining approval is deemed easier. Lungs are much more complex again, and will require work. But we already use pigs – for replacement heart valves.

> 'Britain started a lot of this with Dolly the sheep'

Ethical questions fester. Scientists behind any new procedure are aware of what is sometimes known as 'the "ugh" factor' – loosely defined as the amount of time it takes the public to accept something that may sound alarming. It happened with human-human transplants, IVF, laser eye surgery… but today even leaders within Christianity, Judaism and Islam appear open to the idea of pig xenotransplants. If the need is great enough, they seem to agree, human life comes first.

Animal-rights activists are less swayed. The pigs here are expertly cared for by specialist workers, but they also spend their lives inside. Modifications for xeno do not harm the animals (indeed, Wolf reckons a vet wouldn't be able to tell the difference between a GM and non-GM pig), and when organs are explanted, the pig is put under such strong anaesthesia that death is painless. Whether it is psychologically distressing is less clear.

Their pens are far larger than those on an industrial pig farm, too, where conditions are cramped and animals are slaughtered after five or six months. 'Recipient' pigs for breeding could have several litters over two or three years here, before Kessler kills them. They should, she thinks, then be sold for meat, to make it more sustainable, but food regulators won't allow it. But the point is: if you eat pork, you haven't a trotter to stand on.

'There are animal ethicists who are against the use of any animals, they will be difficult to convince, but I am also against any animal experiments if they are useless,' Wolf says. 'In this case, the benefits are extremely obvious.'

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eeting with a local group of doctors against animal experiments for 'an open discussion', Wolf didn't get very far, since they declared all testing on animals unnecessary. 'And that is simply not true. Before you do xenotransplants on humans, you just have to do it on baboons, to learn techniques, and how the heart behaves.'

He cites an experiment using a pig heart in a baboon. It went well until scientists realised that if you put the heart of an animal that would grow to be 45 stone in a five-stone monkey, the heart wants what the heart wants: to grow. It crowded out the baboon's organs, and soon failed. Today, embryos

Professor Dr Eckhard Wolf, scientific director at the centre

are tweaked to ensure the pig's growth is capped.

Relative to the organ's importance, attaching a new heart is 'quite a simple plumbing job', as one surgeon put it. But in any transplant, xeno or not, the immune system rejecting the new organ is the great risk. Labs have introduced modifications to combat this. David Bennett's new heart had 10 of its 30,000-odd genes altered; Wolf's team's hearts have five, the reasoning being that fewer refinements means less chance of something going wrong. Plus, 'it makes it much easier to identify what the problem area is, if there is one'.

P

revious to Bennett's case, approved on New Year's Eve, the US Food and Drug Administration (FDA) had never given permission for a pig-human heart transplant. Bennett wasn't eligible for a normal transplant, leaving his options limited to being a test case or likely death. He underwent four psychiatric examinations before giving consent.

Wolf is eager to know more about precisely how it took place, but says that a pig would have been transferred to, or near, the hospital alive, then anaesthetised, its heart explanted and kept in a special cool box until the surgeons needed it. A heart can be kept outside a body for 'four or five hours' until it is at risk of failing before it's even reached the patient, 'but there is a new technique involving some saline fluid, and some cocaine, which means it can get to 10 hours'.

When surgeons first took the heart out of its box for Bennett, it didn't look great. 'It had an opaqueness that was off-putting,' cardiothoracic surgeon Bartley Griffith told *The New Yorker* recently. He wondered if they had done 'something wacky'. That was until they connected it all up and let blood flow through it. 'It was as if we'd turned on a light… The heart just brightened up. And it went from trembling to pumping.'

The wait time is one of many inefficiencies in the process: wheeling a pig into (or close to) a hospital every time a transplant is needed just isn't feasible, and currently there are only a handful of facilities like LMU Munich's. The world leader is the Virginia-based Revivicor – originally spun out from PPL Therapeutics, the British company behind Dolly the sheep – which supplied the Bennett heart. Wolf doesn't know of any British labs or companies who take a prominent role in the field now. 'It's strange really, when you think that Britain started a lot of this with Dolly,' he says.

The costs are also vast. It has been estimated that each transplant into a baboon costs about $500,000, which not only makes experiments expensive, but hints that Bennett's operation might have been several times that. Cloning is expensive and fiddly, too. The solution is that labs like Wolf's intend only to need that technology to create perfect 'founder animals'. Future generations of organ-donor pigs can be bred from those.

Bennett's eight-hour operation and closely watched recovery now serve as a 'proof of principle' study, potentially nudging open the door to full human trials – crucial to one day receiving regulatory approval to render xenotransplantation a viable option for more than just the odd heavily publicised case. There is still some chance that advances in artificial hearts will scupper the whole field, but that seems very remote.

'There is just no mechanical heart that is as consistent and as good as a real one,' Wolf says, adamantly. I ask what he thinks the picture will look like in 50 years. 'It's difficult to predict how it will go, but I think xenotransplantation will still be an interesting option. I think it will never be normal to have any organ transplant, but we need to wait for some long-term results.'

This is a man who has spent his entire adult life researching a topic that's only recently gaining significant public attention: he is not given to hype or hyperbole. 'A good human heart will still be the preferred option, but there are so many patients who cannot get them, and there just aren't enough.' He gestures around. 'Xenotransplantation is an option to save their lives.'

We have put wellies on, and stand in the Auckland Island piglets' pen, one of a dozen rooms off a long corridor, each of which contains drifts of pigs – from large recipient sows to dachshund-sized newborns. Kessler's dispassionate focus is understandable, but both she and Wolf admit a soft spot for the animals.

Wolf has three adult children – a lawyer, a doctor, a physio – with his wife, who works in youth mental-health services. To allow other staff to have time off, they once spent a Christmas here caring for a litter of fresh piglets. 'Even to this day, they say it was the best Christmas they ever had,' he says, ruffling 12428's head. In the corridor, Kessler walks by with a piglet under one arm, as you might carry a rugby ball, stroking it with her other hand.

In the operating theatre, research continues. Next on the day's agenda is echocardiograms for the Auckland Island piglets, to be conducted by Andreas Lange, a doctoral researcher. The piglets have these every few weeks, as the development of their hearts is, obviously, of utmost interest.

One of 12428's brood is brought to the operating table under anaesthetic. Lange shaves a strip from its side before slathering on ultrasound gel and placing a probe on the piglet's ribcage. Within an instant, the outline of a small, pumping heart appears on a screen in front of him. He moves the probe around, not taking his eyes off the screen. Somewhere in the background, a sow grunts.

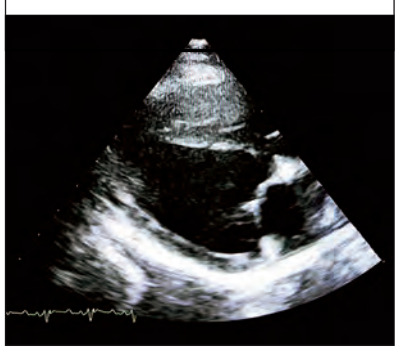
'This looks really nice,' Lange says, squinting at a zoomed-in ventricle.

A moment passes, and I watch the little miracle pulse for a while. Beat, beat, beat, beat. On the table, the piglet stays asleep – oblivious to the procedure, oblivious to its role, and completely oblivious to just how much we might rely on it.

Lange pulls back from the screen. 'Yes,' he mutters, 'it is a good heart.'

Surgeons in Baltimore with the pig heart given to David Bennett in January

An echocardiography of the heart of one of the centre's pigs



MARK TESKE/UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE VIA AP