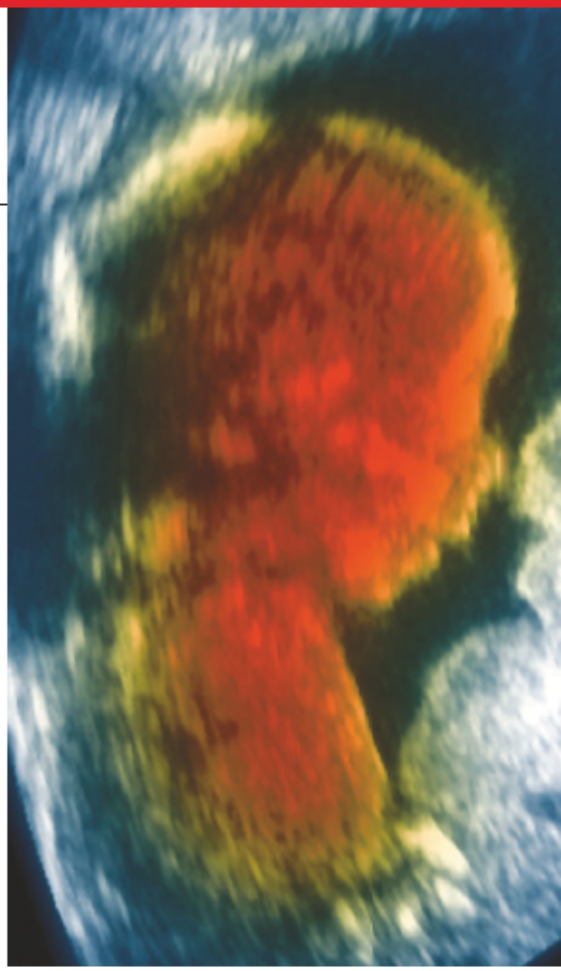
Infertility researchers target uterus transplant



Giuseppe Del Priore has the appearance and the soft-spoken, compassionate manner of a well-paid New York doctor. Just the type, in fact, that a woman might trust to stitch a new uterus into her barren abdomen.

And that is exactly what Del Priore, an obstetrician and gynaecologist at New York Downtown Hospital, hopes to do, along with Jeanetta Stega and other colleagues. A spate of recent media reports has highlighted their plans to provide an infertile woman with a transplanted uterus so that she might bear a child — an operation that, if performed, would be only the second such attempt in the world.

A transplant could potentially help some of the most intractable cases of infertility, such as women born without a uterus, those who underwent a hysterectomy at a young age because of cancer or fibroids, or those in whom an infection has closed up the organ. Many such women are desperate to have their own biological children, and the only way for them to do so at present is by having one of their embryos implanted in a surrogate mother — which is illegal in many countries.

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But some researchers and bioethicists are voicing concern about the prospect of uterus transplants. They argue that the risks are unknown and that the technique may be moving too fast into the clinic. "It's hard to think of another way [of bringing a child into a family] that would be more physically risky or expensive," says Thomas Murray, director of the Hastings Center, a bioethics research institute in Garrison, New York. If a member of his own family was considering it, he adds, "I'd do everything in my power to talk her out of it."

In a uterus transplant, the organ would be removed from a living or recently deceased donor and transferred to a recipient. Embryos previously created by *in vitro* fertilization would be transferred to the uterus and, after a child was born, the uterus would be removed to avoid a lifetime of taking powerful immunosuppressant drugs to prevent rejection.

Del Priore says he realized that the operation was feasible after helping to pioneer a surgical technique for cervical cancer that preserves the uterus. In this process, he explains, the uterus is virtually removed from the body, as it would be during a transplant, but is then reconnected. Many women who have had such a procedure have gone on to have healthy babies.

A human uterus transplant has already been done, in Saudi Arabia in 2000, but it had to be removed after 99 days because of a dangerous blood clot[1]. Most researchers, including Del Priore, say that before attempting the procedure in humans they want to gather more evidence that they can perform three crucial steps in animals: obtain a uterus, transplant it, and show that it can bear healthy offspring. "Yes, I think technically it can be done, but I say that with the greatest deal of caution, because it's a huge undertaking," Del Priore says.

Another leading researcher in this small field, Mats Brännström of Gothenburg University in Sweden, showed more than three years ago that mice could bear babies from a transplanted uterus. However, the donor and recipient were virtually genetically identical, so

Michigan lab axed as Pfizer cuts costs

Pfizer's Ann Arbor laboratory is the largest private-sector employer in the Michigan college town. It is also the birthplace of Lipitor, a cholesterol treatment whose annual sales of $13 billion make it the biggest-selling drug on the planet. So the lab's 2,100 staff were stunned when Pfizer announced on 22 January that it will close the lab by the end of next year.

The closure is part of a move by the world's largest drug company to cut between $1.5 billion and $2 billion from its annual costs, eliminating some 10,000 positions, or about 10% of its workforce. That will include trimming its research and development staff from around 14,000 to 12,500, according to Pfizer's global research chief John LaMattina, and consolidating researchers at four key sites.

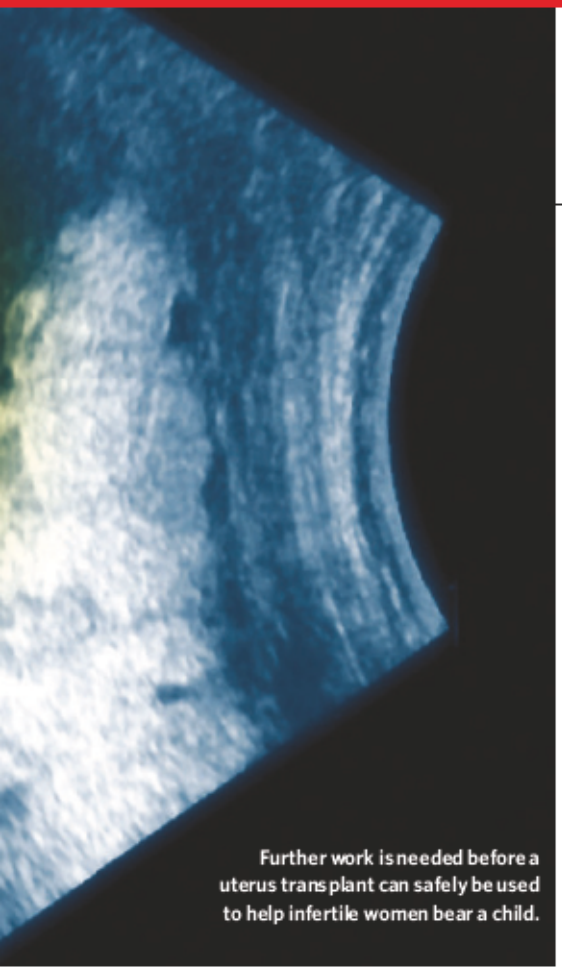
The changes will make Pfizer's research operation more flexible and cost-effective, says LaMattina. "The simplification will add a lot to our efficiencies as well as the speed of our decision-making."

But Michigan academics were left reeling by the announcement's local impact. "It takes decades to build something like that but, evidently, only 18 months to dismantle it," says Stephen Forrest, vice-president for research at the University of Michigan.

Pfizer is facing shrinking profits, expiring patents and a pipeline that is looking short of obvious blockbuster drugs. Late last year, it was forced to withdraw torcetrapib — a cholesterol drug that had been touted as a successor to Lipitor — from clinical trials (see *Nature* 445, 13; 2007).

LaMattina claims the move is needed because the company has so many drug candidates at the expensive, late stages of development all at once, yet needs to control costs. "We're a little bit a victim of our own success," he says.

Pfizer will stop some early-stage work, including efforts to find new skin and digestive-tract drugs, and will cut several layers of middle management.



Further work is needed before a uterus transplant can safely be used to help infertile women bear a child.

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rejection was not an issue[2]. Since then, his team has successfully removed the uterus of a sheep, then replaced it in the same animal, he says. He believes she is now pregnant.

But animal experiments such as these are not ideal models for a human transplant because the uteri have a different anatomy and, in the case of mice, rabbits and pigs, they support multiple fetuses whereas a woman's uterus typically holds only one or two. So Brännström and others say they want to trial the operation in primates before starting in humans.

Stefan Schlatt of the University of Pittsburgh in Pennsylvania, who is collaborating with the New York team, says he has tried and failed to perform the transplants in macaques. He adds that he has just received approval for a further two attempts. If primate experiments succeed, human ones are likely to follow quickly. "Once we show the first monkey baby, people will step up and say they want to do it," Schlatt says. "People are so desperate to have children, they wouldn't wait for ten babies to be born to show it's safe." Researchers interviewed by *Nature* estimate that a human operation could take place within two to five years.

Del Priore says he wants to accumulate animal data and gain more experience with human surgery before trying a human transplant: "Somehow we hope we'll know when it's right." But there is no consensus on what experimental data are required before a human operation is considered an acceptable risk.

The group is already laying the groundwork with donors and recipients. Earlier this year, they showed that it was possible to remove a healthy human uterus from a brain-dead organ donor whose heart was still beating[3]. The researchers are now compiling a list of interested recipients who are being sent information and consent forms to say they are willing to be evaluated for the procedure. The team says the evaluation process will include a psychological assessment and an explanation of alternatives such as adoption.

Del Priore and his colleagues say they are motivated by the number of infertile women who are keen to undergo the operation and who understand the risks. But some bioethicists question how much of the work is really fuelled by doctors' ambition and ego — particularly in the fields of transplant surgery and reproductive medicine, both renowned for aggressively pursuing new methods. "It's a heady cocktail; it brings together two of the more adventurous branches of medicine," says Murray.

Most transplants performed today — such as heart, lung and kidney transplants — are to cure life-threatening or critical conditions. There have been a few exceptions, such as the first face transplant last year, but these are controversial because it is difficult to judge whether the benefits of such transplants are outweighed by the risks.

In the case of uterus transplants, the risk–benefit calculation is even more complex as it must also factor in unknown threats to the future child. Although many thousands of children have been born worldwide to women who have received other transplants, some transplant recipients seem to be at increased risk of pregnancy complications such as high blood pressure and premature birth. It is also not known whether the immunosuppressant drugs might cause subtle effects that become apparent only when the children grow up[4].

Murray suggests that bodies such as the American College of Obstetricians and Gynecologists should investigate the procedure in order to guide future research. An international symposium on uterine transplantation is to be held in Gothenburg in April. "I'm enthusiastic about the possibility of treatment," says Per-Olof Janson, a gynaecologist at Gothenburg University who is co-chairing the meeting, "but I'm hesitant about rushing." ■

Helen Pearson

1. Fageeh, W. *et al. Int. J. Gynaecol. Obstet.* **76**, 245–251 (2002).
2. Racho El-Akouri, R. *et al. Hum. Reprod.* **18**, 2018–2023 (2003).
3. Del Priore, G. *et al. Obstet. Gynecol.* **109**, 101–104 (2007).
4. McKay, D. B. & Josephson, M. A. *New Engl. J. Med.* **354**, 1281–1293 (2006).

Afterwards, LaMattina adds, its laboratories will work at 95% of capacity instead of 65%. Research overhead costs will fall by one-fifth, he says, freeing up hundreds of millions of dollars from bricks and mortar to be spent on science.

The four research sites after the reorganization will be at Groton, Connecticut; Sandwich, UK; St Louis, Missouri; and La Jolla, California. Consolidation into disease-specific groups at these sites will result in "fewer frequent-flier miles and more time at the bench doing science", LaMattina says. The company is planning a new emphasis on bioetherapeutics at St Louis, on cardiovascular work at Groton, and on vaccines at Sandwich and La Jolla.

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But Alan Saltiel, director of the Life Sciences Institute at the University of Michigan and a former cell biologist at the Ann Arbor laboratory when it belonged to Warner-Lambert, before it was acquired by Pfizer in 2000, thinks the separation by disease area has a downside. "What they lose are the opportunities and synergies across therapeutic areas," he points out. "A lot of drug discovery is serendipity."

As well as closing the Ann Arbor site and two smaller Michigan research groups, the company will shut its research facilities in Nagoya in Japan and Amboise in France.

LaMattina says that the company is hoping to transfer, rather than dismiss, up to 70% of workers at targeted facilities. But Tony Butler, a pharmaceuticals analyst with Lehman Brothers in New York, doubts whether as many as that will move.

And Peter Rost, a former vice-president of marketing and strident critic of Pfizer's current management — now in litigation with the company over the circumstances of his departure in 2005 — predicts that there is worse to come. "This is just the beginning," he says. "It is not the bottom. Two years from now, Pfizer will make another announcement, and cut another $2 billion. Just watch." ■

Meredith Wadman

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