Last chance to stop and think on risks of xenotransplants

US regulations are soon to be released allowing trials of animal-to-human transplants. Some feel this is premature, arguing that the risks of creating human diseases remain uncertain, and more preclinical research is needed.

Prospects that the transplant of animal organs, tissues and cells into humans will become a practical proposition are looking increasingly promising, as progress is made towards overcoming the formidable barriers of cross-species rejection. Few doubt that xenotransplantation could eventually bring important medical benefits. But there is still heated debate about the circumstances under which it should be allowed to cross the Rubicon from animal studies into the clinic — if at all.

The dilemma is that, when one tests animal-to-human transplants, one is also carrying out another, unwanted, experiment — testing the remote but real danger that animal viruses might jump to humans and cause man-made pandemics. This concern has come to the fore over the past year just as earlier concerns about animal welfare and the ethics of xenotransplantation have faded (see *Nature* **382,** 197 & **380,** 6; 1996).

Optimism that breeding disease-free animals might overcome viral risks has been dealt a blow recently by the discovery that pigs, the current donor of choice, harbour endogenous retroviruses (PERV) that can infect human cells *in vitro*. Multiple copies of PERV are integrated in the pig genome which suggests that breeding 'clean' pigs will be extremely difficult, if not impossible.

The discovery was made independently by virologists Robin Weiss, at the Institute of Cancer Research in London (see *Nature* **389,** 681; 1997), and David Onions, at the University of Glasgow. It has already prompted the US Food and Drug Administration (FDA) to call a moratorium on porcine transplants until trials can build in adequate tests to screen for the viruses in donor organs, and to monitor for them in the recipients afterwards.

Weiss and Onions' work makes it "painfully evident" that the understanding of the risks is still evolving, said Mary Pendergast, the then senior adviser to the commissioner of the FDA, at a meeting of the agency's advisory sub-committee on xenotransplantation last month. This made development of regulations "difficult," she added.

Regulation of xenotransplantation in the United States is at a turning point with the imminent release of guidelines that will give the go-ahead to clinical trials. The guidelines are expected to be published soon after a public meeting organized in Washington this week by US Public Health Service (PHS) agencies, including the FDA, the National Institutes of Health, and the Centers for Disease Control and Prevention (CDC).

US pre-eminence in medical research means that the guidelines will inevitably influence the development of xenotransplantation internationally (see box, page 322). Moreover, as infectious diseases do not respect national borders, US actions may have consequences for the rest of the world.

The new guidelines will be more stringent than a draft version put out for consultation in 1996. They will give the FDA oversight of all trials, instead of leaving this to local institutional review boards as originally proposed. The creation of a federal xenotransplantation advisory committee along the lines of the Recombinant DNA Advisory Committee is also being explored.

This tougher tone has been welcomed by many, including the American Society of Transplant Physicians (ASTP), which had criticized the earlier guidelines for failing to provide sufficient public health safeguards. The society said the proposal to leave oversight to institutional review boards was a recipe for disaster, arguing that the boards had a narrow view of the issues that could be detrimental to broader public concerns.

Trials might open Pandora's box

The emphasis on the risk of xenozoonosis — the transmission of animal diseases to humans via organ transplants or blood — is relatively recent. Louisa Chapman, an expert on xenotransplantation at CDC, recalls that when the issue was first raised at CDC in 1993 her first thought was "why would we spend taxpayers' money on that, as it's only once in a blue moon that someone puts a baboon or liver heart into someone, they die within 72 hours and that is the end of the story?".

Past transplants of animals' organs into humans have been so rare and unsuccessful as to have never been considered a serious public health issue. But, as the prospect that the techniques may become a clinical reality moves closer, many fear that, as the number of organ recipients grows, so too will the risk to the human population. "We are at the cusp of a possible explosion of xenotransplantation efforts," says Pendergast.

Commercial interest is already strong. The Swiss company, Novartis, the main corporate player in xenotransplantation, is prepared to invest up to US$1 billion in the technology in the near term. And the market may be worth up to $6 billion in 2010, estimates Peter Laing, an analyst at Société Générale Strausse Turnbull in London, who predicts that Novartis could account for more than half.

But there is a broad consensus that substantial preclinical research is needed before xenotransplantation is likely to succeed in the clinic, and that more time is needed to study the nature of the risks. And some scientists are worried that the proposed regulations may herald a premature and dangerous acceleration of clinical applications.

What is mainly fuelling this momentum is the shortage of human donor solid organs, such as hearts, kidneys, lungs and livers. But the numbers of patients involved at present is relatively small in public health terms (although a reliable source of organs could greatly expand use of transplants). Most scientists also believe that, whereas success in implanting animal cells may be within reach, the ability to transplant solid animal organs is many years away (see page 324), despite claims to the contrary by some biotech-

Allan: 'precautionary principle' must be followed.

This briefing has been written by Declan Butler, European correspondent for *Nature*, with additional reporting by Meredith Wadman in Washington, Sally Lehrman in San Francisco and Quirin Schiermeier in Munich.

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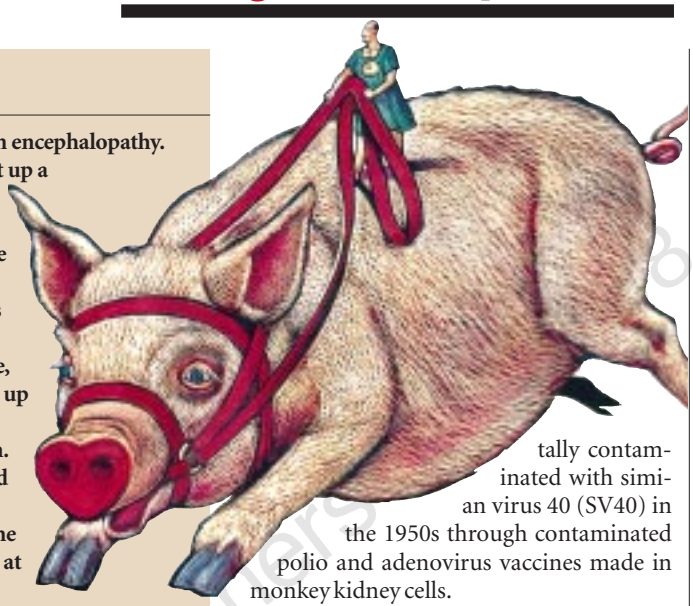
UK ahead in moves to regulate

No country has yet judged that the risks of xenotransplantation so outweigh the potential benefits that they justify a permanent ban on clinical trials. Debate is advanced in the United Kingdom and the United States, but is only just beginning in most other countries and at the international level.

The United Kingdom has, for the moment, the most stringent position of any country, having last year introduced a moratorium on clinical trials until further research shows that transplants are safe and that the science is sufficiently developed to offer transplant recipients real benefits (see *Nature* 385, 285; 1997). "The moratorium is useful in that it is allowing the science base to catch up and quantify what is a hypothetical risk," says Ron James, chief executive officer of Protein Pharmaceuticals.

The need for a regulatory framework had been prompted by the announcement in 1995 that Imutran, a Cambridge-based biotechnology company, planned to proceed with clinical trials of pig hearts (see *Nature* 377, 185; 1995), and subsequently sharpened by the political climate following the failure of expert committees to prevent the crisis over bovine spongiform encephalopathy. The government has set up a Xenotransplantation Interim Regulatory Authority to oversee the field, and is expected to produce legislation this year.

Elsewhere in Europe, Sweden has recently set up a national commission on xenotransplantation. Researchers have agreed to a voluntary moratorium pending the outcome of discussions at the commission which will meet for the first time this month. A similar moratorium is in place in Germany, while France has created an advisory committee within its national transplant authority and intends to release guidelines. France's national bioethics committee is also to review xenotransplantation this year, as is the European Commission's group of advisers on ethical aspects of biotechnology. The commission itself has not taken a position on xenotransplantation.



nology companies and a few bravado transplant surgeons.

Solid organs are only the tip of the iceberg of xenotransplantation. Less spectacular implants of animal cells and tissues offer potential benefits to much larger numbers of patients — transplants of pancreatic islet cells could cure diabetes, while implants of neuronal tissue could treat Parkinson's and Huntingdon's disease, multiple sclerosis and the effects of strokes. Excessive haste in moving to the clinic might create a public backlash that could set the field back years, warns the ASTP.

But the dangers of rushing remain strong. Pressure from patient groups and surgeons to move ahead with trials has coincided with an anti-regulation climate in the United States. "It is hard to say stop," says Jonathan Allan, a virologist at the Southwest Foundation for Biomedical Research in San Antonio, Texas and a member of the FDA advisory subcommittee on xenotransplantation. "I'm not optimistic that they [PHS agencies] will do the right thing, and put public health first."

The Trojan pig

As the FDA subcommittee on xenotransplantation was meeting last month in the United States, hundreds of thousands of chickens were being slaughtered in Hong Kong to try to contain an outbreak of H5N1, a fatal flu virus that previously infected only chickens and ducks. Although the virus had jumped species, it seems to have infected only people who have come into direct contact with fowl, and does not seem to be contagious (see *Nature* **389,** 554; 1997).

If a viral stowaway in a xenotransplant similarly affected only the recipient, it would just be one more of the many infectious complications to which immunosuppressed transplant recipients can succumb. The big unknown is whether animal viruses might spread from recipients to others, and possibly cause pandemics. Natural precedents abound — Ebola and Marburg monkey viruses have caused large disease outbreaks in humans while there is compelling evidence that HIV originated from monkey retroviruses.

Some argue that natural outbreaks merely put the risks of xenotransplantation in a useful perspective, in that animals have transmitted viruses to humans throughout history. Paul Herrling, scientific director of Novartis, says the Hong Kong flu outbreak shows "that the risk from other sources is much greater, and that the added risk in view of the life-saving nature of a successful xenotransplantation might be minimal".

Other researchers are less sanguine. "I take the same data and turn it around, saying 'look, this can happen'," says virologist Robin Weiss. Indeed, accidents have already occurred: millions of people were accidentally contaminated with simian virus 40 (SV40) in the 1950s through contaminated polio and adenovirus vaccines made in monkey kidney cells.

Weiss points out that the pathogenicity of viruses can change unpredictably when they jump species. SV40 does not seem virulent in infected individuals, but many viruses lying dormant in animals, in particular herpes viruses and retroviruses, can become activated and deadly in humans.

He argues that activation of animal viruses might be favoured under transplant conditions, as these remove many barriers to natural means of infection. Viruses that might not usually infect humans would enjoy intimate cell–cell contact in xenotransplants that might favour both infection and recombination with human viruses, a mechanism known to generate pandemic viruses. "I'm not saying you shouldn't do this [clinical xenotransplantation], I'm asking you, 'have you stopped to think?'," says Weiss.

Shutting the barn door?

The PHS guidelines represent an attempt to find a "middle path," says Pendergast, by allowing trials to proceed despite the scientific uncertainties, while attempting, through monitoring of patients, to contain any risk that emerges.

The science and public health issues are "so complicated" that the FDA must strictly regulate the field, she says. "In our job, we hear a lot of quibbling. Isn't a small trial sufficient, do we really have to run so many tests, does it matter that we haven't validated this assay? We are going to expect and demand the best. The stakes are too high not to."

An important part of FDA oversight will be to encourage trial sponsors to generate better data on the risks, according to Amy Patterson, interim deputy director of the Division of Cellular and Gene Therapies at FDA and a leading authority on xenotransplantation. While everyone agrees on the need for more research, there is little consensus as to whether such studies should be done before further trials, or in parallel with them.

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The message to the FDA from its sub-committee on xenotransplantation is that clinical trials should be done with extreme caution, she says.

Paul Noguchi, director of the FDA's Division of Cellular and Gene Therapies, says: "We are committed to examining all the studies very critically and should anything happen we are prepared to halt activities."

The discovery that pig retroviruses can infect human cells *in vitro* has sent researchers scurrying to see whether patients who have already received porcine transplants show signs of infection. "It behoves everyone to 'stop for a moment' and evaluate those people that have already been transplanted," says Marian Michaels, a specialist on risks of xenotransplantation at the Children's Hospital of Pittsburgh.

Novartis is studying 150 patients who have had pig skin transplants for serious burns, implants of pancreatic islet cells, or who temporarily underwent perfusion using pig liver 'bridges' while awaiting a human liver.

In Sweden, studies are tracking ten renal diabetic patients who received fetal pig islets in the early 1990s, and two patients who had outside perfusions using pig kidneys. Twenty-four neural tissue recipients are being tracked in Boston, Massachusetts. Ann Tibell, a researcher at the Karolinska Institute in Stockholm who is leading the pig islet study, recently reported antibodies reactive to swine influenza in all ten patients, porcine parcovirus in five, and five other pig viruses. Only one of the patients is ill, with parcovirus. Tibell is checking whether the results may be accounted for by cross-reactivity with human viruses, and retrovirus assays have yet to be completed.

"As a result of these studies we will have much more data [on risk] in a year from now," says Louisa Chapman, from CDC. But Jonathan Allan, a virologist who sits on the FDA's advisory subcommittee on xenotransplantation, thinks the agency is failing to pay sufficient attention to the 'precautionary principle'. "Xenotransplant researchers haven't done their homework," he says.

Allan is particularly concerned about the threat that, were a xenozoonose to behave like HIV or HTLV, it could spread quietly for decades before being detected, by which time it might also have contaminated the blood supply. The FDA is attempting to address such concerns by requiring monitoring of all future xenotransplant recipients for infectious diseases over their entire lifetime, and prohibiting them and their close contacts from donating blood.

Some argue that this approach could amount to shutting the barn door after the horse has bolted. But this interpretation is disputed by André La-Prairie, official at Health Canada, the country's equivalent of the FDA, which is drafting guidelines similar to those of the United States. He admits that monitoring may not be a guarantee against infections escaping into the population, but argues that "it should tell you as soon as possible if and when the horse has left the barn," and allow trials to be quickly stopped.

Similarly, virologist David Onions points out that what is under discussion is experimental clinical trials, not therapeutic programmes involving thousands of recipients. "Five to ten people you know about are not going to start an epidemic," he says.

But Allan and others argue that the proposed monitoring measures are burdensome, and that their implementation is likely to be unworkable and vulnerable to human errors. "If you are putting your bets on containment, it's a lost cause," he asserts.

Indeed, the draconian monitoring measures being proposed are unprecedented in medicine. They would transform the nature of informed consent into a 'binding contractual agreement'. Patients would surrender the traditional right to withdraw from experimental procedures at any time, and be obliged to accept lifetime monitoring.

Recipients might even face quarantine, in much the same way as astronauts returning from the Moon were initially isolated for several months in case they brought back weird diseases, according to Abdullah Daar, a transplant surgeon at the Sultan Quaboos University in the Sultanate of Oman, who is an authority on the ethics of transplantation and chairman of the xenotransplantation advisory committee set up last year by the World Health Organization.

Trials jump the gun on science

The stringent precautions that xenotransplantation seems likely to require, and the prospect that it may never be possible to eliminate its potential risk to the public, raises the question of whether the risks would be outweighed by the benefits. There is a broad consensus that eventually, if xenotransplantation proves technically feasible, the answer will be 'yes'. There is less agreement on whether the science is sufficiently advanced to justify moving to clinical trials now.

Optimism that clinical applications might be near rose in 1995 when Imutran announced that it had overcome one of the

Confronting the risks of 'xeno-havens'

The announcement last year of the cloning of Dolly the lamb led to an international response unprecedented in medical ethics. Within hours, Presidents Clinton, Chirac and Santer had called on their ethics committees for advice on the implications for humans, while international agreements on bioethics that had been all but finalized by the Council of Europe and Unesco were quickly modified to include a ban on human cloning for reproductive purposes.

"The wrong issue for a moral panic," sighed at the time David Shapiro, then executive director of Britain's Nuffield Council on Bioethics, arguing that if there was an area of medical ethics in dire need of international regulation it was not cloning but xenotransplantation. For, however hard countries such as the United States or United Kingdom attempt to regulate xenotransplantation to reduce the risk of creating human diseases, their efforts will be in vain if other countries adopt weaker or no regulations. Such countries could become 'xeno-havens' for unscrupulous surgeons, allowing animal viruses to escape into the human population (*Nature* 385, 378; 1997).

"The prospect scares the hell out of me," says Daniel Salomon, a scientist at Scripps Research Institute in California, and member of the board of the American Society of Transplant Physicians, a body that has long waged war on the trafficking of human organs in developing countries. The exorbitant costs of meeting the stringent regulatory requirements for clinical xenotransplantation now being developed in the United States and other industrialized countries will create a strong incentive for traffic in xenotransplants with 'xeno-havens' providing cheaper alternatives, argues Salomon. The big risk, he says, is that humans will end up with virus-laden organs from baboons and chimpanzees, rather than from specially bred pigs which — even given the acknowledged dangers — should nevertheless be safer.

The European Commission has yet to take a position on clinical applications of xenotransplantation. Ironically, one reason is that the agenda of the scientific steering committee that advises the commission on technical issues is currently jammed with issues arising from the aftermath of the bovine spongiform encephalopathy crisis, according to Paul Vossen, a commission spokesman.

One official from the World Health Organization (WHO) admits that the growth of interest in xenotransplantation has caught the organization off guard. It has since moved speedily, setting up a xenotransplantation advisory committee last autumn, and planning to release guidelines on the technology within the next few months.

But many argue that WHO guidelines are not enough, pointing out that WHO is not a regulatory authority, so any regulation of xenotransplantation technology at the national or international level will be up to national governments. "We need some kind of formal binding international agreement," says Salomon.

major barriers of cross-species rejection, hyperacute rejection (HAR), a violent immune response involving the complement system that is unleashed when organs are transplanted between distant relatives such as pigs and humans. HAR destroys the blood vessels in the organ, cutting off oxygen, and killing it within minutes.

Imutran's announcement followed experiments in which the company claimed cynomologus monkeys given genetically engineered pig hearts heterotopically survived for as long as 60 days, with none of the hearts sufferering from HAR, whereas control animals died within one hour of transplantation. David White, the company's medical director, said the technology was now "ready for testing in humans" (see *Nature* **377,** 185; 1995).

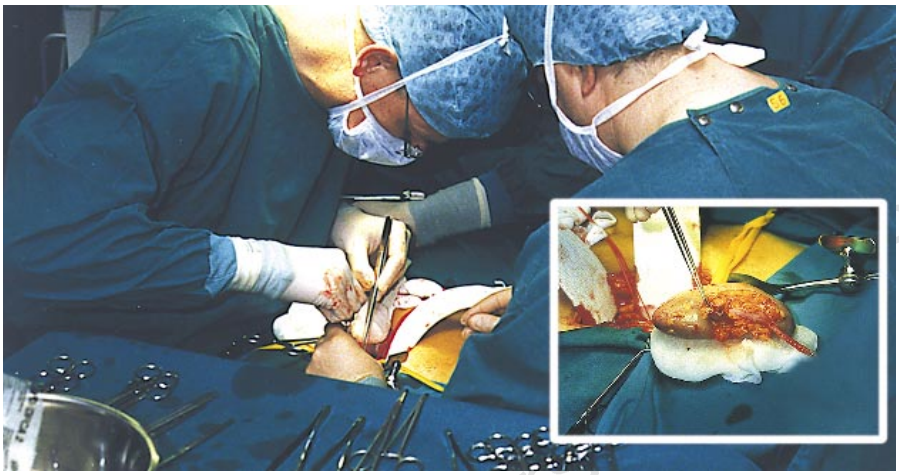
At least three other companies have also engineered pigs to overcome HAR: Protein Pharmaceuticals, Alexion of New Haven, Connecticut, which is linked to US Surgical Corporation, and Nextran of Princeton, New Jersey, a subsidiary of Baxter. But there is now a growing awareness that, even if HAR is overcome, this alone is unlikely to be sufficient to prevent rejection of organs, admits Paul Herrling, research director of Novartis, which bought Imutran in 1996.

Delayed xenograft rejection, which occurs within days when macrophages and natural killer cells invade the organ, is widely considered as formidable a barrier as HAR. And, although the remaining major barrier, the T-cell response, should in principle be able to be controlled using conventional immunosuppressors, recent research suggests the T-cell response to xenografts is subtly different and may require the development of new immunosuppressors.

Herrling rejects White's optimistic projections as premature, and says the company has no immediate plans for clinical trials of transgenic hearts, because it feels that not all the "physiological and pharmacological issues have been satisfactorily solved". He says Novartis is investing heavily to try to "develop clinically acceptable immunosuppressive regimes," and that this is likely to require new approaches to those used in allotransplantation — transplants using human organs, cells or tissues.

Hype hides obstacles

Some accuse capital-hungry biotechnology companies of generating excessive 'hype' about the prospects of xenotransplantation and of having created unrealistic expectations among patients, fuelling pressure to proceed to clinical trials. The ASTP warns that the domination of the research by companies "may not be in the best interests of the community," arguing that "early clinical trials may be sought without adequate documentation or publication of support data in order to facilitate corporate interests".



NOVARTIS

Kidney transplant: a victim of its own success.

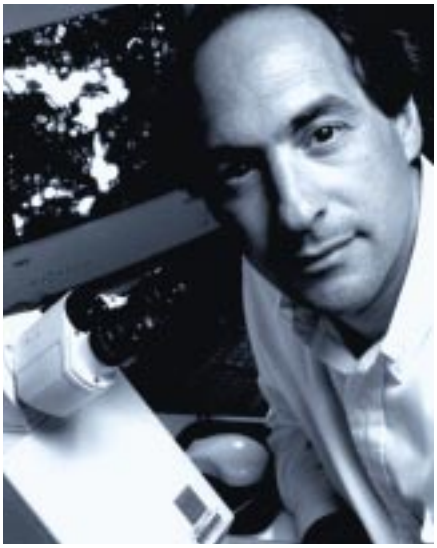
Herrling says excessive hype has become "much less of a problem since the acquisition of Imutran by Novartis". The buyout means that Imutran has "no short-term financial pressure to rush into clinical trial prematurely as might be the case with a standalone biotech company dependent on shorter-term financial goodwill".

Need for novel approaches

In the cold dawn of the 4th International Conference on Xenotransplantation last autumn in Nantes, France, it was clear that optimism resulting from progress in overcoming HAR had given way to the realization that many other factors playing a role in organ rejection are still far from understood.

Analysts are similarly sceptical about the short-term prospects for clinical success. "The immune system is unbelievably complicated and poorly understood, making xenotransplantation one of the most speculative of all areas of biotechnology," says Alex Zisson, an analyst at Hambrecht and Quist in New York. "Companies are years away from having a product on the market."

Daniel Salomon, a scientist at Scripps Research Institute in California and member of the board of the American Association of Transplant Physicians, says he believes the risks of xenotransplantation are "manageable," but feels that the current lack of scientific understanding of rejection and organ function precludes clinical application for some time to come. He thinks a case can be made for trials with the minimum number of patients needed if this yields information that can "move the field forward," however.



Salomon: 'science base still insufficient'.

The holy grail of allotransplantation, completely avoiding the problem of rejection by re-educating the recipient into recognizing donor tissues as 'self', is being pursued by the team of David Sachs, a professor of surgery at Harvard Medical School and director of the transplantation biology research centre at Massachusetts General Hospital, in cooperation with Bio-Transplant, a company linked to Novartis. Applied to xenotransplantation, this technique would similarly overcome the T-cell response, but would itself be insufficient to overcome cross-species rejection and would need to be used with techniques to overcome hyperacute and delayed xenograft rejection.

The concept is elegantly simple. Bone marrow cells from the donor are first engrafted into recipients, while at the same time temporarily disabling their immune system; as the system recovers, the recipient develops tolerance to the organs and tissues of that donor. Sachs points out that this would, in principle, avoid the lifelong immunosuppression currently needed by transplant patients.

In a major breakthrough, Sachs's group reported last year that they had induced permanent tolerance pig skin grafts in mice using this technique (see *Nature Medicine* **2,** 1185 & 1211; 1996). Stephen Squinto, vice-president of research at biotechnology company Alexion, admits that the technique is "scientifically interesting". But he points out that its clinical applicability will require a more gentle technique for disabling the immune system than that used by the group

Primate risks 'still going unheeded'

One controversial aspect of the proposed US guidelines on xenotransplantation is the lack of an explicit ban on the use of organs from non-human primates, such as baboons. Although these are less susceptible to rejection because of their close similarity to human organs, they are nonetheless widely considered unsuitable for transplantation because of their much higher perceived disease risk, and the fact that it would be impractical to breed the large numbers of 'clean' animals that would be needed.

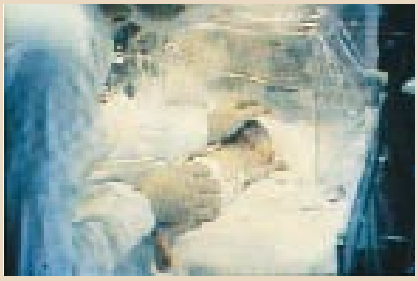
Such considerations led an ethics panel set up by the UK government to rule out the use of primates as donors on the grounds that pig pathogens are better characterized and the animals are easier to breed in large numbers under clean conditions.

But many scientists are unhappy about the lack of a US ban on the use of primates, given their unsuitability. US agencies appear to have felt that the issue was not the species used, but rather the level of disease risk. Applications for clinical trials would be judged on the basis of how well-defined the pathogens of a particular species were, how easily they could be removed, and on the risks that they harboured unknown viruses, says Louisa Chapman, an official at the US Centers for Disease Control and Prevention. She argues that in practice non-human primates will have much greater difficulty in meeting these criteria than pigs.

Such assurances are met with scepticism by critics who point out that the US Food and Drug Administration (FDA) approved a controversial trial of baboon bone marrow in AIDS patient Jeff Getty in 1995 (see *Nature* 378, 756; 1995).

Suzanne Ildstad, director of the Institute for Cellular Therapeutics at Allegheny University of the Health Sciences in Philadelphia, who oversaw this trial, is keen to continue with further trials.

At least one other surgeon also has plans to transplant solid organs from non-human primates. Leonard Bailey, from the Loma Linda University Medical Center in California, one of the country's top heart transplant surgeons, says he intends to apply to the FDA to transplant hearts from the centre's baboon colony into children. "We don't want to risk the public health, but we don't think we need to hold back on the basis of speculation about risks to public health."



Baby Fae: despite failure, new operations with baboon hearts are still being planned.

In 1984, Bailey carried out the most celebrated xenotransplant operation, placing a baboon heart into a two-week old baby — Baby Fae. The child died three weeks later after her immune system destroyed the organ. Bailey now claims to have obtained "prolonged survival" in animal studies (see *World Journal of Surgery* 21, 943–950; 1997) and intends to try again.

But another surgeon who also pioneered early baboon xenotransplants, Thomas Starzl, from the University of Pittsburgh, says he has decided not to proceed for the time being. Starzl carried out a series of unsuccessful baboon-to-human kidney transplants in the early 1960s and again in the 1990s. But he says lack of scientific understanding means that "we are too far from being able to do anything [clinically]; we are tremendously interested but we think the research endeavours are going in the wrong direction".

Concern about the use of non-human primates has been heightened by a loophole in the guidelines that would seem to risk allowing the use of virus-laden wild primates. The revised guidelines do not explicitly ban the use of these, saying only that departures from ideal husbandry would need to be justified by the trial sponsor.

— whole-body irradiation, thymectomy and purging the body of T-cells.

Closer to the clinic?

Cells and tissue xenotransplants are less vulnerable to hyperacute rejection than organs because they have no blood vessels for HAR to attack, relying instead on the supply of blood from the host, although they must overcome a strong cellular response.

The potential for such implants looks promising, as shown by the recent report by Michael Thomas, from Baylor College of Medicine at Houston, Texas (*Nature Medicine* **3,** 978–983; 1997), in which bovine adrenocortical cells implanted into immunodeficient *scid* mice were able to develop into functional adrenal tissue in the kidneys of mice from which the adrenal glands had been removed. This suggests that the only absolute barrier to wider use of such implants is the immune system.

Clinicial trials are already under way worldwide. Ole Isacson's team at Harvard Medical School, for example, are transplanting patients with immortalized mouse fibroblasts, producing retrovirus vectors to deliver a therapeutic gene to brain tumours, and with fetal pig neurons to try to replace dopaminergic neurons destroyed in Parkinson's disease (*Nature Medicine* **3,** 964; 1997).

The fact that cells and tissues seem closer to clinical success means that trials involving these are much more likely to be approved than ones involving solid organs, predict US regulatory officials. Indeed, even if rejection can be overcome, maintaining the complex functioning of solid organs in a human host "for a sufficient time to make clinical sense," remains a major challenge, says Herrling.

Call for moratorium

As the potential risks of xenotransplantation would affect the general population were they to materialize, approving trials through the traditional regulatory approach could be interpreted from an ethical standpoint as tantamount to exposing the public to these risks "without their consent or awareness," according to Bob Arnold, from the Center for Medical Ethics at the University of Pittsburgh. He poses the question of whether the public should be given a direct say in weighing up the risks and benefits of the technology, while at the same time noting the difficulty of defining "what sorts of public action would constitute consent".

Although the US PHS solicited broad public comments on its initial guidelines, the subsequent decision-making process itself has been restricted to within the regulatory agencies. "It is odd that a small number of people in the federal government are making unilateral decisions about something that could have such long-term consequences for the public," says Allan. He points out that expert committees have not been infallible in their handling of such issues where the risks are remote but the public health consequences potentially serious, as has been amply shown by the bovine spongiform encephalopathy (BSE) crisis, and the contamination of blood supplies with HIV during the 1980s.

Bach: calling for a moratorium.

Fritz Bach, a leading xenotransplant scientist from Harvard Medical School, Boston and a proponent of continuing basic research in this area, argues that, before expert committees issue regulations on clinical trials, there should be a wide "informed" public debate on the question of whether such trials should be allowed to proceed at all at present (see *Nature Medicine* **4,** 142–145; 1998). The question is ultimately an ethical, and not a technical, one, says Bach: "Is the risk to the public, which we can't quantify but which we know is greater than zero, justified by the help we are going to give individuals?" The FDA is "neutral" on the question of whether a moratorium is needed, says Noguchi.

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