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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