nature medicine
VOLUME 4 • NUMBER 2 • FEBRUARY 1998

Does biomedical research need another moratorium?

Xenotransplantation has the potential to alter dramatically many areas of medicine. It also has an as-yet undefined, and in all probability very low, risk of spreading new infectious diseases throughout the community. This potential danger to the population demands a new paradigm for assessing the risk-versus-benefit equation associated with xenotransplantation. New clinical trials of this technique should be delayed until this has been achieved.

Despite the experimental nature of protocols for xenotransplantation, it is estimated that more than two hundred patients have been exposed to cells, tissues or organs from other species. Some 20 procedures took place in 1994 and there were more than 100 in 1997, suggesting that under current guidelines we could soon see thousands of patients treated each year. If only one or two of these trials demonstrates efficacy—and there are already signs that at least some will—there are many millions of patients who could benefit.

Today's protocols have been designed to replace failing organs and to treat a wide variety of disorders including neurodegeneration, diabetes and infectious diseases. Just as the diseases being treated are varied, so too are the protocols applied to them. Some simply call for the patient's blood to be passed over columns of xenogeneic cells (such as Circe Biomedical's extracorporeal treatment for liver failure) whereas others involve whole organ transplantation. It seems intuitive that such different procedures will have different risks, but they all have one thing in common—the possible transmission of infectious agents from donor to recipient. In January 1998, a US Department of Health and Human Services (DHHS)-sponsored meeting discussed this risk of infection and other scientific, ethical and public policy issues surrounding xenotransplantation.

Because of a unique set of ethical concerns, cost and a greater perceived risk of xenosis, the routine use of higher non-primates as donors is likely to be ruled out, leaving pigs as the donor of choice. Much progress has been made in overcoming the hyperacute rejection that follows transplantation of vascularized porcine tissue into humans. Hyperacute rejection happens as a result of circulating natural antibodies that recognize antigens on the surface of pig cells and subsequently activate the complement cascade. By blocking or removing the antibody/antigen binding or preventing complement activation, many groups have been able to reduce tissue rejection to levels that may be treated effectively with immunosuppressants. However, as Robin Weiss (Institute of Cancer Research, London) pointed out in a recent Commentary (*Nature* **391**, 328; 1998), the very procedures designed to minimize tissue rejection may increase the risk of viral infection. This combined with the potential of widespread infection, from donor recipient to others in the community, should be enough to give all those involved in the field pause for further thought. Such a pause would have many advantages.

A concern of many of those attending the DHHS meeting was an overall lack of data on which to base risk estimates. Although protocols are now being established to test donors for known infectious agents and to screen recipients for the appearance of these agents, much of the archived tissue from earlier trials and experimental procedures has not been exhaustively studied. This material is an important resource and retrospective testing should be undertaken. With the results of this screening, perhaps a start can be made on estimating some of the risks involved.

It was recently discovered that pig endogenous retroviruses (PERV) can infect human cells. Indeed acting on this, the US Food and Drug Administration (FDA) in October 1997 temporarily halted all pig to human trials pending establishment of new procedures to monitor PERV transmission. It has been proposed that a combination of breeding programs and genetic engineering might make it possible to remove all known PERVs from donor pigs, thus eliminating what is probably the largest single component of the xenosis risk.

A pause in human xenotransplantation would also provide an opportunity for all interested parties to achieve a better consensus on some key issues. As Hugh Auchincloss (Massachusetts General Hospital, Boston) reported, the December 1997 meeting of the Xenotransplantation Subcommittee convened to advise on appropriate assays for detecting PERV in donors and recipients, could not reach a consensus on some core issues: Should it be required to test all tissues and organs for presence of PERV or only samples of animals or organs from each herd? Is it absolutely necessary for patient informed consent to be extended to close contacts of the patient? Should pig xenotransplantation continue given that "it is reasonable to assume that all pig tissue has potentially infectious PERVs"?

Finally, and as discussed by Bach *et al.* in an opinion piece in this issue (page 141), a temporary hold on new trials would allow the FDA and others to convene a more public and broad ranging forum in which to address the important question of whether a well-informed society will support and encourage clinical xenotransplantation. As Margaret Somerville (McGill University, Montreal) pointed out, if the community is put at risk of infection, then the community's informed consent becomes a necessary step before clinical xenotransplantation can proceed.