Xenotransplants: proceed with caution

Sir — The US Public Health Service (PHS) agencies have rejected recommendations for a moratorium on clinical trials of xenotransplants, and left the door open for nonhuman primates to be donors. Your Briefing on xenotransplantation[1] summarizes the important elements of this subject, and captures perfectly the split between those who want to get it right and those who want to get it right now.

In the Briefing, Jonathan Allan, a virologist on the Food and Drug Administration (FDA)'s advisory subcommittee on xenotransplantation, points out the neglect of the precautionary principle in a situation where it is most needed, given the risk of public exposure to xenozoonoses. The United States is fortunate in having bodies such as the Centers for Disease Control and Prevention, the National Institutes of Health and the FDA, which give it the confidence to halt activities "should something happen" — but containment is the wrong strategy here, and any epidemic that starts may involve countries other than the United States.

Many countries, and not just those in the developed world, are likely to want to benefit from xenotransplantation. Given that nothing is to stop them from going ahead, apart from their national governments — if even that — the need for international cooperation in risk minimization and containment becomes obvious.

Recognizing and responding to this global dimension of the risk calls for interdisciplinary and international dialogue to harmonize guidelines, research, surveillance methods and the response in case of adverse outcomes. National registries will need to be compatible, and archived tissue perhaps accessible to scientists from other countries. Many of these issues were agreed upon at the World Health Organization consultation on xenotransplantation in Geneva last October.

With traditional research funding drying up in universities, biotechnology companies are increasingly involved in cutting-edge research. Transparency through peer-reviewed publication cannot be guaranteed and, although companies linked to major pharmaceutical companies will probably be guided by long-term interests, some venture-capital companies may seek short-term rewards. The long-term effects are unpredictable but, given that the public is being put at risk, an argument can be made for greater public debate, as suggested by Bach *et al.*[2], and perhaps novel means of public supervision. A challenge in the days ahead is to define these means and to define what might constitute public or community consent.

Xenotransplants will almost certainly be too expensive in the early years to be the answer to the shortage of human cadaveric organs for transplantation. Furthermore, it is not yet known if xenogeneic organs will adequately replace the function of complex metabolic organs such as the liver. We must therefore continue to strive for other means of increasing donation of human organs and certainly ensure that xenotransplantation does not undermine allo-donation.

Xenotransplantation may also affect traditional transplant ethics[3] by eroding the 'gift' metaphor and the confidentiality principle; through the complete reification and commodification of organs and the rewriting of the meaning of consent to include the community; and through erosion of the courtesy and cooperation between centres working with a very scarce resource.

Finally, no sensible person would want to hold back development of such a potentially useful technology were it not for the risk to public health. There may be reason to be confident that the risk of xenozoonoses is small, but the risk would be justified only if large numbers of patients could be saved in the very near future and we had no hope of improving our risk assessment capabilities quickly. This is not the case at present: xenotransplantation will have no immediate effect on overall transplant numbers; and risk assessment is improving.

We understand the similarity to the early days of genetic engineering and the call for an embargo then, which has proved unnecessary. However, one similarity should not constitute a cliché; the risk is serious enough and the immediate benefits are small enough to require this situation to be assessed in its own right. This is particularly true because, although most comments have been about clinical trials, the reality is that even minimal perception of success in trials will soon lead to xenotransplants as therapy and will encourage many unprepared units to 'do' xenotransplants. The immediate effect of the permissive US PHS guidelines will be that other countries will want to follow suit, so speeding further a process that the PHS itself felt obliged only a few weeks ago to halt as a result of new evidence on porcine endogenous retroviruses.

The PHS is listening and responding. Its guidelines are, fortunately, still evolving. Common sense would dictate caution even without a formal embargo. The guidelines are tougher than originally envisaged and may become tougher still. It would be a recognition of its global reach for the US PHS to acnowledge that it is here dealing with a global rather than a US issue and that there is no reason to hurry past prudence.

A. S. Daar
Sultan Qaboos University, Muscat, Oman
e-mail: asdoc@gto.net.om

Sir — We, the American Society of Transplant Physicians (ASTP) and the American Society of Transplant Surgeons (ASTS), reject the call for a moratorium on clinical trials of xenotransplantation in the United States[2]. Bach *et al.* assert that the potential infectious risks of xenotransplantation could create a public health problem, that a broad public discussion is therefore required and that a moratorium is justified until the latter is completed. But their opinions represent, at best, a minority among US transplant professionals.

They also appear to ignore the remarkable public discussion organized over the past four years by US Public Health Service (PHS) agencies, including the Food and Drug Administration (FDA), the Centers for Disease Control and the National Institutes of Health. Public meetings, the most recent in January, have brought together hundreds of professionals in transplantation medicine and surgery, infectious disease, veterinary medicine, ethics, public policy and law, as well as patients, families, animal rights representatives and companies. This knowledge base has been shared at meetings organized by the Institute of Medicine (Washington, June 1995), Health Canada (Ottawa, November 1997) and the World Health Organization (Geneva, October 1997). All the issues raised by Bach *et al.* have already been clearly articulated, widely discussed and published[1,4–6], and have received substantial media coverage. Between November 1996 and October 1997, some 230 articles discussing xenotransplantation were published in major newspapers in the United States, while more than 435 were published in the UK national press in 1996–97.

The consensus that has emerged from the PHS discussions is that it is time to proceed cautiously with well-defined and highly controlled clinical trials. To support this process further, the PHS has developed several important mechanisms, including a Xenotransplantation Advisory Subcommittee and plans for a National Patient Registry, Biological Specimen

Repository and a National Advisory Committee. We strongly endorse this consensus opinion, and commend the PHS for its efforts in support of our patients, their families and the general public. We agree fully with the recent public statements of William Raub (Deputy Assistant Secretary of Health and Human Services) and Michael Friedman (Acting Commissioner, FDA) rejecting the call for a moratorium.

Daniel R. Salomon
(Xenotransplantation Committee, ASTP)
Department of Molecular and Experimental Medicine — SBR5, Scripps Research Institute, La Jolla, California 92037, USA
e-mail: dsalomon@scripps.edu
Ronald M. Ferguson
(President, ASTS)
Ohio State University Medical Center, Columbus, Ohio
J. Harold Helderman
(President, ASTP)
Vanderbilt University Medical Center, Nashville, Tennessee

Sir — As a clinician involved in clinical allotransplantation and experimental xenotransplantation (heart-lung and lung), I should like to comment on your attitude to xenotransplantation[1].

The European Union has provided a ECU1.5 million (US$1.6 million) grant (1997–2000) to establish a working group of several non-UK countries to address different topics of xenotransplantation. The unique aspect of this group is that it is composed of a physician, researchers (in biochemistry, immunology, genetics and virology), a sociologist, philosophers and so on.

Although heterogeneous, this group has a unique question in mind: is xenotransplantation of clinical benefit for a human being? Although you have published quite a lot on this subject, as far as I know none of the authors has been at the bedside of a patient. They cannot feel the frustration of patients who die while waiting for an organ nor the wonderful sensation of being able once more to breathe or to move without effort. What about the parents seeking a therapeutic solution for children with terminal diseases? As a clinician, is it really ethical for me to have no solution or should I be more concerned with infection and social arguments?

In the laboratory in which I work, we have recently used the nude mouse to host a human trachea derived from human embryonic cells. After several months, we transplanted up to 10 cm^3 of human trachea into piglets to test whether the process might be used in human babies as an alternative to their death. All the experiments were successful (without immunosuppression, human grafts were not rejected). Do I have the right to propose this technique to the parents? I think I do and we are in the process of asking for permission to do it.

I believe that people dealing with xenotransplantation should give more thought to the patient rather than to ways of raising funds for research that may never be applied in clinical practice because it is too complicated. Have such researchers any idea what a child looks like after several years of immunosuppression treatment?

The time has come for clinicians rather than basic researchers to give their opinions on clinical xenotransplantation.

Paolo Macchiarini
Department of Thoracic & Vascular Surgery, Hôpital Marie-Lannelongue, Paris-Sud University, 133 Avenue de la Resistance, F-92350 Le Plessis Robinson, France
e-mail: paolo@pratique.fr

1. Butler, D. *et al. Nature* **391,** 320–325 (1998).
2. Bach, F. H. *et al. Nature Med.* **4,** 141–144 (1998) & *Nature* **391,** 326 (1998).
3. Daar, A. S. *World J. Surgery* **21** (9), 975–982 (1997).
4. Chapman, L. E. *et al. New Engl. J. Med.* **333,** 1498–1501 (1995).
5. Institute of Medicine, *Xenotransplantation: science, ethics and public policy* (National Academy Press, Washington, DC, 1996).
6. Weiss, R. A. *Nature* **391,** 327–328 (1998).