

Report of the Workshop on Xenotransplantation

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Summary — Although the basic concept and medical promise of xenotransplantation appears simple, clinical and scientific, realisation has proven elusive, with success unlikely in the near future. Speakers in this workshop discussed the current European perspective on xenotransplantation; the range of clinical protocols under consideration and the health problems they are designed to address; alternative approaches with an emphasis on reducing the need for transplantation, while increasing the supply and utilisation of human organs; and animal welfare aspects of xenotransplantation research and potential clinical applications.

Dr Jon Richmond, Chief Inspector, Animals (Scientific Procedures) Inspectorate of the UK Home Office, discussed the current status of xenotransplantation development and regulation in Europe. He noted that xenotransplantation raises unique, important issues beyond those encountered with other novel surgical techniques. Because of these ethical and public health concerns, there is a need for coordinated transnational approaches to the regulation of clinical trials and the introduction and use of these techniques in clinical practice.

Within this framework, the Committee of Ministers of the Council of Europe (COE — a confederation of 42 Member States), in 1997, recommended establishing mechanisms for regulation and registration of aspects of xenotransplantation, including basic research, clinical trials, source animals, clinical programmes and review and follow-up of recipients. This was followed, in 1999, by action of the Parliamentary Assembly of the COE, calling for a moratorium on all human xenotransplantation, including clinical trials. This led to the Committee of Ministers establishing a Working Party to review and report on the state-of-the-art in xenotransplantation research and related topics such as ethics, animal welfare, legal principles, safety, efficacy and efficiency; to make recommendations; and draft guidelines on xenotransplantation. Their outputs are generally consistent with those of the European Commission, the Organization for Economic Cooperation and Development, and the World Health Organization.

Individual national authorities, faced with an immediate need to deal with developments in xeno-

transplantation, have sought to devise and implement appropriate national measures pending creation of coordinated transnational positions.

In the United Kingdom, the government commissioned (1995) an independent Advisory Group on the Ethics of Xenotransplantation, which, in 1997, issued a report, *The Ethics of Xenotransplantation: Animal Tissues Into Humans*. Concepts discussed in this document include the insight that ethical considerations of the issues involved in xenotransplantation must be continuous and revisited as new information becomes available, provided certain safety and efficacy concerns can be addressed. Also addressed was the use of pigs as source animals being ethically acceptable, but not non-human primates. The report further recommended the establishment of a formal regulatory body to oversee the development of xenotransplantation in the United Kingdom. The resulting United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) was formed later in 1997. Its mandate is to: advise on the regulation of and developments within the field of xenotransplantation (worldwide); provide a focal point on the issue within the government; and issue publications on various aspects of the subject.

Despite all of this activity, several important issues remain to be resolved. Pre-clinical and clinical xenotransplantation systems remain many and varied, being underway or under discussion in several countries, with animal studies taking place in at least twelve. Development of a transnational approach is still in the future. On what will it be based? What levels of risk are acceptable? What performance standards are required? Where are such issues best discussed and resolved?

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Dr Louisa Chapman, Assistant to the Director for Biological Therapeutics of the Centers for Disease Control (USA), delivered a presentation on the current status of xenotransplantation, with an emphasis on the range of clinical research protocols. The United States Public Health Service now broadly defines xenotransplantation as the transplantation, implantation or infusion into a human recipient of either live cells, tissues or organs that have had *ex vivo* contact with live non-human animal cells, tissues or organs. This characterisation reflects an historical shift in the focus of clinical xenotransplantation to a greater emphasis on the use of cells rather than whole organs. Dr Chapman discussed the growing disparity between the number of patients on organ transplant waiting lists and the available supply of suitable human organs and the specific example of the public health impact of diabetes mellitus, which may be treatable by using animal cells.

Clinical investigations require oversight by the Food and Drug Administration (FDA), with xenotransplantation studies primarily falling under the Investigational New Drug Application (IND) approach. As of 1 December 2001, 40 xenotransplantation INDs were received, the first in 1992 — a gene therapy clinical trial for the implantation of a murine producer cell line. Of these INDs, 21 involved direct implantation, 7 *ex vivo* contact, 7 extracorporeal haemoperfusion and 5 direct implantation with a barrier. Source animals for these protocols included 17 utilising pigs, 11 mice, 4 rabbits, 3 fruit-flies, 3 non-human primates and 2 cows. Currently, 13 of the projects are still in effect; 10 withdrawn (4 never in effect); 9 on hold (7 never in effect); 4 remain inactive; 2 on partial hold; and 2 pending. The suggested clinical applications included cancer, liver failure, diabetes and neurological disorders.

Of the approximately 470 patients treated under these xenotransplantation INDs, several were involved in gene therapy protocols; most were associated with the use of porcine or murine cells; with the majority receiving implanted products or undergoing haemoperfusion. As of 1 June 2002, the FDA has approved no xenotransplantation products for marketing.

There is a general consensus that the potential for cures or amelioration of disease remains greater for xenotransplantation products than for other suggested alternatives. Biological replacements are superior to mechanical approaches. Chapman suggested that human organ donations will never match the clinical demand and that it may take decades to determine whether other theoretical approaches will be effective.

For the future, in the absence of significant breakthroughs in the science of xenotransplantation, Dr Chapman expects basic research to continue at a slower pace with the greatest perceived potential being for cellular therapies providing a

functional cure for diabetes, biological dialysis of patients with liver failure and restoration of irreversible central nervous system damage associated with diseases such as Parkinson's and Huntington's, as well as stroke.

Alan H. Berger, Executive Director of the Animal Protection Institute (USA), discussed the potential alternatives to xenotransplantation, noting that prior to using animal organs, intensified efforts to reduce the need for transplants and to enlarge the pool of human graft donors should be adopted. He cited a 1998 study by the US General Accounting Office, documenting failures to increase the number of potential organ donors, identifying several new policies to achieve that goal and suggesting that the number of available undonated but usable organs was significantly higher than previously indicated. Mr Berger further articulated the potential benefits of mandated choice and presumed consent laws to bring the number of donors in line with estimates of public support for such activities. He cited a Pennsylvania State mandated choice law, which increased organ donor referrals ten-fold and the positive experience of several European countries that utilised presumed consent laws to dramatically increase the supply of organs and tissues for transplantation.

In addition to new legal options, Mr Berger reviewed new medical advances in surgical techniques and repair (e.g. ventricular remodelling), bionic and artificial organs, genetically engineered cells and tissues and the growing potential of stem cell-derived organs and tissues as alternatives to reliance on the use of animal organs, cells and tissues in human patients.

Mr Berger ended his presentation with a consideration of how, as a society, greater emphasis on preventive measures would reduce the need for organ transplantation. Although multiple studies have shown that more education in health maintenance and disease prevention is the most cost-effective use of biomedical research dollars, the emphasis remains on using such financial resources on curing diseases. Mr Berger reminded the participants of the non-medical factors at work in support of xenotransplantations. If genetically modified animal organs and tissues are successfully developed, this will generate enormous profits for the pharmaceutical industry, bioengineering firms that supply the source animals and associated medical professionals.

He concluded that xenotransplantation, despite the favourable picture routinely painted by researchers and pharmaceutical companies, is not the answer to the shortage of organs for transplantation. We cannot continue to cure human lives by the wholesale taking of animal lives. Rather, we must learn to take better care of each other, by being organ donors, and of ourselves, through preventive measures.

Dr John McArdle, Executive Director of the Alternatives Research & Development Foundation (USA), discussed the animal welfare issues associated with xenotransplantation research and potential clinical applications. These can be grouped into four categories: research protocols, transgenic manipulations, donor animal production and new infectious agents. Since the number and severity of injuries and clinical complications associated with xenotransplantation experiments often involve greater degrees of pain and distress, these are not typical biomedical research animal models.

Dr McArdle reviewed general problems associated with transgenic animals: lack of one-to-one gene and phenotype correlations, disruptions of existing gene functions, damaged chromosomal repair and creation of new pleiotropic effects; and with transgenic pigs, such as pulmonary hypertension, congestive heart failure and respiratory distress; and a partial list of proposed transgenic manipulations designed to make pigs suitable organ and tissue donors.

He specifically discussed the known negative consequences of such genetic changes in GAL knockout mice and single GAL allele pigs, while noting potential limitations on the ability of pigs to absorb so many transgenic manipulations without creating serious damage to the animal's quality of life. He asked at what point should limitations be placed on such changes, especially since negative conse-

quences for the pigs may be delayed, pending some stimulus associated with the unique animal production environment.

Potential problems associated with the production of donor animals reflect the creation of a new class of pigs — neither agricultural nor research. Dr McArdle reviewed the traditional five freedoms desired for domestic farm animals, noting that all but one would be absent in xenotransplantation specific pathogen free (SPF) facilities. SPF production is characterised by psychological, social, environmental and maternal deprivation; reduced human contact; lack of appropriate enrichment; caesarian birth and isolation; use of confinement apparatus; and sterilised/irradiated foods. More specific xenotransplantation-related concerns are antibiotic and drug contamination of organs and tissues; repetitive fluid and tissue sampling; euthanasia protocols; the possibility of sequential use of individual animals; and the risk to xenotransplantation and domestic pig herds of new porcine viral diseases created by transgenic and natural genetic alterations.

Dr McArdle concluded by suggesting that all of these welfare considerations may require special care and use regulations for animals used in xenotransplantation research and production.