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Xenotransplantation: progress and promise

BMJ 1999; 319: 1311 [Full text]

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Alix Fano (16 November 1999)

Public Health Risk of Xenotransplantation Must Not Be Dismissed

16 November 1999



Emanuel Goldman,
Professor
*New Jersey Medical
School, Newark, USA*

Send response to journal:

Re: Public Health Risk of
Xenotransplantation Must

Not Be Dismissed

Xenotransplantation of organs from animals to try to save sick humans is a very seductive, but inherently dangerous idea. The risk is not just to the patient, who, if past precedent is any guide, will likely die in the short term after the procedure. The stakes are much higher than the fate of one individual, because the entire human population on this planet is put at risk by this kind of procedure. Viruses that inhabit animals, some of which are even intrinsic to the animal's own genetic material, will gain a route of entry into the human population which is not ordinarily available to them. As noted by Dr. Vanderpool, pig DNA contains endogenous retroviruses (the same class of viruses which cause AIDS), and these have been shown to be able to infect human cells in tissue culture.⁽¹⁾ Dr. Vanderpool does not mention that post-mortem analyses of two human patients who died 70 and 27 days after receiving baboon livers revealed two simian viruses which had apparently

replicated following the transplant.(2) Our state of knowledge is far too incomplete to suggest that it might be possible to breed totally virus-free animals, because it is almost certain that we do not even know all of the viruses there are which would need to be eliminated.

We do know that viruses can and do jump species even without our help, and there are enough frightening precedents of animal to human virus transmission, as far back as the swine influenza pandemic of 1918 which killed 20 million world-wide, to scare anyone contemplating xenotransplantation. In more recent times, one need only recall the millions of chickens which had to be slaughtered in Hong Kong two years ago, because of the unexpected jump to humans of an avian influenza virus; or the tens of thousands of English cattle destroyed because of the apparent jump to humans of the prion-based bovine spongiform encephalopathy ("mad cow disease").

The spectacular advance of one of the great scourges of our era, AIDS, resulted from a virus given new routes of entry into recipient hosts: the widespread increase in certain lifestyle practices provided a conduit for efficient transmission without which the virus would likely have had much less impact, if at all, at least in Western countries. HIV- 1, the virus responsible for AIDS, also likely resulted from a virus jump from simian to human. The deadly Ebola virus is another example of a virus which can be transmitted to humans from primates, and there are at least another 10 known primate viruses which can infect humans, including a deadly form of herpes. Pigs aren't much safer: there are about a dozen known pig viruses which can be transmitted to humans, often with serious pathologic consequences.

Not considered by Dr. Vanderpool is that there are much better alternative approaches, including lifestyle alterations (diet and exercise) which would significantly reduce the numbers of transplant candidates, and presumed consent policies for human donors, which would significantly expand the pool of available organs. Finally, research on unwanted human embryos is much more promising as a solution, but this is held hostage to the abortion politics in the USA. The medical potential of human tissue and organ cultures seems

unlimited and at negligible risk compared to xenotransplantation, but research on this cannot presently be federally funded. So instead of pursuing an avenue for transplantation that really might work, without introducing new viruses into humans, we are absurdly rushing down a path fraught with danger. Have we learned nothing from the AIDS epidemic?

(No competing interests.)

(1) Patience C, et al. (1997) Infection of human cells by an endogenous retrovirus of pigs. *Nat. Med.* 3:282-6.

(2) Allan JS, et al. (1998) Amplification of simian retroviral sequences from human recipients of baboon liver transplants. *AIDS Res Hum Retroviruses.* 14:821-4.

Xenotransplantation: Perils and Plagues

16 November 1999



Alix Fano,
Director
*Campaign for Responsible
Transplantation*

Re: "Xenotransplantation: Progress and Promise" (BMJ 13 November 1999; 319: 1311)

Send response to journal:

To the Editor:

Re: Xenotransplantation:

Perils and Plagues

In the American newspaper, *Newsday*, (Nov. 5, 1999, p.A53), bioethicist Art Caplan wrote, "Nature is making it very clear that lurking out in our world are still more mutating viruses and pestilent bacteria . . . Medicine has to learn an important lesson. The lowliest organisms can confound even the mightiest medical experts. Whatever medicine's achievements . . . humility is a better guide to dealing with the dangers and risks in the world around us than is hubris." These are wise words which should be heeded by pro-xenotransplantation "bioethicists" like Harold Vanderpool.

It is naïve to believe that extensive research in xenotransplantation "is being propelled" by drug companies' beneficent desire to alleviate human suffering, rather than the promise of billions of dollars in profits from the sale of "humanized" pig parts and expensive anti-rejection drugs. For there would be much safer and more-cost- effective[1] ways of dealing with the perceived

human organ and tissue shortage. One would be aggressive investment in population-based prevention programs to prevent organ disease in the first place; another would be passage of presumed consent laws, which have increased organ donation rates in Austria, Belgium, Singapore and other countries.[2] Cultivating human tissues for transplantation would provide a much safer source than animals.

It is ironic, given the multitude of known and unknown viruses lurking in animals,[3] that proponents of xenotransplantation continue to claim the technology can be made “safe.” It will be impossible to breed animals that are free of all infectious pathogens and endogenous retroviruses. Moreover veterinarian M.M. Swindle asserts that “it will be impossible to provide complete individual animal screening in a timely fashion prior to performing a xenograft transplant.”[4] Therefore, all recipients of porcine cells, tissue, or organs would be exposed to viruses and possibly other infectious organisms.[5]

Public health authorities admit that xenotransplantation could transmit deadly animal viruses to humans. Known pig viruses include the porcine endogenous retroviruses (PERVs) – a family of AIDS-like viruses that have infected human cells. And there may be dozens of unknown viruses, many with long latency periods, waiting to be discovered.

None of the alleged “safety” studies performed to date[6] account for latent or unknown viruses. Virologist Jonathan Stoye says: “the absence of infectious virus in, say, the first two hundred patients does not mean it will not occur in the two hundred and first. This implies that the chance of some hazard arising can never be zero . . . The greatest danger would come from something causing disease with a very long latency period.”[7] HIV-1, for example, was transmitted silently from human to human until it was recognized as a causative agent for AIDS in the early 1980s.

A retrospective Novartis/CDC study, designed to allay safety concerns about porcine xenotransplants,[8] raised more questions than it answered: 30 patients who underwent “splenic perfusions” in Russia tested positive for Porcine

Endogenous Retrovirus (or PERV) DNA; 23 had pig cells circulating in their bodies 8.5 years after treatment; and four patients injected with pig cells produced antibodies against pig PERV – suggesting a potential active infection by pig viruses. Data from some patients were deemed “uninterpretable” due to a lack of sufficient DNA for analysis, and technological limitations; none of the patients were exposed to tissue or organs from transgenic pigs; a majority of the study samples tested were from extracorporeal perfusion patients, exposed for very short periods - on the order of minutes to hours. Data from such experiments are hardly relevant to the kinds of conditions that would apply in whole organ xenotransplants. Only 14 patients were actually injected with porcine pancreatic islet cells, but important information about these patients’ exposure times and health and immunological status was missing.

This is hardly a solid study, and certainly not one to base claims of “safety” upon, particularly in light of the fact that “our understanding of the retrovirology of xenotransplant source animals is incomplete,” and that “little or nothing is known about the pathogenic potential of endogenous retroviruses introduced directly into other species.”[9]

Within the last 20 years, 30 novel infectious diseases, including AIDS, Ebola, and Creutzfeldt Jakob Disease, have been discovered. In 1998 -99, the Malaysian “Nipah” viral encephalitis virus jumped from pigs to humans, infected 269 people, killed 102, left dozens brain-damaged, and led to the mass slaughter of one million pigs. The swine flu epidemic of 1918 killed 20-40 million people worldwide. A novel pig virus, contracted via xenotransplantation, could spread to other humans undetected, causing a world-wide plague.

We continue to be baffled as to why xenotransplant researchers and drug companies insist on going down this perilous path, rather than focus their energies on safer, less problematic and humane solutions to the perceived organ shortage. And we are even more baffled that our public health authorities, mandated to protect public health and prevent disease, are encouraging the development and application of xenotransplantation, while simultaneously acknowledging that it could unleash deadly viruses upon

society. This may prove to be legally problematic for these authorities.

Let's not kid ourselves, xenotransplantation will never be "safe" for human beings, and its long-term efficacy has yet to be proven. All human recipients of whole animal organs have died, most within hours or days. Transplanting pig organs into nonhuman primates, as several biotech companies are doing, cannot tell us how pig organs and tissues will perform in human beings, whose physiology, metabolism, and immune responses are different from other animals.

Last year (May 1998), a group of international physicians pointed out in the British Medical Journal, that "the number of people living in absolute poverty has more than doubled since 1975." Global poverty, they said (and resultant lack of access to basic health care and adequate sanitation) is the world's number one health problem. Today, some 50 million Americans (over a third of them minorities and the working poor) lack access to basic health care, and another 50 million are underinsured. If we really wanted to save lives, we would be improving access to basic health care and sanitation, investing in disease prevention, and (in the case of organ failure patients) passing legislation to increase human organ donation. If we are not doing these things, we are simply lining the drug industry's pockets.

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1. Preliminary cost-benefit analyses (using industry's own figures) reveal that first-year implementation costs for xenotransplants in the U.S. would be \$35 billion (see Alan Berger, MBA, CPA "Animal-to-Human Transplants: A Frightening Cost-Benefit Analysis," Animal Protection Institute, Sacramento, California, October 1999, available on www.crt-online.org) This excludes

expensive follow-up care, regimens of anti-rejection drugs, screening assays and screening programs for new viruses, hidden costs of breeding, maintaining, testing, and disposing of herds of transgenic animals, the costs of hiring skilled hospital personnel, surgical staff, infectious disease experts and veterinarians capable of properly monitoring xenograft patients and source animals. And there may be unpredictable legal and medical costs associated with disease outbreaks as a result of xenotransplantation.

2. M.F.X. Gnant, "The Impact of the Presumed Consent Law . . . : Quadruplication in the Number of Organ Donors," *Transplantation Proceedings*, Vol. 23, No. 5 (October 1991): 2685-6. L. Roels, et al., "Effect of a Presumed Consent Law on Organ Retrieval in Belgium," *Transplantation Proceedings*, Vol. 22, (1990): 2078-9.

3. Dominic C. Borie, et al., "Microbiological Hazards Related to Xenotransplantation of Porcine Organs Into Man," Vol. 19, No. 5 (May 1998): 355-65; Frederick A. Murphy, "The Public Health Risk of Animal Organ and Tissue Transplantation Into Humans," *Science*, Vol. 273 1996): 746-7; Jennifer Brown, et al., "Xenotransplantation and the Risk of Retroviral Zoonosis," *Trends in Microbiology*, Vol. 6, No. 10 (October 1998): 411-14.

4. M.M. Swindle, "Defining appropriate health status and management programs for specific-pathogen-free swine for xenotransplantation," *Ann NY Acad Sci*, Vol. 862 (December 1998): 111-20.

5. See Dominic Borie, et al., "Microbiological Hazards Related to Xenotransplantation of Porcine Organs into Man," *Infection Control and Hospital Epidemiology*, Vol. 19, No. 5 (May 1998): 355-65, for an extensive description of porcine viruses, bacteria, parasites, fungi that could be transferred to humans via xenotransplantation.

6. See footnotes 16 and 17 in H. Vanderpool, *BMJ*, 13 November 1999.

7. Jonathan P. Stoye, et al., "Endogenous Retroviruses: A Potential Problem for Xenotransplantation," *Annals of the New York Academy of Sciences*, Vol. 862 (1998): 73.

8. K. Paradis, et al., "Search for Cross-Species Transmission of Porcine Endogenous Retrovirus in Patients Treated With Living Pig Tissue," *Science*, Vol. 285 (20 August 1999): 1236-41.

9. Jonathan P. Stoye, et al., "Endogenous Retroviruses: A Potential Problem for Xenotransplantation," *Annals of the New York Academy of Sciences*, Vol. 862 (1998): 68.

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