Dissent From Within

Why does Dr. Fritz Bach want a moratorium on clinical trials for xenotransplantation, and why should the public listen to him?

When a leading transplant surgeon and xenotransplantation researcher publicly speaks out against the direction of his own field, where he stakes his career, you know that there is serious issue at hand.

For the past eight years, Dr. Fritz Bach, a professor of surgery at Harvard Medical School, has argued for a long-term moratorium on all clinical trials involving xenotransplantation (i.e. transfer of animal tissue into humans) until the public fully understand its risks and benefits\(^1,2,3\). Dr. Bach began his campaign to inform the public about the risks of xenotransplantation in 1996, after two independent research groups documented the transmission risk of animal retroviruses infecting human cells from the procedure\(^4,5\). Even though the Food and Drug Administration (FDA) responded by halting all clinical trials on xenotransplantation, it lifted the freeze a year later after enacting stringent regulations for monitoring of transplant patients\(^3\). However, Dr. Bach believes that the FDA’s actions were inadequate because they did not properly address

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the societal risks of xenotransplantation nor did they sufficiently inform the public about the procedure’s risks and benefits. He believes that the ethical, religious, and safety dilemmas of xenotransplantation need to be resolved in the eyes of the public before any more patients receive this form of therapy. Additionally, Dr. Bach sees a more “generic problem” at hand with the way that researchers and corporations disclose risk. The public unknowingly bears the burden for technological developments when they are implemented without an analysis of their downside.¹² For example, the pesticide DDT was widely used in the United States, until activists documented its harmful effect on human health and the environment⁶. Even though the risks from xenotransplantation seem small at the present, Dr. Bach wants its risks publicly acknowledged and discussed in a manner that sets a precedent for handling of future technologies.

For many years, the risks of xenotransplantation were not visible to the public. The earliest human recipients of animal organs lived for only days or hours after the procedure. From the first attempted baboon kidney transplant in 1964, until the 1980s, animal transplantations have not been an option for most organ-failure patients because the procedure was both rarely performed and unsuccessful. This is because at the time, researchers did not know enough about the human immune system to prevent rejection of animal organs in the human body⁷. Nonetheless, in the early 1990s breakthroughs in immunosuppressant drugs allowed researchers to propose new organ transplantation trials involving liver and kidney tissue from pigs, rather than apes. Researchers determined that the genetic resemblance of primates to humans

makes them a poor donor of organs. The resulting molecular similarity of primate
cells to those of humans leads the human immune system to attack them
because they resemble infected human cells, leading to whole organ rejection.
Successful pig-organ transplantation will require the use of immunosuppressant
drugs to hide the foreign tissue from the human immune system. Pig cells have
also shown promise for treatment of more than organ failure: pig skin is under
study for use in treating burn victims, while swine neural cells are used in a cure
for Parkinson's disease.\textsuperscript{7,8} As the technical issues limiting xenotransplantation
are overcome it is only a matter of time before the procedure becomes
commonplace. Dr. Bach believes that the procedure’s safety and ethical issues
should be addressed before this happens.

Immunosuppressed xenotransplantation patients are a potential haven for the
incubation of trans-species diseases. Research studies \textit{in vitro} show that porcine
endogenous retroviruses (PERVs) can infect human cells after genetic
recombination with human pathogens\textsuperscript{4,5,8}. Even though, xenotransplantation-
destined pigs will be raised in a sterile environment to prevent contamination by
external pathogens, nothing can currently be done about the endogenous
retroviruses present in the pig genome\textsuperscript{7}. Endogenous retroviruses are viral DNA
sequences present in the genome of every organism. While human endogenous
retroviruses are harmless towards our own species, recombination of other
species’ endogenous retroviruses with active viral DNA is responsible for most of
the major flu outbreaks in the last century, as well as for HIV/AIDS, Mad Cow

\textsuperscript{7} Kuby, Janis. Immunology. (WH Freeman, 2003)
\textsuperscript{8} Nicolle, Lindsey E. Xenotransplantation: an animal future? (Canadian Medical Association Journal, 1999
Nov 16;161(10):1291)
Disease (i.e. Bovine Spongiform Encephalopathy) and Creutzfeldt-Jakob disease. In fact, both the Spanish flu outbreak during 1918-1919, which killed over 50 million, and the more recent Asian Bird Flu were traced back to mutations of PERVs. So why hasn’t the risk of a PERV-related disease outbreak prevented researchers from continuing xenotransplantation research, especially when major diseases and flu outbreaks can traced back to endogenous animal retroviruses?

As mentioned previously, the FDA halted clinical trial on xenotransplantation in 1996, after disclosure of the PERV-related risk. At the time, oversight of all clinical trials was done by local institutional review boards, but the FDA has since created a federal xenotransplantation advisory committee to screen all animal-transplantation proposals. In order to combat the risk of PERV-related infections, it was evident to the FDA that long-term (possibly lifelong) monitoring of xenotransplantation patients and their family was required; yet, this created two large problems. First, no easy diagnostic test existed for monitoring PERV transmission, and second, the FDA had never considered requiring this level of consent from a patient or their family. With typical medical procedures, a patient gives informed consent allowing their doctor to perform the procedure, but the patient can choose to withdraw at anytime. In the case of a xenotransplantation, the FDA decided that patients must consent to a lifetime of testing before undergoing the procedure. While Dr. Bach agrees with FDA’s assessment of risk in this case, as well as the need for patient monitoring, he disputes the decision-making process that led to the ruling. “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 Bach. In his writings and in interviews he argues that the FDA should do more than “solicit public comment” on its guidelines for xenotransplantation, but rather commission informed public debates\textsuperscript{1-3}. Previously, expert committees in the FDA as well the US Public Health Service (PHS) failed to prevent the emergence of mad cow disease and the contamination of the US blood supply from HIV-infected donors\textsuperscript{3}. With all their other responsibilities, the FDA and the PHS can only respond to public health threats, not prevent them. Their fallibility is known and it is foolish for the public to rely blindly on them for their health and safety.

Another reason for Bach’s advocacy for increased public oversight of xenotransplantation is the recent rise of commercial interest in the field. Peter Lain, a biotechnology analyst at Société Générale Strausse Turnbull, predicts that a $6 billion to $10 billion a year market will emerge for xenotransplantation by 2010\textsuperscript{3}; not only because of the shortage in available human donor organs such as hearts, kidneys, lungs and livers, but also out of a need for skin and neural cell transplants. There are opportunities for companies to do everything from manufacturing immunosuppressant drugs, to raising transgenic pigs for organ harvesting. Leading the foray into this research is Novartis, a Swiss biotech-giant that has previously embroiled itself in scandals over the toxicity of their genetically modified food products, as well a funding scandal with the Department of Plant and Microbial Biology at Berkeley\textsuperscript{9}. Public input on the FDA oversight of these companies is needed to ensure that safety is not sacrificed as

\textsuperscript{9} Washburn, Jennifer. “The Kept University. (The Atlantic Monthly, 2000 March, p40)
companies seek profits from the commercialization of their research. Xenotransplantation should not undergo clinical trials or be commercialized before the technology is ready.

It is important to involve the general public in the debate over xenotransplantation so that the review boards at the FDA hear a balanced selection of testimony. Currently, passionate patient groups, surgeons, and corporate executives are the dominant lobbyists to federal government health agencies. Jonathan Allan, a virologist at the Foundation for Biomedical Research in San Antonio, and a member of the FDA advisory subcommittee on xenotransplantation, admits that “it is hard to stop” the progression of clinical trials “and put public health first” with all these groups urging for clinical trials. The challenge of solving xenotransplantation’s technical issues is so engaging that peer-reviewers believe greater public involvement would be a distraction to the research. However, the traditional FDA regulatory approval process is not designed to review medical therapies that pose a danger to the general public. Amidst the excitement and the enthusiasm over animal-transplants, the public must ultimately scrutinize them for its own safety.

Dr. Bach admits that the American public accepts dangers from modern technology that are worse than those presented by xenotransplantation. Genetically modified crops were introduced into American food supply without the proper assurances about their safety. While the proper safety precautions may have been taken to prevent unnecessary allergic reactions from their consumption, consumers don’t know about them because they were not involved
in the scrutiny of their development. The public has been burned from the toxic side effects of products such as pesticides, lead paint and asbestos, and Bach simply wants biotechnology to avoid the previous follies of technological revolution. There is a lack of public knowledge about the potential dangers from the biotechnology, which creates fear and suspicion of a field that truly wants to help humanity.

Bach is a wise man in his field. Rather than a risk a backlash against xenotransplantation down the road, he wants the public to accept its risk before the procedure goes mainstream. The leaders of other industries and disciplines should aspire to his level of confidence with the public and seek their approval rather than sidestep their oversight. There’s something for everyone to gain.