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US guidelines on xenotransplantation

As *Nature Medicine* went to press, the US Department of Health and Human Services was poised to release new guidelines concerning the use of non-human primate xenografts in humans. A copy made available to the journal describes what is in effect a temporary halt to the use of non-human primate tissues for medical intervention. Although this move will not please many researchers in academia and industry, it is sensible from the point of view of both safety and ethics.

There are those in the transplantation community who argue that successful xenografts, whether from primates or non-primates, are for the foreseeable future unlikely to be commonplace, because of the formidable immunological barriers yet to be overcome. Although it is true that the two dozen or so animal-to-human organ xenografts attempted over the last 30–40 years have all failed, the pace of discovery is increasing so much that the prospect of such medical interventions can no longer be ignored. The most successful transplants have used organs from chimpanzees, a species that is unlikely to ever be accepted as a donor because of the emotional ties associated with using an animal so phylogenetically close to humans and whose numbers are so limited. However, it was established many years ago that organs from more distant primates, such as baboons, can be shielded from hyperacute rejection. Whereas the more gradual innate rejection seen in such procedures is still a principal problem, recent advances towards a better mechanistic understanding of the nature of this rejection, and the development of transgenic techniques that may soon allow the engineering of donor animals with a much-reduced incompatibility, suggests that successful xenografts are no longer simply a good idea. Indeed, if the very substantial investments that chief pharmaceutical companies and smaller biotechnology companies are making into xenograft research and technology are anything to go by, it may be closer to reality than we think.

Many countries are moving towards regulating the practice and, as recently reported (*Nature Med.* 5, 361; 1999), some have taken steps to prohibit the practice, pending a better and more-open understanding of the societal risks that may be involved. Canada in particular should be applauded for preparing to launch a very thorough and well-funded public consultation exercise to assess the community's response to the prospect of xenotransplantation. Several other countries, including Britain and The Nertherlands, have already put xenotransplantation on hold pending further research into the risk of cross-species infection—an area in which precious few facts are available.

The US is often looked on as a leader in biomedical research, and as such it carries a higher-than-average responsibility to advance cautiously, balancing the needs of the patient community with those of society. The shortage of human solid organs is severe. It is estimated that up to half of those with end-stage organ failure, for whom transplantation is their only hope, die on the waiting list. At the same time, although it is at present impossible to quantify, there is general agreement that the transfer of animal organs and tissues into people carries a risk of transferring both known and unknown viruses and viral sequences. Because of the unpredictable behavior of viruses when they cross species barriers and their ability to emerge as more virulent and pathogenic, this risk cannot be ignored. It is for these reasons that the guidelines, to be released under the auspices of the Food and Drug Administration (FDA), are a welcome, albeit late, development.

The guidelines, which are directed at those who may seek FDA approval for proposed human trials, build on a series of public workshops sponsored by the US Public Health Service (which includes the FDA, the National Institutes of Health, the Centers for Disease Control and Prevention, and the Health Resources and Services Administration). Although the new guidelines are restricted to procedures involving non-human primates, they represent an 'about-turn' for the agency, which in January 1998, during the last of the workshops, resisted a call for a moratorium on human xenografting.

The guidelines, which provide only a very brief assessment of the scientific and ethical questions surrounding xenotransplantation, conclude that "the use of nonhuman primate xenografts in humans raises substantial public health safety concerns," and that "the public at large, would be exposed to significant infectious disease risk". They therefore rule that "clinical protocols proposing the use of nonhuman primate xenografts should not be submitted to the FDA," given that agency is of the opinion that "there is not sufficient information to assess the risks posed by nonhuman primate xenotransplantation".

The agency must now decide how it will handle applications for human trials using organs and tissues from non-primates. Indeed, it is the use of transgenic pigs as a source of organs that is from a scientific perspective the most promising and is receiving the lion's share of the research attention. Although the agency is said to be committed to examining the issues surrounding the potential use of non-primate tissues, and presenting its findings in a set of revised guidelines, it has given no indication of when these guidelines can be expected. Those experts who worked hard to lobby the agency with regard to primate tissues must now shift their attention to this next phase. Only with a similar pause for thorough reflection will the public, including patients, be guaranteed a thoughtful and informed decision on what is already a pressing concern.