Alternative interpretations of the same data: flaws in the process of consulting the Canadian public about xenotransplantation issues

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Xenotransplantation is the transplantation of living cells, tissues or organs from one species to another.[1,2] Until recently, hyperacute rejection posed an absolute barrier to xenotransplantation, but this has been greatly diminished by advances in genetic engineering. Although other immunological[3] and physiological[4] hurdles still exist, pig-to-human xenotransplantation may soon be feasible. While there are concerns that xenotransplantation could promote the transmission of animal infections to humans,[5] the use of specific pathogen–free donor pigs should prevent the transmission of known zoonoses. However, there is a small, but not entirely negligible, risk from other agents.[6]

In 1996, Health Canada began formal consideration of potential regulatory frameworks for xenotransplantation clinical trials. A multidisciplinary Xenotransplant Expert Working Group (XEWG) was formed to consider ethical issues (both human and animal), safety, logistical questions, and so on, to propose a regulatory framework and to construct standard operating procedures that would minimize the pain and suffering for animal donors, provide maximal protection of recipients, health care workers and the public, and promote successful xenotransplantation.[7] However, because of the complex ethical, health, social, legal and economic issues associated with xenotransplantation, the XEWG recommended public involvement in the decision regarding whether to proceed. As a xenotransplantation researcher and as a XEWG member, I supported the recommendation.

In 2000, Health Canada provided funding to the Canadian Public Health Association (CPHA), with which it formed an arm's-length Public Advisory Group to perform the public consultation and report to the federal minister of health. The Public Advisory Group was asked to educate and then consult the public using the following question: "Should Canada proceed with xenotransplantation and if so, under what conditions?" After over a year of public consultations, the CPHA released its final report containing 7 recommendations.[8] The primary recommendation suggests banning xenotransplantation clinical trials for now. In this commentary, I examine the consultation process, the interpretation of the results and the validity of the recommendations.

The CPHA's search for public opinion began with a general-population telephone survey of 1519 Canadians. Among respondents, 65% favoured proceeding with xenotransplantation, 24% said "no" and 11% had no response; however, 70% of respondents stated that they were not knowledgeable about xenotransplantation. Then, to obtain information from "stakeholders" (i.e., "organizations that cover a broad range of interests such as animal welfare, faith, cultural, human rights, industry, legal, health and safety, consumer, organ recipient, scientific, medical, seniors, youth, hospitals, governments, universities and colleges"), 3700 surveys were mailed; 5.8% were returned. Among the respondents, 39% voted "yes"; 58%, "no"; and 3% had no response to the key question. The survey was also posted on an informative Web site; 367 Web site surveys were completed (26% yes, 69% no, 5% no response).

The final instrument was a series of 6 regional citizen forums. At each forum, panellists selected to be representative of their region and Public Advisory Group members checked into a hotel on a Friday night and viewed David Suzuki's television program about xenotransplantation, "Spare Parts." On the Saturday, a transplant recipient and 5 "experts," each representing one of the following areas: transplantation, infectious disease, law, ethics and animal welfare, gave 10-minute presentations covering their topic in a manner suitable for the layperson, and then answered questions for several hours. (If the Halifax experience is representative, the vast majority of the questions were directed to either the transplantation or the infectious disease experts.) On Sunday, the lay panellists met, discussed and rendered their final votes. Final votes were categorized as follows: "no" (i.e., never), "qualified no" (i.e., not yet) and "qualified yes" (i.e., if carefully regulated and overseen).

In an attempt to identify trends, voting occurred daily throughout the consultations (see the Table on the *CMAJ* Web site for details). The executive summary noted the following trend: "At the start of the forums, positions of panelists were similar to those surveyed by telephone. As panelists became better informed, … there was a dramatic shift towards not proceeding".[8]

There are several fatal flaws in this study. First of all, the question that the public was asked is too vague. It ignores the fact that there are several broad categories of xenotransplantation that probably have vastly different levels of associated

public health and personal risk. Although I would personally agree with the panellists that it is premature to proceed with vascularized whole-organ xenotransplantation clinical trials, few people should see harm in transplanting encapsulated cells derived from a cell line that has been genetically engineered to secrete synthetic opiates into the cerebrospinal fluid of patients with terminal cancer who have intractable pain.[9,10] Ex-vivo perfusion of transgenic pig livers in patients with terminal liver failure (and no available liver donor), transplantation of fetal porcine dopaminergic cells into patients with Parkinson's disease and transplantation of encapsulated porcine pancreatic islets into patients with diabetes are other therapies worthy of consideration for clinical trials now.

A more serious problem is the variability of the data (see Table on the *CMAJ* Web site). In 3 forums (Saskatoon, Toronto and Yellowknife), at least 60% of the panellists voted to permit xenotransplantation to proceed. In fact, if you delete the results of only one forum (i.e., Vancouver), which had only a 12.5% "yes" rate, the remainder of "informed" Canadians (52%) favoured proceeding. Why was there such variability from region to region? Are these genuine regional differences? After reviewing the list of experts who made presentations to each citizen forum,[8] I suspect that the main source of regional variability may have been the experts.

As experts, we were given few instructions on what to present and our backgrounds were quite varied. In 3 forums, either the transplantation expert or the infectious disease expert were members of the XEWG (i.e., Saskatoon, Halifax and Toronto); 57% of these panellists voted "yes." In the other 3 forums, neither the transplantation expert nor the infectious disease expert had a background in either xenotransplantation research or regulation; only 36% of the panellists at these 3 forums voted "yes." Clearly, the presence of someone conversant in all of the thorny issues related to xenotransplantation would tend to facilitate discussion and engender confidence. Having specific knowledge of proposed methods of regulation might tend to help allay fears for some individuals, or possibly confirm them for others. Is it not likely that panellists who were exposed to these experts would be better prepared to make informed decisions than panellists who were exposed to experts who may have prepared for their presentation and questioning by reading a review article? In stark contrast to the conclusions of the Public Advisory Group, my analysis suggests that better informed panellists favoured proceeding.

Unfortunately, the report does not describe precisely how the transplantation and infectious disease experts were selected. I was approached 3 weeks before the Halifax forum, having been recommended by a transplant surgeon who had refused to take part. At the Halifax forum, one of the organizers asked participants if they could suggest the name of an infectious disease expert who might take part in the Vancouver forum on the following weekend: How much time could that individual have had to prepare? Clearly, to have obtained optimal results, each forum should have had access to the same information. This marked variability makes the results highly suspect and interpretation problematic.

As for the survey data presented earlier, the Public Advisory Group interprets these as also supporting their hypothesis that more knowledgeable respondents favour banning xenotransplantation clinical trials. Once again, I disagree. A very low response rate to the mailed survey and a likely bias of Web site respondents (see Table 21[8]) render these results meaningless.

The CPHA report offers 7 recommendations of which several are simple statements of obvious truths about encouraging organ donation, disease prevention and healthy lifestyles (ignoring many potential recipients with conditions that are not a result of lifestyle). They also recommend that preclinical xenotransplantation research should continue; however, it seems unlikely that funding would flourish in a country in which its clinical application had been banned for the foreseeable future.

Personally I find the fifth recommendation bothersome, "that stringent … regulations be developed to cover all aspects of xenotransplantation clinical trials," because this regulatory framework already exists.[7] Why did the Public Advisory Group not summarize the *Proposed Canadian Standard* in layperson terms and then present this? Would it not have helped the panellists with their difficult deliberations to know that the government had formed a committee of multidisciplinary experts in 1996 who developed proposed standards to be implemented if xenotransplantation trials were ever to proceed, and that these guidelines had been revised and updated multiple times to reflect the input of numerous and diverse external reviewers? Considering that 35% of the "no" votes were qualified (i.e., not yet) and that one of the major concerns expressed by the public concerned the development of appropriate regulations, how can the results of this expensive exercise be valid when this key information was withheld? Surely the whole object of the exercise was to educate the panellists before asking them to vote?

Even under the best of circumstances, the distinction between a "qualified yes" and "not yet" is probably ill-defined and very much dependent upon the dynamics unique to each forum. By ignoring this, the Public Advisory Group has missed what I believe to be the only valid conclusion fully supported by the data. Panellists were provided (albeit unevenly) with our best available information on potential risks, benefits, alternatives and other potential implications (i.e., legal, societal and ethical) of xenotransplantation. In this context, 34.9% of panellists voted "never" and 65.1% voted for either a "qualified yes" or a "qualified no" (see Table on the *CMAJ* Web site). This suggests that two-thirds of informed Canadians support xenotransplantation as a potential future clinical modality, if its safety and efficacy can be demonstrated. Unfortunately, public consultation cannot provide any insight into this question. Ultimately, the only way to determine whether xenotransplantation is safe and efficacious is to allow small, well-regulated clinical trials involving types of

xenotransplantation that are perceived to have minimal risk. These should occur when warranted by preclinical data, and not by public opinion. Without the ability to perform even limited trials, little information can be obtained.

As a member of the XEWG, I support the concept of public consultation pertaining to xenotransplantation. Public consultation is an important mechanism of prioritizing and rationalizing health services in the context of limited funding.[11,12] It is also potentially a valid way to determine society's reactions to emerging technologies. Therefore, it is appropriate that the public help decide whether xenotransplantation is potentially an appropriate future health care technology. However, a major principle defining useful public consultation is that the "consultees must have sufficient information to make meaningful comment."[13] Because it is not possible in one weekend to provide lay people with more than superficial knowledge about the science of xenotransplantation, the decisions of "when" and "under what circumstances" xenotransplantation clinical trials should be allowed to go forward cannot be decided by public consultation.

I do not pretend to be an expert in methods of evaluating public opinion; however, I am a scientist and I recognize inconclusive and poorly interpreted data when I see it. In this context, I believe that the Public Advisory Group is bold and self-serving to offer its last recommendation, "that the citizen forum model be strongly considered for future consultations on complex and not widely understood policy issues." Until the methodology used in this current consultation has been fully analyzed and corrected, another experiment like this is both unwarranted and dangerous.

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References

1. Daar AS. Animal-to-human organ transplants — a solution or a new problem? *Bull World Health Organ* 1999;77:54-61.
2. Appel JZ III, Alwayn IP, Cooper DK. Xenotransplantation: the challenge to current psychosocial attitudes. *Prog Transplant* 2000;10:217-25.
3. Soin B, Vial CM, Friend PJ. Xenotransplantation. *Br J Surg* 2000;87:138-48.
4. Hammer C, Thein E. Determining significant physiologic incompatibilities. *Graft* 2001;4:108-10.
5. Michaels MG. Infectious concerns of cross-species transplantation: xenozoonoses. *World J Surg* 1997;21:968-74.
6. Patience C. Determining and preventing the potential PERV problem. *Graft* 2001;4:133-4.
7. Health Canada. Proposed Canadian standard for xenotransplantation. Ottawa: Health Canada; 1999. Available: www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/btox/standards/xeno_std_e.html (accessed 2002 June 2).
8. Animal-to-human transplantation: Should Canada proceed? A public consultation on xenotransplantation. Ottawa: Canadian Public Health Association; 2001. Available: www.xeno.cpha.ca/english/finalrep/page1.htm (accessed 2002 June 2).
9. Abicht A, Lochmuller H. Technology evaluation: CRIB (CNTF delivery) CytoTherapeutics Inc. *Curr Opin Mol Ther* 1999;1:645-50.
10. Hentall ID, Sagen J. The alleviation of pain by cell transplantation. *Prog Brain Res* 2000;127:535-50.
11. Bowie C, Richardson A, Sykes W. Consulting the public about health service priorities. *BMJ* 1995;311:1155-8.
12. Khan U. Public consultation. Up and ATAM (aims, timing, audience,

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The xenotransplantation question: public consultation is an important part of the answer

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In his commentary in this issue (page 40),[1] James Wright disagrees with the central conclusion of the recent Canadian Public Health Association (CPHA) report on its public consultation on xenotransplantation. Whereas we have some sympathy with some of the concerns he raises, both he and the CPHA are missing the point. They see the public consultation as a voting exercise, the result of which can be used to determine policy. And that is wrong.

The CPHA report summarized the findings of a "comprehensive consultation with Canadians on the complex issue of xenotransplantation" through citizen forums.[2] Delivered to the federal minister of health, the report made 7 recommendations. It was the principal recommendation "That Canada not proceed with xenotransplantation involving humans at this time …" that bothered Wright the most.

Wright takes issue with the consultation process, arguing that on the whole it was poorly designed. And he raises some important concerns. For example, the central question that was repeatedly asked of the lay participants "Should Canada proceed with xenotransplantation and if so, under what conditions?" was indeed vague and difficult to answer simply. The great variation in responses from the different lay panels is also cause for concern, and the suit-