REPORT OF THE

NATIONAL FORUM ON XENOTRANSPLANTATION
CLINICAL, ETHICAL AND REGULATORY ISSUES

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TABLE OF CONTENTS

PREFACE

Health Canada's Therapeutic Products Programme (TPP) is cooperating with provincial/territorial Ministries of Health to develop strategies for improving the availability, safety and equitable distribution of organs and tissues for transplantation. As a key element of this strategy, TPP sponsored a National Consensus Conference on Safety of Organs and Tissues for Transplantation in 1995. Following this conference, an Expert Working Group was established and safety standards for organs and tissues for transplantation as well as for subsets such as solid organs and tissues were developed in 1997. A process has now begun to recognize these as National Standards of Canada.

The Expert Working Group has recommended the creation of a specific subset committee to develop a xenotransplantation standard. It was also recognized that there are other issues concerning xenotransplantation which need to be addressed, including the clinical, ethical and social aspects of this technology. Consultation with stakeholders, including the public, is essential for all of these issues.

I am pleased to forward to you the report of the National Forum on Xenotransplantation - Clinical, Ethical and Regulatory Issues. The forum was sponsored by the Therapeutic Products Programme and held in Ottawa, from November 6-8, 1997. This conference, with attendance by experts and stakeholders, represents another step in our consultation process addressing the safety of organs and tissues for transplantation and the development of a risk management framework for compliance and oversight. The scientific knowledge and technologies of xenotransplantation are advancing rapidly: accordingly, this Report reflects information current at the time this Forum was held. The workshop synopses, forum summaries and recommendations in this Report are not consensus positions and do not necessarily represent the views of Health Canada. They represent the forum objectives, which are to present information, identify key regulatory issues, define areas where research and new information is required, and initiate discussion on the risks, benefits and ethics of xenotransplantation.

I wish to acknowledge the contribution of the co-chairs, Drs. Margaret Sommerville and Michael Gross, the expert advisors and the organizing committee for their efforts in planning this forum. Also acknowledged are the efforts of workshop chairs and rapporteurs, special guest speakers and all invited participants from across Canada.

Dann Michols
Director General
Therapeutic Products Programme

FORUM PURPOSE

To present information and initiate discussion on the risks, benefits and ethics of xenotransplantation; to identify key regulatory issues; and to define areas where research and new information is required.

FORUM OBJECTIVES

- To present information and promote discussion on the risks and benefits of xenotransplantation.
- To identify areas where information on xenotransplantation is lacking and research is needed.
- To examine the ethical and scientific issues raised by xenotransplantation, including:
    a) the use and source of animals and their potential genetic modification
    b) transmission of known and unknown pathogens to patients and the community
- To consider ethical and societal issues in the regulation of xenotransplantation, including:
    a) principles and practice guidelines for clinical trials
    b) a risk management/regulatory framework that coordinates the establishment of standards, oversight and surveillance methods
    c) responsibilities of federal agencies, health care providers, industry and the community in addressing research, clinical and policy issues
- To solicit comments and make recommendations concerning:
    a) a draft standard for xenotransplantation
    b) a national registry for patients of xenotransplantation
    c) establishment of a national ethics committee
    d) international harmonization

SUMMARY OF KEY ISSUES AND RECOMMENDATIONS

1. Public Consultation

A highly significant issue, conveyed by the extent of interest and comment during the Forum, is the need for the education of and discussion with the Canadian public. Particular topics that warrant public consultation relate to the potential risks of xenotransplantation to the population versus the perceived benefits to the patient; and the ethics of the use of animals for xenotransplantation. The public must be involved in all stages of discussion on these issues and have their perspectives incorporated into decision-making.

2. Use and Care of Animals for Xenotransplantation

- **Ethics:** The use of animals for food or in medical research does not automatically justify their use for xenotransplantation. Whether animals should be used as sources of donor organs and tissues for humans, should be publicly reviewed. Animals should only be considered if suitable alternative therapies are not available. The number of animals utilized in xenotransplantation should be minimized by (i) coordinating surgeries to ensure simultaneous harvesting of as many organs or tissues as possible from each animal in a single operation; (ii) creating an international registry of transgenic strains to eliminate the duplication of establishing founder strains in several locations; and (iii) improving the equity and availability of donor tissues and organs from human cadaver donors.

- **Animal sources:** Tissues and organs from nonhuman primates are more immunologically compatible with humans. However, the higher overall risk of infection from infectious agents transmitted from primates, would most likely preclude their use as donors for xenotransplantation. In addition there are other ethical concerns and practical issues that may make nonhuman primates unsuitable as donors. Therefore, pigs will likely provide the most acceptable source of organs, tissues and cells

- **Standard of Care**: Current animal care standards for research should be reviewed and expanded upon to ensure a high level of biosecurity for xenotransplantation source animals, taking into consideration the social and behavioural requirements for animals in this environment. Appropriate monitoring practices of transgenic and non-transgenic herds for disease and adverse effects should be established and optimized.

A National Animal Care Committee and a central registry should be established to address issues pertaining to the use and care of animals for xenotransplantation.

3. Regulatory and Advisory Bodies

It was strongly recommended that a National Advisory Board on Xenotransplantation be created. Such a board would consist of public representatives, patients, and experts in: infectious diseases (both human and animal), animal welfare, ethics, media and legal communities, and industry. The board mandate would be to advise regulatory bodies and Research Ethics Boards. The initiative to create a National Advisory Board on Xenotransplantation should come from Health Canada.

4. Preclinical Research

Preclinical research in Canada should be strongly encouraged. Additional research is needed to answer critical scientific questions about immunological barriers and infectious disease risks in xenotransplantation. Ideally, research models should include non-human primates as recipients.

As part of the risk assessment process, surveillance results from clinical trials held outside Canada should be summarized and made available for stakeholders, including the public. Other sources of information on infectious disease risks include surveillance of individuals with previous occupational exposure to animals and recipients of biological products produced from animal materials.

5. Immunological Risks

Although strategies are being developed to overcome acute rejection in non-related species, chronic rejection and the inherent biological incompatibility between species are limiting factors for the successful transplantation of whole organ porcine grafts into humans. Many other experimental approaches are being pursued with the goal of reducing the necessity for lifelong immunosuppression, thus enhancing the safety, efficacy and feasibility of xenotransplantation.

There are some applications that may present less immunological difficulties and may be more promising in the near future. These include the implantation of encapsulated tissues (such as pancreatic islet cells) or the implantation of cells into immunologically protected sites (such as fetal pig neurons into the brains of Parkinson's Disease patients). In cases where a patient exhibits temporary but life-threatening liver failure, it may be possible to cleanse the blood by temporarily circulating it through an isolated animal liver.

Forum participants endorsed the need for increased research to reduce the immunologic barriers and related risks of xenotransplantation.

6. Xenozoonosis

Additional research is greatly needed to address the risks of zoonotic infection transmitted by the transplantation of animal cells, tissues or organs into humans (i.e. xenozoonosis). This research is needed to: (i) develop and validate tests for identifying xenozoonotic agents; (ii) increase our knowledge of the pathobiology of retroviruses and prions; and (iii) discern whether concomitant practices in xenotransplantation (such as immunosuppression of the recipient or genetic modification of the donor animal) might inadvertently enhance the potential for xenozoonotic transmission.

It was noted that information available to date, on short term and limited clinical trials, had not demonstrated the transmission of xenozoonotic diseases. Thus, it was considered acceptable to proceed with limited, well designed clinical trials under controlled circumstances.

7. Clinical Trials

Participants felt that the many unanswered questions regarding both immunological and infectious disease risks should be addressed in preclinical trials before proceeding with clinical trials. It was also recognized that carefully controlled clinical trials would be the best strategy for advancing the development of successful xenotransplantation practices. Clinical trials should be governed by the regulatory authority of Health Canada and should be subject to ethical review by the proposed National Advisory Board as well as by the local Research Ethics Board.

It was suggested xenotransplantation clinical protocols should be integrated into existing programs and facilities. The cost/benefit analysis and clinical introduction of these new technologies should be consistent with the evaluation for the introduction of other new biotechnologies or medical procedures.

8. Patient Ethics

Unlike human-to-human transplantation, there will likely be a need for patient consent to include lifelong xenozoonosis surveillance.

Current legal and ethical frameworks for obtaining patient informed consent are appropriate for clinical trials involving xenotransplantation, with the following caveats:

a National Advisory Board should supplement the mandates of the local Research Ethics Board

there is a need for participatory consent from third parties to the patient (i.e. close contacts)

there are potential limits on patient autonomy and privacy to facilitate surveillance and

monitoring for infection

for initial trials, potential recipients should be evaluated based on likelihood for compliance with surveillance; and

there should be a requirement for all xenotransplant recipients to have autopsies upon death.

Oversight committees that would look at each case and the requirements for counselling of the potential transplant recipient and close contacts, should be considered in the process of obtaining informed consent.

9. Standards and Regulation

A standards-based regulatory approach is recommended by the participants as the best method for regulating xenotransplantation. A standards-based regulatory approach for xenotransplantation means that in addition to the usual regulatory process invoking the Food and Drugs Act, standards would provide supplemental information on the acceptable protocols and practices under which xenotransplantation would be conducted. This would enhance the ability to update protocols and procedures in a flexible and timely manner. Standards could be referenced in the Food and Drug Regulations, and therefore would carry more legal authority than the issuing of guidelines.

The essential elements of the standards to be developed should be arrived at by a process involving key stakeholders, including the public.

Relationships and legal authorities that could be applied to the oversight of xenotransplantation, must be clarified. This would include the advice offered by the proposed National Advisory Board on Xenotransplantation and the proposed National Animal Care Committee. Other potential mechanisms which may be useful in the oversight of xenotransplantation include the accreditation of institutions, animal care facilities and professional staff.

10. Surveillance (Registries and Sample Banks)

Lifetime monitoring of xenotransplant recipients and their close contacts is highly desirable. Consequently, at least for initial clinical trials, participants should be selected based on the likelihood that they and their close contacts will comply with surveillance measures.

Duplicate specimens should be obtained and archived at two different locations, one that is national and another that is local.

National registries should be established to address surveillance issues for individual and public safety; scrutinize xenotransplantation protocols in order to verify compliance and efficacy; to indicate areas for future research; and to compare various xenotransplantation protocols.

Critical components of databases for epidemiological investigation (patterns of adverse events) should include well-defined data elements to:

enable linkage of national registries to corporate and international xenotransplantation registries;

facilitate free exchange of information among key stakeholders while protecting the confidentiality of individual patients and investigators; and

provide the means by which non-confidential generic information for patient and public education could be easily derived and automatically updated.

11. International Harmonization

Canada should actively contribute to the development of international regulatory approaches, standards, research, registries (animal and human), and policies for xenotransplantation, especially those concerned with animal welfare, feasibility, xenozoonosis, surveillance and monitoring issues.

The issue of “transplant tourism,” where nationals of one country may seek a xenotransplant in another country, is recognized as an international concern.

I-1. XENOTRANSPLANTATION: ETHICS AT THE HUMAN/ANIMAL/GENE/MACHINE INTERFACE

Dr. Margaret Somerville,
McGill Centre for Medicine Ethics & Law
Montreal, Quebec

Abstract

Xenotransplantation raises profound ethical issues, which means that ethical concerns and analysis must be embedded in the research and development of this technology. These issues are not ones that can be addressed adequately just by scientists, physicians, ethicists or ethics committees. They require public debate by an informed public. Indeed, it is an ethical requirement that the public be fully involved in the development of Canadian public policy on xenotransplantation.

We must first ask whether xenotransplantation is intrinsically acceptable, that is, is it inherently right or wrong? This raises ethical questions in two areas: First, the ethics of the use of animals as a source of organs for human transplantation, in particular, our treatment of these animals in order to make them suitable as organ donors and the ethics of modifying the genome of animals to include human genes. Second, are the risks of xenotransplantation, especially possible unknown risks, of such a nature and seriousness that we ought not to run them? The major risk usually considered in this context is that of the transfer of an animal virus across the species barrier to humans with potentially tragic results, not simply for the person who received the organ, but for other people, including possibly the community at large who could subsequently be infected by this virus. This means that we must balance, not only harms, risks and benefits to potential individual xenotransplant recipients, but also harms to them in not having access to these transplants and risks to the community in allowing them, in deciding whether xenotransplantation is intrinsically acceptable.

If we decide that, in principle, xenotransplantation is ethically acceptable, we must then examine the ethical issues raised by research, development and use of this technology, in particular, the ethics of human subject research; the ethics of the allocation of scarce health care resources, including opportunity costs in both research and health care; and the ethics of access to xenotransplantation.

Finally, and at the broadest and deepest level, we need to consider the impact that the advent of xenotransplantation technology will have on our societal paradigm, that collection of attitudes, values, myths, beliefs, symbols - the "shared story"- that we buy into in order to form society and which we use to give meaning to our individual and collective lives. For instance, does this take us yet one more step away from an integrated theory of personal identity - seeing ourselves as unique, indivisible human beings - and further along the line of a modular theory of human identity - that we are simply a series of interchangeable parts, and these parts can now include animal parts - and a "gene machine" view of human life? Or could the "miracle" that this technology makes possible deepen our sense of awe and wonder about ourselves, our world, and life in general?

I-2. SCOPE OF XENOTRANSPLANTATION

Dr. Calvin Stiller
Professor of Medicine
University of Western Ontario
London, Ontario

Abstract

Xenotransplantation has been a dream of both scientists and practitioners to solve the problem of organ availability in order to save human lives. The biological and social hurdles have not been overcome, but plausible strategies are now available with the imminent application in humans of the first clinical trials. A combination of vision and pragmatism is required in order to meet the growing human need without ignoring the serious down sides that might occur. A review of the opportunities and obstacles, with a description of benchmarks to be achieved will be presented.

I-3. OVERVIEW OF THE NEED FOR XENOTRANSPLANTATION IN CANADA

Dr. Gary Levy
Director, Multi-Organ Transplants
Toronto Hospital, Toronto, Ontario

Abstract

Transplantation is now recognized as the most effective treatment for patients with end stage organ failure. The short term results of transplantation using allografts from humans are excellent with one year patient and graft survival rates approaching 80-90% and five year

survival rates of 70-80%.

However, the success of transplantation has brought with it the problem of obtaining an adequate supply of human organs. As the indication for transplantation continues to grow, the shortage of organ donors has emerged as the major barrier to transplantation. Currently, greater than 52,000 people are waiting for organ transplantation in the United States and over 2,800 people are waiting in Canada. In 1996, in Canada, 1551 transplants were performed and thus, there is a severe discrepancy between the number of candidate recipients and number of donors available for transplantation at the present time.

Furthermore, the overall number of solid organ transplants has declined steadily, at a rate of 1% per year between 1988 and 1994. Thus, nearly 4% of kidney patients awaiting transplantation will die, whereas the mortality among prospective heart or liver graft recipients is approximately 8% and 11% respectively. Additionally, those patients who are waiting a replacement renal allograft can anticipate a median wait time of greater than 2 years, whereas patients awaiting replacement of liver allograft now wait 6 months to one year.

Although a number of attempts have been made to improve organ donation rates, it is clear that allotransplantation will never solve the problem of donor shortage. Thus, a solution to the shortage of human organ donors is the development of xenotransplantation, the transplantation of organs from animal species into humans.

I-4. REPORT OF THE EXPERT WORKING GROUP ON XENOTRANSPLANTATION STANDARDS

Dr. Michael Gross,
Chair for Xenotransplantation Expert Working Group
Queen Elizabeth II Hospital, Halifax, Nova Scotia

Abstract

A uniquely Canadian initiative brought together all interested parties; governments, federal and provincial, patients, surgeons and other interested parties, to address the issue of transplantation of organs and tissues.

The National Consensus Conference on the Safety of Organs and Tissues for Transplantation was sponsored by Health Canada, Therapeutic Products Programme in 1995. An expert working group was established and the standards for the transplantation and tissues were developed in 1997 and will become incorporated as national standards for Canada.

A Xenotransplantation Expert Working Group was struck to explore the potential of

drafting guidelines in a similar manner for xenotransplantation. It rapidly became apparent to the members of the group that the issues surrounding xenotransplantation are broad, not well focussed and open to much debate. As such, the committee felt that all of the issues needed to be explored in a forum that allows for free exchange of information, free debate, open exploration of ethical concerns and an attempt to inform the public of these issues.

This xenotransplantation forum should be seen as an opportunity for experts, interested parties and the public to explore these many issues, address this safety, the potential benefits and disadvantages and the way that new technology should be monitored and applied, the ethics of human and animal interactions and co-dependencies.

There are no hidden agendas. We have very rough drafts of guidelines that are not meant to restrict or influence this debate. The role of the Xenotransplantation Expert Working Group is to listen, to advise, to take notes and to produce recommendations based upon your input in this meeting. We will endeavour to communicate all recommendations back to participants and the general public at large.

Our goal is to set in process a program that will maintain Canada's pre-eminent role in the care of its citizens, while exercising due diligence to protect those who are more dependent on us.

PLENARY SESSION II – INTERNATIONAL PERSPECTIVES PANEL ABSTRACTS

II-1. THE U.S. APPROACH TO XENOTRANSPLANTATION

Dr. Amy Patterson
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Abstract

A fundamental public health dilemma in xenotransplantation is how to balance the potential clinical promise with the problem of potential transmission of infectious agents to both individual patients and to the population at large. Within the U.S. Department of Health and Human Services, the Public Health Service (PHS) agencies, including the National Institutes of Health (NIH), Centres for Disease Control and Prevention (CDC), the Health Resources and Services Administration (HRSA) and the Food and Drug Administration (FDA), are working together to address the public health issues raised by xenotransplantation.

Lessons learned in human allotransplantation, gene therapy and human cell and tissue therapy are being applied in the development of public health policy in xenotransplantation; these will be briefly discussed during the presentation. The draft PHS Guideline on Infectious Disease Issues in Xenotransplantation, published in September 1996, is a visible public statement of current U.S. PHS perspectives. The draft Guideline foreshadowed additional tools, currently under development, to address public health issues raised by xenotransplantation.

Other components of what may be viewed as a matrix of public health tools will be presented and include: Department of Health and Human Services Committee on Xenotransplantation, a Pilot National Xenotransplantation Registry Database, biologic specimen archive(s), regulatory oversight, and possibly a national xenotransplantation advisory body and other continuing venues for public discussion and public accountability in xenotransplantation.

II-2 THE U.K. APPROACH TO XENOTRANSPLANTATION

Dr. Lucy Thomas
Director of Regulatory Affairs
Novartis/Imutran
Cambridge, England

Abstract

The UK Government commenced work on xenotransplantation when it established the Advisory Group on the Ethics of Xenotransplantation, under the Chairmanship of Professor Ian Kennedy. Their report, Animal Tissue into Humans, was published in January 1997. Its main recommendations were that xenotransplantation could be acceptable provided that certain criteria were met and that there should be some national committee to oversee developments.

However, the main conclusion was that key pre-conditions of safety and efficacy had not yet been demonstrated and that it was not therefore appropriate to allow xenotransplantation in human, nor is it appropriate to use primates as organ donors.

In response to this report, the Government established the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) to regulate the development and implementation of xenotransplantation, as they believed that existing legislation on medicines and medical devices was not adequate to cover all xenotransplant therapies.

Proposals for xenotransplantation may be submitted to the UKXIRA, which will advise on whether they are acceptable. Proposals must also be considered by Research Ethics Committees and comply with other relevant legislation on genetically modified organisms and the use of animals in scientific procedures.

II-3. THE NEED FOR INTERNATIONAL HARMONIZATION

Dr. Clara Witt
World Health Organization
Geneva, Switzerland

Abstract

Research and development in xenotransplantation technology is occurring at a very rapid rate. If its implementation becomes a reality, it may serve to alleviate the chronic shortfall in human organ donations. Also, its potential for application as a treatment modality for diseases with no other effective therapeutic intervention, such as for Parkinson's disease, or for which xenotransplantation could offer additional therapeutic approaches, such as Diabetes mellitus, is being investigated. Xenotransplantation also carries with it a risk for the transmission of animal-origin infectious agents - xenozoonoses. The potential of xenozoonotic infections and disease is not solely a community or national issue.

In today's shrinking world, it is an international issue. While the development of the technology is occurring in the developed world, its usage, if proven possible, will occur over a wide geographic distribution. Therefore, the development of effective and realistic national approaches to xenozoonotic disease prevention and control requires international coordination and cooperation, and it requires the input from a variety of social, cultural and religious perspectives. The WHO believes that the harmonization of national approaches to addressing the issues surrounding xenozoonotic disease prevention and control can contribute to the safe and effective implementation of this new and exciting technology internationally.

II-4. REVIEW OF INTERNATIONAL POLICIES ON CONSENT AND HUMAN CLINICAL TRIALS FOR XENOTRANSPLANTATION

Professor Bartha Maria Knoppers
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University of Montréal
Montréal, Québec

Abstract

A comparative international review of official policy statements on xenotransplantation will reveal both common and different positions on: ethical concerns, safety issues, patient perspectives and personal and social effects. Even guidelines that do not purport to cover ethical, legal and social issues offer information on possible directions. The reports of the: Biotechnology Unit of the OECD 1996 Institute of Medicine, Washington, 1996 Nuffield Council on Bioethics,

U.K., 1996 and the Advisory Group on the Ethics of Xenotransplantation, U.K. 1997, will serve as the basis for this comparison.

II-5. CANADIAN REGULATORY APPROACH TO TRANSPLANTATION

Dr. Keith Bailey
Director, Bureau of Biologics and Radiopharmaceuticals
Therapeutic Products Programme
Ottawa, Ontario

Abstract

Transplantation science has developed rapidly during the past several years. To keep pace with rapid change in this field, an appropriate regulatory approach to issues of safety, efficacy, quality and supply is essential. As a commitment to promoting safety, Health Canada organized a National Consensus Conference on Safety of Organs and Tissues for Transplantation in October 1995. There has been a continuous consultation process since that time. An Expert Working Group developed a draft Canadian General Standard (CGS) on Safety which was widely distributed for public comment in September 1996. Subsequent activities of organ/tissue specific expert sub-groups have led to proposed tissue- and organ-specific standards, using the CGS as a template. Xenotransplantation has been included among the subset standards being developed.

The regulatory framework environment to be developed is standards-based, designed to be responsive to future requirements in many emerging areas including somatic cell, gene, blood and transplantation therapy. The pillars of this new approach are consensus building, transparency, staged and consistent stakeholder involvement, flexibility and rapid regulatory response. It is proposed that standards will be accredited as National Standards of Canada and referenced in Regulations. Continuous input and feedback from client and stakeholder groups is an integral part of the Therapeutic Products Programme's refreshed approach to regulation.

PLENARY SESSION III: SCIENTIFIC, MEDICAL AND ETHICAL ISSUES ABSTRACTS

III-1. RISK OF ZOONOSES

Dr. Lorne Babiuk
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Saskatoon, Saskatchewan

Abstract

Viruses have evolved various methods of interacting with their hosts, ranging from acute infections to persistence. These persistent infections are often difficult to detect and therefore can serve as a source of infection to naive individuals. Furthermore, since viruses are so adaptable, evolutionary pressures can alter the host range of viruses resulting in new emerging diseases. Thus, what was not normally a zoonotic virus may rapidly adapt to replicate in a new host, especially if the host is immunosuppressed.

Thus, the risk of assisting virus evolution and emergence of new diseases may be enhanced in such individuals. These factors must all be taken into consideration in xenotransplantation. Examples of accidental and natural transmission of viruses to humans will be described.

III-2. PORCINE ENDOGENOUS RETROVIRUSES (PERVS)

Dr. Robin Weiss
Institute of Cancer Research
London, England

Abstract

Certain C-type retroviruses released from pig cells can replicate in human cells in culture. We have characterized two distinct porcine retrovirus isolates with human cell tropism. While most of their genome sequences are highly similar they possess distinct gp70 sequences in the *env* gene. Retroviral vectors constructed with the porcine *env* genes indicate that the two viruses recognize distinct receptors on human cells.

Using our specific probes, each retrovirus is found to be endogenous with numerous genomes in porcine DNA of diverse breeds, showing some polymorphism. This means that it will be difficult to eradicate them. These retroviruses are sensitive to inactivation by human

complement when released from pig cells but become resistant upon passage in human cells. Complement sensitivity of enveloped viruses occurs by the same mechanism as hyperacute rejection of xenografts.

References:

1. Patience, C., Takeuchi, Y. and Weiss, R. A. (1997). Infection of human cells by an endogenous retrovirus of pigs. Nature Medicine, 3; 282-286.

2. LeTissier, P., Stoye, J. P., Takeuchi, Y., Patience, C. and Weiss, R. A. (1997). Nature, 389; 681-682.

III-3. IMMUNOLOGICAL HURDLES TO XENOTRANSPLANTATION

Dr. Fritz H. Bach
Harvard Medical School
Boston, Massachusetts

Abstract

Transplantation of a pig organ into a human (xenotransplantation) leads to additional forms of rejection as compared with those that we have been dealing with in allotransplantation (transplantation of an organ from one human to another) . The pig organ evokes an inflammatory response in a primate recipient (non-human primates are used as a pre-clinical model for transplantation to humans) that leads to hyperacute rejection (HAR) of the organ in just minutes to one or two hours. Even when we overcome HAR, the xenograft is rejected by a process called delayed xenograft rejection (DXR), which is an inflammatory response involving changes in the endothelial cells (EC) lining the blood vessels of the pig organ. Lastly, we expect that if both HAR and DXR can be overcome, we shall see a reaction quite similar to the T lymphocyte mediated rejection of an allograft.

HAR has been overcome by inhibiting either one of the two factors in the recipient that together precipitate HAR. The primary approach that has been taken is to inhibit recipient complement, which if not inhibited acts on the EC of the organ graft and leads to rejection. Since the molecules in the pig EC that inhibit pig complement do not function to inhibit human complement (a molecular incompatibility), my colleague Dr. Gus Dalmasso and I showed that if one expresses the human inhibitors of complement on the pig EC surface, one can prevent the action of the human complement on those cells. As such, several companies have now produced "transgenic pigs" (pigs that express a human gene) expressing the human inhibitor of complement. The organs from these pigs when given to primates that are immunosuppressed, are not rejected hyperacutely.

With regard to DXR, less progress has been made. However, promising approaches are

being developed that may contribute therapeutically to overcome DXR. These potential therapeutic approaches in part involve further genetic engineering of the EC. These include expressing certain molecules such as thrombomodulin and ATPDase (CD39) on the EC to help prevent thrombosis (platelet aggregation and pro-coagulation) and also expressing genes within the EC that prevent EC activation, which if allowed to occur will lead to an inflammatory response that will in turn lead to rejection. Rendering the EC (the first-encountered or most prone cell type of the pig xenograft) resistant to immune and pro-inflammatory processes may be a key element in the survival of the xenograft. This approach focuses on the importance of the defense or resistance of the xenograft rather than the type or level of immune attack.

It is also likely that immunosuppressive agents can be found that will help overcome DXR. One must be very careful however, not to have the immunosuppressive therapy be toxic to the patient, as is very likely the case with immunosuppressive therapies tested to date. Genetic engineering has the likely advantage of suppressing a given rejection factor locally in the organ and thus being less toxic than an immunosuppressive agent given orally or by vein.

The T lymphocyte response that is the cause of rejection of an allografted organ, and which is the target of most immunosuppressive agents currently being used, will almost certainly occur in some form in xenograft rejection. There is controversy whether the immunosuppressive agents that we currently have will suffice to suppress the xenograft rejection response.

A likely reason why the xenograft rejection response is so strong is the existence of other molecular incompatibilities in which the molecules associated with EC and others do not adequately function on the human system. The reactions are intended in part to avoid the very factors that seem to cause xenograft rejection. As such, some of the major regulatory systems that prevent pro-coagulation and thus blood clotting do not function across this species barrier.

More work needs to be done regarding the inflammatory responses, and understanding the physiological significance of molecular incompatibilities at the human blood / pig EC barrier.

I believe that there is good reason to be optimistic that we shall reach the point of clinical trials of organ xenotransplantation. Yet, I do not think we are ready to have such trials. The findings often presented about weeks of survival of a transgenic pig heart that expresses a human inhibitor of complement in immunosuppressed, non-human primates, while quite dramatic, must be tempered by several facts. First, in order to achieve such survival, very heavy immunosuppression has been used; levels that may not be applicable in humans. Second, these findings have been with heterotopically placed hearts (hearts transplanted in a position in the body where they do not have to work to pump blood and keep the recipient alive). When transplanted orthotopically and asked to do work the survival is not nearly as impressive. Third, the results of various of these studies have not been published, making evaluation of them very difficult.

Nonetheless, I find the progress that has been made in the last few years in both our understanding and in devising of therapeutic approaches very encouraging. It is just that it seems to me that we have additional problems that need solution before clinical activity is begun.

III-4. ETHICAL USE OF ANIMALS FOR MEDICAL TREATMENT

Dr. Gilly Griffin
Canadian Council on Animal Care
Ottawa, Ontario

Abstract

The Canadian Council on Animal Care (CCAC) is the national agency responsible for the oversight of the care and use of animals used for research, teaching and testing in Canada. The keystone of the oversight afforded by the CCAC rests at the local Animal Care Committee (ACC) level. These ACCs are established at each institution which uses experimental animals, according to Terms of Reference laid down by the CCAC and are responsible for providing ethical review of any proposed animal-based study.

ACCs are asked to adhere to the CCAC guidelines on: animal use protocol review in making their ethical judgements. ACCs must attempt to reconcile public demands for medical, scientific and economic progress with demands for reduction in animal use, pain and suffering. The cost in terms of animal welfare and integrity must be measured against the expectation of a proportional contribution to the understanding of fundamental biological principles, or to the improvement of human or animal health or welfare.

ACCs are also responsible for ensuring that animals receive proper housing, husbandry and veterinary care and that any procedures are carried out by qualified personnel according to Standard Operating Procedures or best practices.

PLENARY SESSION IV -- CLINICAL TRIALS AND SURVEILLANCE ABSTRACTS

IV-1. CLINICAL TRIALS IN XENOTRANSPLANTATION

Dr. Daniel Salomon
Director of Transplantation Research
Scripps Research Institute
La Jolla, California

Abstract

Clinical trials in xenotransplantation are already underway. The best examples are fetal pig neural cell transplantation to patients with severe Parkinson's disease and the extracorporeal perfusion of pig hepatocytes to rescue patients with acute liver failure. Thus, the need for regulatory bodies to establish working guidelines for clinical trials is based on a very real and present challenge. That process requires a clear idea of the problems this new field must overcome for clinical trials to be successful.

One of the first questions will be what donor species should be used for a given clinical trial. Therefore, I will describe some of the options such as heart, kidney and liver transplantation in the context of donor selection, specifically pig vs. non-human primate. How and based on what kind of parameters, will we decide when a given set of experiments based in the laboratory warrants the initiation of a clinical trial? Three general issues must be considered:

1) Who is in the best position to evaluate or validate this process: the investigator, a company, the local institutional review boards, the local animal use committees or a more central authority of experts at the federal level?

2) How will we integrate concerns over patient-centered efforts with possible public health implications? In other words, a patient at high risk of dying will have a very different view of risks in xenotransplantation than the public.

3) What is an appropriate expectation for success to justify a clinical trial and how do clinical trial designs and scope impact on issues of informed consent, potential conflicts of interest and safe advancement of the field?

Once we decide to go forward with conduct of a clinical trial, how do we insure the best management of resources, the safety and the efficacy? What are the responsibilities of the various participants: investigator, physician colleagues, vested biotechnology companies, large

pharmaceutical industry backers, local institutional reviewers, federal regulatory bodies as well as patients and patient families? Should we have central registry, how closely should this be tracked, what should be done if a problem is identified and in a practical world, who should pay for this work?

In the final analysis, the tremendous potential of xenotransplantation must be respected and all our efforts designed to facilitate this development. Thus, any guidelines or regulations established must be considered in the context of protecting and enhancing the conduct of clinical trials, necessary to bring xenotransplantation into practice. That goal will require a delicate balance protecting the interests of the patients and the public while remaining flexible enough to permit the innovation absolutely required for success in a new endeavour.

IV-2. PATIENT REGISTRIES IN DISEASE SURVEILLANCE

Dr. Maura Ricketts
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Health Canada
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Abstract

Surveillance systems for the detection of pathogens resulting from xenotransplantation must be designed for their purpose: the detection of novel infectious disease or the detection of novel infections in the recipients of xenotransplants. To do this, they must be capable of detection of previously unrecognized pathogens, capable of rapid detection, reporting and response, and they must monitor populations of people over long time periods.

Such a system will need to be networked to other surveillance systems, be public health oriented, have secure long-term funding and be able to accurately follow every recipient over the long term. Participation of clinicians, patients, biotechnology companies and health care provider organizations in such surveillance must be compulsory until xenotransplantation can be demonstrated to be safe from novel infectious disease for both the individual recipients and the general public.

IV-3. PROPOSED METHODS FOR PATIENT SURVEILLANCE

Dr. Khazal Paradis
Clinical Research
Novartis Pharma Limited
Basel, Switzerland

Abstract

One of the major safety concerns that has been raised regarding xenotransplantation is the potential for transmission of zoonoses from the donor animal. The risk to the patient could be considered to be part of the general individual risk of undergoing a transplant, along with the risks of over immunosuppression, a non-functioning graft and the potential of lymphoma for example. The concern is primarily one of public health, if a zoonotic infection were to establish itself in the recipient and if that could be transmitted to the contacts of the xenograft recipient.

Close monitoring of the recipient for life is therefore probably necessary, until such time as the inherent risks of the procedure are better known. Pre-transplant counselling will be essential. Contacts of the recipient, defined as being at risk of contact with the recipient's bodily fluids should probably have baseline samples archived, as well as samples drawn whenever a mucosal barrier is broken.

Prior to entering any xenotransplant trials, Novartis is conducting a study looking at the potential for transmission of the porcine endogenous retrovirus (PoERV) in patients who have been in intimate contact with porcine tissue (islet cell transplants, extracorporeal liver or hepatocyte perfusion, skin grafts, extracorporeal splenic perfusion etc). The PoERV agent may not be the only potentially infectious agent involved and monitoring will be required for the detection of new, previously undetected agents. Novartis proposes to establish a system for patient surveillance composed of 3 parts:

1) database of information on organ donor animals including health status and test results,

2) a registry to follow all patients containing safety relevant information, contact numbers, inventory of samples and test results, intimate contacts and health care personnel, which will be linked to the donor; and finally,

3) an archiving facility for all retention samples from donor animals and patients. This system would be at the disposition of health authorities in each country, act as a tool for analysis of xenotransplant results and assure a common, worldwide standard of health surveillance for all patients included in Novartis trials.

IV-4. US PHS NATIONAL XENOTRANSPLANTATION REGISTRY DATABASE PILOT STUDY

Ms. Tina Moulton
Division of Cellular and Gene Therapy
Office of Therapeutics Research and Review
Centre for Biologics Evaluation and Research, US PHS
Bethesda, Maryland

Abstract

The US-PHS National Xenotransplantation Registry Database is a proposed national data collection system that will systematically collect data from all clinical centres conducting clinical trials in xenotransplantation and all biomedical animal facilities supplying animals/xenografts for clinical use.

A pilot study to test and implement this database has been initiated (fall 1997). The most immediate purpose for this registry database will be to provide the means for rapid recognition, accurate assessment and appropriate response for identification of any infectious agents or other adverse clinical events that are associated with xenotransplantation and which may have public health consequences.

If adverse transplant-associated events are identified in recipients of xenografts, a national registry database could be used to:

(1) identify and notify other patients that have received similar xenografts;

(2) identify close contacts of the recipients;

(3) locate stored serum or tissues from patient and individual source animal for laboratory testing;

(4) link patients by cause of death as indicated on death certificates and

(5) locate source animal and herd health records. Data quality and the use of an internationally recognized medical terminology and controlled vocabulary will be used to facilitate any future international collaborations, the sharing of data or possible linkages to other databases.

IV-5. PORCINE FETAL NEURAL CELLS FOR TREATMENT OF PARKINSON'S AND HUNTINGTON'S DISEASE

E. Michael Egan
Senior Vice President, Corporate Development
Diacrin, Incorporated

Abstract

Over two years ago Diacrin, Inc. initiated clinical trials using porcine fetal ventral mesencephalon cells for treatment of Parkinson's disease. As part of this phase 1 clinical trial, 12 patients were transplanted. Safety and preliminary efficacy data are being generated. In addition, 12 patients have been entered into a phase 1 program using porcine fetal lateral ganglionic eminence cells for the treatment of Huntington's disease. These trials will be discussed along with the qualification of the cells for transplantation . This effort includes the screening of animals for porcine infectious diseases which would be of concern.

Once screened, the animals are maintained in a Biomedical Animal Facility (BAF) to maintain their health status, additional viral screens are conducted during this period. After artificial insemination, intact uteruses are harvested from donor pregnant pigs at specific gestational ages. Fetuses are collected and cells isolated under GMP conditions. Cells are implanted using standard stereotactic techniques. Extensive follow-up testing is done on final product as well as on the patient samples, including the testing for porcine endogenous retrovirus (PERV) in peripheral blood monocyte cells (PBMC). Samples of patient PBMCs, up to two years post transplantation, which were tested for PERV have been shown to be negative.

WORKSHOP REPORTS

WORKSHOP A-1: IMMUNOLOGY

Chair Dr. Uri Galili
Department of Microbiology and Immunology
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Rapporteur Dr. Bhagirath Singh
Department of Microbiology and Immunology
University of Western Ontario
London, Ontario

WORKSHOP QUESTIONS:

1. SOURCE MATERIAL:

What cells, tissues or organs offer the best prospects for immunological success (i.e. transgenic/non-transgenic isolated or encapsulated cells, solid organs, bone marrow, etc.)?

2. IMMUNE SUPPRESSION AND MODULATION (consider organs and cells separately):

Which immune modulation strategies are most effective? What risks are associated with them? For what type of xenotransplantation would they be most appropriate?

What are the limits of acceptable immunosuppression? Which types of xenotransplants would require the least immunosuppression?

How should recipients of short-term bridging xenotransplants be treated once the xenograft is removed?

Could tolerance to the xenograft be induced?

Could vaccines be developed to prevent xenozoonotic infection or disease? (See also Xenozoonoses workshop.)

3. ANIMALS:

What animal models are most appropriate for xenotransplantation into humans? If an appropriate model exists, should it be a requirement for pre-clinical studies?

What evidence from pre-clinical studies should there be before limited human trials can proceed? *(See also Clinical Trials workshop.)*

WORKSHOP DISCUSSIONS

PREAMBLE

Initial discussion in this Workshop focused on mechanisms of acute rejection, particularly those involving the carbohydrate α-galactosyl (Gal) epitopes that are present on endothelial cells lining the vascular system of whole organ xenografts. Although many antigens are able to stimulate an immune response in xenografts, in discordant xenografts, for example those from pigs to humans, the endothelial cells are almost immediately destroyed by naturally occurring anti-Gal antibodies that circulate in high concentration in human blood. This process is mediated by complement and is essentially irreversible once initiated.

Humans and other old world primates are unique from other mammals in that they lack the terminal Gal carbohydrate on their cells. Conversely, humans have developed "naturally occurring" anti-Gal antibodies in response to the presence of the Gal antigen on bacteria in their gut. The anti-Gal antibodies represent about 1% of total circulating immunoglobulin G in humans, and since a single endothelial cell may express high levels of Gal antigens, the potential for immune interaction is difficult to eliminate.

Nonetheless, a number of strategies to overcome Gal/anti-Gal mediated acute rejection are being pursued. These include removal or neutralization of anti-Gal antibodies prior to transplant, induction of tolerance to the Gal epitopes, and elimination of Gal on the xenograft cells by genetic manipulation. Modifications of various pig proteins needed for complement-mediated tissue destruction are also being investigated. However, most approaches to resolving the immunological incompatibilities are still at preliminary stages of development.

1. SOURCE MATERIAL -- *What cells, tissues or organs offer the best prospects for immunological success?*

There was agreement that transplantation of solid, vascularized organs is still premature and requires significant preclinical research before clinical trials proceed. But the extracorporeal perfusion of solid organs as short term bridges to transplant is more promising, eg. ex-vivo liver perfusion for patients with organ failure, perhaps in conjunction with immunoadsorbent filtration

to remove specific antibodies and/or the use of a semi-permeable membrane to separate xenogeneic tissues from the patient's blood. Acute rejection may also be addressed by using transgenic animals which are engineered to reduce activation of human complement.

Other potential source materials include encapsulated pancreatic islet cells for diabetic patients and neural cell implants. In fact, limited clinical trials with porcine neural implants are already underway in the United States for patients with Parkinson's disease. Both of these source materials are somewhat protected from the patient's immune system -- islet cells by nature of the semi-permeable encapsulating material; and neural implants due to their location in the brain, a site afforded some degree of natural immunological protection.

Some participants claimed that well designed and controlled limited clinical trials were the best strategy for advancing the development of successful xenotransplantation practices. Others believed that outstanding issues regarding immunological and infectious disease risks (eg. retrovirus infection of human cells) were too numerous to sanction clinical trials at the present time. It was recommended that the risk assessment profile of each application be considered individually.

2. IMMUNE SUPPRESSION AND MODULATION (a) *Which immune modulation strategies are most effective? What risks are associated with them? For what type of xenotransplantation would they be most appropriate? (b) What are the limits of acceptable immunosuppression? Which types of xenotransplants would require the least immunosuppression? (c) How should recipients of short-term bridging xenotransplants be treated once the xenograft is removed? (d) Could tolerance to the xenograft be induced? Is this theoretically possible? (e) Could vaccines be developed to prevent xenozoonotic infection or disease?*

In light of the current knowledge base and very limited chance of long-term success, these questions were all viewed as premature for the transplantation of vascularized organs. Nonetheless, each was addressed briefly. (a, d) Induction of immunological tolerance appears to be a promising approach in experimental models but is still at a very preliminary stage of practical development. (b) Under most circumstances, and assuming that absolute tolerance has not been induced prior to grafting, regimens of immunosuppression now used for allografts should be adhered to. An exception for consideration would be the use of higher levels of immunosuppression for very short term treatments. (c) Once patients are disconnected from an extracorporeal xenograft, there is no reason to continue immunosuppressive therapy. Although high levels of antibody to xenograft antigens may develop during exposure to the graft, these antibodies are not expected to be problematic after graft removal. (e) Regarding vaccines, the first challenge is to identify the pathogens of interest. Once relevant infectious agents are identified then vaccines should certainly be developed. The vaccine strategy (eg. inactivated, subunit, DNA) would depend on the nature of the pathogen and the host immune response.

Participants agreed that further experimental studies are needed before clinical xenotransplantation trials involving solid organs are carried out. Participants also strongly supported the view that preclinical research should be conducted in Canada.

3. ANIMALS: *What animal models are most appropriate for xenotransplantation into humans? If an appropriate model exists, should it be a requirement for pre-clinical studies? What evidence from pre-clinical studies should there be before limited human trials can proceed?*

There was an understanding that pigs will likely provide the most acceptable source of organs and tissues, and there is a great deal of interest in engineering pigs to make them as safe and suitable as possible. Workshop participants thus limited their discussion to pig-sourced materials. Tissues and organs from primates would be far more immunologically compatible, but the risk of infection from primate viruses make this an undesirable source.

From a scientific perspective, the most appropriate animal model would be pig to primate (eg. baboon) transplants. But this would be very expensive, might not be practical, and would raise numerous ethical concerns. Some useful but limited information may be obtained from small animal models, in particular mice with genetic knockouts for Gal. But of course this would not involve the Gal/anti-Gal response, and other antigen - antibody responses would be different than in pig to human transplants. Ultimately, studies in primates will be required to simulate parameters of the human immune response.

RECOMMENDATIONS

- Transplantation of solid, vascularized organs is still premature and requires significant pre-clinical research before clinical trials proceed.

- Some participants claimed that well designed and controlled clinical trials were the best strategy for advancing the development of successful xenotransplantation practices. Others believed that outstanding issues regarding immunological and infectious disease risks (eg. retrovirus infection of human cells) were too numerous to sanction clinical trials at the present time. It was recommended that the risk assessment profile of each application be considered individually.

- Further experimental studies are needed before clinical xenotransplantation trials are carried out for solid organ, vascularized xenografts.

- Preclinical research should be conducted in Canada.

- Pigs will likely provide the most acceptable source of organs and tissues.

WORKSHOP A-2: XENOZOONOSES

Chair Dr. Louisa Chapman
Centers for Disease Control and Prevention
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Rapporteur Dr. Harvey Artsob
Head, Zoonotic Diseases
Laboratory Centre for Disease Control
Health Canada
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WORKSHOP QUESTIONS

1. REDUCING RISK:

Can we determine a graded risk scale for zoonoses based on different types of xenotransplants (i.e. cells, tissues, organs)?

Should some animal sources be excluded (particular animals, or particular tissues)?

Would short-term bridge transplants be significantly safer than long-term transplants?

Can the breeding, selection and screening of animals reduce infectious disease risks to acceptable levels?

Could vaccines be developed to prevent xenozoonotic infection or disease? (See also Immunology workshop.)

2. PREVENTING WORST-CASE SCENARIOS:

What science/research can be done to define and quantify the risks that (a) recombination of endogenous retroviruses may occur in xenotransplant recipients; and (b) if this occurs, such viruses may cause disease which may be transmissible to others?

3. PUBLIC HEALTH:

Which has the potential to be a greater risk to public health -- endogenous or exogenous viral zoonoses?

Why does xenotransplantation present any greater risk to public health than other animal-human contact (eg. farmers, slaughterhouse workers, butchers)?

At the present time, is it safe to proceed with limited clinical trials?

WORKSHOP DISCUSSIONS

Question 1: *Which infectious agents have the greatest potential to be a risk to the public health?*

The greatest risks are those infectious agents which are not known to exist in the donor species (because it does not produce overt disease), produce silent persistent infections in humans, are readily transmissible among humans, produce delayed onset of significant disease, and for which no curative therapy exists or is likely.

A good example of this would the family of retroviruses. The human immunodeficiency virus (HIV) is a retrovirus thought to have crossed the species barrier from monkeys or other nonhuman primates to humans sometime after the Second World War [1,2] and is now known to be the causative agent of AIDS. Not only is the infection innocuous (silent) but the virus ultimately destroys the immune system. A curative therapy for AIDS is unlikely since to date antiviral drugs suppress but do not eliminate viral infections. The retrovirus family shows a high genetic variation and this molecular adaptation quickly allows the agent to circumvent the recipient's immune defences and acquire resistance to clinically administered therapies. Hence, a key issue for the containment of retroviral infections is and remains prevention.

Relevant to this issue in xenotransplantation, in 1997 a research team lead by Dr. Weiss demonstrated that pig tissues harbour several expressed pig endogenous retroviruses (PERVs), that do not cause disease in pigs. It was also shown that these PERVs can productively infect human cells in laboratory experiments. It is not known whether PERVS can infect humans in real life, whether infected human could transmit PERVs among humans, or whether human infections would result in disease or be the source of a new AIDS-like epidemic. Clearly, this is a major concern for xenotransplantation. In addition, there may be other unrecognized agents harboured by donor species. For example, the prion mediated diseases have been transmitted across species lines and may be transmissible from animals to humans. Diagnostic assays for prions are not available, making these another concern.

Question 2. *Can the breeding, selection and screening of animals reduce infectious disease risks to acceptable levels?*

This question was divided into two parts. First, the breeding, selection and screening of animals can reduce the risk of xenozoonoses, particularly for agents that are transmitted horizontally and which are currently identifiable. However, it is more problematic for agents that are vertically transmitted (i.e. through the placental or incorporated into the genome) and/or presently unidentifiable.

Second, a key question is what is an acceptable risk? A risk of infection may be more acceptable for the near-death patient than for the population as a whole. In the latter case, a new epidemic might cause significant disease and death within the healthy population and this may be unacceptable. Thus, the problem emerges as to how to compromise between these two diametrically opposed viewpoints of infectious disease risks associated with xenotransplantation.

Question 3. *Should some animal sources be permanently excluded (i.e. a particular animal species, or particular tissues)?*

No animal source should be permanently excluded. Instead exclusion should not be by species affiliation but by associated disease risk. There should be minimal standards established for safety and all source animals of any species should meet these standards.

However, primates may exclude themselves because they are only one or two generations removed from the feral state and therefore carry more exogenous infectious agents than domesticated pigs; in addition, compared to pigs the breeding time is longer and offspring are fewer. For these reasons, it may be much more difficult to clean up the herd if primates were used rather than pigs. Finally, for ethical reasons or reasons having to do with perception of the appropriate use of animals, it may societally be less acceptable to use nonhuman primates than pigs (which are widely accepted in society for industrial uses) even if the infection risk can be equalized between the species.

Question 4. *Can we determine a graded risk scale for zoonoses based on different types of xenotransplants?*

The answer as to whether we can determine a graded risk was no. The answer as to whether or not there is a graded risk was maybe but information concerning risk factors and their impact on xenozoonosis are lacking. Research questions identified include: is risk reduced by sequestering of the xenograft (from the circulation) or the absence of vascular connections between the graft and the host? Is risk increased by an "increased tissue (viral) load", by the proliferation of xenograft cells (supporting viral replication), or by the use of immunosuppressive agents (decreased recipient resistance to infectious agents)? Finally, the question was poised, is

there a higher risk with bone marrow transplantation from a different species?

Question 5. *Would short term bridge transplants be significantly safer than long term transplants?*

No, but this is an interesting and important area for research.

Question 6. *Could vaccines be developed?*

Yes they can be developed but it is highly improbable that vaccines will solve problems with xenozoonoses for the following reasons. First, vaccine development requires the identity of the infectious agent where in fact, the major risk in xenotransplantation relates to unknown agents. Second, vaccines protect against disease occurrence but do not produce sterile immunity (i.e. the infection still occurs). Even vaccines supplemented with immune sera (which may hasten the removal of the invading agent), would not likely be more effective than vaccines used alone. Finally, attempts to develop a vaccine for common retroviruses (HIV) have been unsuccessful to date due to the complexities of developing lasting immunity against a virus that mutates as rapidly as HIV and other difficulties associated with the development of vaccines for RNA viruses.

Question 7. *Why does xenotransplantation present any greater risk to public health than other animal-human contact that occurs (i.e. farmers, slaughterhouse workers, butchers)?*

The current public health burden of infectious diseases that is sustained in human populations by animal-human contact is, in fact, very high (including salmonellosis, E. coli 0157 and other food borne diseases perhaps including prion-mediated diseases). However xenotransplantation poses a unique risk due to the routes of exposure that bypass the normal host defence mechanisms including intact barriers, associated immunosuppression (to prevent the rejection of foreign tissue) and the potential to result in new diseases not normally encountered in human populations.

It was suggested that animal handlers such as farmers, butchers, researchers and slaughterhouse workers, be tested for exposures to PERVs (by looking for antibodies and by PCR), and for other 'unknown' infectious agents which may be derived from animals.

Question 8. *How likely is it that*

a) recombination of (or active expressing infections with) endogenous retroviruses will occur in xenotransplant recipients?

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b) such viruses/infections would cause disease?

c) these viruses could be transmitted to other humans?

Most participants felt that some sort of viral infection will occur in xenotransplant recipients. It is not clear whether endogenous retroviruses such as pig retroviruses could recombine to create a new strain of retrovirus capable of infecting humans. There is also insufficient information to assess whether such infections will cause disease in humans and/or start a new epidemic. Presently, the information on short-term and limited clinical trials from outside of Canada, do not indicate that a new epidemic or even limited individual infections have occurred. However, the absence of evidence does not necessarily indicate absence of risk, especially when longer term follow-up is needed for confirmation.

Question 9. *Is it safe to proceed with limited clinical trials?*

The question was reformulated by the participants as follows: "Is it acceptable to proceed with limited clinical trials?"

No consensus was reached on the above. However, a consensus (with regulatory representation abstaining from the vote) was reached on the following points. There is no known evidence to date (in the limited studies performed so far) suggesting infectious disease transmission associated with xenotransplantation. Thus, the participants concluded it would be acceptable scientifically to proceed with limited clinical trials under certain circumstances following expert review and approval and with ongoing regulatory oversight and surveillance.

References:

1. Wain-Hobson S, Immunodeficiency viruses: 1959. Nature, 391: 531, 1998.
2. Zhu T et al. An African HIV-1 sequence from 1959 and the implications for the origin of the epidemic. Nature 391:594, 1998

SUMMARY AND RECOMMENDATIONS

The following concerns, issues or recommendations were derived from the participants discussion in the A2 Workshop on Xenozoonosis and/or from discussions on this topic during the National Forum on Xenotransplantation:

- We need to develop and validate diagnostic methods for the detection of PERVs, and other potential human pathogens (derived from animal sources), so that we can better assess the infectious disease risks of xenotransplantation.

- Regulators and the National Advisory Committee need to examine the screening results for infectious agents in past or on-going clinical trials of xenotransplantation which are occurring outside of Canada. Summaries of their conclusions should be made public as part of the public consultation process prior to deciding whether or not

xenotransplantation clinical trials will occur in Canada.

- We need to validate what are appropriate schedules for screening of recipient blood samples, and to establish sample banks and registries (including samples from close contacts of recipients) if limited trials in xenotransplantation were to occur in Canada.

- More attention should be placed on the research and development of strategies to reduce the inherent risk of xenozoonosis, including the establishment of pig herds where endogenous retroviruses have been inactivated by gene knock-out technology. There may be other approaches, such as the development of tolerance inducing schemes to replace the need for long-term immunosuppression therapy, the latter which may make the recipient more vunerable to infectious agents.

- We need to study the conditions underwhich endogenous retroviruses might be activated or recombine as may present in post-transplantation conditions. This could include radiation exposures (medical diagnostics) and the effects of various drugs commonly used in transplantation (immunosuppressive drugs, steroids etc.). Such investigations could include pre-clinical evaluations (i.e. pig to primates), on-going studies of human recipients as performed outside Canada, and in test-tube laboratory experiments.

- While genetic modification of donor animals appears to be necessary to prevent rejection of solid organs, it would be important to evaluate these changes in terms of the augmentation of infectious disease risks. (For example, does making the donor organ more biocompatible with human systems also increase the likelyhood that an infectious agent will cross the species barrier and cause disease in humans?).

- We need to look for evidence of xenozoonosis in animal handlers such as farmers and slaughterhouse workers by screening for PERVs, antibodies to PERVs, and using other appropriate tests yet to be developed.

WORKSHOP A-3: USE AND CARE OF ANIMALS

Chair: Dr. Donald Casebolt
Atlantic Veterinary College
University of Prince Edward Island
Charlottetown, Prince Edward Island

Rapporteur: Dr. Francine Lord
Canadian Food Inspection Agency
Agriculture Canada
Ottawa, Ontario

WORKSHOP QUESTIONS:

1. USE OF ANIMALS:

Does using animals for xenotransplantation differ from using them for medical research, or as a food source?

If xenotransplantation proceeds, how can the number of animals be minimized (including animals involved in development of transgenics)?

Is genetic modification of animals legitimate if it puts them at increased risk of disease? Is increased risk of disease likely to occur?

2. CARE OF ANIMALS:

What new considerations are introduced into animal care by transgenic and cloning technologies, as these may be applied to xeno-sourced animals?

What level of animal seclusion is needed to maintain a disease-free environment for potential donors? Is this compatible with current animal care standards?

3. REGULATIONS:

Who within Canada has the responsibility to regulate appropriate care and use of animals for xenotransplantation?

Should there be a National Animal Care Committee? Should public consultation be

incorporated?

Is there a need for internationally accepted regulations/standards?

Should there be an international registry of transgenic strains?

WORKSHOP DISCUSSIONS:

1. USE OF ANIMALS

Does using animals for xenotransplantation differ from using them for medical research, or as a food source?

The consensus was that the use of animals for xenotransplantation is different, and not automatically justified because they are currently used for food, research, or other activities. Animals should be used only if alternatives are not available. Alternatives include prevention of disease and maximizing the use of human organs.

A review of the ethics of using animals for xenotransplantation needs to be discussed and wide public consultation is necessary. This needs to be done with appropriate education of the public to make an informed decision.

If xenotransplantation proceeds, how can the number of animals be minimized (including animals involved in development of transgenics)?

The total number of animals produced and used would be difficult to control in a production scenario. However, one should strive to maximize the simultaneous harvesting of as many organs and tissues per animal as possible. The group was unanimous in that sequential surgical harvesting from a given animal should not be allowed on ethical grounds.

Thus, by regulatory influences and for economic reasons, the use of animals would be minimized. Eventually if efficiency of cloning were to be improved, cloning of transgenic animals might supersede the breeding of transgenic pairs where in some cases, only 25% of the offspring may have the trait in the homozygous state. Cloning might reduce the total number of animals bred and harvested, since 100% homozygous animals could be produced.

Is genetic modification of animals legitimate if it puts them at increased risk of disease? Is increased risk of disease likely to occur?

Genetic modification of animals has already been occurring for centuries through selection techniques and more recently by transgenics and cloning approaches. Although

breeding of animal strains is associated with increased risk of disease due to loss of heterozygosity, it is difficult to predict the level of risk of disease associated with selection for a given trait. Similar unknown risks occur with the production of transgenic animals. In order to address these risks, it is imperative that monitoring for adverse effects be optimized.

2. CARE OF ANIMALS

What new considerations are introduced into animal care by transgenic and cloning technologies, as these may be applied to xeno sourced animals?

While animal care standards should be identical for transgenic animals and nontransgenic animals, risk assessment and monitoring for animal welfare becomes very important for these animals destined to become xenograft donors. Alterations to the host defence system to make transgenic animals more compatible with the host defences of humans, may result in potential adverse effects such as decreased resistance to disease.

What level of animal seclusion is needed to maintain a disease-free environment for potential donors? Is this compatible with current animal care standards?

A high level of biosecurity for xenotransplantation source animals will be necessary to maintain pathogen-free herds. Current animal care standards for research are compatible with this level of biosecurity, but should be reviewed and will likely need to be expanded upon. The most important issue discussed was the social and behavioural requirements for animals raised in this environment.

3. REGULATIONS

Who within Canada has the responsibility to regulate appropriate care and use of animals for xenotransplantation?

The participants felt that Health Canada should be the regulatory body. As a model, the regulatory framework of the Food and Drugs Act should be discussed further. The Canadian Council on animal Care (CCAC) is not a regulatory agency, but is a voluntary compliance organization. However, there can be a link between Health Canada and CCAC to provide regulatory and compliance authority.

Should there be a National Animal Care Committee? Should public consultation be incorporated?

There was consensus that a National Committee was necessary and that public consultation should be incorporated. The justification for such a committee is that local animal

care committees may not have the range of expertise or authority to effectively address all of the complex issues involved in xenotransplantation, nor have the expertise to evaluate animal care concerns with xenozoonosis, biocompatibility or immunological compatibility.

Is there a need for internationally accepted regulations/standards?

There was a consensus that there is a requirement for international harmonization for animal care in xenotransplantation. International harmonization of regulations or standards regarding the import and export of animals, organs, cells or tissues is particularly important.

Should there be an international registry of transgenic strains?

Yes, because shared knowledge and accessibility of established transgenic strains may eliminate the duplication of work and reduce the number of animals used in establishing founder strains.

WORKSHOP A-4: PATIENT ETHICS

Chair: Dr. John Dossetor
Director, Bioethics Centre, University of Alberta
Edmonton, Alberta

Rapporteur: Mr. Michael Hudson
General Counsel, Canadian Blood Secretariat
Health Canada
Ottawa, Ontario

WORKSHOP QUESTIONS:

1. PATIENT CONSENT:

Given all the implications of xenotransplantation (i.e. scientific, ethical, public health), what constitutes a truly informed consent?

What is the minimum information that must be presented and understood for a patient to make an informed decision?

Should informed consent extend to a spouse or other close contacts?
Is lifetime surveillance acceptable or feasible?

Should various lifestyle restrictions be recommended in early trials, eg. regarding blood donation, unprotected sexual contact?

2. PATIENT SELECTION:

Should some patient groups be excluded from initial trials, for example because of age, sex, ability to comply?

Should there be minimum benefit criteria for the patient?

WORKSHOP DISCUSSIONS:

The Workshop's initial discussion focused on the ethical framework of the entire field of xenotransplantation, and then focused on the ethics of patient consent and patient selection. It was concluded that the questions provided are premature. Despite the fact that these questions seem fairly obvious - and that there was a desire to answer these questions - the workshop participants were uncomfortable in trying to answer them.

And that in itself is a message.

In trying to approach these ethical questions it was agreed that a clear pre-condition of an informed public - both before, during and on-going - is necessary. How this could be achieved was not determined. A Royal Commission style of cross country consensus gathering or debate is a costly but valid way of achieving this goal. There may also be other ways by which public opinion may be sounded and opinions aired. There was also absolute agreement that a societal debate is important which has not happened to any extent and is the number one prerequisite.

In the process of public debate it may also be determined that some forms of xenotransplantation activity is totally unacceptable. Any trials considered acceptable would be conducted as research and none should initially be considered as conventional clinical practice.

The existing informed consent models are valid, but there is a critical need for an adequate information. Some limitations exist due to the limited knowledge base at the present time.

Current legal and ethical frameworks for informed consent are also valid. Obviously information must be fairly placed before patients who are being asked to accept this risk. The consent requirements should reflect the research nature of the activities. The informed consent model for research, and not clinical practice, is preferred as it has a stricter level of disclosure. Additional elements to consider in the consent process include the possible impact on third persons, society at large and potential future limits on patient autonomy and privacy.

There is a need to ask for participatory consent from third parties to the patient, specifically those who are in intimate contact and in likelihood to exchange fluids or intimacies. Consideration should be given to limiting patient autonomy so that proper surveillance and monitoring could be done.

Hazards to patients's privacy and confidentiality, and the issue of information sharing should not be viewed as a single process problem to be solved. It will start well before and continue indefinitely into the future of individual patients, should it ever get to that point.

The use of special oversight committees that would look at each case and requirements for psychological counselling of the potential transplant recipient are additional safeguards surrounding informed consent should be considered.

In the deliberations it was also realized that patient risks varied with the kind of xenotransplantation considered. Risks to the solid organ patient may be greater than that for tissues or cellular transplants. There was also a very strong concern by some workshop representatives that commerce and science may be driving xenotransplantation, rather than patient need.

WORKSHOP B-1: SURVEILLANCE AND PATIENT REGISTRIES

Chair: Dr. Jay Fishman
Transplant Infectious Diseases, Massachusetts General Hospital
Boston, Massachusetts

Rapporteur: Dr. Cam Hobson
The Bruce Denniston Bone Marrow Society
British Columbia

WORKSHOP QUESTIONS:

1. REGISTRIES – ORGANIZATION AND ADMINISTRATION:

Should xenotransplantation registries be part of existing solid organ and/or tissue registries? Should they be operated by industry or government?

Is a central monitoring agency needed for xenotransplantation? If so, who should pay?

Should all public health agencies have open access to patient registries and patient records?

Should/could the xenotransplantation registry be linked internationally? Should/could the registry be used for other means?

How can adverse event reporting be brought into surveillance systems? What kind of access should companies have?

Who keeps the samples? How often is sampling and testing done? Who should be responsible for doing the testing?

2. PATIENT ISSUES:

Should close relatives and contacts be monitored? Is this feasible?

How anonymous and yet 'identifying' should registry data be?

How can we ensure lifetime surveillance?

WORKSHOP DISCUSSIONS

In order to address the questions provided, this workshop first established a set of principal assumptions for surveillance registries:

Added value: Surveillance (registries and sample banks) regulation must provide some added value. There must be some reason for it; otherwise we are being burdensome without benefit.

Appropriate: The less we ask of reporting corporations and individuals the more likely we are to achieve compliance. We should therefore not ask for things that we do not need

Regulation: Some degree of regulation is necessary because of the potential risk of infection in xenotransplantation -- even though we do not know the level/degree of that risk. It is not clear that the expertise required by programs, institutional review boards (IRBs) protocols, physicians and scientists exists - even by those that are now prepared to carry out xenotransplantation. Regulatory bodies are required to address the risks and the desire for appropriate levels of expertise and applied standards. The exact format and linkages of these bodies is open to discussion.

Defined goals: Well defined goals are essential for both regulations and registries to work.

Goals should be established before the registry is developed. These goals will reflect the concept/belief that the information required within the data base i.e. the data elements to be collected, should be determined by those who will have access to that particular database. For xenotransplantation, this group will primarily be public health authorities, but subgroups of data might be made available to research or corporate entities.

Goals: The principal goals of a xenotransplantation registry are really very simple:

to address surveillance responsibilities for individual and public safety

to scrutinize xenotransplantation protocols to verify compliance and efficacy, and

possibly to indicate areas for future research and for comparison of various xenotransplantation protocols.

Activities needed to achieve these goals will evolve over time and with experience: there is some analogy with allotransplant registries: over time we may require less information, i.e., we may be able to specify more important information, and they may therefore become less burdensome.

Some added benefits will also accrue, as the goals of a registry are not limited to detection of infection and adverse events. These complementary benefits include:

Regulatory interests: adverse event reporting (especially for xenozoonosis); monitor adherence to protocols; epidemiological monitoring (patterns of adverse events); source animal-related events; development of guidelines (rapid regulatory response); and outcomes.

Public interest will focus on assurance of the monitoring of patients; public information and education; consensus building; and mechanisms to provide public comment.

Improvements in protocol development is achieved by determining the patterns of adverse events associated with specific protocols and facilitating the availability of specific micro-biologic assays.

Optimization of animal sources and animal protection/Scientific (and clinical) collaboration through the assembly of scientific and research data.

In order to address the public health concerns associated with xenotransplantation, national registries are needed to assure the safety and efficacy of ongoing investigations. Therefore, both corporate and national registries should be maintained. It is important that these registries be carefully linked by shared software, computer links and prospectively well defined data elements, so that there is free exchange of information. They should also include references to stored/archived specimens so as to correlate these with adverse events.

In Canada, the consensus of the group was that a National Agency for Transplantation will best reflect the ongoing national effort in Canada to establish a standards-based risk

management framework for all transplantation- including xenotransplantation. This national agency would facilitate the compliance and maintenance of standards and the collection of outcome and adverse event data by centre. Xenotransplantation would be a component of this national agency and database. Additional data requirements for this sub-component would reflect the desire to address the potential infectious risks associated with xenotransplantation.

International linkage of databases was the question identified as the most important of the all questions provided to this workshop. The role of these databases and how to develop international collaborations still needs to be defined. International linkage of databases for epidemiologic investigations, for example, is desirable but there are significant concerns about the amount of data that governments routinely collect and share.

Protection of personal liberties and independencies is also important and all parties should be encouraged to establish international collaborations and have access to shared data, while protecting confidentiality of individual patients and investigators.

There is still a tremendous amount of work to be done to establish international collaborations in xenotransplantation. It is important to prospectively coordinate with the principal countries that are performing xenotransplants a common set of (computer-based) definitions for data elements. To encourage a common data set- even if we do not share data immediately- will help to ensure that ultimately there can be collaboration. Without the ability to link databases, and therefore link information by shared definition, data sets will not be comparable.

Payment for the registries became an area of interest and a preferred model was proposed. For the current, largely pre-clinical and early clinical trial status of xenotransplantation, the registries and archives for blood and tissue samples should be maintained at public expense because they benefit the public domain. However, funding from corporate entities could be expected based on the rationale that, at present, xenotransplantation is primarily driven by corporate interest and entities. Initially payment for maintenance of registries and archiving of samples should therefore be born by the corporate sponsors of each trial. It is not likely that this would be a particular popular response, but this was the general consensus.

It was also noted that institutions should not be expected to incur this expense. This may inhibit cooperation with central registries if the cost are going to be passed back to the institution. Most institutions now do not have the finances to pay for non-reimbursable expenses. These added costs will have to be incorporated into the cost of the trials.

Which data sets should be included in the national registries? A central goal should be to maintain anonymity of the individual. Therefore, the minimal amount of data is desired, as long as the complete data set collected is accessible by other established means (i.e. the concept of

linked databanks) on a routine basis. To achieve this end, each of the corporate sponsors or medical centres must agree to maintain a database in a pre-determined format subject to regulatory review.

Patient identifiers must be carefully designed to prevent identification of individuals. The small numbers of potential xenograft recipients at this time means that any individual data element - such as co-morbidity of illnesses, or the date of transplant - might be able to identify an individual. Therefore data made available to the public must be presented in some sort of pooled set to blur the identity of individuals. This is an important point and fields such as geography, dates of procedures and other information available must be carefully screened out before the data become accessible to the public or others that do not require identifiable information. The phrase “sanitization of the databank” was used by this workshop to describe this desired action.

The data collected must reflect the goal of public safety. Although serious adverse events are important and must be reported, lesser clinical diagnosis using the sensitivities of the clinician caring for the patient - such as a viral syndrome or respiratory illness - must also be collected and pooled to capture clinical events.

It is important to stress that those who take care of transplant patients observe tremendous numbers of infections or infections like syndromes in transplant patients. Therefore the background "noise" of infectious disease among those truly related to xenotransplantation is very high (i.e. respiratory syndrome, urinary track infections...).

In order to recognize sentinel events within the larger data set, we may need, initially, to generate a large amount of data including lesser events even though they may not be interpretable initially . There must be a way - again the idea of defining what those categories are in advance - to standardize what is collected and how it will be formatted.

Who needs access to the data? The registries that we have described have been from the perspective of health care authorities, disease surveillance and corporate interest. A very strong point was made that in addition to public health authorities, patient education (a component of informed consent) must be served by the data collected. This information will have to be in a different format . A synopsis of each approved clinical protocol should also be available with summary data, updated at intervals chosen to address confidentiality including adverse events by category, technical complications, infections, serious reportable adverse events, potentially sources of financial support, regulatory concerns. This is key to the public's acceptance and understanding of clinical xenotransplantation.

Presentation of raw data may in fact be a disservice to the public. This kind of information

may not be interpretable or may provide bad impressions (i.e. we do our first xenotransplant and the patient died--an expected result from most investigators' perspectives.) Therefore, a subset of the data must be made available in an "accessible" form to the public. The amount of these data should be as much as is possible without affecting confidentiality.

Counselling and education go hand in hand. Therefore the education of the public should be coordinated with counselling of the individual recipients, so as to provide good background information and to not stigmatize the individuals in the community.

Question of surveillance: Duplicate specimens should be obtained and archived at two different locations: one that is national and another that is local.

Which individuals get sampled? This was a topic of great interest and agreement. The concept that as many samples as possible should be obtained from donors, recipients, sexual and social contacts is both highly desirable and unlikely. That we may be able to maintain complete monitoring beyond the immediate period for any significant amount of time is also unlikely. Although complete surveillance is highly desirable, we expect that the sexual contacts of xenotransplant patients (and the patients themselves) will wander out into the environment and potentially share whatever it is they have acquired with their good friends and neighbours.

It is also accepted that we cannot guarantee all autopsies will be performed It is likely that public health surveillance will be incomplete. Therefore, this workshop has emphasized that whatever we do, we must up front assure the safety of the procedures themselves - because we really cannot guarantee absolute long term monitoring. Therefore we must maximize the data that we can collect, and recruit individuals into clinical trials who are most likely to comply with clinical protocols and stay “in the neighbourhood”. i.e. IT IS ESSENTIAL THAT WE THINK ABOUT COMPLIANCE ISSUES PRIOR TO BEGINNING ANY PROTOCOLS.

WORKSHOP B-2: CLINICAL TRIALS

Chair: Dr. David Grant
London Health Science Centre
London, Ontario

Rapporteur: Dr. Francis Rolleston
Medical Research Council of Canada
Ottawa, Ontario

WORKSHOP QUESTIONS:

1. PATIENTS AND TESTING:

How long should the assessment period be after initial clinical trials, before proceeding with larger trials? Who should determine this? What questions need to be answered?

How should the issue of "xenotransplantation tourism" be addressed? Should initial trials exclude foreign nationals?

There are no comprehensive screening tests for xeno sourced animals. How much emphasis should be placed on the ability to test and screen for infectious agents?

What evidence from pre-clinical studies should there be before limited human trials proceed? (See also Immunology workshop.)

2. FACILITIES:

Can existing transplant facilities perform xenotransplants, or are specialized facilities and staff required before trials can proceed?

3. ECONOMICS:

Should cost-benefit considerations be different for xenotransplantation than for allotransplantation?

WORKSHOP DISCUSSIONS AND RECOMMENDATIONS:

In order to answer the questions put to participants attending this workshop, we adopted the premise that clinical trials are, indeed, appropriate. It was acknowledged, however, that the status of clinical xenotransplantation in Canada has yet to be defined.

We re-ordered the questions posed to our group, starting with preclinical issues, then clinical issues, and finally follow-up issues. We also introduced two additional questions that we considered pertinent.

Question 1:

What evidence from pre-clinical studies should there be before limited human trials proceed? Who should decide?

Answers:

We agreed that there was not enough knowledge at this time to justify starting clinical trials in the near future. Because this field is rapidly evolving, we felt that a national xenotransplantation advisory body should be formed, mandated to review applications for clinical trials and advise regulatory bodies and local Research Ethics Boards regarding these submissions. We had a lengthy discussion about whether this body should be advisory or regulatory, but the consensus was that this panel should be advisory and that we should continue to use existing mechanisms for giving permission to conduct clinical trials.

A generic answer is impossible

Requires protocol-by-protocol decisions based on good science and good medical practice within an ethical framework.

Evidence from primate studies will be required before initiation of clinical trials in most, but not all, cases.

Decisions should be made in the context of the existing mechanism for review of clinical trials with input from a national xenotransplantation advisory body - the local Research Ethics Board must remain responsible for approval of trials within a given institution.

Recommendation:

- We recommend the formation of a National Xenotransplantation Advisory Board mandated to provide advice to regulatory bodies and REBs.

Question 2:

How long should the assessment period be after initial clinical trials, before proceeding with larger trials? Who should determine this? What questions need to be answered? Are standards an appropriate way to regulate this?

Answers:

We felt it was impossible to define generic time limits because the time to assess efficacy might be different than the time required to assess safety; evaluation has to be a continuous process. The decision to expand clinical application would require case-by-case decisions based on good science, good medical practice, and an ethical framework. Furthermore, we felt everyone involved in these studies should have an international perspective. Finally, any standards must be based on solid evidence.

The length of assessment for clinical trials would have to be decided on a protocol-by-protocol basis, according to the current knowledge at the time of submission.

Decisions to expand trials will require case-by-case decisions based on good science and good medical practice within an ethical framework.

The working group felt strongly that we must preserve "a pathway to discovery" within the boundaries provided by public debate. Standards are only appropriate when based on solid evidence of best practice.

Question 3:

How should the issue of xenotransplantation tourism be addressed? Should initial trials exclude foreign nationals?

(Editorial comment: The term "xenotransplantation tourism" describes the situation where people cross national borders in order to obtain treatment involving xenotransplantation, and then return. By such action, elements of society potentially become subject to risks that may not have been considered or accepted. It illustrates the potential confounding aspect of travel on regional or national societal decisions regarding the acceptability of xenotransplantation and indicates the value of an international approach).

Answers:

We felt we could not address the really big issue of public health concerns but thought

that there are existing public health measures in place that could or should be used to deal with problems when, and if, they arise; the availability of legislation to actually quarantine individuals, if necessary, was raised.

that there are existing public health measures in place that could or should be used to deal with problems when, and if, they arise; the availability of legislation to actually quarantine individuals, if necessary, was raised.

A majority believed that foreign nationals should not be included in the initial trials, but there were strong dissenting views.

Existing public health measures should be used to deal with the xenotourist when needed.

(Editorial Comment: Existing legislation was designed to address concerns about contagious disease and would not be helpful for xenozoonosis.)

Recommendations:

HPB, industry, and scientific community should work with other nations to develop common principles for xenotransplantation.

Question 4:

Can existing transplant facilities perform xenotranplants, or are specialized facilities and staff required before trials can proceed?

Answers:

We felt very strongly that it is desirable to integrate xenotransplantation within existing facilities and existing programs. These programs have evolved in a way that aims to provide excellent patient care. It was also pointed out that there may well be programs, such as neurosurgical programs, that are not considered transplant programs but should be included within the concept of "existing facilities".

In the initial phases of development, xenotransplantation should be integrated into existing facilities.

Recommendation:

In the initial phases of development, xenotransplantation should be integrated into existing facilities.

Question 5:

Should cost-benefit considerations be different for xenotransplantation than for allo-transplantation?

Answers:

No.

Costs must be identified in all clinical trials.

Eventually, costs may be higher because we will be paying for the organ itself (which is currently free); surveillance will be more intensive; and the opportunities / indications for transplantation will expand.

Recommendations:

Cost/benefits analysis and clinical introduction of these new technologies should be consistent with the measures applied to the adaptation and introduction of other medical procedures.

Question 6:

How much emphasis should be placed on the ability to test and screen for infectious agents?

Answers:

While acknowledging that testing and screening for infectious agents is very important, we did not attempt to address how much emphasis should be placed on testing; the details will vary from case to case.

The required information must conform to a very high standard and be available in a timely fashion.

The testing facilities do not necessarily have to be on site.

Recommendations:

Consider consent to an autopsy as a requirement for inclusion in the initial clinical trials.

WORKSHOP B-3: ETHICS REVIEW BOARDS

Chair: Dr. Henry Dinsdale
President, National Council on Bioethics and Human Research
Kingston, Ontario

Rapporteur: Ms. Ann Bourke
Policy and Consultation Branch
Health Canada
Ottawa, Ontario

WORKSHOP QUESTIONS:

1. COMPOSITION:

Does a local Institutional Review Board (IRB) have the necessary expertise to review proposed xenotransplant trials?

Should an IRB have access to broader expertise (eg. a National Advisory Board, or *ad hoc* members) for reviewing xenotransplantation trials?

2. RESPONSIBILITIES:

How can an IRB balance patient benefits *vs*. community risks?

Should there be a National Advisory Board? If so, who should be on it and how should it be supported?

WORKSHOP DISCUSSIONS:

The overriding consensus was that there should be a national xenotransplantation advisory board or group. While the opinion of some in the group was that certain REBs may have some capacity to address limited aspects of xenotransplantation, there was general agreement that the issues are so new and complex that the average REB does not have the necessary expertise, and would require additional access and support from a broader-based committee of appropriate experts.

There was also a very strong concern by some workshop representatives about the possible infectious disease risk to the public at large. From this concern is the belief that the public must be involved early in this debate, bringing an important perspective to all decisions.

The public needs to be informed and have a method of input. Terms of reference and regulatory linkages for such a body was not discussed, but there was a general agreement that the initiative should come from Health Canada. This is a matter that concerns public health and it was agreed that this proposed group's reporting structure should include the Minister of Health.

It was suggested that there must also be interaction and linkage with other groups such as the Medical Research Council, other funding councils, provincial health departments, and REBs. A relationship structure would need to be defined if this proposal moves forward.

As a national advisory board, this proposed group should address fundamental issues about the ethics of xenotransplantation research. There was a general feeling that one would carry on with the pre-clinical research, but it was the application of the research and the implications of it that really needed to be discussed in a very fundamental way by this national advisory group. However, whether this group should be limited to an advisory capacity or should be broadened to participation in regulatory oversight was not resolved.

In terms of the makeup of the national advisory board, this group should be capable of addressing all issues on a national level. It should be broadly based, with a goal to interface with the public. There was no decision on how the members of a national advisory board would be selected. Ideally, it should have representatives from the scientific and medical groups, including experts in both human and animal infectious diseases. There is a need for animal welfare to be represented in this group, unlike the traditional needs of a board reviewing clinical trial protocols for research involving humans. Clearly the patients, who are the people most at risk, should be represented. Representation from the ethics, media and legal communities is important. Industry should be involved in helping to develop guidelines, in determining the nature of the research which should proceed, and also by the sharing of their expertise and points of view more effectively.

The influence of a national advisory board cannot work on the basis of guidelines and moral suasion alone. In addition to regulatory review, there are mechanisms through accreditation and other procedures by which pressure can be brought to bear upon institutions. Dr. Thérèse Leroux, for instance, has recently produced a paper about the various modes in which REBs can demonstrate compliance in meeting certain standards and other requirements for approving research [1].

The workshop did not discuss in detail how REBs function in Canada. At this time there is no registry of REBs in Canada , and there is some question as to the current state of compliance of REBs with respect to guidelines from the MRC. In addition, it is anticipated that

[1] T. Leroux et al. Étude comparée des mécanismes élaborés à l'étranger pour examiner les enjeux éthiques et sociaux des biotechnologies." Office of Consumer Affairs, Industry Canada, March 1998.

the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans will be implemented in 1998. These are important considerations which are obviously in the background as we consider any proposed interaction and review of REBs.

Finally, a national body (perhaps as an advisory implementation to a regulatory group) should consider the international implications of ethical issues in xenotransplantation. It was pointed out that to do nothing in terms of research in this area, and to take advantage of research carried out in other countries, goes against basic moral principles. In a country such as Canada there is an ethical implication in not being involved in this area of emerging biotechnologies.

It was further suggested that because of the global aspects of this technology and the potential movement of patients and tissues across borders, that it would be quite appropriate for Canada, in addition to the development of a national advisory group, to also take an initiative in the international field. Similar harmonization activities have been discussed and proposed throughout this Forum with respect to some of the databanks, guidelines, standards and other activities which require an international dialogue.

WORKSHOP B-4: STANDARDS AND SCREENING

Chair: Dr. Jim Wright
Dalhousie University
Halifax, Nova Scotia

Rapporteur: Dr. William Freeland
Medical Devices Bureau
Therapeutic Products Programme
Health Canada
Ottawa, Ontario

WORKSHOP QUESTIONS:

1. STANDARDS:

How can standards be written that encompass a variety of tissue types and source animals (primate and porcine, solid organs, tissues, encapsulated cells, etc.)?

Should the standards address the scaling of risk (eg. the immunosuppressed patient vs. the non-suppressed, vascularized organs vs. cells, etc.)?

Is a standards based approach to regulation appropriate for xenotransplantation?

Should extra precautions be taken by staff and caregivers who handle xenograft specimens?

2. SCREENING:

What should be done if a recipient tests positive? (eg. Notify all participants in the trial? Stop the trial? Begin anti-retroviral therapy for the patient? Increase surveillance?)

What tests are now available for xenozoonoses? Are they sufficient for the potential endogenous and exogenous retroviruses?

How long should monitoring continue? At what intervals?

WORKSHOP DISCUSSIONS:

It should be pointed out that there was good debate on all the questions provided, but that the Health Canada regulators sustained from the decision process in concluding the positions reached below.

The first question discussed was "*is a standard base approach to regulation appropriate for xenotransplantation?*"

The short answer is yes.

We considered three different options:

- a complete regulatory option where all requirements would be described in detailed regulations
- voluntary guidelines only, and
- a standards-based regulatory approach.

It was felt that the complete regulatory control model would be an inappropriate way to address this and that it would be a very labour intensive to initiate change. Because of the current lack of knowledge that exists in this field, it was agreed that the approach must be flexible.

Voluntary guidelines only was ruled out, as this approach did not have enough "teeth" to verify compliance.

A fluid standards based regulatory approach was thought to be the best.

It was further recognized that this field includes many areas lacking enough information and knowledge. The standards would reflect this and would include statements with "must","shall" and "should".

The key elements of the standards should be arrived at by a consensus process, and all stakeholders should be involved in the discussion. There must be "due process" and an auditing of the due process.

It is unclear at this time what kinds of legal authorities can be applied to xenotransplantation and the proposed standards, and this will have to be clarified later. Another advantage of the standards based approach is that it can enable better international coordination.

The second question that we approached was how can a standard be written that encompasses a variety of tissue types in source animals primate versus porcine, solid organs versus tissues or encapsulated cells?

We envisage the xenotransplantation standards as a subset of the Canadian General Standards for transplantation, but with a series of umbrella documents addressing such issues as animal source or the type of graft, cell versus encapsulated tissue versus vascularized organs.

Another issue discussed was that there might be some differences based on the required interval between harvesting the tissue and transplanting. For example, cells that could be harvested and kept in culture or cryopreserved for a period of time would allow for a significant range of donor screening, safety and quality assurance measures applied. A vascularized organ has a very short shelf life before the transplantation and would not have the same time frame to apply a complete battery of tests.

We also wanted to interject a note of caution that writing standards implies a knowledge that is not yet available. Therefore, the advantageous feature we would like to see in these standards would be malleability. They should not inhibit advances in the field of xenotransplantation, but they would need to give some authority to intervene if and when necessary.

The next series of questions addressed were: *should standards be addressed to the scaling of risk?* i.e. immunosuppresssed patients versus non suppressed, vascularized organs versus cells. Then we looked at precautions for staff and caregivers who handle the xenograft specimens and patients.

As far as risk was concerned, we identified three groups essentially at risk:

- the patients
- health care workers involved in the transplant process and taking care of the patients
- the public.

In identifying risk variables there is a presumption that we can also determine the hierarchy of risk - but there is really no hard data available to support this. Cells potentially maybe less of a problem then vascularized organs, but that is not in any way proven at this point. We would also expect that there would be less risk with non immunosuppressed patients then there would be with immunosuppressed.

The source of animal also suggests a similar kind of expectation: that a more ‘distant’ donor source is probably less dangerous as far as transmitting disease to man, but that once again

is really just speculation.

Likewise, it is unclear whether the length of graft exposure is an important factor. It is possible that infection can occur very quickly (e.g. even during bridging transplants) and length of exposure may not be an issue at all. However, for the possibility of recombination of viruses, there is an expectation that longer exposure increases risk. All of these are areas that are worthy of study but that there is really no way to make any absolute recommendations related to any of these at this time.

The second major issue that we were giving to deal with is the area of screening and once again we have reordered the questions here, starting with question 1, *what tests are now available for xenozoonosis? Are they sufficient for the detection of potential endogenous and exogenous retroviruses?*

It has been identified throughout this whole forum there are a number of types of tests that are available, PCR, RT-PCR, serology, co-cultivation, etc.. There are a number of known zoonoses and it is presumed that these would be screened out of source animals. The more important issue is the development of tests for new xenozoonoses. As each new infectious agent is identified there must be probes developed for screening.

Although it was noted that some probes are being developed which will be able to identify closely related viruses of known retroviral families, there is obviously further work in this area that must be done.

Positive identification of a pathogen in the donor animal may be different than identification in the donor organ or in the patient cells after transplantation and will have different implications. It will be important to have technologies available that can further confirm the positivity of a screening test. This would initially involve repeating the screening test, and then - if available - using more specific testing.

It is expected that a list of pathogens to screen for will continue to expand for a long time - possibly exponentially. Due to the high costs associated with screening for all of these pathogens there needs to be a mechanism available to discard screening tests that – over a period of time – seem to have no consequence. That would be something that we would like to have built into the screening expectations.

The second question set asked *what should be done if a recipient tests positive*? Some suggestions included in the question were: notify all participants in the trial, stop the trial, begin anti retroviral therapy in the patient, increase surveillance etc..

Again, this hypothetical question is difficult to address because of the of lack of knowledge in this area, but it is felt that algorithms could be applied that would address the transplant recipient: does the pathogen cause infection and does it cause disease? Disease scales of severity would also be important: whether or not the disease was treatable, transmissibility of the disease, the method of transmissibility of the pathogen. All of these are important variables for which complete information may not be immediately available, so it may be difficult to generate such algorithms. So no specific recommendations were generated at this time.

And, lastly, there was question 3, *how long should monitoring continue and at what intervals?*

There was complete agreement that there should be intense screening at the time of transplantation, and this level of observation should probably continue for 12 to 24 months.

Beyond that time period, active screening (surveillance) should continue, but it would tend to be less frequent. It was felt that a"common sense approach" be applied - but that screening, of some sort, should be life long.

CLOSING REMARKS:

Margaret A. Somerville, AM, FRSC
Forum Co-Chair

A Retrospective Overview of the Discussion of the Ethical Issues

Some major conclusions and questions with respect to the ethical issues raised by xenotransplantation emerged from the Forum.

First, we recognized that xenotransplantation research on human subjects involves decision making in conditions of uncertainty with respect to risk. While this is true for all medical research on human subjects, the difference with xenotransplantation is that the risks not only are to the immediate subjects of the research, but also could be to the public at large. The transplantation of animal organs into humans involves crossing the species and immunological barriers, which carries the risk of transmitting to humans an infective agent that could, in turn, be passed on to others. This possibility of risk to the public in general from xenotransplantation, raises special ethical concerns.

One area of special ethical concern, was the use of animals as the source of organs. The ethical issues in this area involve, first, the ethics of the use, itself, of the animals and, second, the ethics of the way in which they would need to be treated in order to be an acceptable source of donor organs. The question which must be addressed is, is it inherently wrong to use animals for xenotransplantation or to treat them in the way that is necessary to make them suitable as organ donors? The majority of participants appeared to agree that this could be justified, provided certain ethical requirements were fulfilled. These included that everything reasonably possible was done to reduce the animals' suffering; that the animals used were provided with as high a quality of life as possible; and the number of animals used was reduced to the minimum.

The issue of which animal species should be chosen as a source of organs was also a focus of discussion. Although primates were the closest genetic relatives of humans, they were rejected on several counts, including the following: in some instances, for instance, chimpanzees, the species is endangered; the suffering experienced by primates as a result of the living conditions required to make them suitable as organ donors was thought to be unacceptable (this same reasoning was not applied to pigs, but there was more an assumption that this differential treatment was justified, than an explanation of why this was the case); primates would be more difficult and much more costly to care for and manage than other animals that could be used, in particular pigs; the use of primates would be unacceptable to the general public; and the likelihood of the transfer of infective agents was more likely between more closely related species, that is between primates and humans than between pigs and humans. The sense of the meeting seemed to be that if it were ethically acceptable to use animals, then pigs (which were often referred to by the more derogatory term swine) were the animals of choice. There

was little discussion of whether the choice in this respect reflected ethically relevant and justifiable differences between primates and pigs, or perhaps just greater personal identification with primates than pigs (the former look more like us), that is, a certain degree of anthropomorphism, and different cultural attitudes to primates as compared with pigs.

A second ethical aspect related to the use of animals involves the human-animal interface: the transfer of human genes into the animals in order to decrease the likelihood of organ rejection by the human recipient, and the transfer of animal organs into humans. Again, the participants did not seem to regard this as raising ethical difficulties that could not be overcome and that would require the prohibition of xenotransplantation. It was pointed out that the ethical questions surrounding the use of animals and the mixing of human and animal genes and organs, raise issues not just with respect to the physical realities they create, but also with respect to important societal values and, in particular, with respect to maintaining respect for both human and animal life. There was no dissent from the view that we have serious obligations to ensure that these values are not damaged.

The major ethical issue articulated at the forum, on which the **participants were seriously divided in their views**, was whether clinical trials of xenotransplantation in the human context should be allowed to commence. Leaving aside risks to transplant recipients, the central issue was expressed as whether, at this time, xenotransplantation can be regarded as sufficiently safe in terms of the risks of the transfer of an infective agent from an animal to a human that could put at risk the general public, for limited, carefully safeguarded, clinical trials to commence. The argument in favour of proceeding with a limited number of sentinel cases of xenotransplantation is that this is a life saving intervention for people with no other medical alternative and should be developed. This requires research on human subjects. The argument against this is that this could put the health and lives of others at risk.

In addressing this dilemma there was agreement, first, that the ethics of xenotransplantation must be embedded in the science - bad ethics is bad science and, in this area in particular, ethics cannot just be an add-on after the science has been carried out. Second, it was agreed that it is essential to proceeding with any human trials of xenotransplantation that there first be an informed public debate and that, ultimately, it is Canadian society which must decide whether xenotransplantation will proceed and, if so, under what general conditions. In short, these decisions must be taken by all stakeholders, not just the scientists or industries involved in xenotransplantation. It was acknowledged that we have insufficiently developed mechanisms for engaging in a broad, in-depth public debate, and it was recognised that there is an ethical requirement to establish the means through which this can be achieved, including possibly, setting up a National Advisory Committee.

It is relevant to note that most of the workshop reports which examined and articulated the ethical and scientific requirements for carrying out human trials on xenotransplantation, made

these recommendations simply assuming, for the purposes of discussion, that it was ethically acceptable to proceed with xenotransplantation. In other words, they did not decide whether or not it was ethically acceptable to proceed. Rather if it were ethical, then the recommendations which they made were the ethical and scientific principles which should be applied. Some of the recommendations made in the workshops to govern xenotransplantation were it to proceed, would be unique to this form of research. For instance, recipients would be required to agree to long term - indeed lifetime - monitoring, informed consent would be required from the sexual partners of the recipients to the risks which these partners could run, etc. **As well, of course, all the usual ethical and legal requirements governing medical research on human subjects would apply.**

The crucial question, therefore, is are we ethically justified in creating unknown risks with xenotransplantation? In answering this question, as was discussed at the Forum, the allocation of the burden of proof will be crucial. It was my sense of the meeting that there was agreement that those who wish to undertake xenotransplantation, have the burden to show that this is both *reasonably safe and ethical*. This means that if there is equal doubt as to whether either of these requirements are fulfilled, xenotransplantation research on humans cannot proceed until this doubt has been resolved in favour of proceeding.

At a broader level, major insights that I saw the Forum as eliciting included that:

The xenotransplantation debate is of great importance to society with respect to the ethics of protection of both human and animal life, and not simply in the present, but also with respect to future generations.

We should take the 'medical and scientific cloak' off xenotransplantation. Xenotransplantation is a very important area of medical and scientific research, but it does not just involve *medical and scientific decision making*. Rather, it involves *decision making in a medical and scientific context.* This latter description should tell us that there is a much broader range of people and institutions, and considerations and concerns, that must be taken into account in deciding what we do about xenotransplantation, than simply the medical and scientific ones.

The decision makers and the range of issues must definitely include the public and their concerns.

We need credible, informed, wise and courageous discussion and decision making about xenotransplantation.

Organ transplantation has always been at the crossroads of new medical science and technology, on the one hand, and, the impact of these on individuals and society, including on

our moral and ethical values, on the other hand. The birth of modern bioethics is often regarded as having taken place on the day on which Dr. Christian Barnard carried out the first human heart transplant in South Africa. We thought at that time, when we had dealt with the major ethical, legal and social issues that this raised, that we had solved most of the problems that the transplantation of organs would create for us. But we were surprised by the new issues that constantly arose in this context, and, interestingly, these were usually at the forefront of where we were pushing both our science and bioethics. Xenotransplantation is the latest situation in which transplantation science is challenging us to state where we stand on some very important and fundamental principles of human ethics. In a sense, transplantation is like the bioethics canary in the societal mine shaft. Therefore, how we handle the ethics of the science of xenotransplantation affects not only that area, but our society in general. Consequently, the xenotransplantation debate should be added to the other major societal debates in which we are engaging at the end of the twentieth century, many of which involve medicine or medical science (for instance, the debates surrounding genetics, human cloning, new reproductive technologies, euthanasia, allocation of and access to health care, etc.) which in combination will be a major force in determining the nature of the society that we will become.

CLOSING REMARKS:

Michael Gross, FRCS (C & Lond)
Forum Co-Chair

In addition to my role as the co-chair of this forum, I am also the chair of a Xenotransplantation Expert Working Group tasked by Health Canada's Therapeutic Products Programme to explore the potential of drafting standards for xenotransplantation. This group of experts quickly came to the realization that the issues surrounding xenotransplantation are many and the questions of safety go beyond those of the potential recipient. Transplantation of viable cells, tissues or organs from animals into humans is not an accepted therapy at this time and any standard we would generate must describe a complete ethical and scientific framework for proposed clinical trials.

Before xenotransplantation trials can be considered - and before a draft standard for xenotransplantation should be circulated for comment - this committee recommended that Canadians must be informed of the potential benefits and risks of xenotransplantation and have an opportunity to participate in this important discussion.

The ***National Forum on Xenotransplantation: Clinical, Ethical and Regulatory Issues*** represented the first step in the exercise of education and participation of Canadians on the important issues surrounding xenotransplantation. A balanced forum of Canadian and international experts, interested parties, stakeholders and potential consumers were brought together by design to discuss the safety, the potential benefits and risks, the ethics of human and animal interactions and co-dependencies, and the way that xenotransplantation should be monitored and applied. This forum allowed for free exchange of information, free debate, and open exploration of ethical concerns. There were no hidden agendas.

As the co-chair of the forum it is as my role to ensure that all participants' voices are heard, as a member of the Xenotransplantation Expert Working Group it is to listen, to take notes and to bring back recommendations, and as a citizen to represent and communicate the public's interest in this discussion.

There were many expectations presented at this forum, both formally and informally. Patients and future patients have expectations that their individual needs are going to be met. Society expects that the risks are going to be identified on an ongoing basis and that the appropriate safeguards will be put in place to protect all Canadians. The many issues of animal welfare and their importance to medical research and therapies also have to be addressed. Industry has expectations that there will be a stable and efficient environment through which they can meet the demands of patients through their caregivers. And finally Health Canada, the regulator who sponsored this important Forum, has the expectation that they can participate in

this ongoing process that will allow safeguards to be put in place to balance the need to serve the patient and protect the public.

This Forum held in November 1997, represented the first step in this exercise of educating and involving Canadians in the many issues of xenotransplantation. The release of the Forum report is now a continuation of this important process. Our expectations as an expert committee and from the forum participants is that we will communicate as broadly as possible the results of the Forum, the observations made, the key issues and recommendations that were identified.

I encourage you to review this report and forward your comments and suggestions to the Therapeutic Products Programme. The issues and recommendations from this forum - together with comments received from the forum report - will be reviewed by the Expert Working Group on Xenotransplantation as it continues to define the steps that must be followed in order to review xenotransplantation and determine if it can be performed ethically, successfully and safely in Canada.

As co-chair of this forum I wish to express my thanks to everybody that participated. I have never had such a great learning experience myself. I feel I have been wonderfully educated and have also exposed the depth of my ignorance, which is always a good thing. I would like to say thank you very much to the Therapeutic Products Program, the staff, the forum planning and advisory committee members and everyone who has been involved in making this an excellent first step in addressing the possibilities of xenotransplantation in Canada.

XENOTRANSPLANTATION CORRESPONDENCE:

Health Canada's regulatory system is designed to address the needs of Canadians within the context of the Canadian health system, Canadian medical practices and Canadian values. As a regulatory body of Health Canada, the Therapeutic Products Programme (TPP) is committed to making well-informed decisions for xenotransplantation.

As part of a transparent and informed decision-making process for xenotransplantation, TPP encourages all interested individuals and organizations to forward their comments on the Forum report or any other issues relating to xenotransplantation. Please forward correspondence to the TPP contact:

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Thank you in advance for your efforts to assist us in this work.

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ANNEX 5
BIOGRAPHIES

Dr. Lorne Babiuk
Director, Veterinary Infectious Disease Organization (VIDO)
University of Saskatchewan
Saskatoon, Saskatchewan

Lorne Babiuk, a Saskatchewan native, obtained his B.SA., M.Sc. and D.Sc. degree at the University of Saskatchewan and a Ph.D. from the University of British Columbia. He was appointed as Professor of Veterinary Microbiology at the Western College of Veterinary Medicine in 1973, Associate Director (Science) of the Veterinary Infectious Disease Organization in 1984 and Director of VIDO in 1993. Dr. Babiuk also serves on numerous national and international committees in setting scientific policies, in addition to being active in the scientific community.

For the past 23 years Dr. Babiuk has focused his research activities on understanding how viruses and bacteria cause disease and how animals respond to infection. During this time, he has assembled and trained a group of researchers in biotechnology and immunology to help identify protective proteins of disease-causing organisms and to determine ways to enhance the immune response of animals using cytokines. As part of these activities his group at VIDO produced and licensed the world's first engineered vaccine for any animal species, when they developed Pasteurella leukotoxin to control respiratory disease in cattle. Subsequently, they developed additional subunit vaccines for use in pigs and cattle. In addition, the VIDO group is developing live-vectored vaccines for poultry and other livestock. These research achievements have been published in over 300 peer reviewed manuscripts and 63 review articles and lead to 7 patents awarded and 5 patents pending.

Dr. Babiuk has been instrumental in transferring technology from the research laboratory to industry. As a result, VIDO has a number of industry interactions with multi-national companies as well as having played a pivotal role in spinning off a local company, BIOSTAR Incorporated. BIOSTAR Inc. raised over 10 million dollars in private funds to develop technologies originating at VIDO. In recognition of this University /Industry interaction he was awarded the Xerox Canada Forum Award in 1993.

Dr. Fritz H. Bach
Harvard Medical School
Boston, Massachusetts

Fritz Bach, born in Vienna, Austria, received his A.B. degree from Harvard College and his M.D. from Harvard Medical School. After a residency in internal medicine at New York University, he joined the Laboratory of Genetics at the University of Wisconsin, Madison in 1965. He was promoted to Full Professor in 1973, and in the following year took on Directorship of the newly-established Immunobiology Research Center at that University. Dr. Bach was awarded Full Professorship at Harvard medical School in December 1994 and Lewis Thomas Professorship in November 1995.

In 1979, Dr. Bach moved to the University of Minnesota, Minneapolis, as Professor of Laboratory Medicine, Pathology and Surgery and to function as the Director of the Immunobiology Research Center. As of July 1, 1992, Dr. Bach became Director of the Sandoz Center for Immunobiology at Harvard Medical School. He also directs a Laboratory of Transplantation Biology at the Vienna International Research Cooperation Center in Vienna, Austria.

In 1964, Dr. Bach published a paper in Science, one of more than 500 in his bibliography, in which he described a method, the mixed leukocyte culture (MLC), for testing tissue compatibility between donors and recipients for organ transplantation. This test has served not only as a major approach to determine compatibility of donor and recipient for transplantation, but also became the basic experimental method for studying the response of one of the two principle types of immune cells, the T lymphocytes. Dr. Bach used this method to make several key observations in cellular immunology. He used genetic studies with the MLC to help define HLA, the major histocompatibility complex in humans, which plays such an important role in determining the fate of a graft and in controlling immune responses. He performed, based on testing compatibility in MLC, one of the first two successful, matched bone marrow transplants ever done, and did compatibility testing for the second. He made the all-important observation that there are different classes of antigens associated with HLA that perform different function in regulating the immune response. He also devised a number of additional tests, based on the MLC, that were key elements in the evolution of transplantation biology and basic Immunology.

All during this time, Dr. Bach has played a leading role in the field of transplantation immunology. He has written a large number of the major reviews in various aspects of the field and is one of the most sought-after lecturers at national and international meetings. During the last three years, Dr. Bach has again turned his attention to the area of xenotransplantation, and has played a major role in revitalizing that field with his suggestion that it is activation of endothelial cells of the donor organ that is the fundamental event leading to vascular rejection in that situation, his proposing of an overall model for the basis of rejection by primates of xenografts from a species such as pig, and his view of the future.

Dr. Bach has received numerous honors during his career. These include election as Foreign Member of the Royal Dutch Academy of Sciences, the Emilio Trabucchi Medal, election as an Honorary Member of the American Society of Transplant Surgeons, as well as Distinguished Achievement Awards from Modern Medicine, the Milwaukee Academy of Medicine and The American Red Cross.

Dr. Keith Bailey
Director, Bureau of Biologics and Radiopharmaceuticals
Therapeutic Products Programme
Ottawa, Ontario

Keith Bailey studied chemistry at St. Catherine's College, Oxford, and received his D.Phil. in the chemistry of natural products. He conducted post-doctoral research work and taught chemistry at the University of Oxford for two years, and at Trent University, Ontario, from 1967-1969.

He joined the research laboratories of the then Food and Drugs Programme as a Research Scientist in 1969. His early studies of the chemistry and forensic characterization of hallucinogenic substances

developed into general interests in pharmacology and toxicology of drugs, on which he published over fifty original articles. Progressing to Section Head and Division Chief, he was appointed Director of the Bureau of Drug Research in 1984 and moved to the Bureau of Biologics and Radiopharmaceuticals, as Director in 1994.

Dr. Bailey is a Fellow of the Chemical Institute of Canada. He is Canada's Member-at-Large to the United States Pharmacopeial Convention and has served on various international task forces and committees for the OECD, PAHO, and WHO.

His hobbies include gardening his one acre in the Ottawa suburbs, theater and singing— he belongs to several choral and operatic groups in the Ottawa area.

Dr. Donald Casebolt
Atlantic Veterinary College
Charlottetown, Prince Edward Island

Donald B. Casebolt received his Bachelor of Science Animal Science in 1979, Doctor of Veterinary Medicine in 1983, and Master of Preventive Veterinary Medicine in 1984 from the University of California at Davis. He completed postdoctoral training in laboratory animal medicine and comparative pathology in 1987 at the University of Alabama at Birmingham. He is board certified by the American College of Laboratory Animal Medicine. From 1987 to 1993, Dr. Casebolt was Assistant Professor in the Department of Comparative Medicine and Associate Director of the Animal Resources Program at the University of Alabama at Birmingham. Since 1993, he has been Assistant Professor in the Department of Pathology and Microbiology and Director of Animal Resources at the University of Prince Edward Island.

Dr. Louisa Chapman
Centers for Disease Control & Prevention
Atlanta, Georgia

Louisa Chapman received a BA degree from Macalister College, St. Paul, Minnesota in 1975 and MSPH and MD degrees from the School of Public Health (1977) and the School of Medicine (1982), respectively, University of North Carolina, Chapel Hill. She is board certified in Internal Medicine and Infectious Diseases. Dr. Chapman has worked with a variety of zoonotic viruses during a decade as a viral epidemiologist at the United States Centers for Disease Control in Atlanta, Georgia. She is currently the medical epidemiologist in the HIV/Retrovirus Diseases Branch, Division of AIDS, STD, and TB Laboratory Research, National Center for Infectious Diseases, CDC and heads the CDC Xenotransplantation Working Group.

Dr. Henry Dinsdale
President, National Council for Bioethics in Human Research
Kingston General Hospital
Kingston, Ontario

Henry Dinsdale is a neurologist and Professor Emeritus (Medicine), Queen's University. A graduate of the Faculty of Medicine of Queen's University, he undertook clinical and research training in neurology at the Maudsley and National Hospital, Queen Square, London and the Harvard Neurological Institute, Boston City Hospital. He returned to Queen's University where he was professor and Head of the Department of Medicine from 1983-1993. Dr. Dinsdale's main research interests and publications have been in the area of cerebrovascular disease and blood-brain barrier permeability.

Dr. Dinsdale has been a member of numerous national and international organizations representing his profession and speciality. He was a founding member and currently is President of the National Council on Bioethics in Human Research. He was member of Council and Vice-President of the Medical Research Council of Canada. He is immediate Past-President of the Royal College of Physicians and Surgeons of Canada. He is Chair of the Health and Public Policy Committee of the Royal College.

Dr. John Dossetor
Director, Bioethics Center
University of Alberta
Edmonton, Alberta

Born in India in 1925 of Australian parents, John Dossetor was educated in England's Marlborough College, Wiltshire and entered Oxford University as an Open Scholar in Natural Science in 1943 to study medicine. After 3 years in Oxford, he completed an Honors degree in Physiology before moving in 1947 to St. Bartholomew's Hospital and obtaining medical degrees from Oxford and London Universities in 1950.

Dr. Dossetor's postgraduate clinical residency training in London during the next 5 years was interrupted for two years of National Service in the Royal Army Medical Corps. He returned to London for residency training at the Royal Post-Graduate Medical School, Hammersmith and at St. Bartholomew's Hospital and obtained the MRCP (UK) in 1955 before moving to McGill University (Royal Victoria Hospital). After years as a teaching fellow and then Chief Resident in Medicine at Royal Victoria Hospital (1956-1957), Dr. Dossetor was awarded a Canada Life Insurance Research Fellowship to do research in circadian rhythms of electrolyte excretion and renal function, leading to a Ph.D. at McGill (1961) in Experimental Medicine. This experience was followed by a post-doctorate fellowship of the U.S. Public Health Service at New York University Medical School, Bellevue Hospital.

In 1961, Dr. Dossetor was appointed Director, Renal and Urologic Research, Royal Victoria Hospital, Montreal and in charge of the renal service, with responsibility for dialysis and the medical aspects of renal transplantation. It is noteworthy that in the mid-sixties the Royal Victoria series of cadaver-donor transplants was the second largest such series in the world. In 1963, he was elected Fellow

of the American College of Physicians. Between 1961-1969 immunological aspects of renal transplantation became the principle research field and in 1968, while at McGill, he was appointed Career Investigator of the Medical Research Council of Canada, an appointment in which he remained active to 1989. Dr. Dossetor is recognized as co-founder of the Kidney Foundation of Canada and founding member of the Canadian Society of Nephrology, the Canadian Society of Immunology and the Canadian Transplantation Society.

In 1969, Dr. Dossetor was appointed Professor of Medicine, University of Alberta and Director of the Division of Nephrology and Immunology, Department of Medicine. In 1970, he was appointed Chair and Co-Director (with Dr. Erwin Diener) of a research group in transplantation established by MRC, Canada, at the University of Alberta. He conducted studies in HLA immunogenetics, with two groups of Inuit in the Arctic and many hutterite communities in Alberta, as well as in immunologic monitoring of kidney transplant recipients. He was elected to Fellowship of the Royal College of Opticians, London, UK, in 1982.

In 1985 his interest in medical ethics precipitated a career change into bioethics after a sabbatical year spent in medical ethics at UCSF, San Francisco, the Bioethics Center in Montreal and the Hasting's Center, New World . As Director of the joint-faculties Bioethics Project at the University of Alberta and the University of Alberta hospitals, he was responsible for bioethics teaching at the undergraduate level, ethics seminars for residents and nurses and a graduate course in healthcare ethics. The Bioethics Project evolved in 1990 into the Division of Biomedical Ethics and in 1993 into the Bioethics Center. Dr Dossetor is Past President of the Canadian Bioethics Society of which he is also a founding member. He was appointed Professor Emeritus of the University of Alberta in January, 1992 and Chair of the University of Alberta Hospitals Ethics Committee from 1992-1995 and has remained an active committee member. He served as Director of the Division of Bioethics and Bioethics Center from 1990-1996. He has over 250 publications and has co-authored 5 books. In 1992, he was awarded the 125th Canadian Confederation Commemorative Medal for work with the Kidney Foundation of Canada and on January 4, 1995, he was appointed an Officer of the Order of Canada for his achievements in the fields of medicine and bioethics. He remains active as the first nominee to the Chair in Bioethics, Faculty of Medicine and is a key consultant in the field of ethics for the Center and the Provincial Health Ethics Network, of which he is Vice-Chair and C.E.O.

Mr. E. Michael Egan
Senior Vice President, Corporate Development
Diacrin Incorporated

E. Michael Egan has been Senior Vice President, Corporate Development of Diacrin, Inc. since June 1993. Mr. Egan joined Diacrin from Repligen, where he was employed from 1983-1993 and since 1989 had been Vice President of Business Development. He was also a member of the Board of Directors of Repligen clinical Partners, L.P. and the Secretary/Treasurer of Repligen Sandoz Research Corporation. Mr. Egan's previous positions at Repligen include director of Business Development and Manager of Business Development. Prior to joining Repligen in 1983, Mr. Egan was a laboratory supervisor at Dana Farber Cancer Institute, Division of Medicine. He received a B.S. in Biology from Boston College and a Certificate of Special Studies in Administration and Management from Harvard University in 1986.

Dr. Jay Fishman
Transplant Infectious Diseases
Massachusetts General Hospital
Boston, Massachusetts

Jay A. Fishman, M.D., F.A.C.P., is Associate Visiting Physician in Infectious Diseases at Massachusetts General Hospital, Boston, Massachusett, and Assistant Professor of Medicine at Harvard Medical School. Dr. Fishman is on the staff of the Infectious Disease (Medicine) and Transplantation (Surgery) Units and is the Clinical Director of the Transplantation Infectious Disease Program at the Massachusetts General Hospital. He received a B.A./B.S. (Biology/lmmunology) from the University of Pennsylvania and the M.D. from the Johns Hopkins University School of Medicine. He completed a residency in Internal Medicine and fellowships in Infectious Diseases and Molecular Biology and Genetics at the Massachusetts General Hospital and at Harvard Medical School. He received additional training in molecular parasitology at the MacArthur Center for Molecular Parasitology at Yale University. He is on the senior scientific staff of the Shriners' Burns Institute (Boston Unit) and Visiting Scientist at the Massachusetts Institute of Technology. He is a consultant to BioTransplant, Incorporated and Diacrin, Incorporated for issues concerning infectious diseases related to the development of swine as xenograft source species. He has served on the United States FDA, Advisory Committee on Xenotransplantation.

Dr. Fishman's laboratory research has focused on studies of the pathogenesis of infection in the immunocompromised host. On-going projects include investigation of the molecular biology of Pneumocystis carinii, viral infections in xenotransplantation and the role of cytokines in pulmonary infection. His clinical research interests are focused on the prevention of infection in solid organ and bone marrow transplant recipients and in other immunocompromised individuals.

Dr. Uri Galili
Allegheny University of the Health Sciences
Philadelphia, Pennsylvania

Uri Galili pursued graduate studies at Hebrew University, Jerusalem, Israel, obtaining an M.S. in Immunology in 1973 and subsequently a Ph.D. in Immunology in 1977. Dr. Galili continued on a Post Doctoral Fellowship in the Department of Tumor Biology, Karolinska Institute, Stockholm until 1979. From 1979-1984, he worked as Assistant Research Immunologist, leading histology and immunology, at the Hadassah University Hospital, Department of Hematology, Jerusalem, Israel. Subsequently, he traveled to University of California, San Francisco where he worked from 1984-1987 as Assistant Research Immunologist in the Cancer Research Institute.

Dr. Galili was appointed as Associate Professor in the Department of Anatomy, University of California, teaching histology and cell biology from 1988-1990. His teaching responsibilities were further expanded at the University of California, from 1989 to 1990, to histology and immunology in the Department of Laboratory Medicine and his specialization in teaching continued there after his appointment

as Professor in Residence, from 1990-1991. Since February 1991, Dr. Galili has pursued teaching immunology, microbiology and molecular biology as Professor in the Department of Microbiology and Immunology, Allegheny University of the Health Sciences.

Dr. Peter Ganz
Manager, Blood and Tissues Division
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Therapeutic Products Programme, Health Canada
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Peter Ganz received both his bachelors (biochemistry, magna cum laude) and doctoral degrees (protein and nucleic acid biochemistry) in Toronto. As a Leukemia Society of America Post-Doctoral Fellow, Dr. Ganz trained in the area of molecular biology (virology) at Harvard Medical School and the University of Toronto. Before moving to Health Canada, he served as Research Director at the Ottawa Blood Center, CRCS. He is well known in Canada for his research in expression of blood factors in transgenic plant systems and in the area of vascular cell biology. Dr. Ganz moved to Health Canada in 1996 and is currently the Acting Manager of the Blood and Tissues Division of the Bureau of Biologics and Radiopharmaceuticals. Dr. Ganz holds a cross appointment in the Department of Biochemistry, Faculty of Medicine, University of Ottawa.

Dr. David Grant
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David Grant is a Professor in the Department of Surgery at the University of Western Ontario. His research interests include xenotransplantation, small bowel transplantation and tolerance induction for transplantation. Dr. Grant is a member of the Editorial Board for Transplantation and Clinical Transplantation and the Director of the International Intestinal Transplant Registry. Dr. Grant has been recognized by receiving the Medal in Surgery, awarded by the Canadian Royal College of Surgery and the Hames IV Travelling Scholarship.

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Toronto General Hospital, Toronto, Ontario

Paul D. Greig is an Associate Professor, Department of Surgery, University of Toronto and Director of the G.I. Transplant Program. He is an hepatobiliary/pancreatic and liver transplant surgeon at the Toronto Hospital. Dr. Greig is the President and Chief of the Board of Directors of the Canadian Organ Replacement Registry (CORR). He has also served as the President of the Canadian Transplantation Society and with Mr. LaPrairie, was the Co-Chair of Organ Sharing Canada. He, in part, authored the document "Safety of Human Organ and Tissue Transplantation in Canada" and currently

serves on the Expert Working Group advising Health Canada in developing the Canadian General Standard for Organ and Tissue Transplantation. He is the Chair of the Subcommittee to the Expert Working Group, on Standards for Perfusable Organs and is also a member of the Subcommittee on Standards for Xenotransplantation.

Dr. Gilly Griffin
Canadian Council on Animal Care
Ottawa, Ontario

Gilly Griffin, Ph.D., is the information officer for the Canadian Council on Animal Care (CCAC). The CCAC is the primary agency setting guidelines for and assessing the quality of institutional animal care and use programs in Canadian science. Since its inception in 1968, it has continuously developed and refined the terms of reference which guide the composition and function of institutional animal care committees and has been the dominant factor in assuring Canadians that high ethical standards are met for animals used in research, teaching and testing. Dr Griffin holds a Ph.D. in physiology and has worked in both medical and agricultural research. She is also the Executive Director of the Canadian Centre for Alternatives to the Use of Animals in Research, based in the Faculty of Health Sciences, University of Ottawa and an Associate Editor of the journal Alternatives to Laboratory Animals (ATLA).

Dr. Michael Gross
Expert Working Group Chair for Xenotransplantation
Queen Elizabeth II Hospital
Halifax, Nova Scotia

Michael Gross is an Associate Professor of Surgery at Dalhousie University in Halifax, Nova Scotia. Dr. Gross is the Medical Director of one of the largest tissue banks in Canada and is keenly interested in the transplantation of tissues. He has served as the Chair of the Tissue Subcommittee of the Canadian Standards Committee for Organ and Tissue Transplantation.

He is also Chair of the Xenotransplantation Subcommittee. As an orthopaedic surgeon, he brings to the conference an understanding of the huge need and potential benefit of transplantation of tissues, both allograft and potentially, xenograft. He is also acutely aware of the need for transplantation from the patients' perspective and the potential benefits that can accrue. He is committed to a consensus process whereby appropriate standards and guidelines can be developed that will respect the desires of the patient and the well-being of those involved in the transplantation process.

Professor Bartha Maria Knoppers
Faculté de Droit, CRDP
University of Montréal
Montréal, Québec

Bartha Maria Knoppers, Ph.D. (Sorbonne, Paris I) is Ful1 Professor at the Faculty of Law, Université de Montréal, Senior Researcher at the Center for Public Law Research (C.R.D.P.) and Counsel

to the law firm McMaster Meighen. She is a graduate of McMaster University (B.A.), University of Alberta (M.A.), McGill University (LL.B., B.C.L) and Cambridge University, U.K, (D.L.S.) and was admitted to the Bar of Quebec in 1985.

Professor Knoppers serves as an expert to committees of the World Health organization (WHO), Geneva and of the National Institutes of Health (NIH), Washington. She is currently Chair of the International Ethics Committee of the Human Genome Organization (HUGO), member of the International Bioethics Committee of the United Nations Educational, Scientific and Cultural Organization (UNESCO) and Co-Director of the Institute for Population Studies (REP). As a consultant to the Ministry of Industry, Ottawa, she was recently appointed to the Standing Committee on Ethics of the Medical Research Council of Canada (MRC).

She was a member of the Central Management Committee of the Canadian Genome Analysis and Technology Program (CGAT), where she also chaired the Medical, Ethics, Law and Social Issues Committee (l992-l995). She is past Commissioner of the Royal Commission of New Reproductive Technologies (1991-1994) and was both past-president of the Canadian Bioethics Society and past Vice President of the National Council on Bioethics in Human Research. She was named Visiting Heritage Scientist by the Alberta Medical Research Heritage Fund (l993-1995) and she co-chaired the Quebec Bar Committee on the Representation of Children in 1993-1995. In 1995, she became Chair of the Social Issues Committee of the American Society of Human Genetics. In September 1996, she chaired the Organizing Committee of the First International Conference on DNA Sampling, Human Genetic Research: Ethical, Legal and Policy Aspcris, held in Montreal and was also named the 'Scientist of the Year' by the CBC French radio network. Finally, in 1997, she received the Medal of the Bar of Quebec.

Dr. Gary Levy
Director, Multi-Organ Transplants
Toronto Hospital
Toronto, Ontario

Gary Levy graduated from medical school at the University of Toronto in 1973. He completed his training in hepatology at the University of Toronto in 1978 and undertook postdoctoral training in immunology at the Scripps Clinic and Research Foundation from 1978-1981. Dr. Levy founded and became the Medical Director of the Liver Transplant Unit in 1987 at the Toronto Hospital and University of Toronto. In 1991, he organized and co-founded the Multi Organ Transplant Unit at the Toronto Hospital and University of Toronto.

Dr. Levy is currently a Full Professor in the Departments of Medicine and Surgery, Director of Gastroenterology at the University of Toronto and Director of the Multi Organ transplant Unit at the Toronto Hospital and University of Toronto.

He has organized and now heads a research group of 11 principle investigators which is focused on studying cellular and molecular mechanisms of inflammation. His research, funded by the Medical Research Council of Canada and the National Institutes of Health has focused on immune-mediated

mechanisms of organ injury due to viruses, alloantigens, and xenoantigens. He has published over 200 original articles and 20 books and book chapters. Dr. Levy has played a leading role in the development of the new cyclosporine microemulsion, Neoral and has demonstrated its usefulness and its efficacy in the setting of liver transplantation

He has received a number of honors including election to the American Society for Clinical Investigation, the Goldie Prize in Medicine, the Canadian Association of Gastroenterology Visiting Research Professorship and the University of Toronto, Department of Medicine Research Award for Outstanding Contributions to Research. He is a member of the following editorial boards: Transplantation Science, Liver Transplantation and Surgery and Current Opinion in Organ Transplantation.

Susan McCabe
Transplant Recipient
Toronto, Ontario

Susan McCabe obtained an undergraduate degree in History at York University and subsequently obtained a Law degree from the University of Windsor. She was called to the Ontario Bar at Osgoode Hall in 1984. Ms. McCabe was past CEO and Chair of the Board of the Canadian Liver Foundation. She is currently serving on the executive committee as Director for Regional Development and as President of Corbrook Enterprises, a provincially funded vocational rehabilitation agency. She has contributed as past speaker and guest panelist on legal ethical issues concerning transplantation at International Association of Nurses and is a member of Health Canada's Expert Working Group formed to provide safety standards for the transplantation of tissues and organs. Ms. McCabe was a recent recipient of Health Canada's Volunteer Achievement Award Certificate of Merit, recognizing individuals who improve the health and safety of Canadians on a national basis.

Mr. Dann Michols
Director General
Therapeutic Products Programme
Health Canada
Ottawa, Ontario

Dann Michols is currently head of Health Canada's Therapeutic Products Programme. Mr. Michols came to the Department of Health on assignment as Assistant Deputy Minister, National Pharmaceutical Strategy. His responsibilities were to facilitate federal/provincial initiatives in the area of national pharmaceutical policy and regulation and to coordinate the results into a comprehensive and cohesive pharmaceutical policy for Canada.

In January, 1993, Mr. Michols assumed the additional responsibility for the management of Canada's drug review agency and for the implementation of the Gagnon Report recommendations and other similar exercises leading to a renewed Drugs Programme. On January 1, 1997, Health Canada's responsibilities for drug regulation and medical device regulation were merged and the new Therapeutic Products Programme was created.

Prior to his work with the Department, Mr. Michols was Director of Operations for the federal Royal Commission on New Reproductive Technologies, responsible for the development and management of all consultation, communication, coordination, and policy analysis activities.

Mr. Michols has had a twenty-seven year career in the Canadian Public Service, the last twelve years at the level of Assistant Deputy Minister. He has served as a senior management advisor to UNESCO in Paris and as Assistant Secretary General of the National Museums Corporation of Canada during the period when new facilities for the Canadian Museum of Civilization, the National Gallery of Canada, and the National Aviation Museum were built.

Born in Calgary, Dann Michols has an MBA from the Harvard Graduate School of Business Administration and a Bachelor of Commerce (Honours) from the University of Calgary.

Ms. Tina Moulton
Division of Cellular and Gene Therapy
Office of Therapeutics Research and Review
Center for Biologics Evaluation and Research, US PHS
Bethesda, Maryland

Tina Moulton is the Alternate Project Officer for th United States Food and Drug Administration (FDA) Contract Task Order for the US-PHS National Xenotransplantation Registry Database (NXRD) Pilot Study and a Consumer Safety Officer in the Division of Cellular and Gene Therapies (DCGT), Office of Therapeutic Research and Review, Center for Biologics Evaluation and Research, FDA, US Public Health Service. She is responsible for overseeing the administration of the NXRD Pilot Study Contract Task Order and she serves as the DCGT liaison responsible for the coordination of xenotransplantation projects.

Dr. Khazal Paradis
Medical Expert, Clinical Research,
Novartis Pharma Limited
Basel, Switzerland

Khazal Paradis received his M.D. degree from McGill University and followed this with a fellowship in pediatric gastroenterology, pediatric hepatology and liver immunology in Montreal, Paris and Minneapolis. Dr. Paradis served as Director of the Pediatric Liver Transplant Program in Montreal, until he joined Novartis Pharma Ltd. in January 1996. He is currently globally responsible for the clinical development of xenotransplantation with Novartis Pharma Ltd. and is located in Basel, Switzerland.

Dr. Amy Patterson
Cellular and Gene Therapies
Office of Therapeutics Research and Review
Center for Biologics Evaluation and Research, US PHS,
Bethesda, Maryland

Amy P. Patterson, M.D. is Team Leader and Interim Deputy Director of the Division of Cellular and Gene Therapies and Medical Officer in the Division of Clinical Trial Design and Analysis at the Center for Biologics Evaluation and Research, FDA. Dr. Patterson is responsible for reviewing both product manufacturing and clinical trial designs in the field of xenotransplantation and in gene and cell/tissue-based therapies for endocrine disorders and in-born errors of metabolism.

She serves as the FDA liaison to the Department of Health and Human Services Committee, responsible for the coordinated development of US Public Health Service perspectives on xenotransplantation. Dr. Patterson received her degrees from Harvard University and Albert Einstein College of Medicine. She completed residency training in internal medicine at the New York Hospital-Cornell Medical Center and Memorial Sloan Kettering Cancer Center and later served as the Assistant Chief Resident in the Department of Internal Medicine at the New York Hospital-Cornell Medical Center. She completed post-doctoral clinical and basic science research fellowships in both pediatric and adult endocrinology and metabolism at the National Institutes of Health, where she is currently an active clinical staff physician.

Maura N. Ricketts, MD, MDSc, FRCPC
Laboratory Centre for Disease Control (LCDC)
Health Canada
Ottawa, Ontario

Maura Ricketts joined Health Canada in 1985 as Head of the National AIDS Case Reporting Surveillance System, LCDC. Deciding to continue her career in LCDC, Dr. Ricketts accepted the appointment as Medical Specialist in the Division of Blood-borne Pathogens, Bureau of Infectious Diseases. The Division of Blood-borne Pathogens is responsible for the risk identification, determination and management, which include surveillance, investigation, policy development and setting national standards.

Dr. Ricketts' current responsibilities are multi-faceted, including consultant for blood-borne pathogens; principle investigator for a both a case control study of CJD and surveillance system for CJD in Canada; country co-investigator for the European Community BIOMED project on surveillance of CJD in the European Union; Canadian principle investigator for the paediatric surveillance for CJD and consultant for infection control practices for prion diseases.

Ms. Frances Rodenburg
Executive Director, Canadian Federation of Humane Societies
Ottawa, Ontario

Frances Rodenburg graduated from the University of Guelph in 1977 with a B.A. in political studies. She joined the staff of the Canadian Federation of Humane Societies in 1982 and became Executive Director in 1992. She works with the Federation's committees on a wide scope of animal welfare issues, including the use of animals in research, animals in food production and the status of animals in law.

Ms. Rodenburg is a community member of a local animal care committee, a CFHS representative to the Canadian Council on Animal Care and a member of the Board of Directors of the Canadian Centre for Alternatives to Animals in Research. She is also Secretary to the Canada Expert Committee on Farm Animal Welfare and Behaviour and an ex officio member of the Canadian Veterinary Medical Association's Animal Welfare Committee.

Dr. Daniel Salomon
Director of Transplantation Research
Scripps Research Institute
La Jolla, California

Daniel Salomon is an Assistant Member of the Scripps Research Institute, Departments of Molecular and Experimental Medicine and Immunology. Dr. Salomon is the Director of Transplantation Research and Medical Director of the Kidney Transplant Program. He is also an adjunct Associate Professor of Medicine, University of California, San Diego. His education includes Northwestern University (Chemistry, 1973) and Stritch-Loyola School of Medicine (MD, 1976). He did his internship, residency and was Chief Medical Resident at Cedars-Sinai Medical Center, University. Nephrology and Transplantation Immunology fellowships were done at the Brigham and Women's Hospital, Harvard Medical School (1980 to 1984). In 1984 he was appointed the Medical Director of the Kidney Transplant Program at the University of Florida and the Heart Transplant Program in 1985.

In 1990, he moved to the Laboratory of Immunology at the NIH to concentrate on basic laboratory work in molecular immunology. These studies have continued since 1993 at the Scripps Research Institute, specifically on mechanisms of human T cell selection in the thymus and human islet cell development and transplantation. In tandem, Dr. Salomon has been active in the design and conduct of clinical trials in transplantation. These include work with the NIH Cooperative Clinical Trials of bone marrow and peripheral blood stem cells in tolerance induction. Dr. Salomon is a Special Government Employee for the US FDA and has served as an advisor in the development of the US Public Health Service guidelines for xenotransplantation. He serves on the Executive Council of the American Society of Transplant

Physicians, the Executive Board of CenterSpan , an internet project for education and research in transplantation and on the Editorial Boards of Transplantation and the Journal of Heart and Lung Transplantation.

Dr. Margaret Somerville
McGill Centre for Medicine, Ethics & Law
Montréal, Québec

Margaret Somerville holds professorships in both the Faculty of Law and the Faculty of Medicine at McGill University, Montreal. She is Gale Professor of Law, as such, she is the first woman in Canada to hold a named Chair in Law, and the Founding Director of the McGill Centre for Medicine, Ethics and Law. She plays an active role in the world-wide development of bioethics and the study of the wider legal and ethical aspects of medicine and science.

Professor Somerville has a background in science as well as in law. She graduated, with distinction, in Pharmacy from the University of Adelaide (1963); in Law, with First Class Honours and the University Medal, from the University of Sydney (1973); and was awarded a Doctorate in Civil Law by McGill University (1978). She has received honorary doctorates in Law from the University of Windsor, Ontario (1992), Macquarie University, Sydney, Australia (1993) and St. Francis Xavier University, Antigonish, Nova Scotia (1996). She was elected a Fellow of the Royal Society of Canada in 1991. She is the recipient of many honours and awards, including the Distinguished Service Award of the American Society of Law and Medicine (1985), the Pax Orbis ex Jure Gold Medal of the World Jurist Association for support and dedication to the cause of world peace through law (1985) and the Order of Australia (1989), awarded in recognition of her international contribution to law and bioethics.

Professor Somerville has an extensive national and international publishing and speaking record. She has wide experience in communicating with large audiences, especially television and radio audiences on topics that raise complex legal and ethical problems for society. She is regularly and frequently involved in such work in Canada and abroad.

Professor Somerville is a consultant to governments and non-governmental bodies, especially regarding public policy. In particular, she has consulted to the Global Programme on AIDS of the World Health Organization, the United Nations Human Rights Secretariat in Geneva, and law reform commissions in Canada and Australia and has been a speaker (including keynote) at UNESCO conferences in Paris. She was the founding Chairperson of the National Research Council of Canada Ethics Committee, and has served on many editorial boards, advisory boards and boards of directors including the Canadian Centre for Ethics in Sport and the American Society of Law, Medicine and Ethics.

She is also active in the clinical sphere, serving on clinical and research ethics committees and consulting for McGill University Teaching Hospitals. Her work in the broad field of medicine, ethics and law has included research, speaking engagements and consultation on issues related to euthanasia, pain relief, genetics, reproductive technology, biotechnology, ecosystem health, aging populations, quality of life, human rights in medicine and health care, the pharmaceutical industry, public health, health care

systems, medical malpractice, human medical research, AIDS, abortion and the allocation of medical resources.

Dr. Calvin Stiller
Chief, Multi-Organ Transplant Service
University Hospital
London, Ontario

Calvin Stiller obtained his medical degree at the University of Saskatchewan in 1965 and his F.R.C.P. (c) in 1970 following post-graduate studies in London and Edmonton. Dr. Stiller is a professor at the Department of Medicine, University of Western Ontario and Vice Chair of the Board at the John P. Roberts Research Institute. He was founder of and is a member of the Multi-Organ Transplant Service at University Hospital in London. Dr. Stiller is also co-founder and Chair of Canadian Medical Discoveries Fund and the Canadian Science and Technology Growth Fund, in addition to being a member of the Order of Canada.

He has served on the Council and Executive of the Medical Research Council and in several capacities in charitable organizations, co-founding the Alan Thicke Centre for Juvenile Diabetes Research, the J. Allyn Taylor International Prize in Medicine and the Canadian Medical Hall of Fame.

Ms. Lucy Thomas
Director, Regulatory Affairs
Imutran Limited, Douglas House
Cambridge, England

Lucy Thomas worked for several years in a toxicology research laboratory in the Biochemistry and Metabolism Department. She moved into Regulatory Affairs in the pharmaceuticals industry in 1986 working for Wyeth-Ayerst UK and Sterling-Winthrop UK before joining Sandoz UK in 1991. She first became involved in the xenotransplantation project in 1996, when Sandoz acquired Imutran, and was appointed the Director of Regulatory Affairs at Imutran Ltd., in 1997.

Dr. Robin Weiss
Institute of Cancer Research
London, England

Robin Weiss is Professor of Viral Oncology at the Institute of Cancer Research, London. Dr. Weiss has spent a significant part of his career studying retroviruses, starting with the discovery of endogenous retroviruses, in birds, 30 years ago. He first demonstrated that CD4 is the primary binding receptor for HIV and he pioneered studies of neutralizing antibody responses in patients infected with HTLV and HIV. Earlier this year, his research group reported a new exogenous human retrovirus , HRV-

5. They have also extensively studied endogenous (inherited) retroviruses in several host species, including humans.

Dr. Clara Witt
World Health Organization (WHO)
Geneva, Switzerland

Clara Witt obtained both her B.A. (1972) and M.A. (1975) in International Relations, at John Hopkins University. She subsequently studied Veterinary Medicine at the University of Pennsylvania and obtained a V.M.D. in 1981. Dr. Witt pursued studies at John Hopkins University under a Comparative Medicine Internship (1982), in Small Animal Medicine and Surgery at the Animal Medical Center and later a Post Doctoral Fellowship (1989) in Immunology and Infectious Diseases. Dr. Witt's board certification includes Diplomate, American College of Veterinary Preventive Medicine (1991) and Diplomate, American College of Laboratory Animal Medicine, (1989).

Dr. Witt was Chief, Laboratory Animal Medicine Section, Office of Laboratory Animal Science (OLAS) at the National Cancer Institute, Bethesda, Maryland from February 1989 to September 1995. Under the general guidance of the Director, OLAS, she was responsible for the activities and direction of the Laboratory Animal Medicine Section, one of three Office sections administering the NCI intramural animal care and use program. She also was responsible for integration of Section activities with those of other sections to assure appropriate and coordinated husbandry and animal care activities.

Since November 1995, Dr. Witt has provided expertise, leadership and guidance in zoonotic and infectious disease prevention and control and laboratory animal medicine and science matters to senior World Health Organization, Headquarters, Geneva, Switzerland and International Agency for Research on Cancer, Lyon, France, policy and programmatic staffs.

Dr. Jim Wright, Jr.
Professor of Pathology
Dalhousie University,
Halifax, Nova Scotia

James R. Wright, Jr. is a pediatric/perinatal pathologist at the Izaak Walton Killam/Grace Health Centre and a Professor of Pathology and an Associate Professor of Surgery at Dalhousie University, Faculty of Medicine, both in Halifax, Nova Scotia. Dr. Wright received a M.D. and a Ph.D. in Experimental Pathology, a M.A. in Medical History, and a B.Sc. in Zoology from the Ohio State University in Columbus, Ohio. He completed a residency in Anatomical Pathology and a NIH sponsored postdoctoral fellowship in Experimental Diabetes with Dr. Paul E. Lacy, both at Washington University School of Medicine in St. Lolls. This was followed by fellowship training in Pediatric and Perinatal

Pathology at the IWK Children's Hospital and Grace Maternity Hospital in Halifax. Dr. Wright has published extensively on experimental diabetes and pancreatic islet transplantation.

ANNEX 6
FORUM PROGRAMME

Thursday, November 6

6:00 - 7:00 p.m.	Meeting of Chairs and Rapporteurs
7:30 - 10:00 p.m.	Reception and Registration

Friday, November 7

7:00 - 8:00 a.m.	Registration

PLENARY SESSION I: Overview

8:00 - 8:10 a.m.	*Opening Remarks* Dr. Peter Ganz, Forum Host A/Manager, Blood and Tissues Division Bureau of Biologics and Radiopharmaceuticals Therapeutic Products Programme, Health Canada, Ottawa, Ontario
8:10 - 8:20 a.m.	*Welcome and Introduction* Mr. Dann Michols Director General, Therapeutic Products Programme Health Canada, Ottawa, Ontario
8:20 - 8:50 a.m.	*Goals and Objectives of Conference* Dr. Peter Ganz, Forum Host A/Manager, Blood and Tissues Division Bureau of Biologics and Radiopharmaceuticals Therapeutic Products Programme, Health Canada, Ottawa, Ontario Dr. Michael Gross, Forum Co-chair Expert Working Group Chair for Xenotransplantation Queen Elizabeth II Hospital, Halifax, Nova Scotia Dr. Margaret Somerville, Forum Co-chair McGill Centre for Medicine, Ethics and Law Montréal, Québec

8:50 - 9:10 a.m.	*Scope of Xenotransplantation* Dr. Calvin Stiller Professor of Medicine University of Western Ontario, London, Ontario
9:10 - 9:30 a.m.	*Overview of the Need for Xenotransplantation in Canada* Dr. Gary Levy Director, Multi-Organ Transplantation The Toronto Hospital, Toronto, Ontario
9:30 - 9:50 a.m.	*Report of the Expert Working Group on Xenotransplantation Standards* Dr. Michael Gross, Expert Working Group Chair for Xenotransplantation Queen Elizabeth II Hospital Halifax, Nova Scotia
9:50 - 10:00 a.m.	Discussion
10:00 - 10:15 a.m.	Break

PLENARY SESSION II: International Perspectives Panel

10:15 - 10:35 a.m.	*The U.S. Approach to Xenotransplantation* Dr. Amy Patterson Office of Therapeutics Research and Review, Center for Biologics Evaluation and Research, US PHS Bethesda, Maryland
10:35 - 10:55 a.m.	*The U.K. Approach to Xenotransplantation* Dr. Lucy Thomas Director of Regulatory Affairs Novartis/Imutran, Cambridge, England
10:55 - 11:15 a.m.	*Need for International Harmonization* Dr. Clara Witt World Health Organization Geneva, Switzerland
11:15 - 11:35 a.m.	*Review of International Policies on Consent and Human Clinical Trials for Xenotransplantation* Professor Bartha Maria Knoppers Faculté de Droit, CRDP, Université de Montréal Montréal, Québec

11:35 - 11:55 a.m.	*Canadian Regulatory Approach to Transplantation* Dr. Keith Bailey Director, Bureau of Biologics and Radiopharmaceuticals Therapeutic Products Programme, Health Canada Ottawa, Ontario
11:55 - 12:10 p.m.	Discussion
12:10 - 1:10 p.m.	Lunch (Main Lounge)

PLENARY SESSION III: Scientific, Medical & Ethical Issues

1:10 - 1:30 p.m.	*Risk of Zoonoses* Dr. Lorne Babiuk Director of Veterinary Infectious Disease Organization, University of Saskatchewan Saskatoon, Saskatchewan
1:30 - 1:50 p.m.	*Porcine Endogenous Retroviruses (PERVs)* Dr. Robin Weiss Institute of Cancer Research London, England
1:50 - 2:10 p.m.	*Immunological Hurdles to Xenotransplantation* Dr. Fritz H. Bach Beth Israel Deaconess Medical Centre and Harvard Medical School Boston, Massachusetts
2:10 - 2:30 p.m.	*Ethical Use of Animals for Medical Treatment* Dr. Gilly Griffin Canadian Council on Animal Care, Ottawa, Ontario
2:30 - 2:40 p.m.	Discussion
2:40 - 3:00 p.m.	Break (Room 104)
3:00 - 5:00 p.m.	Workshops

WORKSHOP A: Xenotransplantation Issues

1. *Immunology*
   Chair: Dr. Uri Galili
   Allegheny University of the Health Sciences
   Philadelphia, Pennsylvania

   Rapporteur: Dr. Bhagirath Singh, Professor, University of Western Ontario, London, Ontario

2. *Xenozoonoses*
   Chair: Dr Louisa Chapman
   Centers for Disease Control and Prevention
   Atlanta, Georgia

   Rapporteur: Dr. Harvey Artsob
   Laboratory Centre for Disease Control
   Health Canada, Ottawa, Ontario

3. *Use and Care of Animals*
   Chair: Dr. Donald Casebolt
   Atlantic Veterinary College
   Charlottetown, Prince Edward Island

   Rapporteur: Dr. Francine Lord
   Veterinarian
   Canadian Food Inspection Agency
   Nepean, Ontario

4. *Patient Ethics*
   Chair: Dr. John Dossetor
   Director, Bioethics Centre
   University of Alberta,
   Edmonton, Alberta

   Rapporteur: Mr. Michael Hudson
   General Counsel, Canadian Blood Secretariat
   Health Canada
   Ottawa, Ontario

5:00 p.m Adjournment of Day 1

ANNEX 1
FORUM CO-CHAIRS AND EXPERT ADVISORS

Saturday, November 8

8:00 - 9:00 a.m.	Summary of Workshops - A

PLENARY SESSION IV: Clinical Trials and Surveillance

9:00 - 9:20 a.m.	*Clinical Trials in Xenotransplantation* Dr. Daniel Salomon Director of Transplantation Research Scripps Research Institute La Jolla, California
9:20 - 9:35 a.m.	Break
9:35 - 9:50 a.m.	*Patient Registries in Disease Surveillance* Dr. Maura Ricketts Laboratory Centre for Disease Control Health Canada Ottawa, Ontario
9:50 - 10:10 a.m.	*Proposed Methods for Patient Surveillance* Dr. Khazal Paradis Clinical Research, Novartis Pharma Ltd. Basel, Switzerland
10:10 - 10:30 a.m.	*Porcine Fetal Neural Cells for the Treatment of Parkinson's and Huntington Disease* Mr. E. Michael Egan Senior Vice President, Diacrin, Inc. Charlestown, MA
10:30 - 10:50 a.m.	*US PHS National Xenotransplantation Registry Database Pilot Study* Ms. Tina Moulton Office of Therapeutics Research and Review Center for Biologics Evaluation and Research, US PHS, Bethesda, Maryland
10:50 - 11:00 a.m.	Discussion
11:00 - 1:00 p.m.	Workshops

WORKSHOP B: Oversight of Xenotransplantation

1. *Surveillance and Patient Registries*
   Chair: Dr. Jay Fishman
   Harvard Medical School and Massachusetts
   General Hospital
   Boston, Massachusetts

   Rapporteur: Dr. Robert Kauffman
   BioTransplant Inc., Charlestown, Massachusetts

2. *Clinical Trials*
   Chair: Dr. David Grant
   London Health Science Centre, University Campus
   London, Ontario

   Rapporteur: Dr. Francis Rolleston
   Medical Research Council
   Ottawa, Ontario

3. *Ethics Review Boards*
   Chair: Dr. Henry Dinsdale
   President, National Council on Bioethics and
   Human Research
   Kingston, Ontario

   Rapporteur: Ms. Ann Bourke
   Policy and Consultation Branch
   Health Canada, Ottawa, Ontario

4. *Standards / Screening*
   Chair: Dr. Jim Wright
   Professor of Pathology, Dalhousie University and
   Isaac Walton Killam - Grace Health Centre
   Halifax, Nova Scotia

   Rapporteur: Dr. William Freeland
   Medical Devices Bureau
   Therapeutic Products Programme, Health Canada
   Ottawa, Ontario

1:00 - 2:00 p.m. Lunch *(Main Lounge)*

2:00 - 3:00 p.m. Summary of Workshops B

PLENARY SESSION V: Perspectives on Xenotransplantation

3:00 - 4:15 p.m.	Panel Discussion and Round Table
Co-Chairs:	Dr. Michael Gross Expert Working Group Chair for Xenotransplantation Queen Elizabeth II Hospital Halifax, Nova Scotia;
	Dr. Margaret Somerville McGill Centre for Medicine, Ethics and Law Montréal, Québec
Members:	Dr. Peter Ganz A/Manager Bureau of Biologics & Radiopharmaceuticals Therapeutic Products Programme, Health Canada Ottawa, Ontario
	Dr. Henry Dinsdale President, National Council on Bioethics and Human Research Kingston, Ontario
	Ms. Frances Rodenburg Executive Director, Canadian Federation of Humane Societies Ottawa, Ontario
	Dr. Paul Greig Director of Liver Transplantation Program The Toronto Hospital Toronto, Ontario
	Dr. Lucy Thomas Director of Regulatory Affairs, Imutran Ltd. Cambridge, England
	Ms. Susan McCabe Transplant Recipient Toronto, Ontario
4:15 - 4:30 p.m.	Closing Remarks Dr. Michael Gross and Dr. Margaret Somerville Co-chairs
4:30 p.m.	Adjournment of Forum

Dr. Peter Ganz

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Novartis Pharma Canada Incorporated

The Canadian Food Inspection Agency

Genzyme Corporation

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